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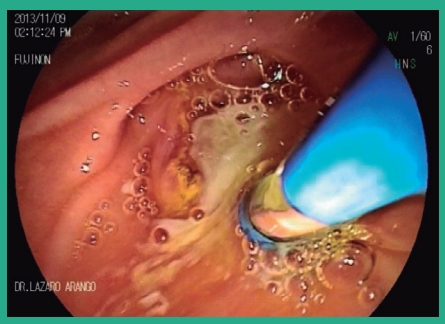
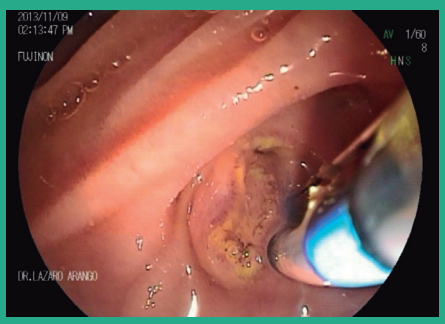
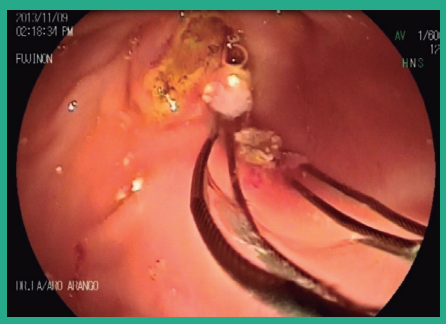

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A. C. G.

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Letter to the editor

Cover: *A. Cannulation of the Wirsung duct. Cloudy material is seen due to chronic pancreatitis (image courtesy of the Union of Surgeons SAS, Lázaro Arango).*
B. Opening cut of the pancreatic duct (image courtesy of the Union of Surgeons SAS, Lázaro Arango).
C. Stone extraction from the Wirsung duct (image courtesy of the Union of Surgeons SAS, Lázaro Arango).
Courtesy by: Lázaro Antonio Arango M., Claudia Patricia Díaz T., Carlos Andrés Caicedo Q.
Article: The current state of diagnosis and management of chronic pancreatitis

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Hybrid technique versus standard technique for endoscopic ultrasound guided fine needle aspiration of solid pancreatic lesions

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Abstract

Endoscopic ultrasound (EUS) is widely used to evaluate pancreatobiliary diseases, especially pancreatic masses. EUS has a good ability to detect pancreatic masses, but it is not sufficient for differential diagnoses of various types of lesions. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is the diagnostic method of choice for pancreatic masses, but its accuracy is affected by various puncture methods. **Materials and methods:** Our objective was to compare the diagnostic yield of examinations of solid lesions in the pancreas by the standard suction technique (ST) with the yield of the hybrid technique (HT) using a prospective, single blind, randomized, controlled design. Patients diagnosed with solid pancreatic lesions who underwent EUS-FNA from May 2014 to June 2016 were included. **Results:** We included 65 patients, 34 of whom (52.3%) were assigned to EUS-FNA with HT, and 31 of whom (47.7%) were assigned to EUS-FNA with TS. We found that the relative frequency that HT successfully obtained an adequate amount of tissue for the cytological diagnosis was 85.2% while ST's relative frequency of success was 71%. The odds ratio was 2.35 (95% CI; 1.2-4.7) in favor of HT. **Conclusion:** This study suggests that the TH is superior to ST for diagnosis of solid pancreatic lesions. Since implementation of this technique does not increase costs and is very simple, we suggest that it become the technique of choice for EUS-FNA.

Keywords

Endoscopic ultrasound, pancreatic cancer, fine needle puncture, cytology.

INTRODUCTION

Solid pancreatic lesions are heterogeneous but can be classified as either neoplastic and non-neoplastic. Neoplastic lesions, the most common, include adenocarcinoma, neuroendocrine tumors, solid pseudopapillary tumors, pancreatoblastomas, lymphomas, metastases, and rare miscellaneous neoplasms. (1) Ductal adenocarcinoma accounts for about 90% of all pancreatic malignancies. (2) It is a significant cause of mortality. Its 5-year survival rate is less than 5% but can reach 20% in selected patients with non-invasive tumors who have undergone surgical resection. The objective is to detect it in early stages. (3) Currently, ultrasound, computed tomography and magnetic resonance imaging are the mainstays used to evaluate 80% to 85% of solid pancreatic lesions. (4) Preoperative diagnosis of solid pancreatic lesions is challenging, despite technological advances in imaging. Endoscopic ultrasound guided fine needle aspiration (EUS-FNA) is the method of choice for detection and diagnosis of these lesions. (5) Its diagnostic yield is highly sensitive and specific, but several factors can affect its performance. Among these are the experience of the echoendoscopist, equipment position, time of day, needle size, technique used, characteristics of lesions, number of passes, whether there is a cytologist in the room, and chronic pancreatitis. (6-16)

The two principal techniques developed to address solid pancreatic lesions are dry suction and wet suction. (17). The dry technique (DT) is standard and consists of placing the patient in the optimal position, locating the lesion with endoscopic ultrasound (EUS), insertion of a 22 gauge needle including a removable stylet, selection of the puncture line, puncturing the lesion with the needle, removal of the stylet, suction by vacuum syringe, movement of the needle from side to side, removal of the needle, and ejection of the sample from the needle using the stylet. (18)

The wet technique has recently been developed to improve sample quality. Prior to puncturing the lesion, the stylet is removed from the 22 gauge needle and pre-washed with 5 mL of saline solution to replace the air column with liquid. A 10 mL syringe is pre-filled with 3 mL of saline solution and used for aspiration after the lesion is punctured. Once the needle is inside the lesion, it is moved from side to side three times. This maneuver is repeated four times (passes) for a total of 12 movements. When the needle is withdrawn, the aspirate is released onto a slide and air is applied. This technique is safer and more efficient for removing the aspirate than is reinsertion of the stylet. (17, 19) A recent metaanalysis has found that patients were more likely to bleed when the stylet was reinserted to remove the aspirate than when the wet technique was used. (20)

The hybrid (TH) technique consists of performing the same steps as the initial wet technique except that a the needle containing a pre-assembled vacuum syringe is used. It is activated once the needle is inside the lesion.

The objective of the present work is to determine and compare the diagnostic yields of the standard dry suction technique and the hybrid wet suction technique when used to study solid pancreatic lesions at a third level hospital institution in Bogotá.

MATERIALS AND METHOD

This study presents our experience at a third level hospital in Bogotá. It is a prospective, single-blind, randomized and controlled study of EUS-FNA techniques for obtaining adequate amounts of tissue for pathological diagnosis of solid pancreatic lesions. Patients who had been diagnosed with solid pancreatic lesion and who underwent EUS-FNA between May 2014 and June 2016 were included in the study. The inclusion and exclusion criteria are summarized in Table 1 and Table 2 The procedures were performed in the gastroenterology ward of a third level hospital in Bogotá under anesthesiologist-guided sedation using a combination of propofol and remifentanil. All EUS-FNA procedures used Pentax brand linear EUS equipment and were performed by an endoscopist who had previously performed more than 1000 such procedures.

Table 1. Inclusion and exclusion criteria

Inclusion criteria
Patients with pancreatic mass referred for EUS-FNA
Exclusion criteria
Patients with decreased functionality: ECOG scale scores of 4 or more (Table 2)
Patients at risk of bleeding (INR> 1.5 or platelet count <50,000/mm^2)
Patients taking 2 or more antiplatelet agents
Patients with a pancreatic mass that is undetectable by EUS
Pregnant women
Patients under 18 years old

ECOG: Eastern Cooperative Oncology Group. INR: international normalized ratio.

Table 2. Eastern Cooperative Oncology Group Performance Status scale of quality of life (21)

Grade	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

FNA 22 gauge (Boston Scientific) needles were used. The hybrid suction technique and the standard dry suction technique (10 mL) with a stylet were used to take biopsies using a total of three passes and four movements within the lesion according to the recommendations described in the literature. (17-19) Samples were spread on slides, fixed in ethyl alcohol, and sent for pathological study by a specialist in cytology of the pancreas who did not know whether the hybrid or dry technique had been used to obtain the samples. Information was recorded in Google Drive. Discrete quantitative variables were obtained and expressed in absolute and relative frequencies from which the risk estimate (odds ratio - OR) was calculated. The capacity of each technique for obtaining a sufficient quantity and sample quality pathological diagnosis was then determined.

RESULTS

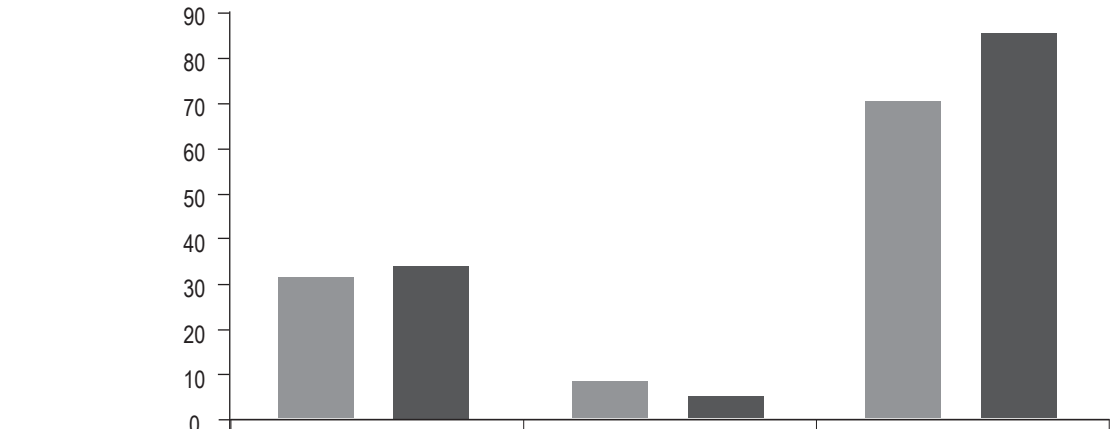
Data were collected from 65 patients who underwent EUS-FNA for diagnosis of solid pancreatic lesions. The hybrid technique was used for 34 patients (52.3%) while the standard dry technique with stylet was used for 31 patients (47.7%). Characteristics are summarized in Table 3. It was found that the relative frequency percentage for EUS-FNA study of solid pancreatic lesions to obtaining adequate amounts of tissue for cytological diagnosis was 85.2% for the hybrid technique and 71% for the dry technique (Figure 1) indicating that the hybrid techniques diagnostic yield is 14.2% higher than that of the standard technique with an OR of 2.35 (95 % CI: 1.2 to 4.7).

DISCUSSION

Endoscopic ultrasound (EUS) offers excellent visualization of the pancreas from the duodenum or stomach. It produces high-resolution images making it one of the most accurate methods for detecting pancreatic focal lesions, especially in patients with tumors measuring 3 cm or less.

Table 3. Patient Characteristics.

	Wet technique	Dry technique	Total patients	*p*
Number of patients	34	31	65	
Gender				ns
Male	15	19	34	
Female	19	12	31	
Age Range (years)	29-87	25-84	25-87	
Mean	65.3	63.5	64.4	ns
EUS diagnosis				
Pancreatic head cancer	26	23	49	ns
Cystadenocarcinoma	1		1	0.32
Lesions in pancreatic head and body	1		1	ns
Lesions in pancreatic body	2	2	4	ns
Focal pancreatic head lesion	2	3	5	ns
Chronic pancreatitis	1	1	2	ns
Solid pseudopapillary tumor	1	1	2	ns
Pancreatic tail cancer		1	1	ns
Lesion size (range in mm)	20-60	17-50	17-60	
Mean	33.3	31.2	32.2	ns
Endoscopic features				
Hypoechoic	27	25	52	ns
Isoechoic	2		2	ns
Heterogeneous	3	5	8	ns
Calcifications	1		1	ns
Mixed	1	1	2	ns
Strain ratio range	12-189	13-140	12-189	
Average	64.3	74	69.2	
Histopathological diagnosis				
Adenocarcinoma	26	17	43	0.0001
Chronic pancreatitis	2	2	4	ns
Solid pseudopapillary tumor	1	1	2	ns
Mesenchymal lesion with atypia		1	1	ns
Oncotic papillary neoplasm		1	1	ns
No diagnosis	5	9	14	0.0001



	Patients	Insufficient sample for diagnosis	Patients' diagnoses (%)
Dry technique	31	9	71
Wet technique	34	5	85,2

Figure 1. Comparison of techniques

(22) In addition, EUS-FNA can obtain samples for pathological diagnosis. EUS is currently considered a safe and accurate imaging technique for tissue diagnosis in patients with pancreatic-biliary lesions and is particularly useful for diagnosing pancreatic tumors and guiding therapeutic decisions. (23) For diagnosis of these carcinomas, it has been found to have diagnostic sensitivity of 54% to 96%, specificity of 96% to 98%, and diagnostic accuracy of 83% to 95%. (24-26)

Attempts to bring its diagnostic yield closer to 100% have included development of several puncture needles including 19, 22 and 25 gauge needles. The 25 gauge needles are easier to handle, cause fewer complications (bleeding), and are less likely to obtain blood-contaminated specimens than are the 19 and 22 gauge needles. (9, 27-29) In addition, 25 gauge needles have been shown to have better diagnostic yields for solid pancreatic tumors than do 22 gauge needles (combined sensitivity: 93% for 25 gauge needles vs. 85% for 22 gauge needles for cytology-based diagnoses). (10)

Nevertheless, the four available metaanalyses on this topic have conflicting results. There is consistent evidence that the cytological quality of samples obtained with 22 and 25 gauge needles are similar, and no convincing advantages of either of the two gauges have been demonstrated in terms of technical performance, ease of use, or safety. Consequently, we decided to use 22 gauge needles for both the wet and dry techniques in this study in order to avoid a confounding factor. (8, 10, 11, 18, 30, 31) Although this technique is considered safe, it is not without complications (0% to 3.4%): the most frequent is mild pancreatitis. (31-33)

Target tissue factors such as masses measuring 20 mm or less and endocrine tumors increase the risk of post-puncture complications. (31-34) Also, serious complications such as bleeding (0.2%), ruptured pseudoaneurysms, pancreatic pseudocysts, abscesses, and cancer seeding have been reported even though they are rare. (31, 35-37) Infectious complications including bacteremia and sepsis occur in 0% to 1%; of punctures of solid pancreatobiliary lesions, but no documented bleeding or infections were reported in this study. (37, 38)

The basic principle of this procedure is to use ultrasound to visualize the target lesion. The puncture site is chosen by taking into account the position of the transducer, presence of blood vessels, amount of tissue between the transducer and the lesion and other factors. The needle chosen is advanced to puncture the lesion, the stylet (if used) is removed, and suction is applied. Then, the needle is advanced and withdrawn through the lesion to obtain cellular material. Finally, the needle is withdrawn and the tissue is collected for cytopathological examination. Variations of this technique have been studied to determine how to improve diagnostic yield. Key factors that can vary include selection of the puncture site, choice of needle, use of a stylet, suction, number of punctures and presence of a cytopathologist. (23, 31, 39)

Some modifications have increased diagnostic yields. Positioning is in first place. The procedure can be performed more comfortably way when the echoendoscope is in a stable position with the tip straight. This allows easy passage of the puncture needle. It is generally better achieved from the transgastric position than from the transduodenal position. (18, 40) It is important to collect samples from multiple sections of a pancreatic lesion using multiple punctures and the fanning technique. Since neoplastic lesions can be heterogeneous with acellular necrotic centers, it is crucial to focus on multiple areas of the lesion, especially on the periphery. Currently, five punctures using the fanning technique are recommended for solid pancreatic lesions. (13, 18, 39) This technique consists of intermittently changing the position of the needle angle using the controls and the elevator to take successive samples from multiple areas of the lesion. This increases the amount of tissue collected, so it was included in the protocol of this study. (13, 31, 41)

A growing amount of evidence also supports the use of Rapid On-site Evaluation (ROSE) with EUS-FNA. ROSE requires the presence of a cytopathologist in the endoscopy room. Using an optical microscope in the endoscopy room, the cytopathologist evaluates the smears and provides the endosonographer with immediate feedback about the quality of the samples for diagnosis and whether additional samples are required. (15, 18, 31, 39, 41)

Numerous studies have confirmed that ROSE increases diagnostic yield by limiting the number of passages and decreasing the number of inappropriate samples. (15, 18, 40-45) Unfortunately, in our setting, the possibility of having a cytopathologist in the endoscopy room is quite limited given the high cost. For this reason, we did not adopt this practice in our study. We decided to perform five punctures and use the fanning technique as recommended by the European Society for Gastrointestinal Endoscopy for puncture protocol. (18)

It is currently known that EUS-FNA commonly fails to result in diagnosis when the cellularity of aspirates obtained is low. This leads to repeated procedures, increased costs and delays in diagnosis which in turn delay early adaptation of treatment strategies. The consequences are higher rates of morbidity and mortality for patients. (44, 45) Initially, wet and dry suction techniques were developed to improve the diagnostic yields of FNA of intra-abdominal solid lesions or those located in the mediastinum. The hybrid technique has not yet been recommended as the overall standard for EUS-FNA. When the dry technique is used, tissue samples have greater cellularity, but there may be more blood contamination which affects the overall quality of the sample. (20, 46)

The wet technique's theoretical superiority is based on a dynamic three-dimensional computational fluid model. Because water is less compressible than air, a needle filled with water should be superior to a needle filled with air since it allows a faster aspiration of the material at the distal end of the needle. (17) The results of our study show that the samples obtained with the wet technique were sufficient to obtain a pathological diagnosis in 85.2% of the cases for which the wet technique was used but in only 71% of the cases in which the dry suction technique was used. The wet technique's diagnostic yield was 14.2 % higher than that of the standard dry technique. These results correlate with the findings of Attam et al. They compared the wet suction technique with the dry technique in 117 patients and found that the wet suction technique significantly increased the acquisition of tissue and had better diagnostic yield: 85.5% versus 75.2% ($P < 0.035$). There was no difference in the amount of blood contamination between the two techniques. (19)

Another pilot study comparing wet, hybrid and dry EUS-FNA techniques in 15 patients with solid lesions was conducted by Berzosa et al. Their objectives were to determine the appropriate sample needed to reach a final pathological diagnosis and to determine the volume of material aspirated and the diagnostic yield (malignant or non-malignant) for each technique. (47) No significant differences were found among the hybrid, wet and dry techniques (87%, 87% and 67%, respectively), but this may be explained by the study's low statistical power. (17)

Although the exact reason why the wet technique provides greater cellularity in the samples obtained is not yet known, theories based on computer models show that a needle filled with water is superior to a needle filled with air since it allows faster aspiration of the material at the distal end of the needle which allows better transmission of the suction applied than that of an air column inside the needle. The saline solution can coat the inner lining of the needle, therefore changing the properties of the surface. This facilitates the movement of the aspirate towards the needle. In addition, the saline column can act as a stylet, potentially reducing tissue contamination during puncture of a lesion while also preventing the needle from clogging. (17, 18, 47)

In addition, the wet technique's saline solution changes the properties of the internal surface of the hollow needle which can reduce friction between the tissue aspirate and the needle wall thereby allowing greater movement into the needle channel. (17) Given the conditions in which this study was conducted, we consider that its main limitation was our inability to have a cytopathologist use ROSE in the endoscopy room. However, we consider that this is not feasible in most endoscopy centers in Colombia even though its absence is likely to result in larger numbers of inadequate samples and therefore lower diagnostic yields. (48) Another limitation is the small sample size although it is much larger than the sample used in the study by Barsa

et al. Also, it would be important for the volume of material in each group to have been measured, even though our goal was diagnostic sensitivity.

CONCLUSION

Our findings suggest that the hybrid wet technique significantly increases cellularity in samples obtained from solid pancreatic lesions above those obtained by the conventional technique. Moreover, the technique is easy to apply in the context of the absence of a cytopathologist in the endoscopy. In addition, the implementation of this has no additional costs. Since this study and another smaller international one suggest the technique's superiority, it should become the technique of choice for EUS-FNA of solid pancreatic lesions.

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Sedation for total colonoscopy with propofol administered by non-anesthesiologists

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Abstract

Introduction: Colonoscopy is a very precise procedure for diagnosis and treatment of diseases of the colon. It allows visualization of the mucosa of the entire colon and the terminal ileum if the examination is adequate. Classically, anxiolysis or conscious sedation has been used through the administration of benzodiazepines, or benzodiazepines plus opiates. However, the use of propofol as a sedative in digestive endoscopy has been gradually spreading in recent years. **Objective:** This study evaluates the evolution of sedation procedures with propofol administered by non-anesthesiologists for total colonoscopies. **Material and Method:** Patients who underwent total colonoscopy who were sedated with propofol administered by appropriately trainedg non-anesthesiologists were evaluated. Hemodynamic and respiratory behavior were measured. Patients were excluded if they were over II on the American Society of Anesthesiologists Physical Status Classification System. **Results:** Three hundred ninety patients were evaluated, 269 (69%) were women, and 121 (31%) were men. Their average age was 53.1 years. The average dose of propofol used was 2.3 mg/kg. Bradycardia developed in 4.9% of the patients according to the definition used. The average dose of propofol in patients with bradycardia was 1.76 mg/kg. **Conclusion:** The use of propofol by non-anesthesiologists can be considered safe as long as the protocols established for this purpose are followed.

Keywords

Colonoscopy, propofol, endoscopy, conscious sedation.

INTRODUCTION

Colonoscopy is very precision for diagnosis and treatment of diseases of the colon. It allows visualization of the entire mucosa of the colon and the terminal ileum if the examination is done well. (1) Classically, anxiolysis (minimal sedation) through administration of benzodiazepines or a combination of these drugs with opiates has been used. However, the use of propofol as a sedative has been gradually increasing in digestive endoscopy in recent years. (2) The administration of propofol is directed by an anesthesiologist in most cases, but 82,620 procedures that have used propofol without presence of an anesthesiologist have been reported by endoscopists. The morbidity rate has been 0.19% while the mortality is zero. (3)

The objective of this project is to evaluate the behavior of patients during total colonoscopy with the administration of propofol sedation by non-anesthesiologists.

MATERIAL AND METHODS

This work was carried out in the diagnostic endoscopy section of the Union of Surgeons in Manizales, Colombia. Patients scheduled for total colonoscopy were evaluated according to protocol and met the inclusion criteria. They were sedated with propofol administered by appropria-

tely trained non-anesthesiologists. Blood oxygen saturation, hemodynamic behavior and respiratory behavior during sedation were all monitored. Patients under 18 years of age and those with ASA (American Society of Anesthesiologists) Physical Status Classifications over II were excluded in accordance with general recommendations for this type of procedure. Intravenous boluses of propofol were administered starting with a 10-30 mg dose and continuing with titrated propofol as needed according to the patient's response. All patients received at least 3 L/min of oxygen by nasal cannula. A heart rate of less than 50 beats per minute was defined as bradycardia for these procedures. This study was approved by the Institutional Bioethics Committee of the Faculty of Health Sciences of the University of Caldas in Resolution CBCS-023-16 of March 31, 2016.

RESULTS

Of the 390 patients evaluated, 269 (69%) were women and 121 (31%) were men. Their average age was 53.1 years, and their average weight was 64.4 kg (Table 1). 70.8% of the patients were ASA I and 29.2% were ASA II. 26.7% of the patients suffered from arterial hypertension, 6.2% had diabetes mellitus, 38.2% had histories of abdominal surgery, 8.2% of the women had had abdominal hysterectomies, 9.5% of the patients were smokers, 8.5% consumed alcohol regularly, and 0.3% consumed other substances (Table 2). The average arterial blood pressure before the procedure was 92 mm Hg, it was 84 mm Hg in the cecum or site of greatest advance, and it was 79 mm Hg after the procedure. The average arterial saturation in the cecum or site of greatest progress was 97% (Table 3). The average dose of propofol used was 2.3 mg/kg (Table 4). Bradycardia (according to the definition used) developed in 4.9% of the patients, and reversal required the use of hyoscine butylbromide although there was no need for atropine or other medications. No relationship was found between bradycardia and ASA I or ASA II classification. The average dose of propofol in patients who presented bradycardia was 1.76 mg/kg, while in those who did not present it was 2.3 mg/kg. The difference was significant ($p = 0.012$ with statistical power of 99%).

Table 1. Sociodemographic variables

N	Female	Male	Average age	Average weight
390	269 (69%)	121 (31%)	53.1 years	64.4 kg

Table 2. Background

ASA 1	ASA 2	AH	DM	ABD S	Cigarettes	Alcohol	Substances	HYST
70.8%	29.2%	26.7%	6.2%	38.2%	9.5%	8.5%	0.3%	8.2%

ASA: American Society of Anesthesiologists; ABD S: abdominal surgery; DM: diabetes mellitus; HYST: hysterectomy; AH: arterial hypertension.

Table 3. Hemodynamic variables

AABP prior to procedure	AABP in the Cecum or highest point of advance	AABP after procedure	Arterial saturation in the Cecum or highest point of advance
92 mm Hg	84 mm Hg	70 mm Hg	97%

AABP: Average arterial blood pressure

Table 4. Propofol dosage

Average propofol dose	Dose bradycardia	Dose without bradycardia
2.3 mg/kg	1.76 mg/kg	2.3 mg/kg

DISCUSSION

This study evaluated the hemodynamic and oxygenation behavior of ASA I and ASA II patients during colonoscopies performed with sedation administered by non-anesthesiologists. Although most of the patient were classified as ASA I patients, we found no real differences in blood pressure levels during the procedure and at the different sites evaluated. Similarly, no differences were found in arterial oxygen saturation. When bradycardia developed, it was reversed with hyoscine butylbromide. Bradycardia may be more closely related to the tension on the mesocolon (vagal reflex) than to the dose of propofol used since patients who developed bradycardia had lower doses of propofol. This association was statistically significant.

To facilitate diagnostic and therapeutic procedures, sedation and/or analgesia is commonly used for medical, dental or surgical procedures by a wide range of health professionals with various qualifications and training. (4) The purpose of sedation and analgesia is to reduce anxiety, discomfort and pain and decrease memories of the event. The appropriate level of sedation ranges from minimal sedation to general anesthesia. (5) Patient comfort is an important measure of colonoscopy quality and outcome and has an

influence on patient satisfaction and acceptance of a new procedure. (6)

Sedation levels range from minimal to moderate sedation to deep sedation and anesthesia. A sedated patient may or may not be awake but maintains an open airway and breathes spontaneously. Similarly, conscious sedation allows communication and response to verbal orders. (7) In general, three types of sedation are used during colonoscopy:

- General anesthesia administered by an anesthesiologist
- Procedural sedation and analgesia (PSA) administered by an anesthesiologist or a gastroenterologist other than the one performing the colonoscopy
- PSA administered by a trained nurse. (8)

Sedation schemes that have been used for invasive procedures include these being midazolam with meperidine, midazolam with fentanyl, and midazolam alone. However, these medications have longer durations of action than does propofol. Their side effects include nausea after the procedure, respiratory depression and accumulation in cases of renal failure. (9) Propofol, developed for induction and maintenance of general anesthesia, has rapid onset of action, less nausea and vomiting. and a short recovery time among its greatest advantages. The latter allows rapid exit of a patient from the endoscopy room. (10)

Propofol is regularly used for sedation, induction, hypnosis, maintenance, anticonvulsant effect and decreasing the cerebral metabolic rate. It acts nonspecifically on lipid membranes and partially in the inhibitory transmitter system (Gamma aminobutyric acid - GABA). (11) It is classified as an ultra-short-acting hypnotic sedative agent that causes amnesia and minimal levels of analgesia. (12)

Injection site pain occurs in more than 30% of patients who receive propofol intravenously. Cardiovascular effects include decreased cardiac output, systemic vascular resistance and blood pressure. Respiratory depression and weakening of cardiac muscular contractions can also occur. (13)

Sedation with propofol for colonoscopy has been shown to be superior to other sedation methods because propofol is associated with a low incidence of cardiopulmonary complications and is superior to benzodiazepines with respect to the speed of sedation of induction and recovery. (14)

Propofol sedation by nurses under the direction and supervision of the endoscopist who is performing the endoscopic procedure remains controversial due to safety-related concerns about the use of an anesthetic for sedation. (15) Recently it has been shown that propofol can be an effective and safe agent when used by non-anesthesiologists to achieve an adequate level of sedation, and adequate evidence supports its use by non-anesthesiologists due to the rarity of life-threatening episodes. (16) In the absence of another person dedicated solely to monitoring the patient and administering medication, administration of sedation by the endoscopist who performs the endoscopic procedure or the nurse who assists is safe and effective. (17) A disadvantage of propofol is its ability to produce rapid changes in neuropsychological function, from conscious sedation to deep sedation, or even narcosis with respiratory depression and apnea. Another disadvantage is that there is no antagonist. (18)

It has been shown that cardiorespiratory complications during colonoscopy may be associated with anesthesia, especially to excessive doses of a drug, inadequate patient monitoring, and/or rapid induction of sedation. (19) A multifaceted specialized training program is needed for individuals who administer propofol. It should include advanced cardiac support and courses designed for this purpose. (20-22) Propofol is one of the medications recommended for sedation grade I and grade II in Colombia. It is recommended by the Colombian Society of Anesthesiology and Resuscitation, the Colombian Association of Gastroenterology and the Colombian Association of Digestive Endoscopy. (23)

CONCLUSION

The use of propofol by non-anesthesiologists can be considered safe for ASA I and ASA II patients as long as the protocols established for this purpose are followed, the person administering the propofol has basic knowledge of the drug and possible complications, and the necessary resources for any untoward eventuality are on hand.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Thyrogastric syndrome: Case Series

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Abstract

A significant percentage of patients with chronic autoimmune atrophic body gastritis (type A gastritis) develop thyroid autoimmune disease (Graves' disease or Hashimoto's disease) and vice versa. This situation is known as thyrogastric syndrome. Its prevalence is unknown, due to incomplete diagnoses. Since the development of atrophic gastritis limits the absorption of vitamin B12 leading to hematological, neurological and metabolic alterations, it is important to perform necessary diagnostic tests and to closely monitor the evolution of patients. Serological detection of autoantibodies against the thyroid gland and the gastric body show the autoimmune etiology and an inflammatory state with tissue damage. Every patient with autoimmune disease should be evaluated to rule out the presence of other pathologies of immunological etiology.

Keywords

Autoimmune diseases, thyroiditis, gastritis, atrophy, antibodies, helicobacter pylori (DeSC).

INTRODUCTION

Thyrogastric autoimmune syndrome (TAS) is defined as thyroid disease of autoimmune etiology (Hashimoto's thyroiditis or Graves' disease) and diffuse chronic atrophic gastritis of the corpus, also called type A gastritis or autoimmune gastritis. It was initially described by Tudhope and Wilson in 1960. (1)

The main cause of vitamin B12 malabsorption is hypochlorhydria or achlorhydria, secondary to atrophy of the gastric oxyntic mucosa. This has been reported in about one third of all people over 50 years of age. There are multiple causes of decreased or absent acid secretion by parietal cells including aggression by autoantibodies against these cells, Helicobacter pylori infections and prolonged use of medications that inhibit gastric secretion (proton pump inhibitors), especially in elderly people. (2, 3)

Diagnosis of TAS depends on clinical suspicion by endocrinologists, hematologists and gastroenterologists. Failure to diagnose can cause serious health problems related chronic malabsorption of essential nutrients such as iron and vitamin B12 (Figure 1). (4)

CASE PRESENTATIONS

Case 1

The patient was a 60-year-old woman with megaloblastic anemia who had been receiving a 1 mg monthly cyanocobalamin supplement to treat vitamin B12 deficiency that had been diagnosed three months earlier. (Table 1). She had developed hypothyroidism three years earlier and was being treated with 75 μg/day of levothyroxine. Esophagogastroduodenoscopy showed atrophic gastritis of the corpus and antrum. Biopsies from the corpus, angular incisures and antrum indicated chronic atrophic gastritis with complete intestinal metaplasia, without dysplasia and without H. pylori. The patient tested positive for parietal

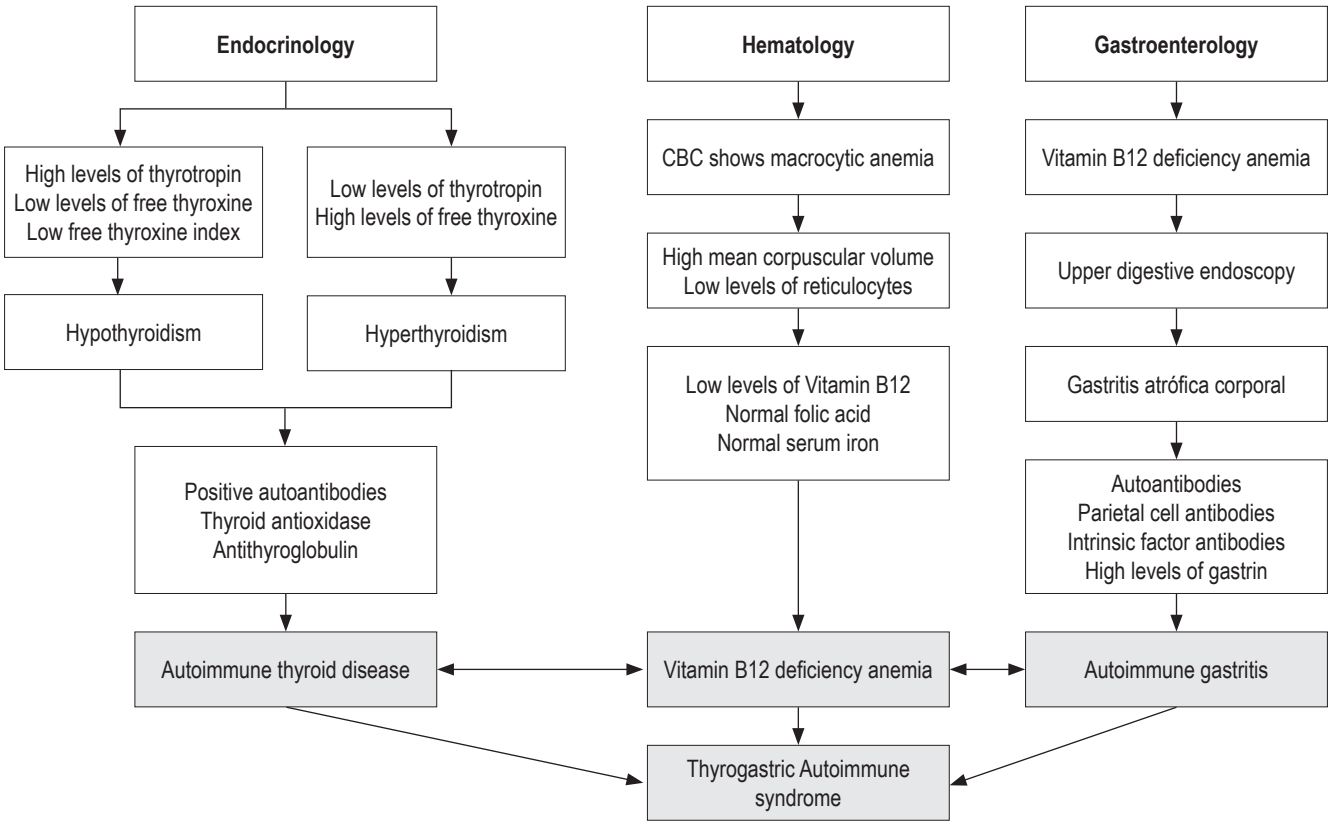

Figure 1. Diagnosis of thyrogastric autoimmune syndrome

Table 1. Patients' laboratory test results

Patient No.	Age	Gender	Clinical history	Vitamin B12 (pg/mL)	Folic acid (ng/mL)	Hemoglobin (g/dL)	Mean corpuscular volume (fl)	Mean corpuscular hemoglobin (pg)	Mean corpuscular hemoglobin concentration (g/dL)	Serum iron levels (µg/dL)
1	60	F	Vitamin B12 deficiency anemia Hashimoto's thyroiditis	150	16	10	110	30	34	80
2	47	F	Iron deficiency anemia Hashimoto's thyroiditis	106	17	13	80	28	32	50
3	63	F	Vitamin B12 deficiency anemia Hashimoto's thyroiditis	54	>20	12	120	30	32	105
4	60	F	Vitamin B12 deficiency anemia Hashimoto's thyroiditis Sjögren's disease	180	18	10	110	26	31	114
5	61	F	Vitamin B12 deficiency anemia Hashimoto's thyroiditis	200	9	15	90	31	33	110

Normal ranges: serum iron: 60-170 µg/dL; Vitamin B12: 200-900 pg/mL (chemiluminescence); hemoglobin: 12-16 g/dL; folic acid: 2.7-17 ng/mL; mean corpuscular volume: 82-98 fl; mean corpuscular hemoglobin: 27-31 pg; mean corpuscular hemoglobin concentration: 33-37 g/dL.

cell antibodies (Table 2). The diagnosis of pernicious anemia plus her history of hypothyroidism antithyroid antibodies (Table 2) result in a diagnosis of TAS.

Case 2

The patient was a 47-year-old woman who had been diagnosed with iron deficiency anemia without a specific cause and who needed ferrous replacement (Table 1). She had no history of digestive bleeding and was not menstruating. She had developed hypothyroidism 7 years earlier which was being treated with 100 μg/day of levothyroxine. Esophagogastroduodenoscopy showed atrophy in the fundus and corpus (Table 2). Two weeks of helicobacter pylori eradication treatment with esomeprazole, clarithromycin and amoxicillin was prescribed. Because of coexistence of hypothyroidism, vitamin B12 deficiency and atrophic gastritis of the corpus, she was tested for thyroid autoantibodies and parietal antibodies (Table 2). A diagnosis of TAS was made and cyanocobalamin treatment was initiated.

Case 3

The patient was a 63-year-old woman who had been referred because of megaloblastic vitamin B12 deficiency anemia. She had been receiving cyanocobalamin due to of 3 months. In addition, she had suffered from hypothyroidism for 10 years and was being treated with 75 μg/day of levothyroxine (Table 1). Esophagogastroduodenoscopy showed atrophy of the corpus and the gastric antrum. Because of the combination of atrophic gastritis and vitamin B12 deficiency, immunological tests for parietal cell antibodies and thyroid antibodies were performed (Table 2) and the diagnosis of TAS was made.

Case 4

The patient was a 60-year-old woman who had been undergoing treatment of Sjögren's syndrome with pilocarpine for five years. The patient had had a combination of megaloblastic anemia (Table 1) and autoimmune hypothyroidism for one year and was receiving 100 μg/day of levothyroxine and 1 mg of cyanocobalamin. Esophagogastroduodenoscopy showed chronic atrophic gastritis and Helicobacter pylori (Table 2). Eradication treatment was prescribed and she was tested for parietal cell antibodies and thyroid antibodies (Table 2). Her results of anemia, hypothyroidism and autoimmune gastritis resulted in a diagnosis of TAS.

Case 5

The patient was a 61-year-old woman with vitamin B12 deficiency anemia who had had hypothyroidism for 10 years. She was being treated with levothyroxine. Her blood tests were positive for thyroid peroxidase antibodies (Tables 1 and 2). Esophagogastroduodenoscopy showed multifocal atrophic chronic gastritis with complete metaplasia, without dysplasia. She was positive for H. pylori. Eradication treatment was prescribed and followed up with a breath test which was negative. She

Table 2. Patient autoantibody and gastric biopsy test results

Patient No.	Parietal cell antibodies	Thyroid peroxidase antibodies (U/mL)	Thyroglobulin antibodies (U/mL)	Gastric biopsy	Helicobacter pylori
1	Positive 1:640	Positive 181	Positive 194	CAGC and CAAG complete intestinal metaplasia	Negative
2	Positive 1:640	Positive >640	Positive 667	CAGC complete intestinal metaplasia	Positive
3	Positive 1:320	Positive 201	Positive 379	GAC complete intestinal metaplasia	Negative
4	Positive 1:2560	Positive 455	Positive 398	GAC complete intestinal metaplasia	Positive
5	Positive 1:64	Positive 76	Negative	CAGC and CAAG Complete intestinal metaplasia	Positive

Normal ranges: thyroid peroxidase antibodies: 0-34 U/mL (chemiluminescence); thyroglobulin antibodies: 0-115 U/mL (chemiluminescence); parietal antibodies: negative (indirect immunofluorescence).
CAAG: chronic atrophic antral gastritis; CAGC: chronic atrophic gastritis of the corpus.

tested positive for parietal cells antibodies (Table 2) and a diagnosis of TAS was made.

COMMENTS

Vitamin B12 deficiency, defined by serum levels of less than 200 pg/dL, is often found in elderly patients. It has been observed in one in twenty people over the age of 65. (5-7)

Hematological, neurological and metabolic alterations secondary to vitamin B12 deficiency are known. An English study over 75 years found vitamin B12 deficiencies in 13% of 1,000 patients and found a clear association between low levels of vitamin B12 and cognitive alterations observed in these individuals, OR = 3.0 (95% CI 1 , 3-6.9). (8)

Vitamin B12 deficiency secondary to autoimmune-caused atrophy of the gastric oxyntic mucosa, also called chronic atrophic corpus gastritis or type A gastritis, causes a type of megaloblastic anemia (classically referred to as pernicious anemia). It is responsible for 25% of all cases of vitamin B12 deficiency. These patients have autoantibodies against parietal cell canaliculi and against the intrinsic factor which leads to the destruction of oxygen glands and induces atrophy. This is evidenced by hypochlorhydria or achlorhydria, G-cell hyperplasia and decreased serum pepsinogen I. It inhibits absorption of vitamin B12. (9, 10)

Vitamin B12 deficiency is also commonly found in patients with chronic multifocal atrophic gastritis (type B gastritis) who do not have any autoimmune etiology. These cases are associated with Helicobacter pylori infections. In contrast to patients with type A gastritis, secretion of intrinsic factor is adequate, but insufficient acid secretion prevents normal absorption of the vitamin. This type of gastritis is common in adults, becoming more common with aging as do neurological and cardiovascular diseases. (11, 12) A study of 75 adult Colombian patients (average age of 56 years) with chronic multifocal atrophic corpus and antral gastritis found vitamin B12 deficiencies in 28%. A third of them tested positive for parietal cell antibodies against. (13)

H. pylori has been found to induce an autoimmune response which causes atrophy of the mucosa of the gastric corpus. Autoantibodies against the gastric mucosa have been detected in 50% to 60% of patients infected with H pylori. Autoantibodies against the luminal membrane of the epithelial cells of the foveoles of the mucosa of both the antrum and the corpus as well as against the membrane canaliculi of the parietal cells of the oxygen mucosa have also been identified. The most important autoantigen is the proton pump H + K + ATPase or acid pump alpha and beta subunits. (14,15)

Gastric autoantibodies, especially H. pylori-induced anti-canalicular antibodies, are associated with histological changes such as increased acute inflammatory activity, hyperplasia of gastrin-producing enterochromaffin cells, decreased production of hydrochloric acid, impaired pepsinogen types I and II, and decreased absorption of vitamin B12. It is known that the majority of patients with autoimmune gastritis are, or were, infected with H. pylori. H. pylori eradication in early stages improves histological changes and decreases autoantibody concentrations. It has been observed that gastritis in the corpus is more severe when anti-canalicular antibodies are identified. (16)

The main tissue damage mechanism is CD4 + T lymphocytes. H. pylori infections induce expression of the major histocompatibility class II complex and costimulation molecules by gastric mucosa cells. This activates intraepithelial lymphocytes. Dendritic cells induce a specific T response against the beta subunit of ATPase which releases cytokines and chemokines (TNF, IL-2, interferon gamma, CXCL8) and increases the number of inflammatory cells. (14) It has been suggested that this autoimmune response may be due to a failure of central immune tolerance. Autoreactive T lymphocytes appear to act on ATPase beta during H. pylori infections or during cell turnover. An increase in gastric cell apoptosis through Fas-FasL molecules has been observed in-vitro when inflammatory cytokines are present. Increased Fas-FasL expression has also been observed in patients with H. pylori where it leads to parietal cell death and where it causes mucosal atrophy. (17)

Several studies have linked H. pylori infections with development of autoimmune diseases such as autoimmune thyroid disease, type 1 diabetes mellitus (DM1), rheumatoid arthritis, Sjögren's syndrome and autoimmune gastritis. (18) Genetic, environmental, and immunological factors are all involved in the etiology of autoimmune diseases. Genetic factors include HLA alleles, mutations, and nucleotide polymorphisms, environmental factors include ultraviolet light, smoking, medications and infections, and immunological factors include T lymphocytes and self-reactive B lymphocytes. (17)

Autoimmune thyroiditis is one of the most frequently diagnosed endocrinopathies. Antibodies against thyroglobulin and thyroid peroxidase have been identified as serological markers of the disease. Molecular mimicry has been postulated as a possible autoimmune mechanism in patients infected with Yersinia enterocolitica bacteria, hepatitis C virus and Helicobacter pylori. Sequences of Helicobacter Cag A cytotoxin and thyroid peroxidase are similar. A reduction in antimicrosomal antibody and H. pylori antibody concentrations has also been observed after eradication treatment. Inflammatory cells, plasma cells that produce autoantibodies against thyroglobulin, peroxidase and the thyrotropin (TSH) receptor, as well as cytotoxic T lymphocytes both of which cause tissue damage have also been found. (19, 20)

Bassi et al. have also found an association between Graves' disease and H. pylori infections. Their study suggests that previous infection may be a trigger for the onset of this disease in patients with genetic predisposition. In addition, other studies suggest that H. pylori infections may worsen autoimmune thyroiditis in immunogenically susceptible patients. This implies that eradication of the infection in high-risk children may prevent autoimmune thyroiditis. It has also been reported that patients with Graves' disease may have elevated levels of gastrin which relates autoimmune hyperthyroidism to autoimmune gastritis. (21) Fallahi et al. have evaluated the prevalence of other autoimmune diseases in patients with autoimmune thyroid disease. The authors' case and control study included 3,069 patients with Hashimoto's thyroiditis and found that the disease's most frequent and significant association was with chronic autoimmune gastritis. (22)

In addition, patients with DM1 also frequently have autoimmune thyroiditis. It has been postulated that patients with one autoimmune disease have a higher risk of developing another autoimmune disease. Approximately 20% of patients with DM1 have antithyroid antibodies and 5% of them develop autoimmune hypothyroidism. (23) Mervat et al. have found a high prevalence of H. pylori infections in patients with DM1 and that glycosylated hemoglobin levels were higher in patients with H. pylori infections than in uninfected patients. In addition, they found that autoimmune thyroiditis was more common in patients with DM1 who had thyroid antibodies and who were infected with H. pylori than it was in otherwise healthy individuals. (24)

Autoimmune gastritis develops in 13% of patients who already have autoimmune thyroid disease whereas 50% of patients who begin with autoimmune gastritis develop autoimmune thyroiditis. (4, 25) Consequently, we believe that pertinent examinations to determine the coexistence of the other disease are justified for all patients with any of these pathologies. Timely detection and determination of potential clinical consequences are need for establishing a program of subsequent surveillance.

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Endoscopic hemostasis in intensive care unit patients with upper digestive tract bleeding

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Abstract

Introduction: Patients hospitalized in an intensive care unit (ICU) are at risk of upper gastrointestinal bleeding. Esophagogastroduodenoscopy (EGD) is the test of choice for these patients. EGD is diagnostic and therapeutic. Many endoscopically identified lesions do not require endoscopic treatment. In Colombia there are no studies on the prevalence of different upper gastrointestinal bleeding lesions in ICU patients, nor on the use of therapeutic EGD in these patients. **Materials and methods:** This is a cross-sectional study conducted at the Clínica Fundadores in Bogotá Colombia between January 2003 and February 2017. Adult ICU patients who underwent EGD due to upper gastrointestinal bleeding were included. **Results:** In the final analysis, 156 patients who underwent EGD were included. Of these, 76.62% (118) had chronic gastritis, 57.79% (89) had erosive esophagitis grades A to D, 47.4% (73) had erosive gastritis, 21.43% (33) had erosive duodenitis, 18.18% (28) had gastric ulcer, 11.69% (18) had esophageal varices, 11.04% (17) had duodenal ulcers, and 4.55% (8) Mallory Weiss tears. Only 15% of patients, including those with esophageal varices, required endoscopic management. **Conclusions:** In this study, 15% of patients with upper gastrointestinal bleeding required endoscopic treatment. Prospective work should be done to establish risk factors to predict the need for therapeutic EGD in patients with upper gastrointestinal bleeding. Patients do not have these predictors should be treated empirically with PPI to avoid unnecessary expenses of diagnostic EGDs.

Keywords

Intensive care, hemorrhage, endoscopy.

INTRODUCTION

Patients hospitalized in the intensive care unit (ICU) have a higher risk of upper gastrointestinal bleeding (UGIB) especially due to stress ulcers. (1, 2) Its appearance is associated with adverse outcomes including 2 to 4 times higher mortality rates and 4 to 8 day longer ICU stays. (3, 4) The incidence of gastrointestinal bleeding in ICUs ranges from 0.17% to 7.0%. (3, 5) An upper gastrointestinal endoscopy (esophagogastroduodenoscopy or EGD) is the test of choice for patients with UGIB, including those in the ICU. EGD can be both diagnostic, macroscopic examination of lesions and taking of biopsies, and therapeutic, various methods of achieving hemostasis. (5, 6) Its performance is well demonstrated in patients with UGIB. (7-10) However, EGDs are more controversial when they are performed in patients admitted to the ICU for other reasons. In addition, the discovery of gastritis, esophagitis, or other GI problems may not require any endoscopic or pharmacological treatment. (5, 7, 11, 12)

Among the causes of UGIB in ICU patients are esophageal varices, gastric varices, esophagitis, ulcers and stress-induced gastritis. (13) It has been estimated that up to 90% of critically ill patients may present gastroduodenal mucosal damage after three days in an ICU and that damage may progress to ulcers and cause bleeding,. Bleeding from ero-

sive gastritis is another potential danger. (14) Nevertheless, UGIB is clinically important bleeding in only 2% to 3% of these cases, and stress ulcers are identified endoscopically as the source of bleeding in less than 50% of these patients. (4, 15, 16) These data have raised a discussion about the real need for EGD given its costs and given the real impact of indiscriminate use on this type of patients, especially since only a small percentage progresses towards manifest and clinically important gastrointestinal bleeding. (17)

Other less common conditions responsible for UGIB are Mallory-Weiss syndrome and vascular lesions. (13) The principal upper gastrointestinal risk factors in an ICU include mechanical ventilation for more than 48 hours, active coagulopathy, liver disease, and kidney disease. (5, 18, 19) Other risk factors are shock, liver failure, kidney failure, sepsis, multiple traumas, burns of more than 35% of the body surface, organ transplantation, skull or spinal cord trauma, history of previous ulcerative disease and hypoalbuminemia. (20-24)

We found no publications on the prevalence of bleeding lesions of the upper digestive tract in ICU patients in Colombia, nor did we find literature on the frequency of endoscopic hemostasis in these patients. Taking into account the limited information available, we decided to perform this study in the Gastroenterology Unit of the Clínica Fundadores in Bogotá by identifying ICU patients who had developed UGIB and had undergone EGD.

MATERIALS AND METHODS

This is a cross-sectional study based on EGD findings from ICU patients at the Clínica Fundadores who underwent EGD because of UGIB. Adult patients over 18 years of age who were treated during the period from January 1, 2003 to December 31, 2017 were included.

Inclusion Criteria

Patients hospitalized in the ICU for critical illnesses were included if they developed UGIB after 24 hours of hospitalization and underwent an EGD.

Exclusion Criteria

ICU patients who had undergone EGD because of any indication other than UGIB were excluded. Patients with incomplete EGDs, those hospitalized in the intermediate care unit and pregnant women were also excluded. Those who were hospitalized in the ICU because of severe UGIB were not included.

Information was obtained from EGD reports of the gastroenterology unit corresponding to the ICU and a review of the medical histories of the patients identified. Variables of each patient were recorded in a data base built for this study. Because only patients with EGD were included, the number of ICU patients with UGIB for whom no endoscopy was performed during the study period is unknown.

Overall Objective

Our overall objective was to determine the need for endoscopic hemostasis in ICU patients with UGIB.

Specific Objectives

- Determine the prevalence of endoscopic lesions in patients with upper gastrointestinal bleeding who were hospitalized in the intensive care unit.
- Identify endoscopic techniques used and compare the prevalence of endoscopic findings according to age groups.

Statistical Analysis

Qualitative variables are presented in the form of absolute numbers and proportions. Prevalence was defined as (the number of patients who underwent endoscopy/the total population) x 100. Prevalence was stratified by age groups. Averages, measures of dispersion, and statistical distributions are presented for quantitative variables. Distributions were evaluated with the Shapiro-Wilk test. Statistical significance was considered to be p less than 0.05.

RESULTS

During the study period, 246 EGDs were performed on ICU patients. Ninety-two of these were excluded:

- Sixty-nine were excluded because they were performed for reasons other than UGIB.
- Eighteen were excluded because patients had nasogastric tube.
- Eight were excluded because they has had endoscopic gastrostomies.
- Seven were excluded due to neoplasia.
- Six were excluded due to abdominal pain
- Four were excluded due to anemia.
- Four were excluded due to dyspepsia.
- Three were excluded due to known cirrhosis.
- Three were excluded due to esophageal varices.
- Two were excluded due to gastroesophageal reflux.
- Two were excluded due to swallowing disorders
- Two were excluded due to esophagitis
- Two were excluded due to exogenous intoxication.
- One was excluded due to an esophageal obstruction

- One was excluded due to an intestinal obstruction
- One was excluded due to an intestinal fistula
- One was excluded due to a tracheoesophageal fistula
- One was excluded due to a bleeding biopsy site.
- One was excluded due to mediastinitis
- One was excluded due to a gunshot wound
- One was excluded due to an esophagectomy and gastric ascent
- Thirteen were excluded due to unrecorded indications for EGD
- Six were excluded due to incomplete studies
- Three were excluded due to inadequate preparation
- One patient did not allow the examination

We included 154 patients who underwent EGDs (Figure 1) including 99 men (64.29%) and 55 women (35.71%). Their median age was 68, and half of them were between 59 and 76 years of age.

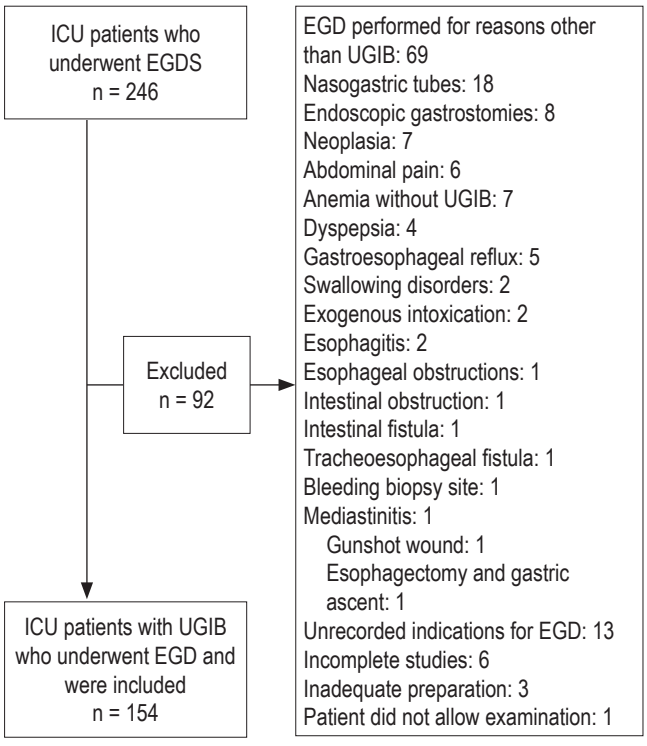

Figure 1. Diagram of patients included in the study.

EGD findings in the esophagus, stomach and duodenum are shown in Figures 2-4.

Twenty-four patients (15.58%) were treated endoscopically, but it was not necessary in the remaining 130 patients (84.4%) (Figure 5). Among the diagnoses recorded in the medical records for esophageal varices, Child Pugh C cirrhosis with encephalopathy, mostly secondary to diabetes mellitus and alcohol was the most common. Other findings were presented with ambivalent information due to the large number of pathologies and comorbidities of these critical patients. They included sepsis, shock, heart failure, renal failure, respiratory failure, and coagulopathy.

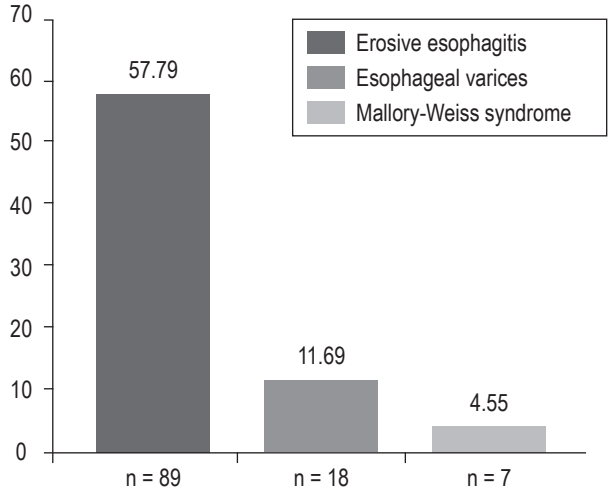

Figure 2. Esophageal findings of EGDs.

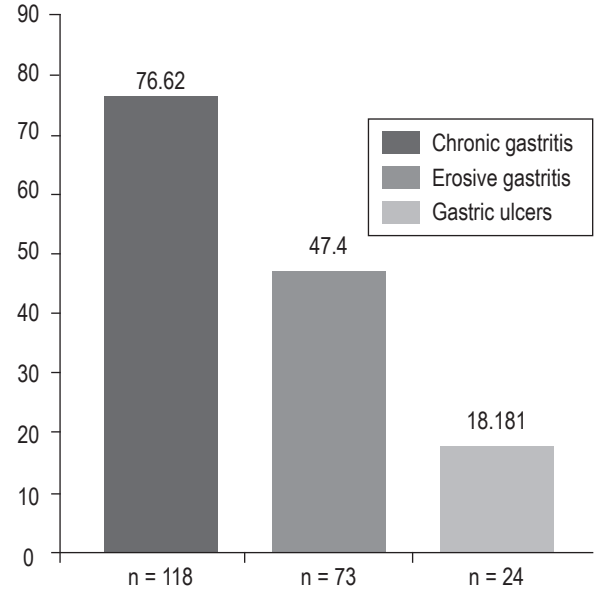

Figure 3. Endoscopic findings in the stomach.

Modalities of therapeutic endoscopy used are shown in Table 1. Hemostasis of bleeding was achieved in all patients.

The prevalences of the primary pathologies responsible for ICU admissions are shown in Table 2.

The prevalence of mechanical ventilation was 20% (n = 30), and the prevalence of prophylaxis with proton pump

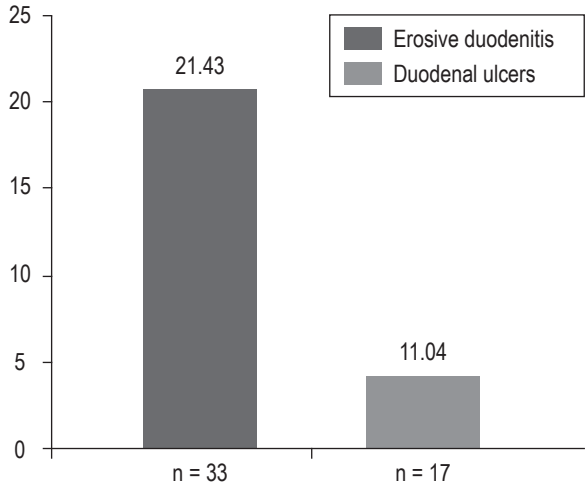

Figure 4. Endoscopic findings in the duodenum.

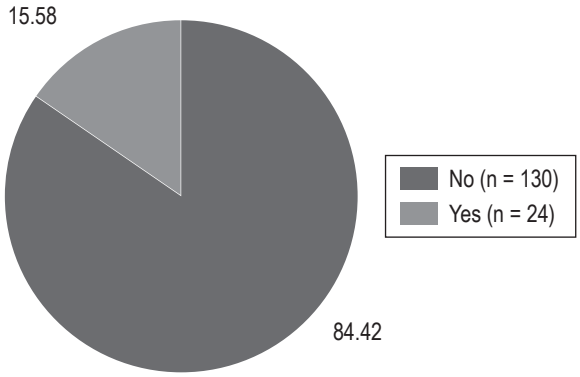

Figure 5. Endoscopic treatment

Table 1. Modalities of therapeutic endoscopic used to treat UGIB

Lesions	Endoscopic treatment	
	Adrenaline injections	Ligation of esophageal varices
Gastric ulcers: 5.85%	n = 9	
Esophageal varices: 4.55%		n = 7
Duodenal ulcers: 3.89%	n = 6	
Mallory-Weiss syndrome: 1.29%	n = 2	n = 1
Prevalence of endoscopic treatment: 15.58%	Total: 17	Total: 8

inhibitors (PPI) was 32% (n = 49). The distribution of lesions by age group is shown in Table 3.

DISCUSSION

Fifteen percent of the ICU patients with UGIB in this study required endoscopic treatment. The need for therapeutic EGD is similar to a study of 66 ICU patients from the University of Pennsylvania. That study found that 15% of those patients merited hemostatic endoscopic therapy. (25) Another study by Kim et al. of 66 patients at the University of Seoul found that endoscopic management of bleeding had been needed in 19% of their patients. (26)

Table 2. Prevalence of pathologies responsible for ICU admissions

Pathology	Prevalence	
	N	%
Lung disease	19	12.36
Cardiovascular disease	38	24.69
Sepsis	31	20.17
Major surgery	8	5.13
Trauma	8	5.13
Neurological disease	12	7.79
Liver disease	24	15.59
Acute renal failure	6	3.95
Diabetic ketoacidosis	8	5.19
Total	154	100

EGDs are frequently requested for critically ill patients with gastrointestinal bleeding for both diagnostic and therapeutic purposes. However, not all mucosal lesions identified by this means require endoscopic treatment which increases the costs of patient care and the likelihood of complications. (7, 27) In general, these patients die due to the severity of the underlying medical condition or due to multiorgan dysfunction rather than due to bleeding. (28)

Lee et al. conducted a prospective study of 105 patients with gastrointestinal bleeding who were in a critical care unit and found that the prevalence of erosive disease was 21.9%. (11) In our study, erosive gastritis had a prevalence of 47.4% (n = 73), but none of these lesions required endoscopic treatment. The clinical relevance of these lesions is controversial, since only a small percentage progress towards overt and clinically important gastrointestinal bleeding. (17, 22)

The most frequent esophageal finding in our study was erosive esophagitis which was found in 59% of the patients, a higher rate than found in previously published studies. (25, 29-31) This finding demonstrates once again that the majority of EGDs performed in ICU patients with UGIB will find lesions that do not merit therapeutic endoscopy. Consequently, there will be no impact on the treatment of these patients. (7) Mallory-Weiss syndrome was found in 8 patients (4.55%), none of whom required endoscopic therapy. Mallory-Weiss syndrome is related to a sudden increase in intragastric or intra-abdominal pressure which is transmitted to the esophagogastric junction. (32) Risk

Table 3. Prevalence of endoscopic findings by age group.

Age	Prevalence of endoscopic findings							
	Chronic gastritis	Gastric ulcers	Erosive gastritis	Erosive duodenitis	Duodenal ulcers	Erosive esophagitis	Esophageal varices	Mallory-Weiss syndrome
20-30	66.67%	11.11%	33.33%	55.56%	11.11%	44.44%	11.11%	11.11%
31-40	100%	0.0%	66.67%	0.0%	33.33%	33.33%	0.0%	0.0%
41-50	72.73%	9.09%	63.64%	0.0%	0.0%	45.45%	0.0%	0.0%
51-60	80%	16.0%	44%	20%	12%	64%	20%	4%
61-70	74.42%	16.28%	41.86%	16.28%	13.95%	51.16%	11.63%	0.0%
71-80	79.07%	25.58%	53.49%	23.26%	9.3%	65.12%	6.98%	11.63%
81-90	70.59%	23.53%	47.06%	29.41%	5.88%	64.71%	23.53%	0.0%
>90	100%	0.0%	33.33%	33.33%	33.33%	66.67%	0.0%	0.0%

factors include severe nausea, vomiting, closed abdominal hypo-trauma, cardiopulmonary resuscitation, coughing, shouting, barotrauma and seizures. In our series, this syndrome occurred less frequently than reported in other publications. The multiple predisposing factors could explain this difference. (10, 33) However, it would be important to minimize related factors since Mallory-Weiss syndrome can deepen and produce transmural rupture which leads to Boeerhäve syndrome. (34).

Gastric ulcers were found in 18.18% (n = 28) of the patients in our study. In 2005, Skok et al. conducted a prospective cohort study of 486 patients in Slovenia which found gastric ulcers in 84 patients (17.3%). (35) However, only 5.8% (9 patients) in our study required endoscopic treatment for gastric ulcers. A retrospective observational study of 88 French patients between 2007 and 2012 evaluated the clinical impact of EGD in critically ill patients with suspected bleeding. It found that only 3.5% of patients required endoscopic management for gastric ulcers. (7) These results are important, since EGDs are relatively expensive and are not risk-free. Both costs and risks increase as the procedure becomes generalized. (35)

Our study found that non-varicose causes occurred twice as frequently as varicose causes (11.03% vs. 4.55%) which is similar to other studies. (36) There were 17 patients with duodenal ulcers (11.04%) which is half of what has been reported in the literature. (29) We do not know the reason for this discrepancy, but it could be related to the prevalence of Helicobacter pylori, the frequency of use of prophylactic PPIs and the type of critical pathology of patients, especially mechanical ventilation, active coagulopathies, liver disease and renal disease. In our study, many patients had these predisposing pathologies, and 32% of the patients used prophylactic PPIs. Prophylactic PPIs have been shown to decrease the rate of clinically significant bleeding below the rate of patients taking placebos (2.5% vs. 4.2%). PPIs are recommended in these circumstances. (2, 37)

Many doctors are still afraid to use PPIs prophylactically because of the theoretical risks of possible adverse effects such as pneumonia, myocardial ischemia, and C. difficile. (15) Nevertheless, the evidence that supports these fears is very weak, and so far only association and non-causality have been established. (38) In our study, the rate of erosive duodenitis was higher than that reported in the literature (21.43% vs. 6%), but we identified no active bleeding related to this pathology in any of our patients. (29, 34)

This study's limitations include its retrospective nature and changing diagnoses due to multiple concomitant pathologies. Also, it was not easy to determine the risk factors that predispose to UGIB which would merit endoscopic treatment and thus avoid the 85% of EGDs which are unnecessary.

In conclusion, 15% of our ICU patients with UGIB needed endoscopic therapy. Prospective studies, preferably multicenter, are needed to identify risk factors that can predict the need for therapeutic EGDs in patients with UGIB. Patients who do not have these predictors should be treated empirically with PPIs which will avoid unnecessary expenses of diagnostic EGDs. To date, the published literature has identified ICU patients at risk of UGIB but has not identified those whose bleeding may require therapeutic EGD.

Conflicts of Interests

None.

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Clinical and histopathological characterization of children with autoimmune hepatitis at a referral center in Bogotá, Colombia

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Abstract

Autoimmune hepatitis (AIH) is a progressive inflammatory liver disease. It is uncommon in children and adolescents, and is a diagnostic challenge for clinicians and pathologists. We describe the clinical, biochemical and histopathological characteristics of 21 pediatric patients with AIH diagnosed in the last 14 years. Liver biopsies were reassessed to analyze histopathological findings in detail. Of the 21 cases evaluated, 12 (57.1%) were girls and young women, the median age was 14 years old, and 17 (80.9%) had type 1 AIH. The most frequent clinical signs were jaundice (66.7%), choluria (44.4%), evidence of portal hypertension with esophageal varices (47.1%), and splenomegaly (41.2%). Histories of other autoimmune diseases were found in 11.8% of these patients. Elevated levels of aminotransferases were found in 89.5% of the patients, hyperbilirubinemia was found in 88.9%, and 60.0% of the cases had low levels of serum albumin. Reassessed biopsies showed portal lymphoplasmocytic infiltrate (94.4%), interface hepatitis (77.8%) and rosette formation (50.0%). Hyaline inclusions were found in Kupffer cells in 42.9% of the biopsies. About 33.5% of the cases showed cirrhosis at the initial biopsy. Despite immunosuppressive treatment, four patients required liver transplantation and two are on the waiting list. AIH in children can manifest with jaundice, choluria, signs of portal hypertension, elevated aminotransferases, hyperbilirubinemia and circulating antibodies. Hyaline inclusions in Kupffer cells may be a useful finding in the histopathological diagnosis of AIH in children.

Keywords

Autoimmune hepatitis, child, biopsy, pathology.

INTRODUCTION

Autoimmune hepatitis (AIH) is a progressive inflammatory liver disease characterized by high levels of aminotransferases and immunoglobulin G (IgG), circulating antibodies, and a favorable response to immunosuppressive therapy. (1-3) Although AIH has a wide clinical spectrum, in children and adolescents it often presents acutely and has a more aggressive course than in middle-aged and elderly patients. It can rapidly progress to cirrhosis and liver failure if diagnosis is delayed and treatment is not timely. (4)

Two types of AIH have been recognized: anti-smooth muscle antibody (antiSMA) and antinuclear antibodies (antiANA) define AIH type 1 whereas liver kidney microsomal (LKM) type 1 antibodies and antigenic antibodies to liver cytosol (anti-LC1) define AIH type 2. (5-7). Before the 1990s, the epidemiology of AIH in children was imprecise,and there was no standard diagnostic method. Since the the International Autoimmune Hepatitis Group's scoring system was created, some countries have begun to estimate the incidence and prevalence of this disease. (8) An article by Boberg has noted that incidence of type 1 AIH among adults and children among Caucasian populations in Europe and North America ranges from 0.1 to 1.9 cases per 100,000 people per year while the prevalence of AIH was 8.0 per 100,000 inhabitants of Iceland between 1977 and 1979

and 16.9 per 100,000 inhabitants of Oslo, Norway in 1995. (9) In addition, AIH type 1 is said to represent two thirds of all cases and usually occurs during puberty while AIH type 2 tends to appear during childhood. (10)

Histological evidence of inflammatory liver damage consistent with AIH is a prerequisite for its diagnosis. (8, 11) The presence of interface hepatitis with portal and periportal lymphoplasmocytic infiltrate, formation of hepatocyte rosettes, and emperipolesis with lymphocytes inside the cytoplasm of injured hepatocytes are the characteristic findings from a liver biopsy. (1-3) Recently, Tucker et al. reported that periodic acid–Schiff (PAS) staining showed the presence of hyaline drops in the cytoplasm of Kupffer cells which is a new histological finding for diagnosis of AIH. (12) Nevertheless, these findings are not pathognomonic and must be considered in the context of the clinical, biochemical and serological findings of each patient. (13)

The objective of this study is to present the clinical characteristics and histopathological findings of pediatric patients with AIH diagnosed in our institution during the last 14 years.

MATERIALS AND METHODS

This is a cross-sectional study performed to identify patients under the age of 18 who were diagnosed with AIH at the Fundación Santa Fe de Bogotá from January 2004 to December 2017. Diagnostic criteria for AIH were those established in the regulations of the International Autoimmune Hepatitis Group published in 1993 and revised in 1999. (14, 15) Clinical and biochemical variables were collected retrospectively from the clinical history registration system available at our institution. Variables collected included each patient's age, sex, form of clinical presentation, clinical manifestations, signs of portal hypertension, family history of autoimmune diseases, association with immunological diseases, liver function tests, bilirubin levels, serum albumin, international normalized ratio (INR), IgG, circulating antibodies and any need for liver transplantation. Similarly, liver biopsies available in the pathology department were reevaluated to make detailed histopathological analyses emphasizing the recently described finding of hyaline drops in Kupffer cells. (12)

The data was analyzed with STATA® version 12.0 (StataCorp LP, College Station, Texas, USA). Continuous variables were described with measures of central tendency and dispersion according to the distribution of the data, and qualitative variables were described in terms of absolute and relative frequencies. This study was reviewed and endorsed by the Corporate Research Ethics Committee of our institution (reference number CCEI-2813-2015).

RESULTS

In the study period, 280 liver biopsies of pediatric patients were analyzed in the Pathology Department. Of these, 22 had histopathological and clinical findings suggestive of, or conclusive for, AIH. Of these 22 patients, 12 (57.1%) were women and 9 (42.9%) were men with a female: male ratio of 1.3:1.0. The median age was 14 years and the age range was from 2 to 17 years. Seventeen (80.9%) had AIH type 1, one (4.8%) had AIH type 2, and three (14.3%) had no record of antibodies. Clinical data, laboratory results and histopathological findings are summarized in Table 1. The most frequent symptoms were jaundice (66.7%), choluria (44.4%) and abdominal pain (27.8%). The least frequent symptoms were nausea, vomiting, headaches, neurological deterioration, and epistaxis. Symptoms were similar to those of acute hepatitis in 72.2% of cases. Physical examinations found that 41.2% (7/17) had evidence of portal hypertension with splenomegaly and about half had esophageal varices found by endoscopy.

The clinical records of two of the seventeen patients (11.8%) included other autoimmune diseases. One had been diagnosed with macrophage activation syndrome before AIH was diagnosed while another case had systemic lupus erythematosus and membranoproliferative glomerulonephritis. Only one patient (5.9%) had a family history of autoimmune disease. High levels of aminotransferases were found 89.5% of the cases, and 88.9% had hyperbilirubinemia. Alkaline phosphatase levels were elevated in 33.3% of the cases, and the INRs were high in 35.7%. Sixty percent had hypoalbuminemia while 44.4% had hypergammaglobulinemia.

Liver biopsy samples were taken from 85.7% of the patients at the beginning of the disease (Figure 1). Reevaluation of biopsies confirmed the diagnosis of AIH based on the presence of interface hepatitis (77.8%), lymphoplasmacytic infiltrate in portal spaces (94.4%) and rosette formation in liver cells (50.0%) . It should be noted that the liver biopsies of 6 of 18 children (33.3%) showed cirrhosis. As of this writing, despite treatment with corticosteroids and azathioprine, four patients have undergone liver transplantation and two are on the waiting list. The presence of hyaline droplets in the cytoplasm of Kupffer cells was verified in 42.9% of cases.

DISCUSSION

AIH is a rare cause of terminal liver disease in children. Failures of immune system regulation, environmental triggers and host genetic susceptibility are the mechanisms of this disease's pathogenesis. (8) Although AIH was first described in a group of young women in 1950 by Swedish

Table 1. Clinical, Biochemical, and Histopathological Findings for Children with Autoimmune Hepatitis

Mode of presentation (n = 18)		**Laboratory findings +**	
Acute viral hepatitis (%)	72.2	Total bilirubin (mg/dL) (n = 18)	3.0 (0.5-22.6)
Insidious onset (%)	22.2	AST (U/L) (n = 19)	163.0 (18.0-4448.0)
Acute liver failure (%)	5.6	ALT (U/L) (n = 19)	143.0 (23.0-3939.0)
Clinical manifestations (n = 18)		ALP (U/L) (n = 16)	245.0 (81.0-1390.0)
Jaundice (%)	66.7	Albumin (g/dL) (n = 15)	3.6 (1.1-4.9)
Choluria (%)	44.4	INR (n = 14)	1.2 (0.9-1.9)
Abdominal pain (%)	27.8	Gamma-glutamyl transferase (U/L) (n = 10)	116.0 (16.0-381.0)
Acholia or fever (%)	22.2	IgG (mg/dL) (n = 8)	2,245.0 (1,041.0-3,972.0)
Anorexia (%)	16.7	**Immunological findings**	
Diarrhea or abdominal bloating (%)	11.1	AntiSMA (n = 15) (%)	73.3
Amenorrhea or pruritus (%)	11.1	AntiANA (n = 18) (%)	66.7
Telangiectasias (%)	11.1	**Pathological findings (n = 18)**	
Nausea or vomiting (%)	5.6	Lymphoplasmocytic infiltrate (%)	94.4
Headache or neurological impairment (%)	5.6	Interface hepatitis (%)	77.8
Epistaxis (%)	5.6	Rosette formation (%)	50.0
Signs of portal hypertension (n = 17)		Kupffer cell hyaline drops (%)	42.9
Esophageal varices (%)	47.1	Cirrhosis, probable or definitive (%)	33.3
Splenomegaly (%)	41.2	No fibrosis (%)	22.2

+ Data presented as median (range); ALT: alanine aminotransferase; antiANA: antinuclear antibodies; antiSMA: anti- smooth muscle antibodies; AST: aspartate aminotransferase; ALP: alkaline phosphatase; IgG: immunoglobulin G; INR: international normalized ratio.

professor Jan Waldenström, it can also affect men and boys who account for 25% to 30% of all AIH patients. It can occur at any age and in all ethnic groups. (2, 5, 16) Of the 21 pediatric patients with AIH described in this study, 42.9% were male and 71.4% were adolescents (over the age of 12 years). About 12% of these patients had other autoimmune diseases although only one patient had a family history of autoimmune disease. This figure is slightly lower than the figures reported in the literature which show that about 20% of children who test positive for anti-SMA/ANA and anti-LKM1 antibodies have associated autoimmune diseases before or after the diagnosis of AIH, and 40% of patients have first-degree relatives who have autoimmune diseases. (17) The reason for these slight discrepancies may be related to limitations of retrospective data collection related to the fact that our institution is a referral center. Some of the liver biopsies processed in the pathology department are referrals from other institutions and access to these patients' clinical information may be limited. Nevertheless, every effort was made to obtain clinical information for all cases by consulting the primary source whenever possible and by checking the clinical history records of the pediatric gastroenterology outpatient clinic.

Three patterns of clinical presentations of AIH among children have been described in the literature:

- Presentation of about 40% of cases is similar to that of acute hepatitis with nonspecific symptoms, such as fatigue, nausea, emesis, anorexia, and abdominal pain followed by jaundice, choluria, and acholia.
- Onset is insidious in 25% to 40% of patients. It is characterized by progressive fatigue, recurrent jaundice, headache, anorexia, amenorrhea, and weight loss which can last for several months or even years before diagnosis.
- About 10% of pediatric cases have no histories of jaundice. Diagnosis of AIH is made due to portal hypertension, splenomegaly, hematemesis due to esophageal varices, and/or chronic diarrhea. (18)

In our series, 72.2% of patients initial symptoms were similar to acute hepatitis and 22.2% had insidious onsets. Nevertheless, it is striking that 41.2% had splenomegaly and 47.1% esophageal varices, signs of portal hypertension and indications of late diagnoses. (19) Although patients with AIH rarely develop fulminant liver failure, one of our cases was admitted with severe liver damage, and 33.3% had initial liver biopsy findings suggestive of cirrhosis. (5, 16) It has

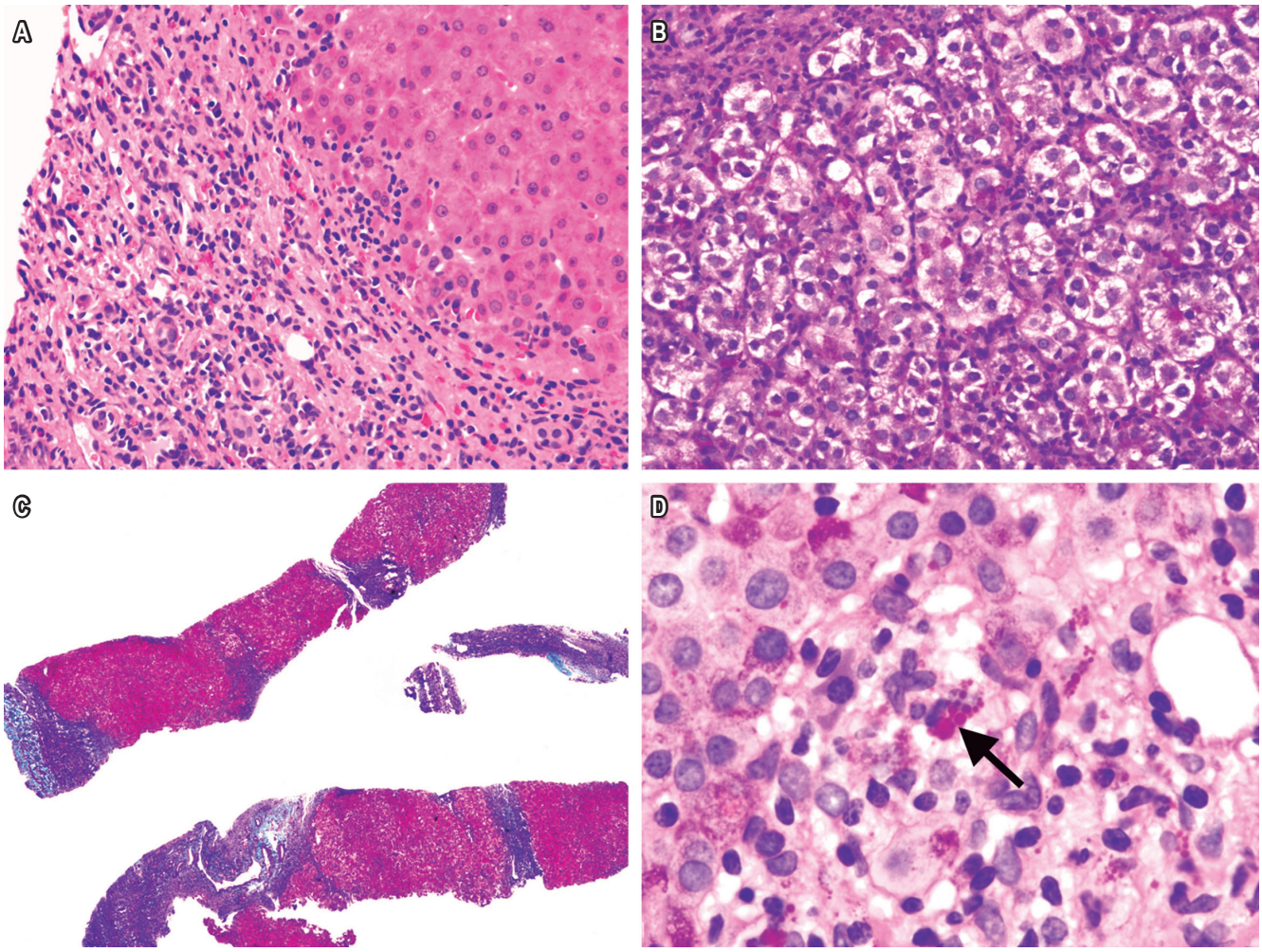

Figure 1. A. H&E stain of liver biopsy from AIH patient shows interface hepatitis and portal lymphoplasmacytic infiltrate (400x). B. Rosette formation (400x). **C**. Masson's trichrome shows regenerative nodules surrounded by fibrotic septa (40x). **D**. PAS-diastase stain shows hyaline drops in Kupffer cells (1000x).

been reported that among AIH patients in the United States, Hispanics have the highest prevalence of cirrhosis (55%) followed by white Americans (30%) and Asians (29%). (20) Similarly, South American patients are commonly young children with severe liver inflammation. (21) We assume that genetic predisposition, risk factors, and socioeconomic reasons including limited access to health care services and delayed diagnosis can explain these differences. (2)

Only 4.8% of our cases were diagnosed with AIH type 2, and only one of our patients had negative antibodies at the time of initial diagnosis. Still, antibody titers may vary during the course of the disease, and individuals who are seronegative at diagnosis may later express these antibodies. (2) For adults, titers are considered significant when they present a dilution of 1:40 or higher by indirect immunofluorescence. For children, dilutions of 1:20 or more for ANA and SMA or 1:10 or higher for antiLKM1 support a diagnosis of AIH when other clinical and laboratory findings also suggest the disease. (2-4) Antibodies are correlated with disease activity in pediatric AIH patients and can be used to monitor response to treatment. (22) Of our patients 89.5% had elevated levels of aminotransferases, 88.9% hyperbilirubinemia, 60.0% had hypoalbuminemia, and 35.7% had coagulopathy. These last two signs are associated with cirrhosis and late diagnosis. It must be taken into account that up to 25% of patients, especially children, the elderly and acute cases, have IgG levels within normal limits. (11)

Liver biopsy results are essential for confirmation of an AIH diagnosis and for assessing severity of liver damage because of the great variability of clinical manifestations and

because serum antibodies and elevated IgG levels are very nonspecific. (5, 8) Interface hepatitis is a typical finding, but it is not exclusive to AIH. It is characterized by portal and periportal lymphocytic or lymphoplasmacytic infiltration with edema of hepatocytes. In cases of acute AIH and during relapses, panlobular hepatitis with bridging necrosis can occur while in fulminant cases massive necrosis often occurs. Other findings include hepatic regeneration with rosette formation and emperipolesis. (2, 5, 8) In 2008, the International Autoimmune Hepatitis Group developed a system of simplified criteria for AIH diagnosis. Interface hepatitis with lymphoplasmacytic infiltrate, rosettes, and emperipolesis are necessary to categorize a case as typical, and all three findings must be present for a 2-point histological score. (23, 24)

Several studies indicate that the simplified criteria have excellent sensitivity and specificity for pediatric patients except those cases with fulminant liver failure. (25) A novel histological finding recently described by Tucker et al. is the presence of hyaline drops in the cytoplasm of Kupffer cells. This provides information that distinguishes AIH from other forms of chronic hepatitis. (12) In our cases, the most frequent histopathological findings were portal lymphoplasmacytic infiltrate and interface hepatitis. Hyaline drops were present in 42.9% of the liver biopsies.

Certain histological changes and their severity serve as markers for disease phenotypes. (1) A study by Miao et al. has shown that emperipolesis is associated with the most severe necroinflammatory and fibrotic changes in AIH. (26) It should be noted that up to 24% of patients have bile duct alterations including pleomorphic and destructive lymphocytic cholangitis. These cases should be investigated for possible association with primary sclerosing cholangitis or primary biliary cholangitis/cirrhosis (AIH overlap syndromes). (1) The initial biopsy provides information on inflammatory activity and the stage of fibrosis which helps guide treatment decisions. Similarly, follow-up biopsies may be necessary to assess response to treatment since residual inflammatory activity predicts relapses after interruption of immunosuppression. (3) Finally, biopsy allows differentiation between AIH and other autoimmune liver diseases such as primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune cholangitis. (6)

In conclusion, AIH should be considered in any pediatric or adolescent patient with acute or chronic liver compromise, especially if they have elevated levels of aminotransferases and/or hyperbilirubinemia which are suggestive of portal hypertension and other autoimmune diseases associated with the presence of serum antibodies and hypergammaglobulinemia. The presence of signs of portal hypertension, cirrhosis, hypoalbuminemia, or coagulopathy indicate a late clinical diagnosis. A liver biopsy is important for both initial diagnosis and for long-term follow-up of AIH. The presence of hyaline drops in the cytoplasm of Kupffer cells is a useful histological finding for diagnosis of AIH in children.

As previously mentioned, the relatively small number of pediatric and adolescent patients with AIH and retrospective data collection are limitations of this study, but our results are comparable to those described in elsewhere in the literature.

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Coexistence of functional gastrointestinal disorders in Latin American infants and preschoolers

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Abstract

Introduction: Coexistence of functional gastrointestinal disorders (FGID) in infants and preschool children has been described, but there is little literature on the main types of FGID coexistence or their characteristics. **Objective:** This study describes the prevalence and possible associations of FGID coexistence among Latin American infants and preschool children. **Methodology:** This is a prevalence study of infants and preschool children conducted in Colombia, Ecuador, Nicaragua and Panama. Children included were outpatients and emergency patients who were identified according to the Rome III Criteria in Spanish as suffering from regurgitation, rumination syndrome, cyclic vomiting syndrome, colic, functional diarrhea, functional constipation and/or dyspepsia. Age, sex and origin of patients were registered. Statistical analyses included Student's T test, chi squared test, Fisher's exact test, univariate analysis, multivariate analysis and calculation of odds ratios and 95% confidence intervals with $p < 0.05$ set as significant. **Results:** Two thousand four hundred and seventeen children were included. Their age range was 2.4 months to 19.8 months of age, and 51.3% were male. The proportion of patients with a diagnosis of at least one FGID was 35.7%. FGID coexistence was found in 3.6% of the patients. The most frequent combination was rumination syndrome plus functional constipation. There were predominances of males, infants and Colombian children in the total sample. **Conclusion:** The most commonly coexisting FGIDs in this group of Latin America infants and preschool children were infant rumination syndrome and functional constipation which were found together most frequently among boys who were under 24 months old.

Keywords

Infants, pre-school, prevalence, gastrointestinal diseases.

INTRODUCTION

According to the Rome IV criteria, functional gastrointestinal disorders (FGIDs) in infants and preschoolers are defined as a diverse and variable combination of recurrent or chronic gastrointestinal symptoms that are not attributable to other medical conditions after adequate medical evaluation. (1) Globally, the prevalence of FGIDs defined by the Rome III criteria ranges between 27.1% and 38.0% in children between 0 and 4 years old. (2) Recently, Robin et al. described a Rome IV prevalence of 24.7% in children under 3 years of age in the United States. (3) Prevalences between 11.6% and 47.8% have been described for these FGIDs in Latin America, according to the Rome III criteria in Spanish. Prevelance varied by place with 47.8% among hospitalized patients, 38.2% in a pediatric emergency department, 26.6% in a private hospital outpatient clinic and 11.6% in an outpatient clinic for growth and development of healthy children. (4)

Although coexistence of FGIDs has been described, there is little literature on primary coexisting FGIDs (c-FGIDs) or the characteristics of this group of children. School chil-

dren and adolescents have been found to have an 8.4%, prevalence of c-FGIDs, primarily coexistence being irritable bowel syndrome and functional abdominal pain which occurs predominantly in girls. (5) Study of FGIDs coexistence will provide a better understanding of the pathophysiology and pathogenesis of the biopsychosocial model of FGIDs in this age group from the genetic, nutritional, environmental, psychosocial, cultural, socioeconomic and infectious points of view. This will allow better definition of its epidemiology, symptoms, comorbidities and effects on health related quality of life of infants and preschoolers.

The objective of this work is to describe prevalence of c-FGIDs and possible risk factors in Latin American infants and preschoolers.

MATERIALS AND METHOD

This is a descriptive, non-experimental, observational, cross-sectional study of prevalence carried out between May 1 and October 31, 2015 using the database of Functional International Digestive Epidemiological Research Survey Group (FINDERS). It was performed by a transnational research group made up of members of the Latin American Society of Pediatric Gastroenterology, Hepatology and Nutrition (SLAGHNP).

Standard data collection methods were used in all participating countries: Colombia, Ecuador, Nicaragua and Panama. Parents who signed informed consent for children under 4 years of age or the recipients were interviewed at hospitals and at outpatient clinics for development of healthy children in Colombia, Nicaragua and Panama, and at an emergency office in Ecuador. Sociodemographic variables recorded included age, sex and country of origin. Children with known histories of organic gastrointestinal disorders such as gastroesophageal reflux disease, cow's milk protein allergy, Hirschsprung's disease, cerebral palsy, vesicoureteral reflux, seizure syndrome, and heart disease were excluded. The Rome III questionnaire for pediatric gastrointestinal symptoms for infants and preschoolers (QPGS-III), which has been validated and tested in Spanish, was used to identify FGIDs. (6) According to the guidelines for Scoring Instructions for Infant/Toddler Report Form for the Rome III Diagnostic Questionnaire on Pediatric Gastrointestinal Symptoms for Infants and Toddlers, the FGIDs identified were infant colic (0-4 months), infant dyschezia (0-5 months), infant regurgitation (0-12 months), infant rumination syndrome (0-24 months), cyclic vomiting syndrome (0-48 months), functional diarrhea (0-48 months) and functional constipation (0-48 months). (7) For the purposes of this study and to allow comparisons of these results with the Rome IV criteria, all possible overlays were taken into account. (1)

Infants between 0 and 24 months of age and preschoolers between 2 and 4 years were studied. C-FGID was defined as the presence of two or more FGIDs in the same child. The study was approved by the Ethics Committee of the Universidad del Valle de Cali in Colombia.

Given the possibility of transcription errors, 10% of the data were reviewed and then compared with the original forms. Statistical analysis using Stata 15 (StataCorp, College Station, TX) included the two-tailed Student's t, chi-square test and Fisher's exact test. Univariate and multivariate analyses were performed for possible c-FGID risk factors, Odds Ratios were calculated between the exposure variable of interest (sex, age, origin) and the effect variable (presence or absence of c-FGID). $p < 0.05$ was considered statistically significant.

RESULTS

We analyzed 2,417 children aged 2.4 ± 19.8 months (range 1 to 48): 1694 from Colombia, 322 from Ecuador, 203 from Nicaragua, and 198 from Panama. Of the total, 67.1% were infants between 1 and 24 months, and 51.3% were male sex. Some type of FGID was diagnosed in 35.7% of these children with functional constipation (19.7%) most prevalent across all age groups followed by infant rumination syndrome (7.2%) among infants and cyclic vomiting syndrome (4.0%) among preschoolers. Data are shown in Table 1.

Table 2 shows coexistence of FGIDs in individual children in the total sample of 2,417 Latin American children. Of the total sample without regard to age, 3.7% had overlapping FGIDs (3.3% with 2 FGIDS and 0.4% with 3 FGIDS). Of the total sample infants, 3.5% were infants with overlapping FGIDs while 0.2% of the total sample were preschoolers with overlapping FGIDs. The most common double overlaps were between infant rumination syndrome and functional constipation (1.0%), and the only triple overlap was among regurgitation, dyschezia, and functional constipation (0.1%).

Possible associations are shown in Table 3. There was a predominance of the male gender (OR 1.84; 95% CI: 1.134 to 3.02; p = 0.0083), of infants (OR 10.52; 95% CI: 3.88 to 39.87; p 0.0000) and of children from Colombia (OR 6.85; 95% CI: 1.78 to 58.37; p 0.0021) when there more than one FGID in the same child.

DISCUSSION

Prevalence of FGIDs in infants and preschoolers

In these 4 Latin American countries, the prevalence of FGIDs by the Rome III criteria in Spanish was 35.7%. This is lower than that described by Rouster et al. of 52.0% for the United States and lower than those reported by Chogle

Table 1. General characteristics of Latin American infants and preschoolers (N = 2,417)

	Latin America	Colombia	Ecuador	Nicaragua	Panamá
Total	2417	1694	322	203	198
Age (months) (X SD)	19.8 (15.0)	19.5 (15.3)	20.9 (13.7)	13.9 (8.9)	26.6 (16.2)
Infant (1-12 months) (n%)	1621 (67.1)	1153 (68.1)	203 (63.0)	186 (91.6)	79 (39.9)
Preschool (13-48 months) (n%)	796 (32.9)	541 (31.9)	119 (37.0)	17 (8.4)	119 (60.1)
Sex (n%)					
Female	1179 (48.8)	825 (48.7)	149 (46.3)	107 (52.7)	98 (49.5)
Male	1238 (51.2)	869 (51.3)	173 (53.7)	96 (47.3)	100 (50.5)
FGID (n%)					
Absent	1555 (64.3)	1008 (59.5)	218 (67.7)	176 (86.7)	153 (77.3)
Present	862 (35.7)	686 (40.5)	104 (32.3)	27 (13.3)	45 (22.7)
Infant regurgitation (n%) ***	89 (3.7)	57 (3.4)	10 (3.1)	16 (7.9)	6 (3.0)
Infant Rumination Syndrome (n%) **	117 (4.8)	110 (6.5)	1 (0.3)	4 (2.0)	2 (1.0)
Cyclic vomiting syndrome (n%) *	81 (3.4)	78 (4.6)	2 (0.6)	1 (0.5)	0 (0.0)
Infant colic (n%) *****	41 (1.7)	38 (2.2)	0 (0.0)	0 (0.0)	3 (1.5)
Functional diarrhea (n%)	24 (1.0)	22 (1.3)	0 (0.0)	2 (1.0)	0 (0.0)
Functional constipation (n%) *	475 (19.7)	354 (20.9)	87 (27.0)	3 (1.5)	31 (15.7)
Infant dyschezia (n%) ****	35 (1.5)	27 (1.6)	4 (1.2)	1 (0.5)	3 (1.5)

SD: standard deviation; FGID: functional gastrointestinal disorder; X: average.
* 0-48 months; ** 0-24 months; *** 0-12 months; **** 0-5 months; ***** 0-4 months.

Table 2. Coexistence of functional gastrointestinal disorders in Latin American infants and preschoolers (N = 2,417)

	Latin America	Colombia	Ecuador	Nicaragua	Panamá
Total	2417	1694	322	203	198
Without FGIDs	1555 (64.3)	1008 (59.5)	218 (67.7)	176 (86.7)	153 (77.3)
With FGIDs	862 (35.7)	686 (40.5)	104 (32.3)	27 (13.3)	45 (22.7)
Without overlap	774 (32.0)	604 (35.7)	102 (31.7)	25 (12.3)	43 (21.7)
With overlap	88 (3.7)	82 (4.8)	2 (0.6)	2 (1.0)	2 (1.0)
With 2 FGIDs	79 (3.3)	75 (4.3)	1 (0.3)	2 (1.0)	1 (0.5)
IRS-FC	25 (1.0)	24 (1.4)	0 (0.0)	0 (0.0)	1 (0.5)
REG-COL	11 (0.5)	11 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
CVS-FC	10 (0.4)	10 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
IRS-COL	5 (0.2)	5 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
REG-IRS	3 (0.1)	2 (0.1)	0 (0.0)	1 (0.5)	0 (0.0)
IRS-FD	2 (0.08)	1 (0.06)	0 (0.0)	1 (0.5)	0 (0.0)
REG-DISC	1 (0.04)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
With 3 FGIDs	9 (0.4)	7 (0.5)	1 (0.3)	0 (0.0)	1 (0.5)
REG-DISC-FC	2 (0.08)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.5)

COL: infant colic; FD: functional diarrhea; DISC: infant dyschezia; FC: functional constipation; REG: infant regurgitation; IRS: infant rumination syndrome; CVS: cyclic vomiting syndrome; FGIDs: functional gastrointestinal disorders.

et al. of 40.0% and 40.5% in Latin American countries, but it is higher than the results of van Tilburg et al. of 27.1% in the United States. (8-11) Vandenplas et al. found that for medical experts worldwide the most likely prevalences are regurgitation (30.0%), colic (20.0%) and functional constipation (15.0%). (12) In this study, the most common FGID in infants was infant rumination syndrome. This differs from the findings of van Tilburg et al. and Rouster

Table 3. Possible risk factors in Latin American infants and preschoolers with coexistence of functional gastrointestinal disorders (N = 862)

	2 or more FGIDs				
	No	Yes			
	774 (89.8)	88 (10.2)	OR	95% CI	*P*
Age groups					
Preschool	259	4	1.00		
Infant	515	84	10.52	3.88-39.87	0.0000
Sex					
Female	388	31	1.00		
Male	386	57	1.84	1.14-3.02	0.0083
Country					
Ecuador	102	2	1.00		
Colombia	604	82	6.85	1.78-58.37	0.0021
Nicaragua	25	2	4.04	0.27-57.43	0.1432
Panamá	43	2	2.34	0.16-33.16	0.3878

FGIDs: functional gastrointestinal disorders.

Table 4. Comparison of prevalence in infants and preschoolers with coexistence of functional gastrointestinal disorders (N = 2,417)

	Velasco N = 2417	van Tilburg[10] N = 264	Chogle[9] N = 1183	Rouster[7] N = 332
2 FGIDs	9.2%	12.6%	4.6%	13.0%
3 or more FGIDs	1.0%	8.6%	0.4%	5.0%

FGIDs: functional gastrointestinal disorders.

et al. in the United States where regurgitation was most frequent. It also differs from the findings of Chogle et al. that the most common FGID in Latin American countries, where was infant colic. (9, 10)

The most common FGIDs in preschoolers in the 4 Latin American countries we studied was constipation as has been found in the United States and other Latin American countries. (8-11) Recently, Robin et al. described a Rome IV FGID prevalence of 24.7% in the United States. Regurgitation was the most frequent in infants while constipation was most frequent for preschoolers. (3) The variability of these prevalences depends on the regions in which the studies are conducted, and genetic, nutritional, environmental, psychosocial, cultural, socioeconomic and infectious factors typical of each country are involved.

Coexistence

The Rome IV criteria for infants and preschoolers do not discuss the issue of FGID coexistence in one patient. This contrasts with the criteria for schoolchildren and adolescents for whom studies have shown that there may be coexistence of more than one functional abdominal pain disorder in one individual patient. However, those studies do not report their characteristics. (5, 13, 14) This study found that the prevalence of one child presenting two FGIDs was 9.2% while the prevalence of one child presenting three or more FGIDS was 1.0%, as shown in Table 4. Rouster et al., Chogle et al., and van Tilburg et al. have reported prevalence ranges for presentation of 2, or 3 or more FGIDS in the same child of 5.0% to 13.0%, 0.4% to 4.6%, and 8.6% to 12.6%, respectively. (8, 10, 11)

Few studies describe which FGIDSs coexist. In this study, the most frequently occurring combination of two FGIDs was infant rumination syndrome and functional constipation. The most frequent coexistence of three FGIDs was regurgitation, infant dyschezia and functional constipation. The study by Vandenplas et al. does not detail coexistence of specific FGIDs, but it does analyze coexistence of clinical symptoms such as flatulence, abdominal distension, constipation, diarrhea, regurgitation and colic. That study found that the most frequent combinations were colic with abdominal distension and colic with regurgitation. (12)

This study found no cases of coexistence of infant dyschezia and functional constipation, but Kramer et al. reported Rome III prevalences for infant dyschezia of 3.9% at one month of age, 0.9% at three months of age, and 0.9% at 9 months of age. Four of the children in that study had coexisting infant dyschezia and functional constipation. (15) Robin et al. have described a 9.6% Rome IV rate of FGID coexistence. (3)

Associations

Robin et al. and van Tilburg et al. found no statistical differences in gender or race, and in contrast to our study, they found that more boys were affected than girls between 0 and 2 years of age. (3, 11)

The strengths of this study include its large sample size and the fact that it was conducted private and public outpatient clinics, hospitals and emergency rooms in several Spanish-speaking Latin American countries. A single methodology, that proposed by FINDERS, was used in all countries to allow comparison.

Among the limitations of the study is the possibility that the results cannot be generalized throughout Latin America even though it includes cities from several countries. In addition, we did not perform a systematic evaluation or anamnesis of the children surveyed, and simultaneous medical diagnoses could have existed that are not described in the study. Also, other possible risk factors other than

sociodemographic factors were not included which may explain the biopsychosocial model of this entity.

In the future, multicenter intercultural epidemiological studies with large sample sizes according to the Rome IV criteria are needed to determine FGIDs' impacts on quality of life. Research on the pathophysiology and genetic, metabolic and neurophysiological characterizations of most FGIDs are also needed since their pathophysiology is poorly understood. (1)

In conclusion, there is a low prevalence of c-FGIDS among infants and preschoolers in Latin America, with a predominances in males and in infants under 24 months. Infant rumination syndrome and functional constipation are the most frequent presentations. This invites future studies to deepen our understanding of FGID coexistence in this age group.

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The current state of diagnosis and management of chronic pancreatitis

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Abstract

Chronic pancreatitis (CP) is an inflammatory condition that leads to fibrosis, damage, and even destruction of the pancreatic parenchyma and ducts. These permanent changes can alter pancreatic exocrine and endocrine functioning, cause biliary and pancreatic stenosis, lead to formation of pseudocysts and even increase the possibility of developing pancreatic cancer. The main clinical characteristic is pain which significantly alters quality of life. To diagnose the CP, we have direct and indirect functional tests and the pancreatic structure test.

The great challenge of these methods is early diagnosis, but this is difficult due to the subtlety of changes. Once CP is diagnosed, management must be staggered. Medical management is the initial step which can be followed by endoscopic management, surgical management, and for the most difficult cases a combination of these. The goal is to manage and understand the whole patient and illness to provide the best possible quality of life. This review article focuses on CP diagnosis and management in light of the currently available evidence.

Keywords

Chronic pancreatitis, diagnosis, treatment.

INTRODUCTION

Chronic pancreatitis (CP) is an inflammatory process in which the pancreatic parenchyma is altered and replaced by fibrous tissue. This permanently changes the pancreatic duct and parenchyma leading to endocrine and exocrine dysfunctions. (1, 2) In most patients, the main clinical characteristic is pain. Other clinical characteristics depend on the degree of pancreatic endocrine and exocrine dysfunction. (3)

This review will focus on diagnostic methods and therapeutic modalities for this entity. Improving each patient's quality of life depends on understanding the disease as a whole and comprehensive management on a case by case basis.

DIAGNOSIS

Advanced CP is more easily diagnosed than are mild or moderate cases whose diagnosis can be challenging. Diagnosis requires evaluation of a patient's clinical symptoms, pancreatic function tests and imaging such as magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS). Diagnostic tests can be classified into functional and structural. The latter evaluates the parenchyma and/or duct anatomy. Functional tests can be direct or indirect. The latter has better diagnostic capacity when the disease is in more advanced stages but has lower sensitivity for detecting early and moderate disease. (2, 4)

PANCREATIC FUNCTION TESTS

Direct tests

Due to their expense, The cholecystokinin test and the secretin test are used almost exclusively at research centers due to the expense of its execution. They consist of the measurement of bicarbonate in the duodenal aspirate after stimu-

lation with secretin or cholecystokinin (CCK). Pancreatic exocrine dysfunction is indicated when bicarbonate levels are below 75 mEq/L (5). These tests have high sensitivity and specificity but because are invasive and expensive. (6)

Indirect tests

Indirect tests do not require hormonal stimulation of pancreatic secretion. Their diagnostic value is limited by their low sensitivity and specificity for detecting alterations, especially in early stages of the disease. (3) These tests include measurement of serum trypsinogen, fecal fat, and/or fecal elastase and a respiratory test. Traditional measurements of endocrine function such as the glycated hemoglobin, fasting blood glucose, and oral glucose tolerance tests require further study before they can be considered for diagnosis of chronic pancreatitis. (7)

Measurements of serum trypsinogen below 20 ng/mL is specific for advanced CP. Fecal fat measurement consists of quantifying fat excreted fat for 72 hours by a patient limited to consumption of 100 g/day for at least 3 days before the test. A finding of more than 7 g of fat/day indicates malabsorption. Like the serum trypsinogen test, the fecal fat test has limited sensitivity for mild and moderate cases. Fecal elastase levels over 200 μg/g of fecal matter indicate slight possibility of exocrine pancreatic insufficiency. (8)

The carbon 13-labeled mixed triglyceride (MTG) breath test is used for diagnosis of exocrine pancreatic insufficiency and has a sensitivity of 92% and specificity of 91%. When administered 6 hours after oral administration of 250 mg of labeled MTG together with a meal with 16 g of fat, a cumulative recovery rate of less than 29% indicates exocrine pancreatic insufficiency. (9)

PANCREATIC STRUCTURE TEST

Diagnostic imaging is used for structural study of CP, but plain abdominal radiography has a very low sensitivity because the pancreatic calcifications characteristic CP can only be seen when the disease is already well advanced. In the past, endoscopic retrograde cholangiopancreatography (ERCP) using the Cambridge criteria for diagnosis of CP was considered to be the definitive method for evaluating changes in the pancreatic duct. This invasive method, which has had associated complications, has recently been displaced. (4)

Abdominal computed tomography (CT) is the first line in the diagnostic algorithm for patients suspected of having CP. It is available and non-invasive nature but has low diagnostic yield in cases of mild to moderate CP. When CT scans are inconclusive, Magnetic resonance cholangiopancreatography (MRCP) is indicated. It is superior to CT scans for detecting incipient parenchymal and ductal changes and has better diagnostic sensitivity for early CP. (10)

The use of secretin increases the diagnostic potential of MRCP since it improves evaluation of ducts and of pancreatic secretion into the duodenum. Imaging techniques including abdominal ultrasound allow us to evaluate ductal changes, pancreatic enlargement, calcifications, and peripancreatic collections. (11)

Today, endoscopic ultrasound (EUS) is the most sensitive diagnostic method,. It can be used to evaluate both the pancreatic parenchyma and the ductal system and has the ability to detect early and late changes in CP. (12-15) The purpose of EUS is to evaluate alterations of the parenchyma and pancreatic duct and to make early diagnoses.

The literature lacks data to support any particular method of criteria based classification and diagnosis of chronic pancreatitis. There are many classifications and criteria which evaluate issues including duct dilation, irregularity, and enhancement, visualization of secondary ducts and calculi as well hyperechoic foci, bands, lobularity and cysts in the parenchyma. The classification systems include the Lees-Wiersema, Milwaukee, Japanese and Rosemont systems which classify findings as definitive or consistent, suggestive, indeterminate or inconclusive (normal) for CP. (13-16)

Recently, the important concept of minimal endosonographic changes which do not meet criteria for diagnosing pancreatitis has appeared. An article by Sheel explains the issue very well. It describes the diagnostic value of the Japanese and Rosemont criteria in patients with undetermined, suggestive, possible or early chronic pancreatitis and shows that criteria that explain a patient's symptoms are not always found. (16) A great majority of patients have pain and typical signs but have normal images even though discrete changes can be seen by EUS. It is important to assess the histories of these patients for social issues, alcohol intake, cigarette smoking, and family histories of disease. If possible, genetic studies and endosonographic follow-up for at least 30 months should be conducted to observe which patients have true chronic pancreatitis, which patients heal, and which patients show improvement of EUS changes. Similarly, patients who have had acute pancreatitis should be followed up to determine who will develop CP. (16)

It is important to determine which EUS criteria help diagnosis the most. In 1993, Wiersema et al. described a scale of the following nine diagnostic criteria. (17)

- Hyperechoic foci
- Fibrous tracts
- Lobularity
- Cysts
- Calculi
- Dilation of secondary branches

- Irregularity of the pancreatic duct
- Hyperechogenic walls of the Wirsung duct .

They gave all of these criteria equal diagnostic values. No optimal cut-off point has been found, but it has been said that the presence of four or more confirms the diagnosis. (17) Given the poor sensitivity of this classification, in the Rosemont International Consensus was proposed in 2007. It includes the following two major parenchymal criteria. (14, 18)

- Hyperechoic foci greater than 2 mm in length and width with acoustic shadow
- Lobularity (greater than or equal to 3 contiguous lobes as in a honeycomb).

In addition, it includes the following four minor parenchymal criteria.

- Hyperechoic foci (> 2 mm in length without acoustic shadow)
- Bands (greater than or equal to 3 mm, in at least two different directions)
- Lobularity (> 5 mm, non-contiguous lobes)
- Pseudocysts (anechoic, with or without septa).

It includes one major ductal criterion:

- Duct stones with acoustic shadow.

It includes four minor ductal criteria:

- Duct dilation greater than or equal to 3.5 mm in the body and 1.5 mm in the tail
- Tortuous duct
- Hyperechoic duct wall
- Dilated lateral duct branches.

A diagnosis is made with one major parenchymal and three minor criteria or with two major parenchymal or ductal criteria or with two major parenchymal criteria. A diagnosis of chronic pancreatitis is suggested by three minor criteria or with only one ductal or pancreatic parenchyma criterion. (14, 18)

In 2010, the Japanese criteria for chronic pancreatitis were issues. They include the following criteria. (19)

- Findings in images
- Histological findings
- Abnormality of pancreatic enzymes in blood or urine
- Abnormal results of exocrine function tests.

Although this Japanese classification is more sensitive and specific, it is difficult to use because it combines multiple variables. The use of endosonography with the Rosemont criteria is easier. Here is a summary list of some findings that can be observed:

- Calcifications or calculi in secondary branches (Figure 1)
- Dilation of the Wirsung duct or stones within this duct (Figure 2)
- Fibrous bands (Figure 3)
- Dilation of the Wirsung duct and enhancement of its walls (Figure 4)
- Wirsung duct dilation, secondary branch dilation and lobularity of the gland (Figure 5)
- Lobularity, fibrous bands and dilation of secondary branches (Figure 6).

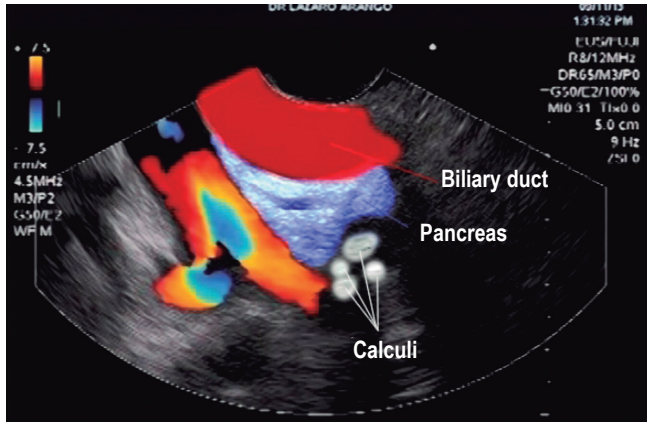

Figure 1. Calculi in the parenchyma of the pancreas and branches seen by Fujinon's linear endosonography (image edited by the Union of Surgeons SAS, Lázaro Arango).

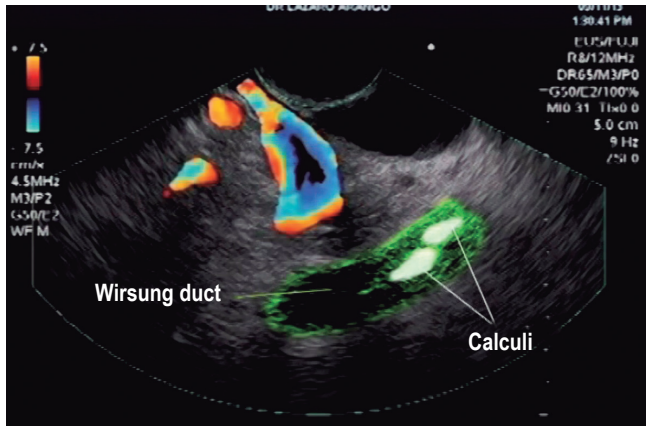

Figure 2. Dilation of the Wirsung duct and calculi within it, seen with Fujinon's linear endosonography (image courtesy of the Union of Surgeons SAS, Lázaro Arango).

EUS also integrates the use of elastography to measure the degree of pancreatic fibrosis and its relationship to the probability of exocrine pancreatic insufficiency. (20)

TREATMENT OF CHRONIC PANCREATITIS

Treatment of CP consists of relieving pain, preventing recurrent attacks, correcting the consequences of endocrine and exocrine insufficiency such as diabetes and malnutrition,

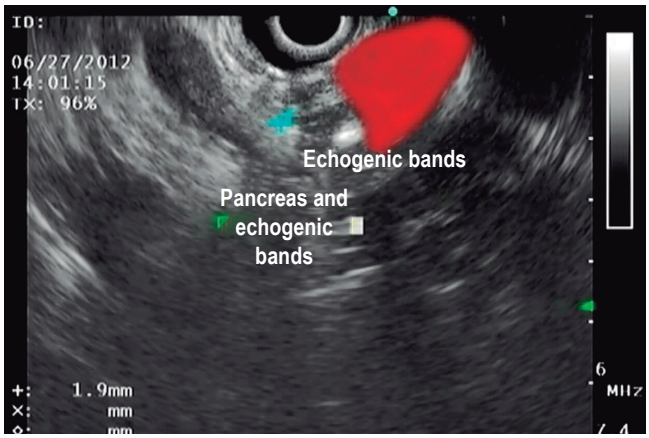

Figure 3. Echogenic bands in Olympus linear endosonography (image courtesy of the Union of Surgeons SAS, Lázaro Arango).

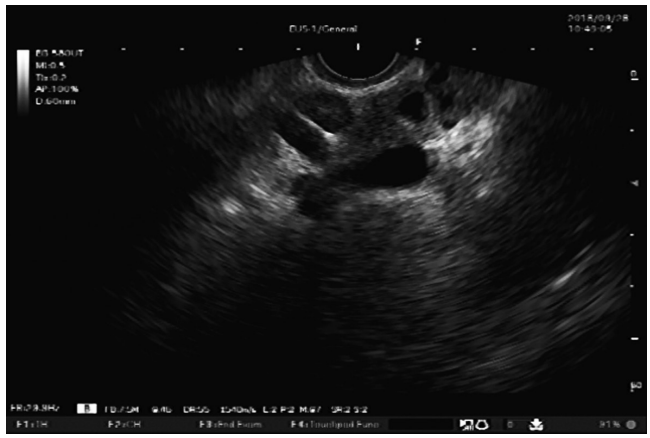

Figure 5. Linear EUS of the pancreas with Fujinon instrument. Wirsung duct dilation, secondary branch dilation, and lobularity of the gland (image courtesy of the Union of Surgeons SAS, Lázaro Arango).

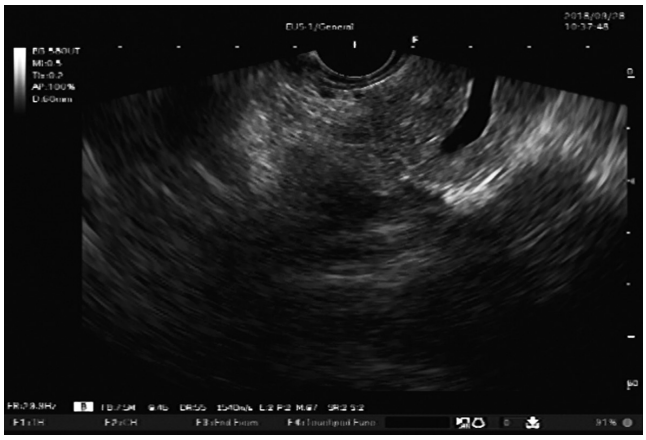

Figure 4. Fujinon's linear EUS. Wirsung duct dilation in the body of the pancreas and enhancement of its walls (image courtesy of the Union of Surgeons SAS, Lázaro Arango).

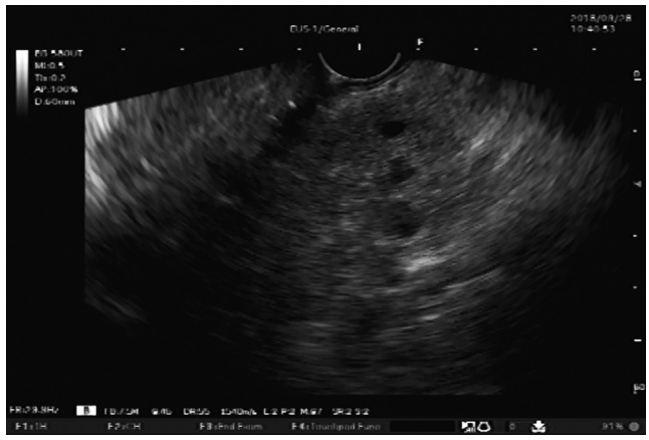

Figure 6. Lobularity, fibrous bands, and dilation of secondary branches (image courtesy of the Union of Surgeons SAS, Lázaro Arango).

and treating any complications that may arise. It begins with medical management. Endoscopic and/or surgical treatment should be used only when medical treatment fails to relieve pain or for management of complications. (21)

Medical Treatment

The initial objectives of medical management are to modify patients' lifestyles by eliminating alcohol and cigarette consumption and to manage pain and manage exocrine pancreatic insufficiency to avoid malnutrition which can lead to sarcopenia, osteoporosis, and increased cardiovascular risk. (21-24)

Pain is the initial symptom of CP in approximately 75% of patients, and it is present during the clinical course of the disease in 85% to 97% of all patients. Hence the importance of its management. Progressive use of the analgesic scale is recommended. Potency of medications should be increased according to the response until adequate pain control is reached. (25)

Exocrine pancreatic insufficiency treatment with pancreatic enzymes is indicated when a patient presents steatorrhea greater than 15 g/day, weight loss, protein or carbohydrate malabsorption, and dyspepsia. The indicated supplement is 40,000 U which must be administered during each main meal. Since intraluminal acid pH decreases the action of lipase, it is suggested that double doses of a proton pump inhibitor be administered to facilitate lipase action. Dietary fat restriction is not indicated as it would lead to insufficient intake of fat-soluble vitamins which

are diminished by the disease itself. (1, 26) In addition, supplementation of fat-soluble vitamins such as A, D, E, K, vitamin B12, micronutrients, antioxidants, calcium and vitamin D is suggested. (1)

Management of endocrine pancreatic insufficiency (type 3C diabetes) is complex. The first-line medication is metformin which is preferred for patients with malnutrition and mild hyperglycemia. Some patients require insulin therapy. Supervision by an experienced endocrinologist is suggested. (27)

Endoscopic Treatment

Endoscopic treatment for CP is indicated in cases with stones that obstruct the pancreatic duct, benign biliary stenosis, pancreatic stenosis, pancreatic pseudocyst drainage, and celiac plexus block. (28)

Primary pancreatic duct stones smaller than 5 mm are managed with standard ERCP maneuvers for stone removal (Figures 7-10). Stones larger than 5 mm require the use electrohydraulic, extracorporeal, or Spyglass-guided elec-

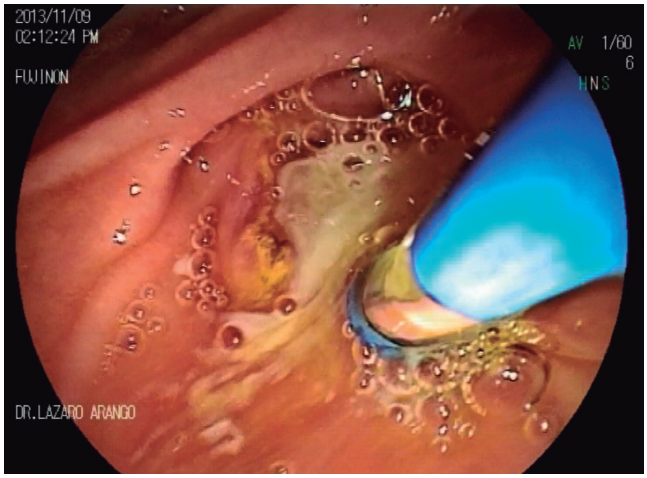

Figure 7. Cannulation of the Wirsung duct. Cloudy material is seen due to chronic pancreatitis (image courtesy of the Union of Surgeons SAS, Lázaro Arango).

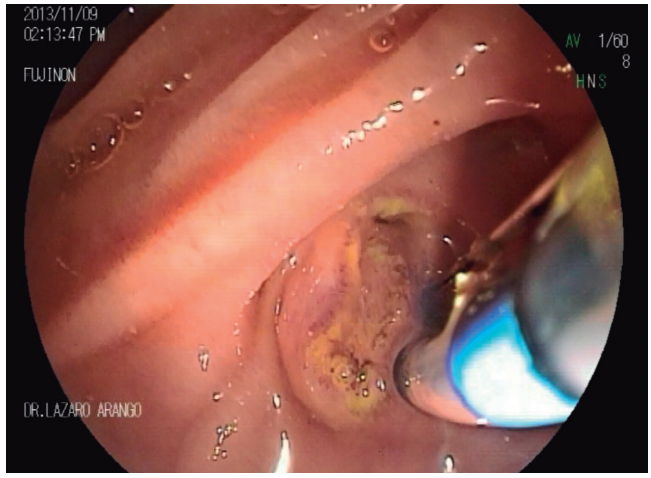

Figure 8. Opening cut of the pancreatic duct (image courtesy of the Union of Surgeons SAS, Lázaro Arango).

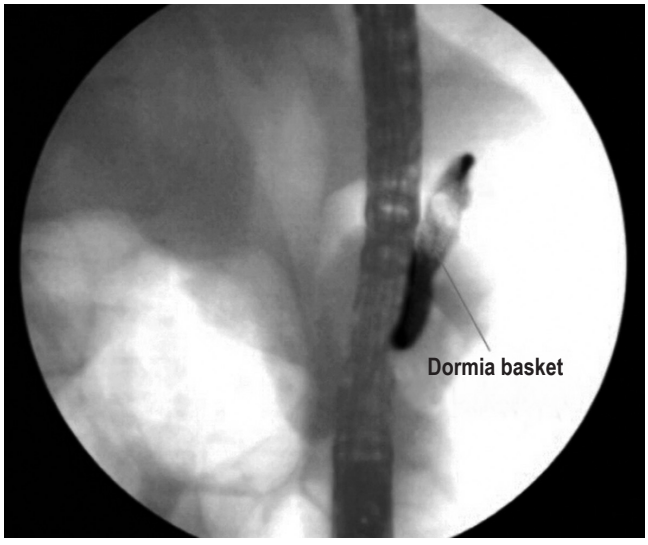

Figure 9. Exploration of the Wirsung duct with Dormia basket (image courtesy of the Union of Surgeons SAS, Lázaro Arango).

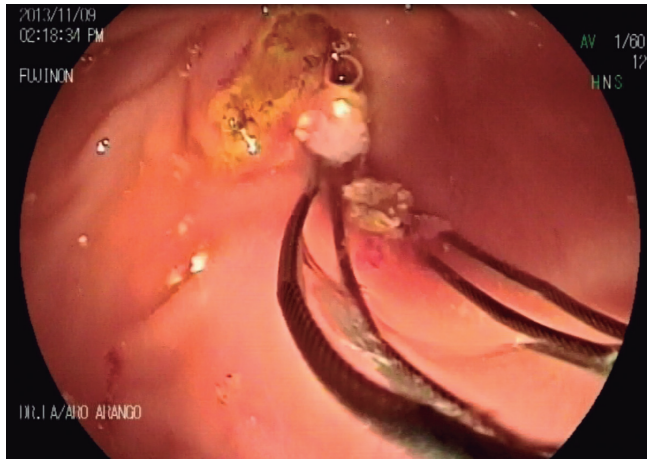

Figure 10. Stone extraction from the Wirsung duct (image courtesy of the Union of Surgeons SAS, Lázaro Arango).

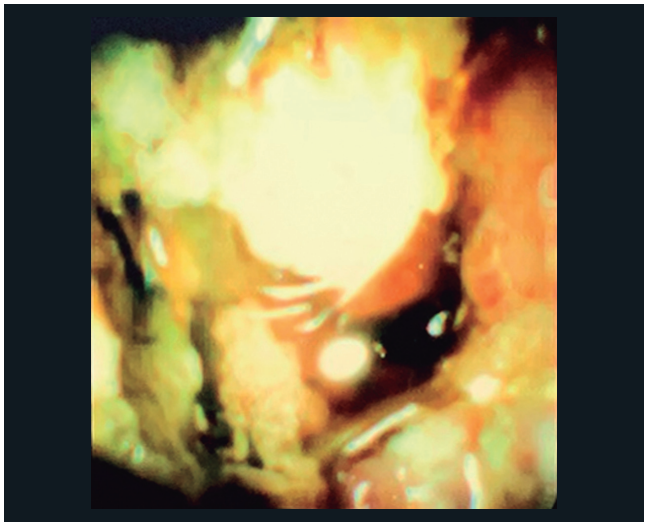

Figure 11. Calculi within the Wirsung duct seen by cholangioscopy (image courtesy of Unión de Cirujanos SAS, Manizales, Colombia).

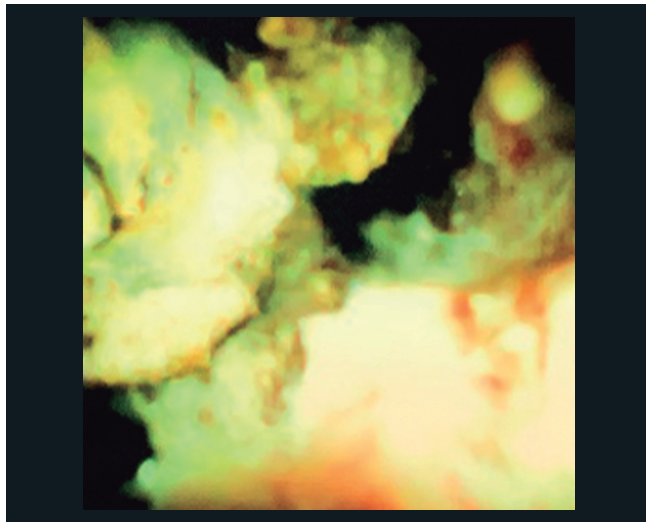

Figure 12. Calculus fragments fractured by laser and ready to be extracted (image courtesy of Unión de Cirujanos SAS, Manizales, Colombia).

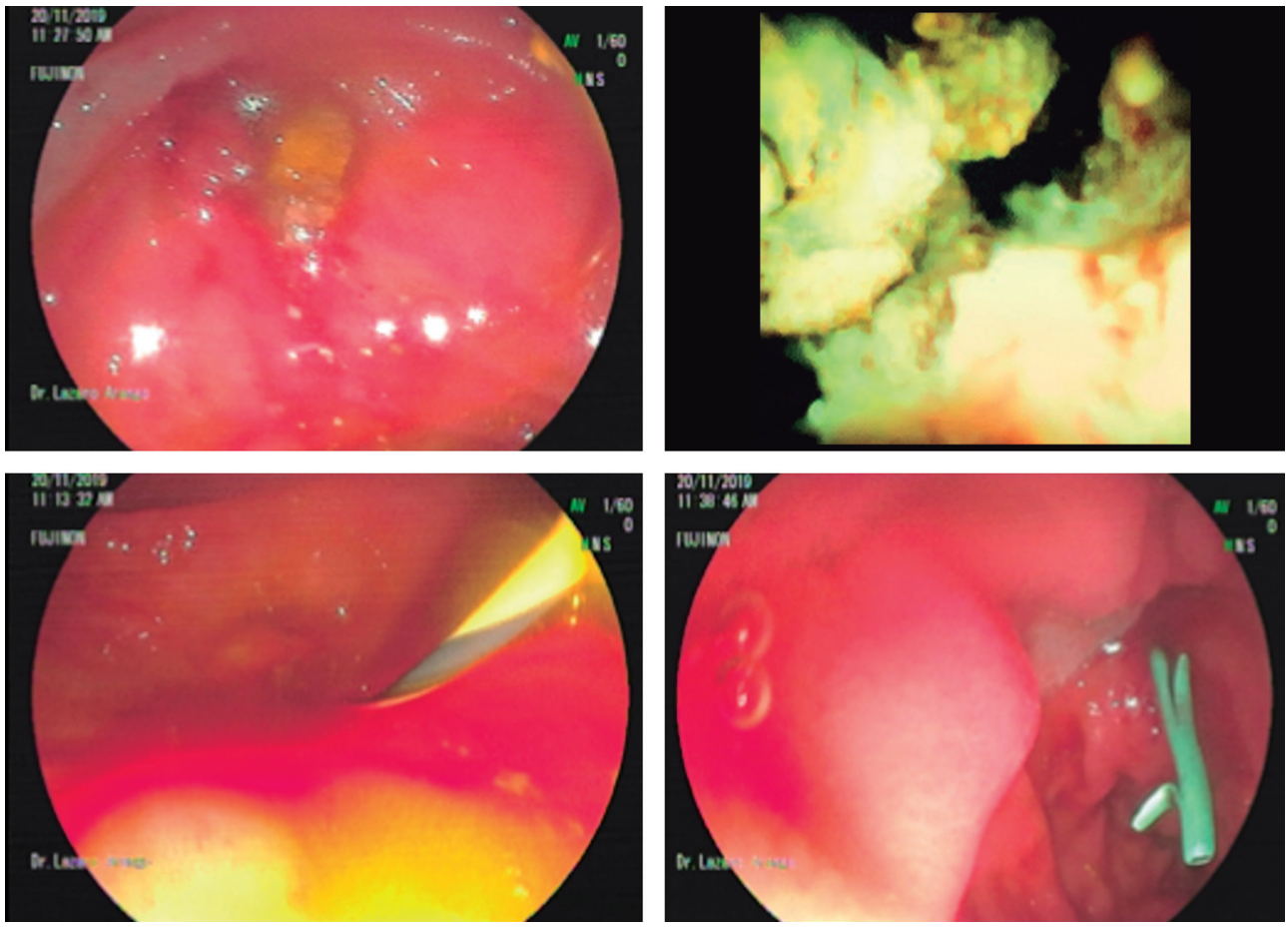

Figure 13. Stones to be removed with lithotripsy are shown in the upper left. The upper right is the same image as in Figure 12. Below left is the guide used to introduce the extraction balloon to sweep or clean the remnants of stones. Below right, the pancreatic stent placed at the end of the procedure is shown.

trohydraulic lithotripsy. In the latter case, the duct can be entered for use of a laser to fragment stones. (29) We have been gaining experience with the use of a cholangioscope which has been very useful for non-surgical management of patients with pancreatic stones. Figures 11, 12 and 13 show the Spyglass inside the Wirsung duct performing laser lithotripsy on a large stone. After the procedure, a pancreas stent is always placed.

ERCP plus sphincterotomy, balloon dilation, and plastic, metal, or biodegradable stents are used to manage biliary strictures and the main pancreatic duct. (30) A pseudocyst should be treated when it becomes symptomatic and can be done by either a transpapillary or transmural (transgastric or transduodenal) route. The ERCP-guided approach is indicated for lesions measuring less than 5 mm which disrupt the main pancreatic duct. For large pseudocysts, EUS-guided transmural drainage is indicated. (28, 30)

A celiac plexus block is used to manage pain, especially in patients who require high doses of narcotics. It relieves pain and reduces the need to administer analgesics, but its effect is temporary. (21) The procedure consists of a guided injection (preferably by EUS) of a steroid and a local anesthetic into the celiac plexus to cut the afferent nociception pathways. (1)

Surgical Treatment

Surgical treatment of CP is indicated when medical and endoscopic management of CP complications have failed. The goals of surgery are to decompress the blocked ducts and preserve the pancreatic tissue. Among the surgical procedures used are the Puestow procedure (lateral pancreaticojejunostomy), partial pancreatectomies and total pancreatectomies with autologous transplantation of pancreatic islets. (21)

CONCLUSION

CP significantly alters patients' quality of life. Management should initially focus on pain management, but should also work to prevent and manage complications. The approach must be comprehensive and multidisciplinary with the judicious use of replacement therapy and early intervention, using endoscopic and surgical therapy only for selected patients.

Acknowledgments

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Liver diseases and pregnancy

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Abstract

Liver diseases develop in 3% to 5% of all gestations. Among the causes are: 1. Physiological changes of pregnancy. 2. Pre-existing liver diseases and conditions. The most common are cholestatic diseases such as primary biliary cholangitis and primary sclerosing cholangitis. Others include autoimmune hepatitis, Wilson's disease, chronic viral hepatitis, cirrhosis of any etiology and histories of liver transplantation. 3. Liver disease acquired during pregnancy, especially viral hepatitis, drug-induced toxicity and hepatolithiasis. 4. Pregnancy-related liver diseases including hyperemesis gravidarum, intrahepatic cholestasis of pregnancy, preeclampsia, HELLP syndrome and fatty liver of pregnancy.

Severity ranges from absence of symptoms to acute liver failure and even death. Severe cases have significant morbidity and mortality for both mother and fetus. These cases require rapid evaluation, accurate diagnosis and appropriate management by a multidisciplinary team including high-risk obstetrics, hepatology, gastroenterology and interventional radiology. Availability of liver transplantation is also important for obtaining good outcomes.

Keywords

Pregnancy, hyperemesis gravidarum, gestational cholestasis, HELLP, preeclampsia, hepatitis B virus, cirrhosis, liver transplantation.

INTRODUCTION

All women, regardless of age, are at risk of suffering some type of acute or chronic liver disease. Optimal management is of vital importance when these pathologies affect women in pregnancy both because of adverse effects themselves and also because of maternal and fetal outcomes. Acute or chronic liver diseases in women, pregnant and not, require changes in gynecological care, contraception, planning of pregnancy, exploration of cervical cancer, papilloma vaccine and postmenopausal hormone replacement therapy.

Women with liver transplants require gynecological care adapted to their immunosuppressed state for both the well-being of the mother and the viability of the fetus.

NORMAL PHYSIOLOGICAL CHANGES DURING PREGNANCY

Many physiological and hormonal changes normally occur in pregnant women's bodies during pregnancy. Some may resemble those that occur in patients with liver disease. Maternal heart rate, cardiac output, and circulatory volume all increase while peripheral vascular resistance decreases. These changes can also occur patients with decompensated chronic liver disease. Physical examination may show palmar erythema and arachnid nevi in up to 70% of pregnant women. Liver blood flow remains constant during pregnancy, and the liver is not palpable because it is displaced a little upwards in the thoracic cavity due to the growth of the

uterus. Gallbladder motility decreases, resulting in increased risk of gallstone development. (1)

During pregnancy, biochemical and hematological indices should be interpreted in light of the normal ranges for a pregnant woman. Alkaline phosphatase increases in the third trimester, as it is produced by the placenta and by development of fetal bone. Alpha-fetoprotein increases in pregnancy and is produced by the fetal liver. Urea levels, hemoglobin levels, and prothrombin times remain unchanged or are slightly reduced due to hemodilution. Elevated transaminases, bilirubin, and prothrombin time are abnormal and indicate disease states which require appropriate studies.

Pregnancy is a procoagulant state in which coagulation factors I, II, V, VII, X, and XII as well as fibrinogen are increased. Small esophageal varices can be seen in up to 50% of pregnant women in the second and third trimesters. They are due to compression of the inferior vena cava by the uterus and consequent reduction of venous return. A liver biopsy is rarely indicated, but if one is performed during pregnancy, the risks are very similar to those for women who are not pregnant. (2, 3) Liver dysfunction during pregnancy may be due to liver disease associated with pregnancy, exacerbation of pre-existing liver disease, or conditions unrelated to pregnancy (Table 1).

Table 1. Liver diseases during pregnancy (4)

Liver diseases related to pregnancy
Hyperemesis gravidarum
Gestational intrahepatic cholestasis
Liver diseases related to hypertension
Preeclampsia/eclampsia
HELLP syndrome
Subcapsular hematoma and liver rupture
Acute fatty liver of pregnancy
Liver diseases not related to pregnancy
Pre-existing liver disease
Viral
Autoimmune (autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis)
Metabolic (Wilson's disease, hemochromatosis)
Cirrhosis and portal hypertension
Post-liver transplant
Other pre-existing liver diseases
Coincident with pregnancy
Autoimmune
Viral
Vascular
Drug-induced hepatotoxicity
Diseases that can be exacerbated during pregnancy
Budd-Chiari syndrome
Hepatic adenoma
Polycystic disease

HYPEREMESIS GRAVIDARUM

Hyperemesis gravidarum (HG), persistent vomiting unrelated to other causes, occurs in 0.3% to 3% of pregnancies. (5, 6) It can lead to dehydration, ketosis, and loss of more than 5% of preconception weight. (5) It usually begins very early in gestation and resolves at week 20. (2, 7) Diagnosis is made by exclusion, and its exact cause is not clear. Numerous theories based on genetic, psychiatric, psychological, cultural and hormonal factors that have been put forward. Others are based on gastric motility alterations, changes in the autonomic nervous system, and Helicobacter pylori infections. (5, 6, 8, 9)

The first trimester peak of human chorionic gonadotropin (HCG) is correlated with the severity of hyperemesis gravidarum, and hyperthyroidism occurs in 60% of patients with HG. (1, 2, 8, 9) HCG activates thyroid stimulating hormone (TSH) receptors leading to thyroid suppression and increased thyroxine levels. (2, 5)

Clearly identified risk factors include molar and twin pregnancies, trophoblastic disease, previous history of HG, previous history of fetal abnormalities, increased body mass index, psychiatric diseases, and diabetes. (2, 7, 8) Alterations of liver biochemistry occur in 50% to 60% of hospitalized patients with HG and are characterized by slight elevations of transaminases. Jaundice and synthetic dysfunction are rare. (2, 7) In addition, patients may present renal dysfunction and electrolyte disorders such as hyponatremia, hypokalemia, and hypochloremic alkalosis. (2, 6) In severe cases, dehydration can lead to orthostatic hypotension, tachycardia, and lethargy. Vomiting can lead to bleeding from esophageal lacerations and vitamin deficiency which has produced neurological disorders in very rare cases. (5, 6) The relationship of HG with fetal morbidity has not been clearly demonstrated in the literature, but some studies have reported higher rates of low birth weight and preterm deliveries. (6, 9)

Management of HG is based on support measures until symptoms resolve with progression of gestational age. (2, 6, 10) Intravenous rehydration, correction of electrolyte disorders, and thiamine replacement are indicated for prevention of Wernicke's encephalopathy, especially in patients who receive dextrose solutions. (6, 9) Vitamin B6 for control of nausea and vomiting is considered the first-line therapy while antiemetics are considered second line. (2, 5) Systemic steroids and ondansetron can be considered for refractory patients, but their safety profiles must be taken into account. (2, 5) Patients who cannot maintain weight and do not respond to antiemetics require advanced enteral nutrition and may even require total parenteral nutrition. (5, 6, 9)

Biochemical abnormalities usually improve with resolution of vomiting and do not leave permanent liver sequelae.

If liver tests are not normalized with resolution of vomiting, other causes should be suspected. (8)

INTRAHEPATIC CHOLESTASIS OF PREGNANCY

Intrahepatic cholestasis of pregnancy (ICP) affects 1 in 140 pregnancies in the UK and is more common among women with family or personal histories of ICP, itching related to oral contraceptives, gallstones, or multiple pregnancies. Some studies suggest a high prevalence in patients with hepatitis C virus infections and non-alcoholic fatty liver disease. (4, 11, 12) It usually occurs in the 3rd trimester of pregnancy, but cases have been reported as early as the eighth week of pregnancy. ICP is characterized by itching, abnormal liver function tests, and increased serum bile acid levels. The symptoms are choluria, acholia, anorexia, fatigue, epigastric pain and steatorrhea due to fat malabsorption. Transaminases are usually elevated. (4, 8, 11, 12)

Itching is predominantly nocturnal and usually affects palms and soles. It can become severe but characteristically improves within 48 hours of delivery. Elevation of bilirubin is rare, but when it occurs, it increases 2 to 4 weeks after the onset of itching and can occur before or after bile acid levels increase. ALT has been found to be a more sensitive marker of ICP than AST because ALT levels increase between two and ten times more than do those of AST. Clinical jaundice occurs in 10% to 15% of pregnant women with ICP and is generally mild, with bilirubin levels not exceeding 100 μmol/L or 5.85 mg/dL. Hyperbilirubinemia usually occurs at the expense of direct bilirubin. Vitamin K malabsorption increases the risk of postpartum hemorrhaging. (4)

ICP is benign for the mother, but when bile acid levels are higher than 40 mmol/L the risk of adverse outcomes including preterm deliveries, fetal distress, meconium-stained amniotic fluid, long-term neonatal ICU care and stillbirths increases. (12, 13)

ICP's pathogenesis is unknown but is related to abnormal bile transport through the canalicular membrane. Multidrug resistance protein 3 (MDR3) is the major phospholipid transporter, and mutation of the gene which expresses it leads to a loss in function and increased levels of serum bile acids. The MDR3 mutation is located on chromosome 7q21.1 and has been identified in 15% of the cases of ICP. Abnormal placental transport of bile acids from fetal to maternal circulation increases maternal bile acids while the immature fetal transport system can contribute to increased bile acid levels in the fetus itself. (4)

When a diagnosis of ICP is ruled out, other causes of cholestasis should be sought. (13) Serum bile acids are the most sensitive and specific test for diagnosis and monitoring of this condition. Usually, a liver biopsy is not necessary for diagnosis, but if one is performed, findings predominate in zone 3. They include centrilobular cholestasis without inflammation and bile plugs in hepatocytes and canaliculi. (4)

ICP is treated with 10-15 mg/kg of ursodeoxycholic acid (UDCA). This is the only drug that has shown to benefit maternal symptoms and liver biochemistry and to have possible beneficial effects on perinatal outcomes. Some studies have shown that it increases the expression of placental bile acid transporters which improves transfer. It is anti-apoptotic and increases the excretion of pruritogens such as progesterone sulfate. Studies suggest that its use has a positive impact on premature deliveries, reduces admission of newborns to the ICU, reduces placental damage and reduces fetal arrhythmias. (2, 4, 12, 14) Other medications, including cholestyramine, S-adenosine L-methionine, and dexamethasone are less effective than UDCA at reducing itching and improving liver function. Cholestyramine has even been found to exacerbate vitamin K deficiency. (8, 12, 14)

Rifampicin may be useful as an adjunct treatment in women with severe or refractory disease, and it improves symptoms and biochemistry in a third of the patients who did not respond to UDCA. Nevertheless, it should only be used if transaminases are not too high. (2, 12) An association between stillbirths in ICP and the 38th week of pregnancy has been found, so many centers have chosen to end these pregnancies before that moment.

Symptoms and liver profile changes usually disappear after delivery, but sometimes they continue. Bile acid and liver enzyme levels should be tested 6 to 8 weeks after delivery. If enzyme levels have not improved, other causes of cholestasis should be sought. There is a high risk of recurrence of ICP in subsequent pregnancies, and some women even experience cholestasis with menstrual cycles or with the use of oral contraceptives and should avoid estrogen-containing medications. (12, 14) There is evidence that those women who developed ICP have high risks of developing hepatobiliary diseases or metabolic syndrome at some point in their lifetimes. (4, 12)

HELLP SYNDROME

Preeclampsia is the most common cause of liver function abnormalities during pregnancy. It is characterized by hypertension and proteinuria after 20 weeks of pregnancy. Pain in the right upper quadrant of the abdomen is suggestive of hepatic involvement and requires close monitoring. (13)

HELLP syndrome is characterized by microangiopathic hemolytic anemia (MAHA), elevated liver enzymes, and decreased platelet levels. This syndrome occurs in 0.2% to 0.8% of pregnancies and 70% to 80% of these cases coexist with pre-eclampsia. Most cases occur in the third trimester of pregnancy. Perinatal mortality secondary to premature

births and maternal complications occurs in 6% to 70% of cases. Risk factors include advanced age of the mother, nulliparity and multiparity. (4, 10)

HELLP is believed to be due to impaired platelet activation, increased proinflammatory cytokines, and segmental vasospasms with vascular endothelial damage. (4) Most patients gain weight and develop abdominal pain in the right upper quadrant, nausea, vomiting, malaise, headaches, visual changes, and peripheral edema. Hypertension and proteinuria occur in 80% of cases. Jaundice only occurs in 5% of patients. Symptoms associated with thrombocytopenia such as bleeding from the mucosa, hematuria, petechiae, and bruising are also unusual. Less common are renal failure with increased uric acid, diabetes insipidus, and antiphospholipid syndrome (APS). (4, 11, 15)

Due to hemolysis, patients have elevated indirect bilirubin levels and increased lactic dehydrogenase (LDH) levels. ALT and AST levels are moderately high. In initial stages, the prothrombin time (PT) and the partial thromboplastin time (PTT) are normal, but in later stages, disseminated intravascular coagulation (DIC) with high levels of fibrin degradation products, D-dimer and thrombin-antithrombin complex can occur. (4) Diagnostic criteria for HELLP syndrome have been standardized by the Task Force of the American College of Obstetrics and Gynecology on hypertension in pregnancy and are shown in Table 2. (15)

Table 2. Recommended criteria for diagnosis of HELLP syndrome (15)

Hemolysis (at least 2 of the following)
Peripheral blood smear (schistocytes, echinocytes)
Serum bilirubin> 1.2 mg/dL (indirect predominance)
Low serum haptoglobin
Severe anemia not related to blood loss
Elevated liver enzyme levels
AST or ALT ≥2, normal upper limit
LDH ≥2, upper limit normal
Thrombocytopenia (platelets <100,000/mm^3)

It is estimated that 1 in every 1,000 pregnant women develops HELLP. Of these, 2% to 3% develop liver complications including liver failure requiring liver transplantation. A ruptured liver is rare but is a life threatening complication. It is usually preceded by hepatic hemorrhaging that progresses from the parenchyma to become a subscapular hematoma contained in the right liver lobe. Uric acid levels of over 464 µmol/L (7.8 mg/dL) are associated with increased maternal and fetal morbidity and mortality. (4, 8)

Once HELLP develops, the only treatment is delivery of the baby. If the gestational age is between 24 and 34 weeks, steroids are required for lung maturation. Delivery take place 24 hours after application of steroids. Continuous maternal follow-up after delivery is required because worsening thrombocytopenia and increased LDH may occur up to 48 hours postpartum. If gestational age is over 34 weeks, of if there is evidence of fetal distress or maternal complications such as severe organ compromise, disseminated intravascular coagulation, kidney failure, pulmonary edema, intrahepatic bleeding, stroke, or placental abruption, the pregnancy should be terminated as rapidly as possible. (4, 8, 15) Indications for transplant include persistent bleeding from bruising, ruptured liver, or liver failure. It has been found that 88% of these patients survive for 5 years after transplantation. (8)

HEMATOMA, INFARCTION AND RUPTURED LIVER

Hemorrhaging and a ruptured liver can complicate preeclampsia, eclampsia, or HELLP syndrome and have been associated with a 50% mortality rate. Patients present abdominal pain, pyrexia and severe hypovolemic shock with cardiovascular collapse. There is a marked increase in transaminases and anemia. Computed tomography and magnetic resonance imaging are the diagnostic methods of choice. (2)

Hematomas that are contained can be managed conservatively with aggressive coagulation support, prophylactic antibiotics, and transfusions. Any evidence of hemodynamic instability should be treated with angiography with embolization of the hepatic artery, liver packing, ligation of the hepatic artery and resection.

Necrotic infarcts can occur as complications of preeclampsia. Often, patients have unexplained increases in transaminases, fever, anemia, and leukocytosis associated with signs of liver failure. In most cases, the liver recovers, but when areas of extensive infarction occur, multiple organ failure and death due to a ruptured liver may ensue. (2) Rupture of the hepatic capsule generates intraperitoneal bleeding. Mortality is highest after a liver ruptures. Treatment is rehydration and either surgery or angiographic embolization, as appropriate. (2, 4, 11)

ACUTE FATTY LIVER OF PREGNANCY

Acute fatty liver of pregnancy (AFLP) is a rare occurring pathology with a reported incidence of 1 in 7,000 to 15,000 pregnancies. A prospective population study conducted in the UK with a cohort of 1.1 million pregnancies has estimated an incidence of 1:20,000 births. (16, 17) AFLP can be life-threatening and is considered an obstetric emergency. It can lead to acute liver failure and, if diagnosis is delayed, to death of the fetus and the mother. Although maternal

mortality rates have improved from 92% before 1970 to less than 10% reported in 2008, they are still very high. (2)

Typically, this pathology occurs in the third trimester between week 30 and 38, but sometimes it is not recognized until after delivery. However, there are reports of cases as early as the 26th week of gestation. (18, 19) AFLP is an infiltrative disease with evidence of microvesicular steatosis upon biopsy. It is a mitochondrial liver disease which is associated with a homozygous fetal mutation (1528G> C) in the gene coding for long-chain 3-hydroxyacyl-CoA dehydrogenase which produces severe decrease or total loss of enzymatic activity. This mutation results in an accumulation of long-chain fatty acids in the placenta which pass into maternal circulation and lead to development of acute liver damage. (20)

AFPL risk factors include histories of previous episodes, multiple gestation, male fetal sex, coexistence of other liver diseases during gestation (HELLP, pre-eclampsia) and a body mass index under 20 kg/m^2. (16, 17) Initial symptoms of AFPL are generally nonspecific with 1-2 weeks of nausea, vomiting, abdominal pain, malaise, and anorexia. Signs and symptoms of acute liver failure such as encephalopathy, jaundice, and coagulopathy may appear with rapid development of moderate to severe hypoglycemia. Approximately 50% of these patients present preeclampsia, although hypertension is generally not severe. (21)

The definitive diagnostic method for AFLP is a liver biopsy. In patients with coagulopathy, it should be performed transjugularly given the high risk of bleeding. In many cases a liver biopsy is not necessary to make the diagnosis. The characteristic histological finding is microvascular fat infiltration, which affects the pericentral zone and respects the periportal zone. When a biopsy is performed at an early stage of the disease, the hepatocytes appear ballooned in the absence of large amounts of fat and giant mitochondria. At later stages, hepatocyte destruction can cause loss of the liver parenchyma and cellular atrophy. (18) There is no adequate correlation between the degree of alterations found in laboratory tests and the severity of histological compromise. (22)

Ultrasound and CT scan findings are inconsistent for detection of fatty infiltration, so diagnosis is usually based on clinical and laboratory findings. The Swansea criteria (Table 3) for diagnosis of AFLP are a proposal that includes symptoms, laboratory findings, and imaging. This model was developed by Ch'ng et al. at the Swansea Midwifery Unit in South West Wales, UK in 2002. It was validated in a cohort study in 2008. When at least six of 15 criteria are present, AFLP is likely. (17, 23) These criteria have demonstrated a sensitivity of 100% (95% CI: 77% to 100%), a specificity of 57% (95% CI: 20% to 88%), a positive predictive value of 85%, and a negative predictive value of 100% for diffuse and perivenular microvesicular steatosis. (24)

Table 3. Swansea criteria

Signs and symptoms	Laboratory findings	Others
Vomiting	Bilirubin> 0.8 mg/dL	Ascites or "bright liver" found by ultrasound
Abdominal pain	Hypoglycemia <72 mg/dL	Biopsy: microvesicular steatosis
Polydipsia/ polyuria	Urea elevated> 950 mg/dL	
Encephalopathy	Leukocytosis> 11 x 10^9/L	
Ascites	ALT >42 U/L	
	Ammonium> 66 µmol	
	Creatinine >1.7 mg/dL	
	PT coagulopathy> 14s or PTT> 34s	

Early diagnosis of AFLP is essential. Initial management is basically supportive to stabilize the mother while avoiding the use of hepatotoxic drugs. In cases with suspected infections, broad-spectrum antibiotics should be administered. Regardless of the severity of AFPL, termination of pregnancy as quickly as possible is the basic treatment. If there is no obstetric contraindication, delivery may be vaginal, although a small study published in 2010 showed a lower maternal mortality rate in the caesarean group than in the vaginal delivery group (16.2% vs. 48.1%). (25, 26)

AFPL is usually reversible with complete liver function recovery and no sequelae. In case of persistent deterioration and development of liver failure, liver transplantation should be considered. (14, 16, 25) A retrospective study of 54 patients with liver disease associated with pregnancy found 18 patients with diagnoses of AFPL who had been referred to a liver transplant center. The study documented that lactate > 2.8 mg/dL had a sensitivity of 73% and a specificity of 75% as a predictor of death or need for liver transplantation. When encephalopathy was added, the sensitivity and specificity increased to 90% and 86%, respectively. (27)

AUTOIMMUNE HEPATITIS

Autoimmune hepatitis (AIH) is a chronic inflammatory process of the liver of unknown cause that is characterized by hypergammaglobulinemia, circulating autoantibodies, interface hepatitis found by biopsy and favorable response to immunosuppression. (28-30) The clinical spectrum is wide and includes asymptomatic patients; patients with nonspecific symptoms such as fatigue, nausea, abdominal

pain and arthralgia; patients with severe acute hepatitis; and even patients with established cirrhosis. (30, 31) Some patients also have other autoimmune pathologies. (28, 30)

The 1993 diagnostic criteria for autoimmune hepatitis of the International Group on Autoimmune Hepatitis (IAIHG), a group of experts, were revised in 1999, (30, 31) but due to their complexity Hennes et al. developed a simplified and much more practical scoring system in 2008. It is based on variables that are independent predictors of autoimmune hepatitis and has sensitivity and specificity over 80 % (Table 4). (29)

Autoimmune hepatitis manifests itself in the same manner in pregnant women as in others and is therefore diagnosed the same way. (8) Autoimmune hepatitis usually occurs in women of childbearing age. Successful pregnancies are possible in this group of patients, but increased morbidity and mortality rates have been reported for both the fetus and the mother. They have been associated with poor control of inflammatory activity from one year prior to conception through pregnancy. (2, 8, 32-38) These complications are more frequent and can be fatal in patients with decompensated cirrhosis of the liver. (38, 39)

Table 4. Simplified autoimmune hepatitis scoring system (29)

Parameter		Score
ANA or ASTHMA	≥1:40	+1
ANA or ASTHMA	≥1:80	+2*
or LKM	≥1:40	+2*
or SLA/LP	Any titer	+2*
IgG	> upper limit of normal	+1
	> 1.1 times the upper limit of normal	+2
Biopsy	Compatible	+1
	Typical	+2
Absence of viral hepatitis	Yes	+2

* The maximum score for autoantibodies is +2.
> 6 points: probable.
> 7 points: definitive.

AIH is most frequently activated in the first three months following delivery. Its incidence ranges from 11% to 81%. It probably occurs due to immune reconstitution after delivery and decreasing blood estrogens. (2, 8, 30, 31, 33, 35, 37, 38) Improvement including spontaneous remission of inflammatory activity has been described during pregnancy. This is probably related to the predominantly immunotolerant state during pregnancy. (30, 32, 38, 39) Despite this, the disease can be activated at any point during pregnancy and has an incidence of 7% to 21%. (7, 20, 30, 33) This activation can usually be controlled with increased immunosuppression, but for some patients, activation of the disease can lead to liver decompensation, the need for liver transplantation, and even death of the patient and fetus. (2, 33, 38)

Immunosuppression with steroids and drugs such as azathioprine is the mainstay of treatment for AIH. (30, 36, 40) However, in pregnancy, optimal management has not been well established. What is clear is that these patients require stable immunosuppression throughout the pregnancy, with greater vigilance in the postpartum period. (30, 32, 33, 38, 40, 41)

Due to the teratogenic effects reported in animals, azathioprine is considered a category D drug in pregnant women. However, multiple retrospective studies have shown that it is safe during pregnancy and lactation. Consequently, the teratogenic potential of azathioprine is outweighed by the beneficial effects of disease control since remission decreases the risk of maternal and fetal complications. (2, 8, 30-33, 35, 37-40) For patients who have been undergoing treatment of AIH with azathioprine before pregnancy, administration of the drug should be continued at the dosage necessary to control the disease during pregnancy. (2, 38) If biochemical hepatitis occurs, it should be treated conventionally with steroids. (2, 8, 30)

Mycophenolate mofetil has been associated with increased teratogenicity and should be discontinued before pregnancy and should not be used during pregnancy. (30, 39, 40) Calcineurin inhibitors can be safely used during pregnancy according to data obtained from transplanted pregnant women. (30, 40) To decrease risks of complications, these patients should plan their pregnancies and have inflammatory activity under control for at least one year prior to becoming pregnant. They should receive treatment throughout pregnancy and deliver their babies in highly complex medical centers with close obstetric and hepatological monitoring during pregnancy and the postpartum period. (2, 30, 32, 33, 38-40) The delivery route should be defined by the obstetrician. (33)

HEPATITIS B INFECTIONS

It has been calculated that up to a third of the world's population may have serological evidence of past or present hepatitis B infections. Between 350 and 400 million people are chronic carriers of the surface antigen (HBsAg) and 240 million have chronic hepatitis. (42-44) Every year more than 50 million new cases are reported. Most of them are transmitted vertically. (42, 45) Data from the United States indicate a prevalence of 0.7 to 0.9 of HBV in pregnant women which translates into 25,000 newborns at risk of infection annually. (46)

The risk of an HBV infection becoming chronic (HBsAg persists beyond 6 months) is related to age at infection. It is

5% in adults, 50% in small children, and up to 90% in infants. (43) The highest vertical transmission rates (70% -90%) have been associated with maternal HBsAg , e antigen (HBeAg), and absence of post-exposure prophylaxis in infants. (47)

The behavior of HBV infections in pregnancy has no important differences with HBV in the general population. Ninety-five percent of acute infections in pregnant women spontaneously resolve, and the risk of liver failure is about 1%. (48) If an infection occurs early in pregnancy, it can cause a miscarriage, but it usually resolves without consequences for the mother or fetus. In this scenario, the possibility of vertical transmission is only 10%, but when an infection is acquired in the final stage of pregnancy, vertical transmission is much more likely and can occur in up to 60% of cases. (49) There are several factors that increase the possibility of perinatal transmission of HBV. (50-52)

- It has been shown that immunoprophylaxis can fail when maternal viral loads are high, especially when they are greater than 6 Log10 copies/mL. (51-53)
- HBeAg is a marker of replication and infectivity which is usually associated with high viral loads
- Lack of immunoprophylaxis is related to possibility of perinatal transmission of over 90% when the mother is HBeAg positive, and 15% when she is HBeAg negative. If adequate immunoprophylaxis is offered, the perinatal transmission rate falls to 2%. The vast majority of these cases occur when viral loads are greater than 200,000 IU/mL (106 copies/mL). (49-54)

Prevention of vertical transmission is based on a combination of vaccination and hepatitis B immunoglobulin (HBIG). This must be provided within the first 12 hours after birth to every child born to an HBsAg positive mother regardless of whether she has received antiviral treatment. (55, 57) This combination has a great impact on viral transmission rates and has caused perinatal transmission to go from 90% (in cases where immunoprophylaxis is not administered) to minus 10% in this combination. (49)

Antiviral treatment is indicated in all pregnant women who are HBsAg positive and have a viral load over 200,000 IU/mL (over 10^6 copies/mL). In these patients, the use of immunoprophylaxis alone has a possibility of failure up to 30%, so they are considered a high-risk group for perinatal transmission. (49, 57, 58) In patients with hepatitis B e antigen (HBeAg)-negative chronic hepatitis B (previously called asymptomatic carrier status) and with viral loads of 200,000 IU/mL or more, antiviral prophylaxis is not indicated. (59, 60)

The goals of treatment in pregnancy are to maintain stable liver function in the mother and to prevent neonatal infection. Levels of aminotransferases should be regularly evaluated during pregnancy, and antiviral medication should be started between the 28th and 32nd week of pregnancy since organogenesis is complete but there is still enough time to reduce HBV DNA levels significantly. (60) Medication should be continued up to 12 weeks after delivery due to the possibility of exacerbation of HBV. This occurs most frequently in patients who are HBeAg positive whose risk is 2.56 times higher when patients who are HBeAg negative. (59-62)

Three antiviral drugs whose fetal safety profile is adequate are available: lamivudine, telbivudine, and tenofovir (63-66). Lamivudine has been falling into disuse due to resistance rates which can be as high as 70% over 5 years. This drug limits future maternal treatment options since use for even a short period promotes resistant viral variants in 20% of cases. (67)

Tenofovir is the antiviral agent of choice during pregnancy. It should be administered orally in doses of 300 mg/day. It is the most potent nucleoside analog, has the lowest resistance rates, and extensive safety data are available for use during pregnancy. (49, 64, 68, 69) Patients with chronic HBV infection treated with tenofovir should continue with this medication. If they have been treated with entecavir, treatment should be switched to tenofovir. (59)

The indication for delivery is obstetric. There is no contraindication for vaginal birth since no studies have found that caesarean sections decrease the possibility of perinatal transmission. (70, 71) There is also no contraindication for breastfeeding for untreated women or for mothers who receive an antiviral agent such as tenofovir. The risk of exposure to this drug in utero is greater than that through breast milk and its use, and tenofovir is recommended during pregnancy. (59, 72-75) What is clear is that breastfeeding should be avoided when the mother's nipples are cracked or bleeding because of the risk of mixing serous exudates with breast milk which could potentially lead to transmission of HBV to the infant. (76)

HEPATITIS C INFECTIONS

Hepatitis C virus (HCV) infection constitute one of the leading causes of chronic liver disease worldwide. (77) The natural history of this entity varies greatly from minimal histological changes to cirrhosis, with or without hepatocellular carcinoma. Worldwide, there are approximately 71 million people who have chronic HCV infections. It is estimated that 1% to 8% of pregnant women have HCV. (78)

Transmission of the infection from mother to child can occur during three different periods:

- Intrauterine transmission is defined by HCV RNA in the serum of the newborn within the first 3 days of life. It accounts for 30% to 40% of cases. Among the proposed mechanisms are the passage of viral particles from mother to fetus, maternal-fetal flow of infected mononuclear cells, and infection of trophoblasts.

- Peripartum transmission is defined by a finding of HCV RNA in the serum of a newborn within the first 28 days after birth. This is the most important period in vertical transmission (60% of cases). It correlates with exposure to maternal blood. For this period, the main risk factors are invasive obstetric procedures (for example, amniocentesis and fetal monitoring), as well as lacerations of the vaginal or perineal mucosa during vaginal delivery and prolonged rupture of the membranes.
- Postpartum transmission is rare and is attributed to breastfeeding. However, despite the fact that HCV RNA is detectable in human colostrum, breastfeeding is not considered a risk factor for mother-to-child transmission. (79)

A 2014 metaanalysis reported vertical transmission rates of 5.8% in viremic women and 10.8% for those who were coinfected with HIV. (80) Transmission occurs almost exclusively from mothers who are HCV RNA-positive, and risk correlates with the mother's viral load titers. Transmission is four times higher for patients with 6 log copies/mL than for those who have lower viral loads (14.3% vs. 3.9%). (81)

There is no universal consensus on screening for HCV during pregnancy. The American College of Obstetricians and Gynecologists (ACOG) and the Centers for Disease Control and Prevention (CDC) recommend screening only for women with risk factors for HCV infections (Table 5). (79) Nevertheless, a retrospective study by Selvapatt et al. that evaluated 35,355 women who had undergone prenatal HCV screening found that a total of 136 mothers (0.38%) tested positive for HCV antibodies. Of these, forty-four (0.12%) had been recently diagnosed with chronic hepatitis C, thirty-four had previous diagnoses, and 58 had negative HCV viral loads. Three cases of vertical transmission (6.8%) were documented in the children of these newly diagnosed mothers. This and other studies have shown that universal screening in pregnancy should be implemented. (82, 83)

Table 5. Recommendations for prenatal HCV screening (84)

Recommendations for prenatal HCV screening
Illegal drug injections (current or past, even those who injected only once)
Intranasal illicit drug use
Hemodialysis use
History of piercing or tattoos in an unregulated environment
HIV or HBV infection
Recipients of transfusions or transplants before 1992 or clotting factors before 1987
Background of incarceration
In vitro fertilization with anonymous donors
Sexual partners of people with HIV, HBV or HCV
Women with unexplained chronic liver disease (including persistently elevated ALT)

There is no evidence that termination of pregnancy by caesarean section decreases transmission of HCV, and breastfeeding is not contraindicated except in cases of cracked or bleeding nipples. These recommendations are the same as those for HBV. (85)

The use of interferon and ribavirin is contraindicated in pregnancy due to teratogenic effects. (86) There are no adequate human data for the use of second-generation direct-acting antivirals during pregnancy, but data obtained from animal studies demonstrate that they do not confer risk to the fetus. Due to the lack of human studies, no direct-acting antiviral therapy has yet been approved for treating HCV infections during pregnancy. (87)

CIRRHOSIS AND PREGNANCY

The prevalence of cirrhosis in women of childbearing age is low because hepatocellular damage leads to metabolic and hormonal changes such as anovulation, amenorrhea, and infertility. (8, 10, 11, 32) Although pregnancy is rare in patients with liver disease, it implies a complicated clinical condition when it does occur. (8) Outcomes of these pregnancies are related to the severity of liver disease. A preconception MELD score of over 10 points is associated with a decompensation risk of 10% while a MELD score of less than six points is not associated with liver complications during pregnancy. (2, 7)

The most frequent causes of cirrhosis in pregnant women are autoimmune factors and hepatotropic viral infections. (10) Physiological changes during pregnancy and fetal needs worsen portal hypertension and increase both maternal and fetal risks. (2, 7, 10) Bleeding varices are the most frequent and catastrophic complications of portal hypertension during pregnancy. The greatest risks of bleeding occurs during the second trimester during which the highest peak of portal hypertension is reached and during delivery due to Valsalva maneuvers. (7, 8)

Increased maternal blood volume and cardiac output associated with decreased peripheral vascular resistance secondary to the effects of progesterone and the development of the placental vascular bed lead to a hyperdynamic state with increased flow to the collaterals. This significantly increases the risk of bleeding varices. (10) External compression of the inferior vena cava by the gravid uterus further increases portal pressure. (8) Pregnant cirrhotic women have nearly 30% probability of variceal bleeding, and this increases to 70% in patients with pre-existing varicose veins. (8, 10, 32) Mortality associated with bleeding is 18% to 50%. (2, 10) Bleeding varices increase the incidences of miscarriage and preterm delivery. Given the high risk of variceal bleeding and its complications, the American College of Gastroenterology recommends screening for

esophageal varices in pregnant patients in the second trimester after completion of organogenesis, but before delivery, at a time of increased risk of bleeding.

Despite limited data regarding prophylaxis and management of acute variceal bleeding in pregnant patients, primary prophylaxis can be performed with endoscopic ligation or with β-blockers just as in the general population. (10) Secondary prophylaxis requires both endoscopic band ligation and the use of β blockers. These drugs are considered safe in pregnancy despite being category C, but they carry risks of fetal bradycardia, intrauterine growth restriction and neonatal hypoglycemia. (2, 7, 10) Treatment of acute variceal bleeding is similar to that for the general population. The mother should be resuscitated and stabilized, then endoscopic ligation of varicose veins is the main therapeutic measure. Endoscopy is safe during pregnancy although it carries a small risk of fetal hypoxia secondary to sedation and patient position. Octreotide is a category B medication in pregnancy. Despite a lack of good studies in pregnant women, it appears to be safe. Terlipressin is category D since it produces uterine ischemia: it is not recommended for pregnant women. (2) Third-generation cephalosporins are the recommended prophylactic antibiotics since quinolones are contraindicated. (10) Emergency Transjugular intrahepatic portosystemic shunting (TIPS) has been successfully performed in pregnant patients. (2, 32)

Ascites and hepatic encephalopathy occur in 24% of pregnant patients with cirrhosis and can appear at any stage of pregnancy. (88) Treatment of ascites is based on salt restriction and the use of diuretics. When spontaneous bacterial peritonitis is found, it the usually treated with third-generation cephalosporins. (10) Hepatic encephalopathy is usually associated with a precipitating event that should be actively sought. Lactulose is a category B drug, while rifaximin is category C. (32)

Ultrasound is considered to be the safest imaging method for visualizing the liver parenchyma and even the bile duct in a pregnant patient. In case a more detailed image is required, MRI without contrast is also safe in the second and third trimesters of pregnancy. The limitations of uncontrasted images for evaluating liver lesions, especially hepatocellular carcinoma, must always be taken into account. (8, 11) Data comparing vaginal and cesarean deliveries in these patients are too scare to recommend one route or the other, so the individual obstetrician must decide. (2, 89)

Pregnant patients with cirrhosis are at greater risk of postpartum hemorrhaging. It occurs in 7% to 10% of cases in relation to coagulopathy secondary to liver dysfunction and thrombocytopenia due to hypersplenism. It is treated with transfusions and agents that promote uterine contraction. (10) The probabilities of fetal complications, spontaneous abortions, preterm deliveries, stillbirths and perinatal deaths all increase. (2, 7, 89)

Due to the high risks of complications, comprehensive management of these patients requires an interdisciplinary group in a highly complex medical center. The group should include gynecologists, neonatologists, hepatologists, endoscopists, and even intensive care specialists. Ideally, these patients' liver disease should be compensated, their esophageal varices managed, and medications contraindicated during pregnancy should be discontinued. Periodic examinations should be done throughout the pregnancy in order to decrease the risk of complications for both the mother and the fetus.

TRANSPLANTS AND PREGNANCY

Perinatal outcomes in women who have had liver transplants are good, especially if they wait at least 12 months after surgery or an acute episode of rejection to become pregnant since this lessens the need for immunosuppressants and lessens the risks of opportunistic infections. The live birth rate is reported to be between 70% and 90%. There are high risks of hypertensive disorders of pregnancy, pre-eclampsia, preterm deliveries, and low birth weights. (11, 12)

Administration of immunosuppressants should continue as part of pre-pregnancy care, and high-dose folic acid supplements (5 mg/day) should be taken. (12) Overall, the impacts of steroids, azathioprine, and calcineurin inhibitors (tacrolimus and cyclosporine) on maternal-fetal abnormalities are small. Neonatal leukopenia has been seen with azathioprine, but this normalizes after the first year of life. Cyclosporine is associated with low birth weights and premature births. Calcineurin inhibitors can cause hyperkalemia, preterm delivery, and renal dysfunction. (4, 11, 90, 91)

In contrast, mycophenolate, sirolimus, and everolimus are all associated with high rates of fetal abnormalities. Mycophenolate not only increases the rate of miscarriages and fetal toxicity, but is related to malformations of many organs and parts of the body including ears, extremities, kidneys, hearts, esophagi and faces (cleft palate and cleft lip). Sirolimus and everolimus have not been sufficiently studied, but their antiproliferative effects can harm a fetus, so they are contraindicated in pregnancy. If possible, a woman receiving this type of immunosuppressant should be switched to an alternative regimen at least 6 months before conception. (4, 11, 90, 91)

Graft survival appears to be unaffected by pregnancy although there are reports of rejection in 2% to 17% of cases during pregnancy and in 3% to 12% of cases in the postpartum period. As in women who are not pregnant, episodes of rejection should be managed by investigating the cause

of rejection and adjusting administration of immunosuppressants. (2, 12)

Prenatal medical examinations should be done every four weeks and should always include screening for normal pregnancy infections. Vaccinations should be updated. Examinations should also include periodic evaluations for cytomegalovirus which can not only cause various malformations in fetal development, but can also compromise graft survival. Once 24 weeks is reached, monitoring of fetal well-being every two weeks is recommended. This should include Doppler of the umbilical and uterine arteries. Women who have had transplants and become pregnant should maintain hemoglobin levels between 10-12 g/dL. Iron and erythropoietin stimulating agents, which are not contraindicated in pregnancy, are recommended for this purpose. (90, 91)

A review of the largest published studies of pregnancy in liver transplant patients shows that the incidences of maternal complications during pregnancy are 33.9% for hypertension, 26.5% for infections, 21.5% for preeclampsia, 8.4% for rejection and 6.7% for diabetes. (90) Cesarean deliveries are preferred primarily out of concern over obstetric complications. (92)

Women who are on steroid-only management are allowed to breastfeed, but breastfeeding is not advised for the vast majority who take more than one immunosuppressant since some effects of immunosuppression on newborns are unknown. (4, 91)

Hormonal contraceptives taken by liver transplant patients have no effects on liver function, incidence of rejection, complications, patients' cardiovascular health and no interactions that would require discontinuation of medications. However, calcineurin inhibitor toxicity associated with inhibition of cytochrome P-450 by oral contraceptives may develop. Consequently, women who have liver transplants who use hormonal contraceptives require strict control of cyclosporine and tacrolimus levels. Intrauterine devices are the most widely used contraceptive method in these patients, since they are safe for graft viability and do not increase the risk of intrauterine infections. (90-92)

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Microscopic Cholitis, An Increasingly Frequent Diagnosis

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Abstract

Microscopic colitis currently includes three subgroups. The classical ones are lymphocytic colitis and collagenous colitis which are distinguished histologically by the presence or absence of subepithelial thickening. The third subgroup is Incomplete Microscopic Colitis which includes patients who do not meet the classical criteria for Microscopic colitis but who have similar histological changes. Although prevalence and incidence are low, recent studies show that it has become slightly more common. Causative factors mentioned include immunological and infectious issue, and it has been related to some medications and to cigarette smoking. Clinically it is characterized by watery diarrhea which sometimes oscillate with periods of constipation. The three subgroups have similar clinical manifestations, so their diagnoses are usually histological. Colonoscopy with biopsy is the diagnostic pillar, and should be complemented by complete blood count, a parasitological examination, immunological studies (antinuclear antibodies, IgG) and thyroid function. Treatment is based on the suspension of related medications, changes in eating habits, and the use of medications such as steroids, bismuth subsalicylate, 5-ASA and cholestyramine. Improvement is achieved in the vast majority of patients, and recurrences are rare.

Keywords

Colitis, microscopic, lymphocytic, collagenase, colonoscopy, biopsies.

INTRODUCTION

The first publication of a case of microscopic colitis is attributed to Lindstrom who reported the case of a patient with chronic watery diarrhea in 1976. Colon biopsies evidenced a significant deposition of subepithelial collagen. (1) In 1980, Read was the first to use the term microscopic colitis (MC) to refer to patients with chronic diarrhea whose enema and colonoscopy studies were mostly normal but whose biopsies showed histological alterations. (2) In 1993, the two now-classic MC subtypes, lymphocytic colitis (LC) and collagenous colitis (CC), were proposed. They are clinically similar but histologically distinguished by the presence or absence of a band of collagen indicating subepithelial thickening. (3-5) In recent decades there have been studies of patients who do not meet the classic criteria of MC, but who present similar histological changes. Now, the term "incomplete microscopic colitis (MIC)" has become universally accepted. (6)

In 2001, in the United States, the incidence of LC was 64 cases per 100,000 people and that of CC was 36 cases per 100,000 people. Prevalence was 2% to 16% in patients with chronic diarrhea. (7) There are only a few studies of microscopic colitis in Latin America, and they were done at the beginning of the last decade. Prevalence of up to 9% was found in patients with chronic diarrhea. (8-10) In the last decade, topical reviews have presented a slight increase in this pathology. (5, 11-13) We have no recent figures for this disease in Colombia.

DISCUSSION

MC is a generic term which includes two main diseases either of which can be chronic or recurrent. Both have similar histopathological characteristics that include superficial epithelial lesions (mild in LC, and moderate to severe in CC), mild or absent architectural distortion in crypts, and occasional focal alterations such as cryptitis and cell metaplasia similar to those observed in inflammatory bowel disease (IBD). (6, 14)

LC is characterized by higher than normal quantities of intraepithelial lymphocytes (IEL) (More than 20 lymphocytes/100 epithelial cells) in the superficial epithelium and in the epithelium of the crypts, normal mucosal architecture with damage in the superficial epithelium, mixed mononuclear inflammatory infiltrate (plasmocytes, lymphocytes), small numbers of eosinophils in the lamina propria, and absence of a subepithelial collagen deposit. (11, 15, 16) CC is defined by a band of thickened subepithelial collagen measuring more than 10 μm thick. Measuring this band is costly and not practical, so the key to diagnosis is the abnormal distribution of the band as well as its the thickness. The band extends within the lamina propria and wraps and trap capillaries and fibroblasts. (11, 15, 17)

MC was initially considered a rare disease, and until 1992 only 446 cases of CC had been reported (18). In recent years, a greater number of studies assessing incidence and prevalence have been done, and they have found important geographical variations. According to a metaanalysis, the 2015 incidence of CC was 4.14/100,000 person-years (95% CI 2.89-5.4) and that of LC was 4.85/100,000 person-years (95% CI 3.45-6.25). (19) According to various studies, MC is more common in women, with a male: female ratio that varies from 1: 4 to 1: 9. (14, 15) CC occurs more frequently in people over 50 years old, although it can occur at any age, while LC occurs in younger patients. (20, 21)

ETIOLOGY

Most commonly, theories about MC attribute it to activation of the immune system of the colonic mucosa in response to exposure to luminal antigenic factors such as toxins, infections, bile acids and drugs. (22) The existence of a human leukocyte antigen has recently been demonstrated. It is directly related to inflammatory mechanisms of the colonic mucosa. (23, 24)

The possibility of an infectious etiology of MC is based on several clinical observations including development of MC after a Clostridium difficile infection and the presence of a greater number of antibodies against Yersinia enterocolitis and other infectious agents in the serum of patients' with CC than in control subjects. Nevertheless, no single pathogen related to MC has yet been identified. (25-27)

The theory that bile acids may affect the development of MC is based on experimental animal models of the disease in which diarrhea frequently occurs due to malabsorption of bile acid after an ileal resection plus the observation of malabsorption in a significant proportion of patients with MC. (22, 28-32). Nevertheless, there is no evidence of an etiological role of bile acids in MC, and no remission of histological lesions has been observed in patients treated with bile acid sequestering agents. (33)

Since the 1990s, continuous use of some medications (Table 1) has been considered to be a cause or precipitant of MC. (34, 35) The MC management guidelines of the American Institute of Gastroenterology include nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, proton pump inhibitors (PPIs), selective serotonin reuptake inhibitors (SSRIs), clozapine and acarbose in this category. However, the purported degree of the cause and effect relationship varies widely in the various reports. (32, 36, 37)

Table 1. Medications associated with microscopic colitis

Cardiovascular	β Blockers
	Vinburnine (vasodilator)
	Lisinopril
	Simvastatin
	Angiotensin II receptor antagonists
Antiplatelet agents	Ticlopidine
	Aspirin
Centrally acting analgesics	Paroxetine
	Sertraline
	Carbamazepine
Gastrointestinal	Proton Pump Inhibitors
	Ranitidine
Others	NSAIDs
	Ferro-Tardyferon (iron supplement)
	Bisphosphonates
	Flutamide

Smoking is the best documented environmental risk factor for MC. Several studies have shown that smoking is associated with CC and LC. The occurrence of the disease has been observed 10 years earlier in a smoking group than in a non-smoking group, but smoking did not influence the subsequent course of the disease. Alcohol intake has also been implicated as a contributing factor to the genesis of MC. (38)

DIAGNOSIS

MC is clinically characterized by chronic watery diarrhea without blood. It can be moderate or severe with urgent defecation, but cases of asymptomatic patients with MC

histopathology have been found. Almost half of patients with MC also meet criteria for irritable bowel syndrome (IBS) such as abdominal pain, bloating, and periods of constipation. (39) Since the clinical manifestations of LC and CC are very similar, it is not possible to clinically differentiate between them. (13)

Generally, the onset of symptoms is gradual, but in 25% to 40% of cases it is sudden. Most patients have a single episode. Remission occurs spontaneously in up to 10% of cases. About 30% of patients suffer chronic recurrences while up to 7% of patients are refractory to treatment. (40, 41)

Diagnosis should include a complete blood count, erythrocyte sedimentation rate, blood chemistry, stool cultures, parasitological examinations, thyroid test and tests for antinuclear antibodies and IgG. Recently, calprotectin measurement has also been recommended. The most important diagnostic study is a colonoscopy. Although up to 80% of cases look normal, biopsy samples must be taken from all segments of the colon. Histology will ultimately determine a diagnosis of microscopic colitis. (13, 42)

TREATMENT

Initial treatment should start with evaluation of medications related to MC for suspension or modification of dosage. Also, suspension of caffeine and lactose may have some benefits. Spontaneous remission occurs in about 30% of patients, so they can be treated symptomatically with loperamide. The medications that have been used in the treatment of MC are steroids (budesonide and prednisone), bismuth subsalicylate, 5-ASA and cholestyramine (a bile acid binding agent). Of these, only budesonide has randomized trials that demonstrate that they effectively induce and maintain clinical remission for both LC and CC. Budesonide is a locally active corticosteroid which is well tolerated and has little systemic absorption. The recommended dose is 9 mg/day during the first month, with a decrease to 6 mg/day in the second month and to and 3 mg/day in the third month. Some studies suggest the use of immunosuppressants, such as azathioprine and antitumor necrosis factor agents, especially for refractory cases. (42-44)

The prognosis of MC is very good with adequate therapy and spontaneous remission is fairly common. Once clinical remission is achieved, the course is benign and most patients remain asymptomatic in the long term. Recurrences occur in less than 30% of patients but normally respond to treatment. Very few cases have reportedly required surgical treatment (ileostomy or total proctocolectomy). MC has not been associated with any significant mortality and there seems to be no potential of malignancy. (13, 45)

CONCLUSIONS

Diagnoses of both lymphocytic colitis and collagenase colitis have become increasingly common. These diagnoses should always be suspected in patients with chronic diarrhea for whom performance of a colonoscopy with serial biopsy will facilitate histological diagnosis. Together with a clinical examination and blood tests, histology is necessary for diagnosis. There is no consensus regarding etiology or diagnostic criteria, but treatment generally achieves symptomatic remission. Nevertheless, relapses occur in almost a third of these patients. This pathology is reported more and more frequently and merits study to establish its true prevalence here in Colombia.

Conflicts of Interest

The authors have no conflicts of interest related to this article.

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How to perform and interpret high resolution anorectal manometry

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Abstract

Anorectal manometry is the most commonly used technique to evaluate anorectal functioning and coordination and detect functional abnormalities of the anal sphincter. In our physiology laboratory we perform approximately 15 high resolution anorectal manometry studies each week. We consider that proper performance and correct interpretation are vitally important. We want to share our high resolution anorectal manometry protocol based on the most relevant literature through this article.

Keywords

High resolution anorectal manometry, dyssynergic defecation, fecal incontinence.

INTRODUCTION

High resolution anorectal manometry is an essential tool for evaluating functional anorectal disorders. From 10% to 25% of the population in developed countries has functional anorectal abnormalities. It is estimated that this figure is on the rise due increases in the elderly population. (1) Functional anorectal disorders are diagnostically challenging since some patients do not seek medical help and correct and complete evaluation of anorectal functioning is essential for proper diagnosis and management. A clinical history considering the Rome IV criteria is important as is knowledge of the clinical utility of diagnostic support studies. High-resolution anorectal manometry records circumferential pressure points through sensors assembled on a flexible probe. Information is presented topographically by colors using averages of the different circumferential pressures. This allows measurement of sphincter and rectal pressures. (2) These pressures are identified during rest, during contraction maneuvers, and during simulated defecation. The percentage of anal relaxation is measured to identify patterns of dyssynergic defecation. This article uses the best available evidence to discuss the procedure in detail and explain how results should be interpreted.

High resolution anorectal manometry (HR-ARM) with complementary studies such as magnetic resonance defecography, fluoroscopic defecography, endoscopic anal ultrasound, and anal sphincter electromyography is recommended for evaluation of anorectal disorders. (3) It is indicated for evaluating fecal incontinence, constipation, functional anorectal pain, before and after anorectal surgery and for functional defecation disorders. (4)

To arrive at accurate diagnoses according to patients' medical histories, the diagnostic principles of defecation disorders as described in the Rome IV criteria are essential, and the effects of age and body mass index on anorectal functions should be considered. (5) Studies by Brochard et al. and Ellington et al. have found that the resting pressure of the anal sphincters of obese people is higher than those of people who have normal weight and those who are overweight. Adipose tissue can increase the thickness of anal sphincters and consequently increase their resting pressures. (6, 7)

Anorectal manometry can identify abnormal motor, sensory and reflex patterns in patients with incontinence and

constipation. These patterns suggest physiological differences which can predict the potentials of different treatments. Otto et al. have demonstrated the reproducibility of anorectal manometry in healthy volunteers and patients. They found a high intra-individual correlation between the pressure of the contraction maneuver and simulated defecation, and between the resting pressure of the anal sphincter and sensitivity. (8)

The reproducibility of sphincter pressure at the time of contraction has been a point of controversy. This is considered the parameter that needs the most cooperation from the person undergoing the exam. This factor is considered to have contributed to the poor reproducibility found in some studies. (9, 10)

MOTILITY LABORATORIES

In addition to trained personnel, adequate space that provides patient privacy in an area with the appropriate equipment and a large enough space for performance of HR-ARM is essential (Figure 1).

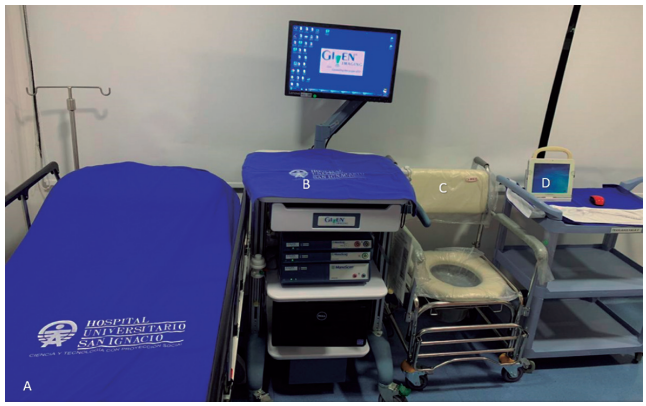

Figure 1. Gastrointestinal motility laboratory. A. Procedure table B. Manoscan™ Eso High Resolution Manometry System C. Defecation simulation chair D. Cybermed Biofeedback

There are various systems with high resolution, high-definition catheters with circumferential pressure sensors along the longitudinal axis (Figure 2). Pressure sensing elements vary among these systems. Two versions of solid state pressure catheter (ManoScan Catheter AR) with external diameters of 4.2 mm are available. One probe has 12 circumferential pressure sensors: 10 sensors at 6 mm intervals along the anal canal and two sensors in the rectal balloon. The other has 8 circumferential sensors including one in the balloon. The manufacturer recommends using a 3.3 cm long latex-free rectal balloon with a maximum insufflation capacity of 400 mL. The catheter is guaranteed for 200 uses, so care and handling of these probes must be done by trained personnel. Pressure sensors are affected by differences in body and environmental temperatures. The software contains a thermal compensation algorithm to correct this phenomenon.

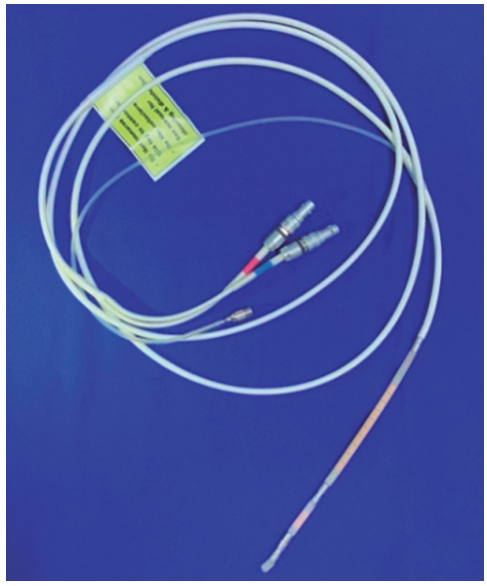

Figure 2. High resolution anorectal manometry probe

HR-ARM can be performed by physicians or nurses. For best results, the physician or nurses must know how to adequately prepare patients and must be able to convey a clear and reliable explanation to the patient.

TECHNIQUE

Patient Preparation

The patient is asked to avoid muscle relaxants and anticholinergic agents prior to the procedure, but is not required to fast. The patient is instructed to take two enemas, the first on the night before the study, and the second two hours before the study.

Positioning

The study must be carried out in a comfortable, private space that is exclusively set aside for the exam. The patient is asked to place herself or himself in left lateral recumbency with the knees bent. The perianal region is inspected to identify fissures, fistulas, wounds and hemorrhoids. Then, the rectal examination verifies adequate preparation of the patient which facilitates introduction of the catheter and anorectal anatomical evaluation. The lubricated probe is gently inserted 14 centimeters into the rectum. The probe is oriented with its dorsal side towards the posterior wall of

the patient. This orientation allows detailed reading of the measurements of the rectum and the anal canal.

At Rest Pressure

After placement of the probe, the patient should be allowed to relax for approximately 3-5 minutes, so that the tone of the anal sphincter returns to baseline levels. Anal resting pressure is usually measured for 20 seconds. Ultra slow waves with frequencies of 1.0 to 1.5 cycles/min which are associated with normal or increased anal rest pressures can then be identified.

Voluntary Contraction

The patient is asked to squeeze the anus as hard as possible for a maximum of 30 seconds, followed by a one minute break. By convention, this maneuver is performed 3 times. It is important to continuously monitor the probe assembly and to be aware of any movement of the probe, especially after the patient performs maneuvers such as tightening, coughing or pressing. The probe should be adjusted when necessary.

Simulated Defecation Maneuver

The patient is asked to push as if defecating. This test is performed using distension of a 50 mL rectal balloon with each push separated from the previous one by an interval of 30 seconds. It is essential to instruct patients not to try to retain the catheter. In fact, training patients while performing maneuvers improves the accuracy of the test.

To simulate a physiological defecation position, the subject is asked to sit in a chair with the HR-ARM catheter in position. A container is placed under the chair to catch the balloon, the probe and any other contents that may be accidentally ejected. The rectal balloon is inflated with 50 mL of air. Then, the subject is asked to sit in the chair and push for 30 seconds, as if he were trying to evacuate. The subject is placed back in bed and the manometry probe is removed.

Rectal Sensitivity

This maneuver consists of intermittent distension of the balloon in the rectum to assess rectal sensitivity and the rectoanal inhibitory reflex (RAIR). Prior to this test, the patient is told to report the moment of the first sensation, discomfort and urgency to evacuate.

The test starts with a balloon volume of 10 mL. The balloon is inflated in increments of 10 mL until the first sensation is reported or until balloon volume reaches 60 mL. Then, the balloon is inflated in steps of 30 mL to a maximum of 320 mL or until the maximum tolerated volume is reached (usually 400 mL).

Rectoanal inhibitory reflex (RAIR)

The RAIR should be tested by inflating the balloon at a rate of 30 mL/s and assessing its presence at 20, 40 and 60 mL. If the reflex is absent, the operator must ensure that there is no fecal impaction. If there is none, the balloon should continue to be inflated in increments of 60 mL to a maximum of 240 mL, recording values when the reflex is observed. (11)

Balloon Expulsion Test

The balloon expulsion test, performed on patients with constipation, has proven its usefulness for diagnosis of defecation disorders with a specificity of 86% and sensitivity of 73.9% for identification of defecation dyssynergia. Studies suggest that the best patient position for this maneuver is in the chair that simulates a toilet. (12)

The balloon is inflated to 50 mL, and the patient is asked to push for a maximum of three minutes or until the balloon is expelled. The time required for expulsion is recorded. Failure to expel the balloon within the one minute is considered abnormal (obstruction to the outflow tract or dyssynergia).

Cough Reflex Test

The cough reflex test assesses the integrity of the spinal reflex pathways in patients with incontinence.

The patient is asked to cough or inflate a balloon. Normally, the increased abdominal pressure triggers the contraction of the external sphincter.

ANALYSIS AND INTERPRETATION OF ANORECTAL PARAMETERS

At Rest Pressure

The internal anal sphincter (IAS) maintains approximately 55% of the anal tone at rest and the external anal sphincter (EAS) maintains approximately 30% of the anal tone at rest. The other 15% is generated by the hemorrhoidal plexus. (7) The basal pressure of the anal sphincter varies according to the sex and age of the patient. Various studies have identified that the at rest pressure is lower in women than in men, and that at it decreases in both men and women as they age. When base pressures are low, the diagnosis is hypotonia of the internal anal sphincter. This diagnosis is useful if the patient presents constipation and may suggest

smooth or striated muscle spasms. It has a sensitivity of 51% and a specificity of 70% for identifying lesions of the internal anal sphincter or the rectal canal (Figure 3). (13)

The most recent studies in healthy women under 50 years of age have identified the resting pressure range at 85 +/- 22 mm Hg. For women 50 and over it is 66 +/- 25 mm Hg. In men, the range is 83 +/- 25 mm Hg. (7)

Voluntary Contraction

Voluntary contractions primarily reflect the strength of the external anal sphincter and the difference between atmospheric pressure and the highest pressure recorded at any level of the anal canal. The contraction must be performed in such a way that the intra-abdominal pressure does not increase simultaneously. The duration of the contraction is the time during which the subject maintains a contraction or 50% of the maximum pressure of the anal sphincter contraction. If this maneuver is abnormal, the diagnosis is alteration or dysfunction of the external anal sphincter. (4)

Evacuation Maneuver (push)

For measurement, two attempts at the push maneuver should be made. The maneuver that most closely resembles a normal push should be used. The defecation index (DI)

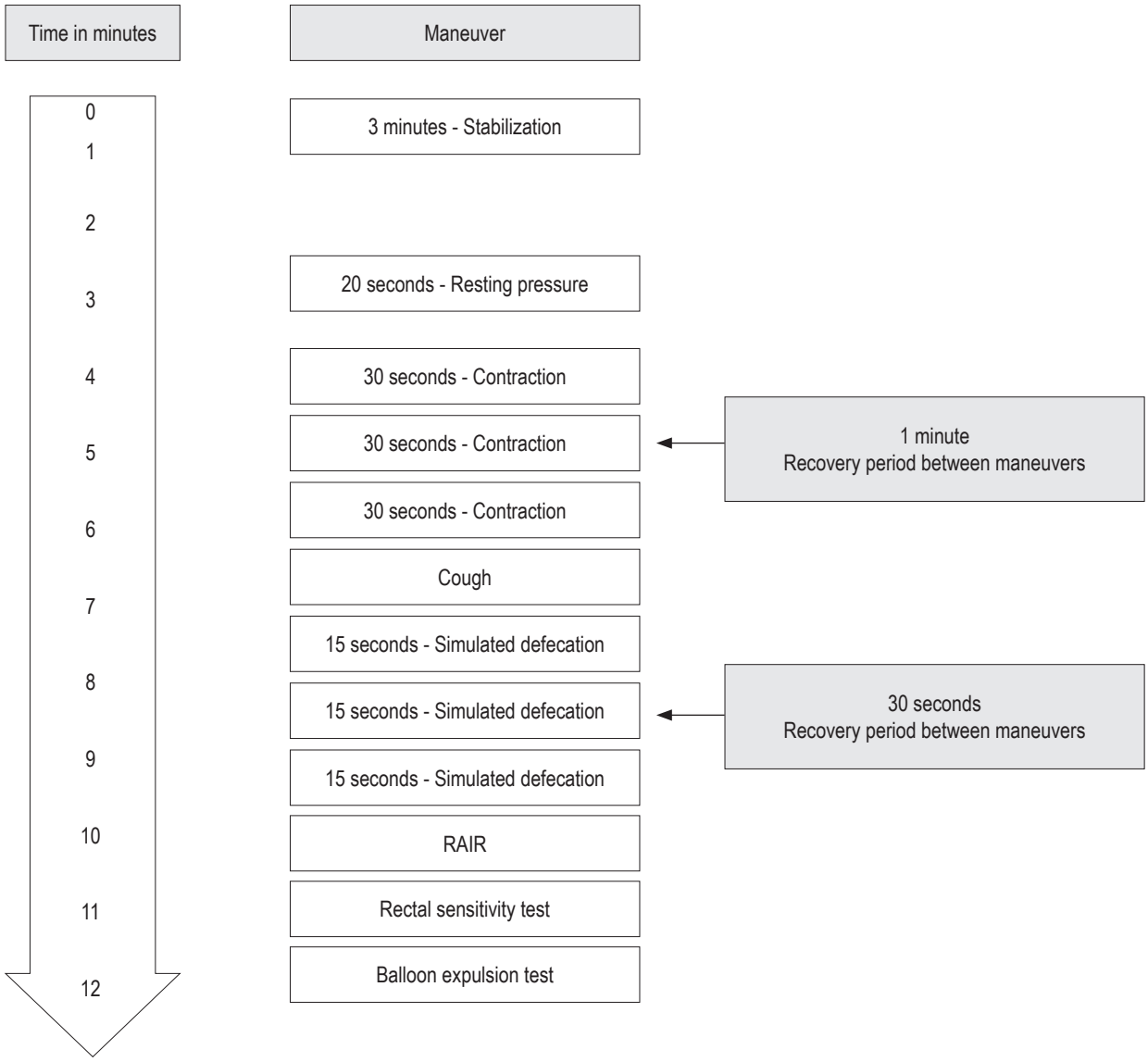

Figure 3. HR-ARM procedure protocol. RAIR: rectoanal inhibitory reflex.

is defined as the maximum rectal pushing pressure/minimum residual anal pushing pressure.

In normal subjects, the push increases rectal pressure while decreasing anal sphincter pressure. A defecation index over 1.2 is considered normal. Inability to perform this coordinated maneuver indicates dyssynergia or a functional obstruction of the passage of the fecal bolus. (4)

The proportion of abnormal defecation findings was 47% for dyssynergic manometry patterns and 52.9% for dyssynergic ultrasonography patterns. Four reproducible patterns have been defined although others may exist although none have been confirmed. (14) We consider normal the push maneuver to be normal when anal relaxation is greater than 20% and rectal pressure is greater than 40 mm Hg.

Dyssynergic defecation Type 1

The subject is capable of generating rectal pressure measuring over 40 mm Hg and adequate pushing force, but with no anal relaxation. Instead, there is a paradoxical increase in anal sphincter pressure (Figure 4).

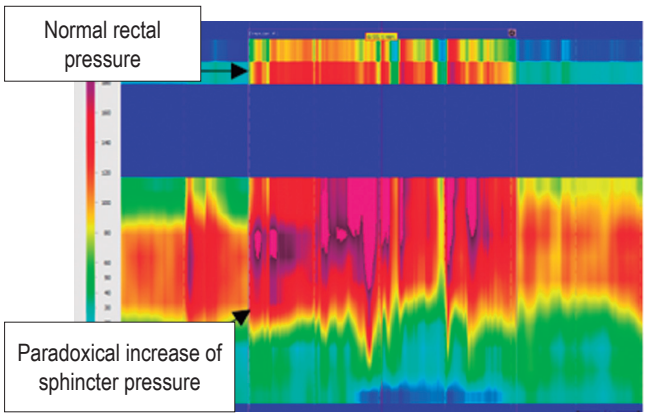

Figure 4. Dyssynergic defecation type 1.

Dyssynergic defecation Type 2

The subject is unable to generate adequate pushing force and presents paradoxical increase in anal sphincter pressure (Figure 5).

Dyssynergic defecation Type 3

The subject is capable of generating adequate pushing force, but has incomplete or absent anal sphincter relaxation (<20%) with insufficient pressure decrease in the anal sphincter (Figure 6).

Dyssynergic defecation Type 4

The subject is unable to generate adequate pushing force and has incomplete or absent anal sphincter relaxation (has a worse response to Biofeedback therapy) (Figure 7).

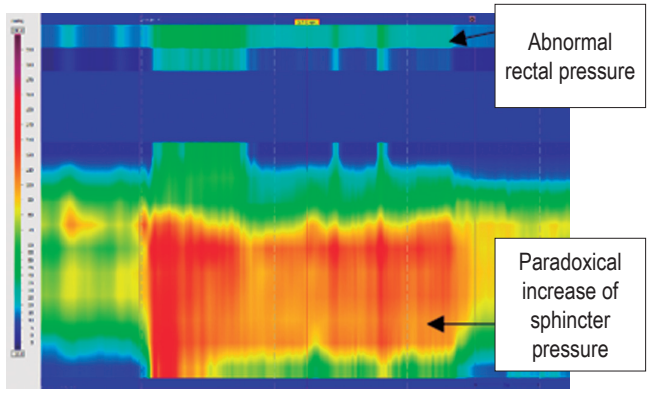

Figure 5. Dyssynergic defecation type 2.

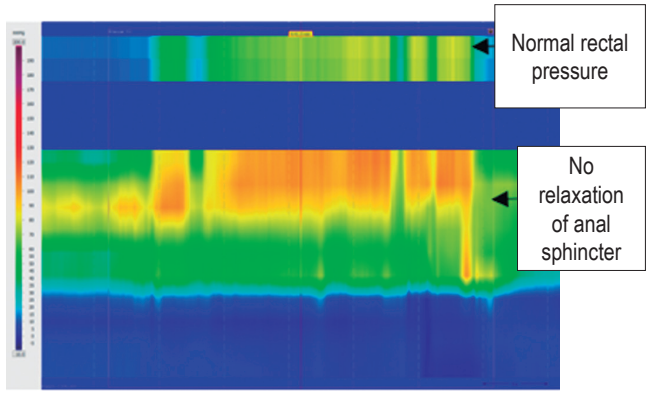

Figure 6. Dyssynergic defecation type 3.

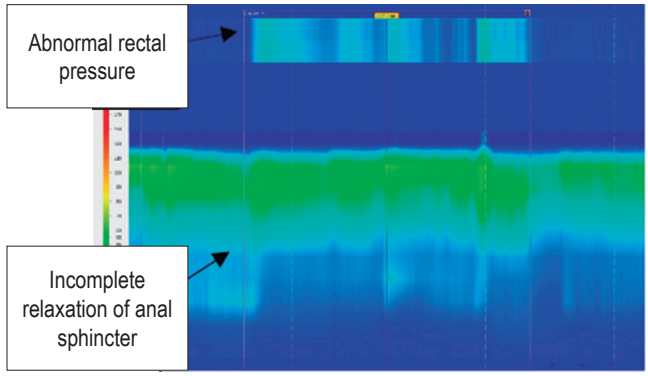

Figure 7. Dyssynergic defecation type 4.

Rectal Sensitivity

Rectal sensation is assessed by measuring perceptions of rectal distention including the first sensation, discomfort and urgency. Normal measurements of rectal sensation depend on the stiffness and configuration of the rectal balloon. Diminished perception is demonstrated by at least two modalities of rectal sensation (first sensation, urgency

of defecation, maximum tolerable volume) and indicates rectal hyposensitivity.

In our physiology laboratory we consider it to be abnormal when the first sensation is achieved at or above 100 mL which indicates alteration of the sensory threshold of rectal hyposensitivity. This is associated with poor prognoses in patients with conditions as varied as diabetes, fecal incontinence and constipation. Two or more lower perception thresholds indicate rectal hypersensitivity including emergency incontinence, proctitis, and irritable bowel syndrome. We consider it to be abnormal when the first sensation is reported at less than 30 mL which indicates sensory threshold e rectal hypersensitivity.

RAIR is the relaxation reflex of the internal anal sphincter in response to rectal distention. It is associated with increased activity of the external anal sphincter which is eliminated by higher volumes of rectal distention. RAIR is modulated by the myenteric plexus of the autonomic nervous system and produced by the release of nitric oxide and vasoactive intestinal polypeptide. The absence of RAIR may indicate Hirschsprung disease, a postcircular myotomy, or anterior lower resection of the rectum. In patients for whom large volumes are needed to identify RAIR, megarectum (300 mL) and Chagas disease (200 mL) should be considered.

Cough Reflex

Coughing induces a reflex response that consists of a rapid increase in intra-abdominal pressure together with increased external anal sphincter pressure. This reflex assesses damage to the sacral reflex arch. Low contraction pressure of the external anal sphincter and a normal cough reflex may reflect an alteration of control of this sphincter, but reduced contraction pressure of the EAS and an abnormal cough reflex suggests a defect in the sacral reflex arch. (13)

Our experience reveals a complete medical history of the patient and adequate training of the personnel who perform the procedure and operate the equipment are both essential. Interpretation of the study should always be in accordance with the most recent information in the literature.

Authors' Note

As published this article does not reflect the London International Consensus of Anorectal Manometry in view of the fact that this consensus was published after the submission of this article.

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Update of high-resolution anorectal manometry interpretation using the London classification

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Abstract

High resolution anorectal manometry is a diagnostic test, used for anorectal motor and sensory disorders. It consists of measurement of basal tone, anal contraction and squeeze, the rectoanal inhibitory reflex (RAIR), and rectal sensory parameters. The conventional interpretation of anorectal manometry focuses on describing the dysfunctional anatomical region in isolation. However, the London classification seeks to standardize the report of these results, grouping them into major, minor and inconclusive findings in a manner similar to the Chicago classification for esophageal motor disorders.

Keywords

Anorectal manometry, anorectal functional disorders, anorectal physiology, London classification.

INTRODUCTION

Fecal incontinence and constipation are the most frequent anorectal disorders. (1) Their origins can be structural or functional alterations so symptoms and initial physical examinations are not enough to determine the cause. Complementary imaging such as magnetic resonance defecography, fluoroscopy, colonic transit, rectoanal endosonography and/or high-resolution anorectal manometry is also required. (2-4)

The American Gastroenterological Association (AGA) introduced the use of anorectal manometry, rectal sensitivity tests and balloon expulsion for diagnosis and evaluation of the anal sphincter and anorectal coordination in 1999. (5) However, throughout the years it has not been possible to standardize performance and interpretation. This has affected the external validity diagnostic results of these tests. (6-8) For this reason, the International Anorectal Physiology Working Group (IAPWG) was formed to standardize anorectal manometry. It consists of 29 gastroenterologists, coloproctologists and physiologists from 12 countries. In August 2019, they published their proposal which is now known as London classification for disorders of anorectal function. (9)

EPIDEMIOLOGY

The overall prevalence of constipation and incontinence in developed countries is said to be close to 20%. (10) However, this deserves careful evaluation since measuring prevalence depends on the diagnostic criteria used for these two pathologies plus patients' ages, study locations, and study factors such as whether patients were outpatients, hospitalized or in geriatric homes. This is why a 9.9% prevalence for fecal incontinence and a prevalence of up to 20% for constipation were found for an over 60 population among whom up to 50% reside in geriatric homes. (11, 12)

INDICATIONS FOR ANORECTAL MANOMETRY

The main indications for anorectal manometry are constipation and fecal incontinence, but less common indications

include anorectal pain, megacolon and megarectum. (1, 14, 15) Table 1 describes the indications for high-resolution anorectal manometry in greater detail.

Table 1. Indications for performing anorectal manometry, rectal sensitivity test and balloon expulsion

Indication	Parameters to be evaluated
Constipation Megarectum/megacolon	Anorectal coordination (dyssynergia and abnormal balloon expulsion test) Rectal hyposensitivity Absence of RIR
Fecal incontinence	Anal sphincter hypofunction Rectal hyposensitivity or hypersensitivity
Functional anorectal pain	Anorectal coordination (dyssynergia and abnormal balloon expulsion test)
Prior to anorectal surgery	Anal sphincter function Anorectal coordination
History of obstetric injury	Anal sphincter function

RIR: rectoanal inhibitory reflex

LONDON CLASSIFICATION OF ANORECTAL DISORDERS

In August 2019, the IAPWG presented the first protocol to standardize performance of high-resolution anorectal manometry, rectal sensitivity tests and balloon expulsion. It is now known as the London classification for disorders of anorectal function. (9)

The IAPWG standards propose the following procedure: 3-minute stabilization of the sensor be followed by taking anal sphincter pressure at rest for 60 seconds, three contraction maneuvers of 5 seconds each, prolonged contraction of 30 seconds, two simple cough maneuvers, three strong contraction maneuvers of 15 seconds each, rectal sensitivity measurement by ballooning at progressive volumes, RIR and, finally, the ball expulsion test. (15)

The London classification focuses on four large groups of anorectal abnormalities that we review in the following order: anal tone and contractility (Figure 1), anorectal coordination (Figure 2), rectal sensitivity (Figure 3), and rectoanal inhibitory reflex (RIR) (Figure 4).

No large studies have been done in Colombia that would allow establishment of normal values for anal resting pressure, contraction pressure and rectal pressure for our

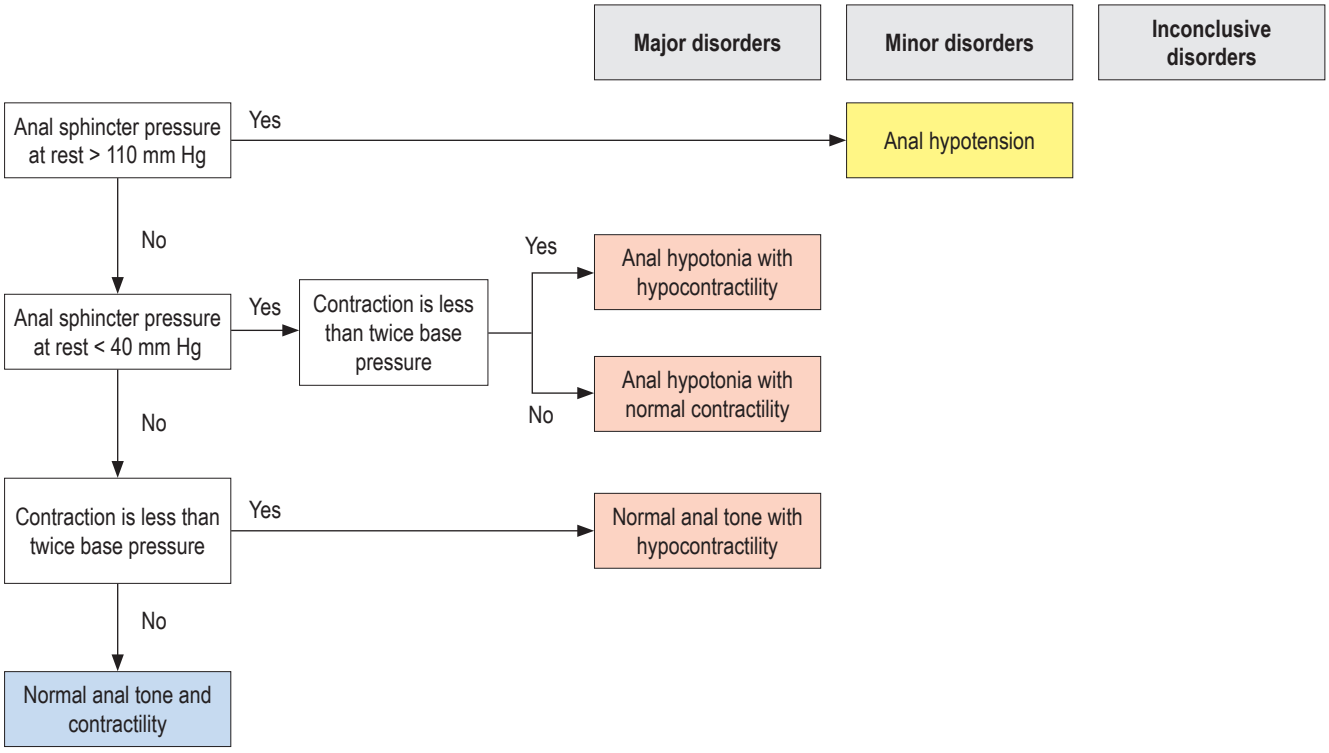

Figure 1. Disorders of anal tone and contractility (9)

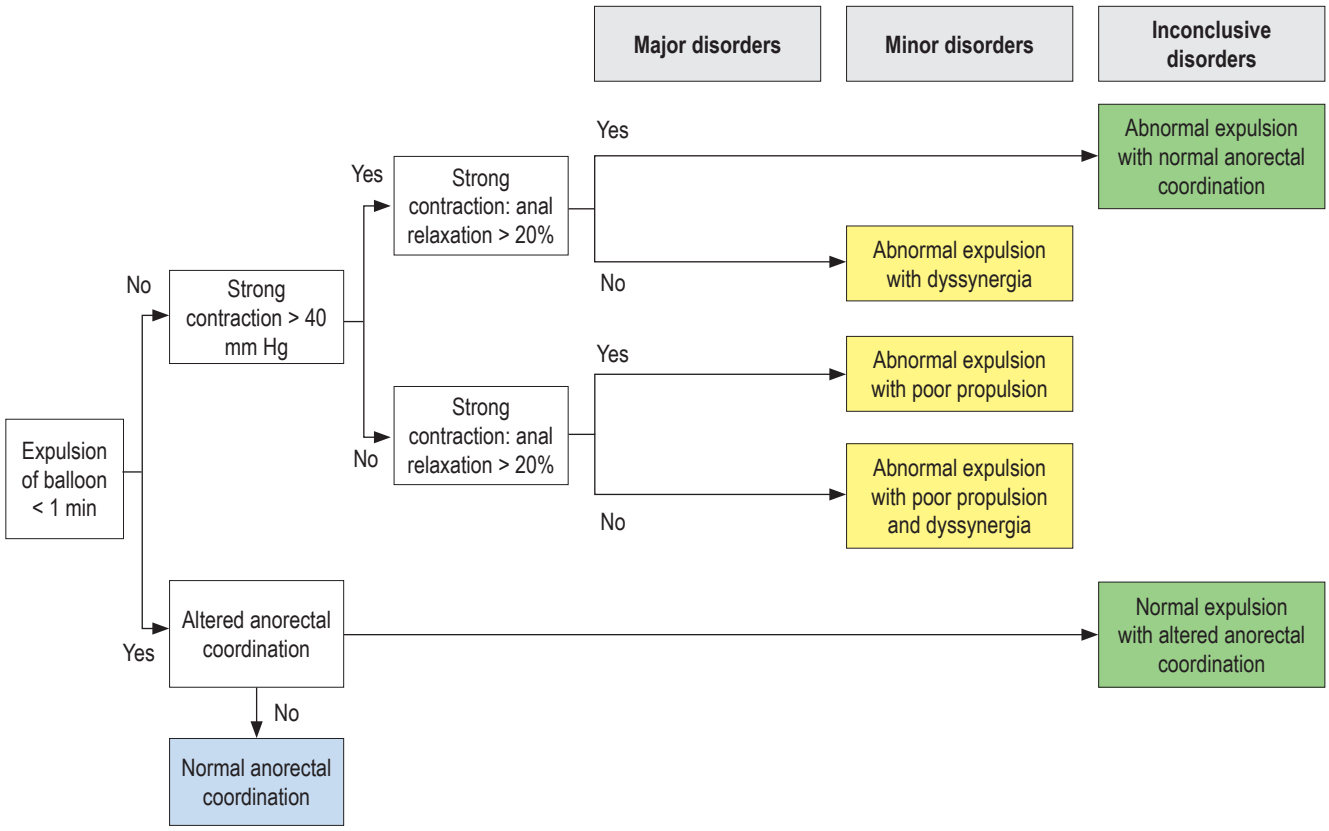

Figure 2. Anorectal coordination disorders (9)

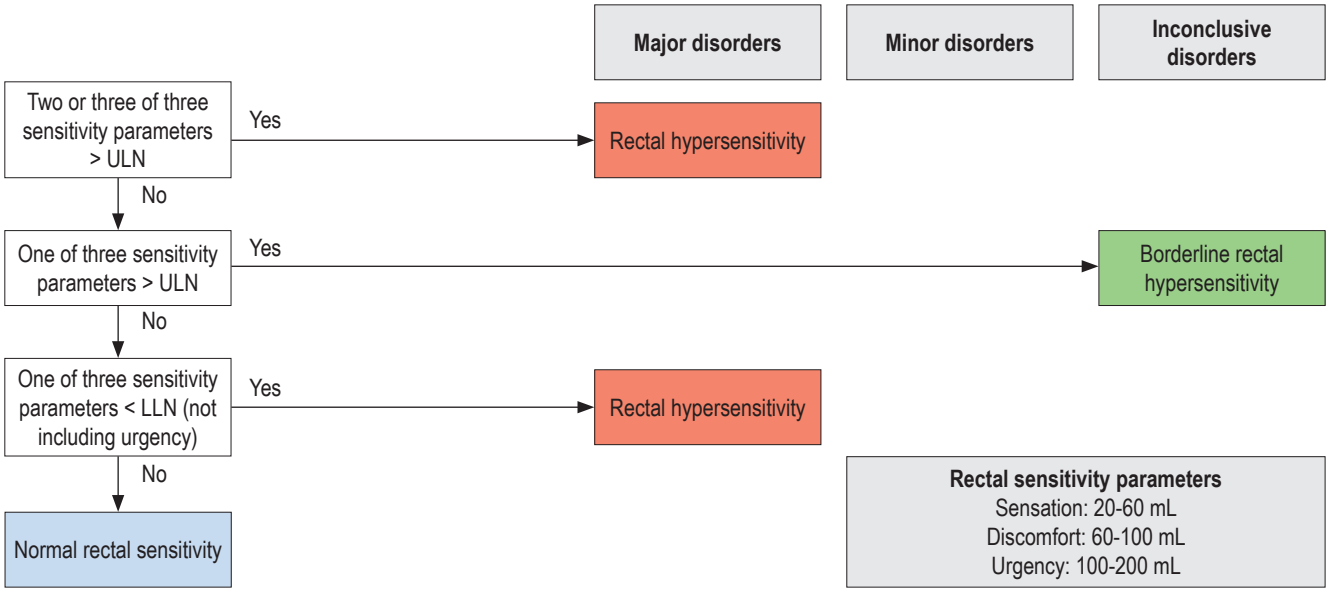

Figure 3. Rectal sensitivity disorders (9)

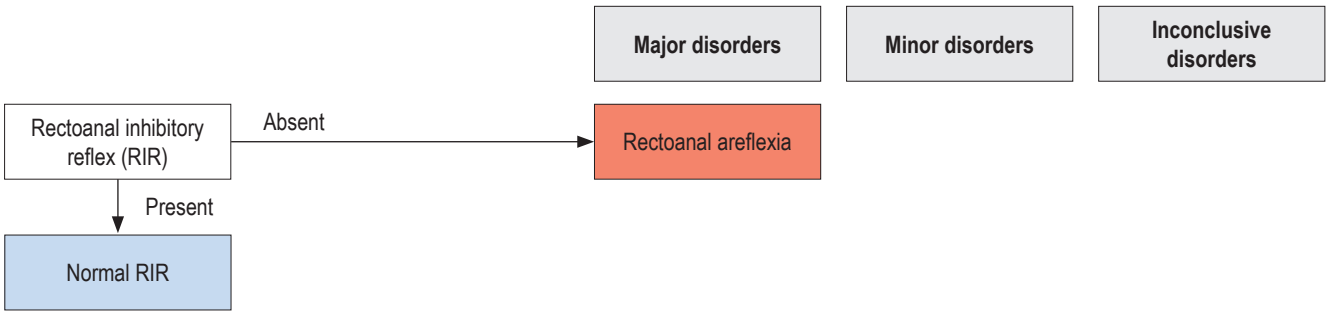

Figure 4. Rectoanal inhibitory reflex disorders (9)

Table 2. Comparison between the London classification and conventional nomenclature for high-resolution anorectal manometry

London Classification	Conventional Nomenclature
Major disorders	
Anal hypotension with hypocontractility	Alteration (hypotonia) of the internal anal sphincter. Alteration of the external anal sphincter
Anal hypotension with normal contractility	Alteration (hypotonia) of the internal anal sphincter
Normal anal tone with hypocontractility	Alteration or dysfunction of the external anal sphincter
Rectal hyposensitivity	Rectal hyposensitivity disorders
Rectal hypersensitivity	Rectal hypersensitivity disorders
Rectoanal Areflexia	Absent inhibitory rectoanal reflex
Minor disorders	
Anal hypertension	Hypertonic anal sphincter
Abnormal expulsion with dyssynergia	Type I or type III defecation dyssynergia
Abnormal expulsion with poor propulsion	Not applicable
Abnormal expulsion with poor propulsion and dyssynergia	Type II or type IV defecation dyssynergia
Inconclusive disorders	
Abnormal expulsion with normal anorectal coordination	Abnormal balloon expulsion
Normal expulsion with abnormal anorectal coordination	Type I - IV defecation dyssynergia
Borderline rectal hyposensitivity	Not applicable

diverse population. Also, there are no values for anal relaxation and rectal sensitivity parameters, so we have taken them from international studies and we adapted them for the London classification. (9, 16-19)

Like the Chicago classification for esophageal motility disorders, the London system classifies anorectal disorders as major, minor and non-significant according to pathological relevance. (20) Table 2 compares the terminology of this new proposal with that of conventional manometry.

CONCLUSION

Anorectal manometry is a useful diagnostic tool for anorectal sensory-motor disorders. Proper performance and interpretation are essential for providing patients with adequate treatment. The London classification is the first proposal that seeks to standardize reporting of high-resolution anorectal manometry results.

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A case report of malignant gastrointestinal melanoma of unknown primary origin

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Abstract

One of the unusual characteristics of cutaneous melanoma is its ability to metastasize in the small intestine. It is often diagnosed during autopsies of cutaneous melanoma patients. Metastatic deposits have been found in 50% to 60% of these autopsies, but less than 2% to 4% of patients diagnosed with melanoma have gastrointestinal metastasis during the course of the disease. Between 4% and 9% of gastrointestinal melanoma cases have unknown primary tumors.

Rapid identification and resection of melanoma in the digestive tract could improve the patient survival rate and prevent complications such as intestinal obstructions from occurring. We present a rare clinical case of gastrointestinal melanoma of unknown primary origin. The patient had a clinical picture of nausea, hyporexia, epigastralgia, fatigue, paresthesias in the right dorsal region and had lost nine kilograms in three weeks. An abdominal CT scan showed three predominantly isodense liver lesions in the parenchyma, with some areas of lower density located in segments 2,5,7 and 8 of the liver. These were biopsied. Upper digestive tract endoscopy took biopsy samples of two hyperpigmented lesions in the second portion of the duodenum. Histopathological examination showed malignant melanoma. All typical locations of primary melanoma were excluded during the diagnostic procedure.

Keywords

Melanoma, metastasis, unknown primary neoplasms, gastrointestinal tract.

INTRODUCTION

Malignant melanomas (MM) are tumors that originate from melanocytes in neuroectodermal cells which are derived from neuroectodermal cells. The primary focus of this cancer is usually diagnosed in the skin, eyeball or anus. Melanomas of unknown primary origin represent 1% to 8% of all cases and are usually diagnosed when patients present clinical symptoms of metastases. (1-3) A definitive diagnosis of melanoma of unknown primary origin requires confirmation of histopathological metastases and exclusion of all possible sites of primary foci. Several theories try to explain the etiology of unknown primary melanomas. (2, 3) One posits that spontaneous regression of the primary focus occurs as an effect of the immune system. Another posits a malignant transformation of individual melanocytes which enter a lymph node without formation of a focus within any organ. (2, 3) The biological behavior of MM is similar to cases with known locations of the primary focus. (4)

Clinically, gastrointestinal malignant melanomas are relatively rare and most frequently metastasize from cutaneous primaries. (5) The incidence of gastrointestinal metastases of unknown primary origin is between 4% to 9% of cases. (6) However, primary melanomas can also originate from certain regions in the gastrointestinal tract including the esophagus, small intestine, rectum and anus. (5) The small intestine has the greatest predilection for the development of metastatic melanoma due to its abundant blood supply.

The anus and rectum are the most common sites for primary gastrointestinal melanomas due to the presence of melanocytes. (7, 8)

Incidence rates of this complex, heterogeneous neoplasm vary by gender, age, ethnic group and region. Every year, approximately 200,000 new cases of MM and 46,500 subsequent deaths are diagnosed worldwide. (9) The approximate global incidence of MM was 2.5/100,000 men and 2.6/100,000 women in 2002. (10) In the last 4 decades incidence has continuous increased throughout the world, especially in regions with white populations. In Latin America, data is scarce. (9) Some previous estimates of incidence in Colombia exist, but there is no central cancer registration system of data covering the entire population of the country. The Cali Population Registry of Cancer is the only one in the country that has been used to calculate the incidence for one specific region. (11, 12)

Cali's crude incidence rate for MM in men was 1.6 in 1962-1966 and 3.5 in 2003-2007. Inn women it was 1.0 in 1962-1996 and 3.2 in 2003-2007. (9)

A rare clinical case of metastasis of melanoma of unknown primary origin to the small intestine and liver is presented.

CASE REPORT

The patient was a 46-year-old woman who came to the emergency department of the Fundación Hospital San Pedro because of nausea, hyporexia, epigastralgia, paresthesia in the right dorsal region, and a loss of 9 kg in 3 weeks. She had a history of chronic gastritis, her sister had died of lung cancer ,and her father had a history of prostate cancer. Two years earlier she had undergone two retinal operations on her left eye. Physical examination found her to be hemodynamically stable, allergic, asthenic, adynamic, and dehydrated. She had amaurosis of her left eye. Her abdomen was slightly distended, had normal abdominal sounds, and experienced pain on palpation of the right upper quadrant but had no signs of peritoneal irritation. Here skin had 2 pedicle lesions on her left forearm and on the right lumbar region of her back. The rest of her skin had no lesions suggestive of melanoma.

Her complete blood count was normal, her serum C-reactive protein (CRP) level was high (15 mg/dL), and electrolytes, renal function, blood glucose and coagulation times were within normal values. Ultrasound of the liver and bile ducts showed multiple focal lesions of possible metastatic origin (Figure 1).

An abdominal CT scan with contrast showed a normal-sized liver with lobulated contour and heterogeneous echogenicity. Three protruding isodense lesions were observed in the parenchyma of segments 5, 7 and 8 with several interior areas of lower density. They measured 149 x 128 mm. There were two other lesions, one with diameter of 51 mm in segment 2, and another whose diameter was 57 mm in segment 7. These findings suggested neoplasia. The rest of the abdominal organs were without alterations (Figure 2).

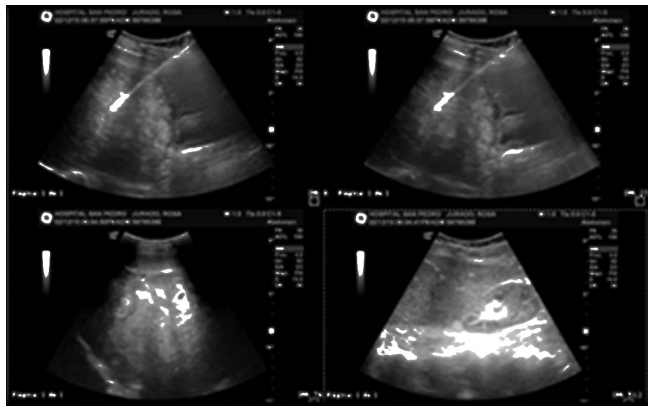

Figure 1. Ultrasound of the liver and bile ducts showing multiple focal lesions of possible metastatic origin.

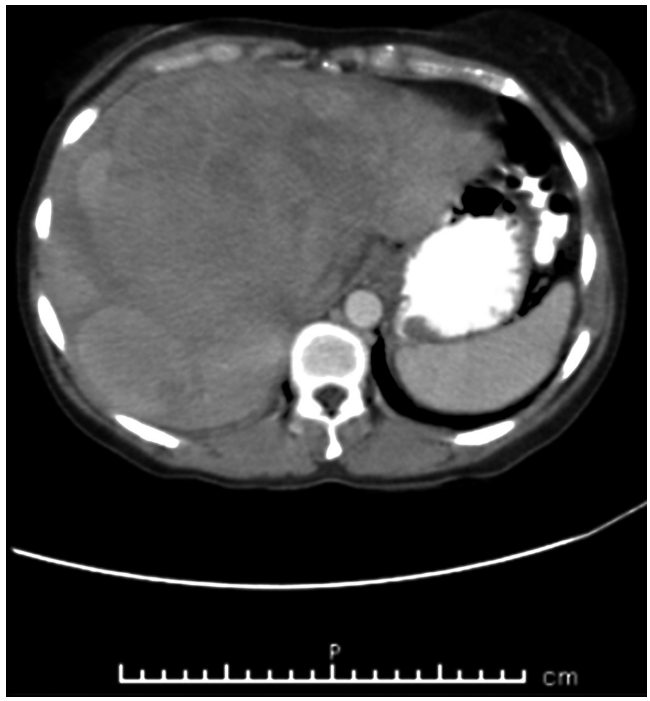

Figure 2. Abdominal CT scan with contrast shows liver with heterogeneous echogenicity, three protruding isodense lesions, with interior areas of lower density inside, located in segments 5, 7 and 8 and two smaller lesions in segments 2 and 7.

Upper endoscopy found antral erythematous gastritis and two hyperpigmented 5 mm lesions in the second portion of the duodenum (Figure 3). Biopsies found malignant proliferations of pleomorphic cells with hyperchromatic nuclei, prominent nucleolus and abundant melanin

pigment distributed diffusely throughout the thickness of the mucosa.

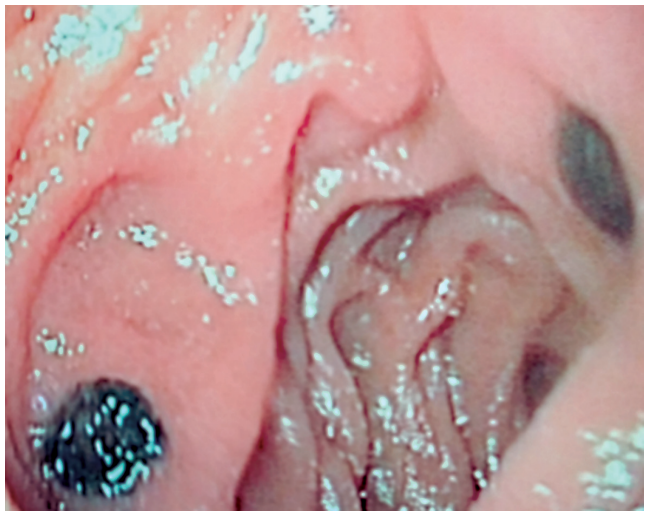

Figure 3. Upper endoscopy. Second segment of duodenum second portion shows two hyperpigmented 5 mm lesions.

The histopathological diagnosis was malignant melanoma. A percutaneous liver mass biopsy identified malignant proliferation of pleomorphic cells with hyperchromatic nuclei, prominent nucleolus and abundant melanin pigment arranged in nests and solid masses.

The patient returned to the emergency department because of her original symptoms plus choluria and hematochezia. Here complete blood count showed a hemoglobin blood count (11.9), slightly elevated liver enzymes (AST: 68 and ALT: 54). Her coagulation times and INR were within normal parameters. A total colonoscopy found grade II internal hemorrhoids but otherwise no abnormalities. Informed consent was obtained for preparation of the case report. The patient is currently undergoing palliative chemotherapy and receiving pain medicine.

DISCUSSION

Malignant melanoma is a tumor that most often occurs in the skin. It occurs less frequently in the eye (choroid layers), leptomeninges, oral cavity, nasal mucosa, pharynx, esophagus, bronchi, vaginal mucosa, rectal mucosa and nails. (11-13) In autopsies, GI metastases have been reported in 50% to 60% of cases, but only 2% to 4% of patients with melanoma are diagnosed with GI metastases during the course of their disease. Primary melanoma in a patient with GI metastasis is most often found in an extremity (15% -57%), followed by the trunk (13% -54%) . They are less frequently found in the head and neck (5% -33%). In 10% to 26% of cases, the primary lesion cannot be found. The period between diagnosis of a primary melanoma and GI metastasis is reported to be up to 54 months. (14) About 70% of patients have symptoms related to the GI tract, while 30% remain clinically asymptomatic. (15)

A CT scan is preferred for diagnosis because it can show the most common compromises such as polypoid intraluminal masses, intestinal invagination, ulcerated lesions, diffuse infiltration and implants. (16) The presence of metastatic lesions has been confirmed by surgical exploration in 80% of cases. Eleven percent have been confirmed by endoscopy and 5% by percutaneous biopsies. (15)

Metastatic melanoma of unknown primary origin accounts for 1% to 8% of all melanoma diagnoses. The diagnosis is made after exclusion of all possible primary focus locations, as was done with this patient. In 33 years of experience treating melanoma, Savoia et al. found that it was impossible to locate the primary foci in 88 of 4,881 patients. In 31 (35.3%) patients, the first clinical presentation was metastasis in the skin and subcutaneous tissue, in 38 (43.2%) patients it was compromised lymph nodes, while another four patients (4.5%) had compromised lymph nodes and skin. In the remaining 15 patients (17%), melanoma presented visceral metastases. (4)

It is very difficult to diagnose primary melanoma of the digestive tract. The suggested diagnostic criteria are absence of another location of melanoma and atypical cutaneous nevi, lesions located only in the small intestine without distant metastases or the presence of a primary focus on the mucosa. Metastases in the liver and duodenum were identified in our patient (Figures 2 and 3) after a detailed analysis of all other possible locations of the primary focus. This could not be identified, therefore, a diagnosis of melanoma of unknown primary origin was made.

When metastasis of melanoma to the digestive tract is suspected, diagnostic images should be taken. The first basic stage of diagnosis is abdominal ultrasound a non-invasive, low-cost exam. Another test is computed tomography, whose sensitivity for identifying melanoma metastases in the digestive tract is only 60% to 70%. In each case, when metastases in the digestive tract are clinically suspected, other tests are necessary when a CT scan is negative. The PET/CT exam has greater sensitivity than CT and should be done if available. (4). In our case, ultrasound and a CT scan revealed metastases in the digestive tract (Figure 1 and 2).

CONCLUSION

Melanoma of unknown primary origin occurs in 1% to 8% of all diagnosed melanomas. It is usually diagnosed when patients develop clinical symptoms related to metastases such as gastrointestinal bleeding, perforations, or alterations of intestinal transit or absorption. It is relevant to

look for the primary focus before making a diagnosis of melanoma of unknown origin. For this, integral evaluation of the patient must take into account the fact that in most cases the primary focus cannot be described.

RECOMMENDATIONS

Complete imaging studies should be done when any patient is diagnosed with malignant melanoma. This will help avoid complications of the underlying metastatic process while making a timely diagnosis of the primary focus (when possible) or arriving at a diagnosis of metastatic melanoma with unknown primary.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Digestive tract hemorrhaging in a patient with Brunner's gland hyperplasia

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Abstract

Objective: This study analyzes the epidemiological characteristics, etiological and pathogenic bases, clinical presentation, diagnosis and treatment of Brunner's gland hyperplasia. **Methods:** We describe a case of Brunner's gland hyperplasia that was diagnosed incidentally during elective endoscopy and review the available literature. **Results:** This neoplasm consists of glandular proliferation preferentially located in the proximal duodenum. Its diagnosis, normally made by endoscopic biopsy, can be associated with complications that, although infrequent, should not be underestimated. **Conclusions:** Duodenal neoplasms are a small percentage of those that affect the gastrointestinal tract. Because diagnosis is usually made by chance during a scheduled endoscopy, treatment should be based on the symptoms and size of the lesion according to the treatment standards of each medical center.

Keywords

Digestive hemorrhage, Brunner's glands, Brunner's gland hyperplasia, Brunner's gland adenoma.

INTRODUCTION

Brunner's gland hyperplasia (BGH), also known as Brunner's gland adenoma or Brunneroma, consists of a proliferation of these submucosal glands of varying sizes and morphology. Usually they are found in the duodenum. The prevalence of BGH is not well established, since most cases are incidentally discovered during an endoscopic examination. Although they are normally asymptomatic, they can produce a variety of gastrointestinal symptoms ranging from nausea and vomiting to gastrointestinal bleeding which is related to their profuse vascularization. Diagnosis is made by endoscopy, echoendoscopy or other imaging techniques. When treatment is necessary, it must be individual, either endoscopic or surgical.

CLINICAL CASE

The patient was a 60-year-old man who smoked and who formerly consumed 30 grams of alcohol daily. He had a history of arterial hypertension, stage IV chronic kidney disease secondary to nephroangiosclerosis, and chronic hepatopathy of enolic origin. There were no data on portal hypertension. He had been taking 25 mg/day of spironolactone and 40 mg/day of enalapril.

He was seen in our endoscopy unit for an upper digestive endoscopy for varicose vein screening. During the exploration, two subepithelial nodular lesions that each measured about 10 mm and were covered with normal mucosa were identified in the second duodenal portion distal to the duodenal papilla (Figure 1). Taking of a diagnostic biopsy

sample from one nodule led to persistent seepage of blood which required placement of a hemoclip to achieve hemostasis. No other lesions or evidence of portal hypertension were identified.

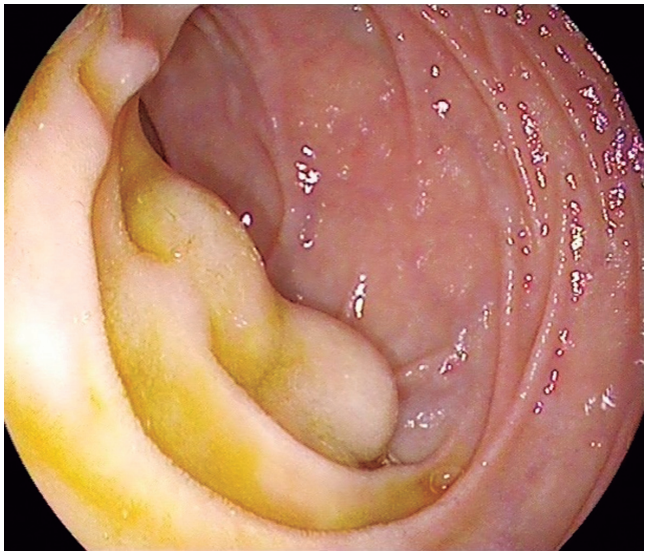

Figure 1. Two subepithelial lesions covered with normal mucosa immediately distal to the duodenal papilla.

Four days later the patient came to the Emergency Department after two days of melena. Upon arrival, he was hemodynamically stable with blood pressure of 110/80 mm Hg and heart rate of 73 beats per minute. He was significantly anemic with hemoglobin of 9.7 g/dL. Previously, it had been 14.3 g/dL. Other parameters were at their usual values. Upper gastrointestinal bleeding was suspected so intravenous treatment with proton pump inhibitors and continuous perfusion was initiated and urgent upper endoscopy was performed. A clot attached to the previously placed hemoclip in the second duodenal portion was identified, but there was no active bleeding. A new hemoclip was placed, which again caused abundant bleeding. Ten mL of adrenaline diluted in 0.9% physiological saline (1:10,000) and 2 mL of Etoxiesclerol® (lauromacrogol 400) were administered at the site, and two hemoclips were placed. This stopped the bleeding. Another blood test found that the patient's hemoglobin had decreased to 7.5 g/dL, so two packs of red blood cell concentrate were transfused. There were no further complications, and the patient was discharged after 5 days.

The histological study of the lesion found proliferation of submucosal glands, so Brunner's gland hyperplasia was diagnosed (Figure 2). Computed tomography (CT) showed no extraluminal extension. Given the small size, iatrogenic origin of hemorrhaging, and subsequent absence of symptoms, a waiting attitude was chosen. The patient remains asymptomatic eight months after diagnosis.

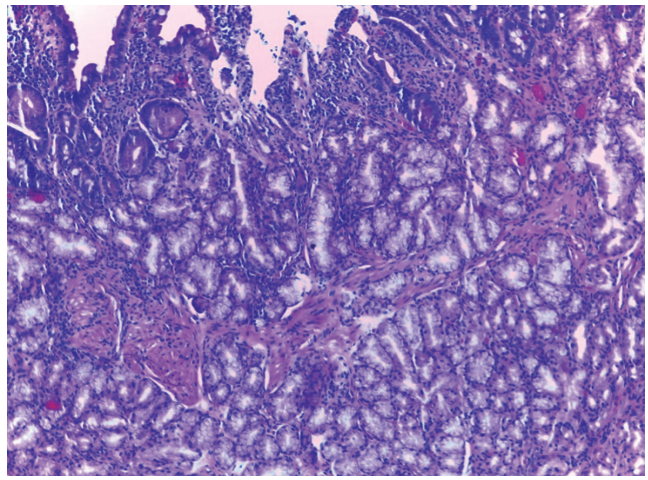

Figure 2. More than half of the mucosa shows correct villus height and Brunner's gland lobes. These lobes are continued with abundant Brunner's glands in the submucosa. The cells show typically clear mucous cytoplasm without cytological atypia (H&E x400).

DISCUSSION

Brunner's glands are acinotubular and are found in the submucosa, most commonly in the proximal duodenum between the pylorus and the duodenal papilla. They are less commonly found in more distal portions of the duodenum and even in the jejunum. Their fundamental function consists of producing and secreting alkaline mucus which helps protect the duodenal mucosa from chime. (1, 2) Although there is no established name for proliferation of these glands, Brunner's gland hyperplasia covers both diffuse hyperplasia (<1 cm) and polypoid lesions (> 1 cm) which are commonly known as Brunneroma. (3) Within this group we can differentiate between hamartoma and adenoma depending on whether or not they have mesenchymal elements. (2)

Although the etiopathogenesis of these lesions has not been clearly established, several theories attempt to explain their formation. The hyperchlorhydria hypothesis is most commonly accepted. Overproduction of gastric acid may act as a stimulus for compensatory proliferation of Brunner's glands, ultimately culminating in an BGH. (4) Other hypotheses place their origin in dysembryoplastic lesions, while others see them as an adaptation to local inflammatory processes such as H. pylori infections or chronic pancreatitis. (1, 2)

BGH appears predominantly in middle-aged patients without differences of gender distribution. (5) In general, primary tumors of the duodenum are rare and represent

less than 1% of gastrointestinal tumors. BGH may have an incidence of 0.008% according to some studies. (5) However, it is difficult to establish its prevalence since most are asymptomatic lesions found incidentally in endoscopy, and only a small proportion are diagnosed clinically. (6-8)

In general, larger polyps tend to have symptoms more frequently. The most common are nonspecific symptoms such as nausea, vomiting and chronic abdominal pain. Other less frequent symptoms are digestive hemorrhaging due to profuse vascularization and found as occult blood in feces, recurrent pancreatitis, obstructive jaundice, and even biliary fistulas. (6, 9) Regarding potential malignancy, Sakurai et al. observed dysplasia in 2.1% and invasive carcinoma in 0.3% of the 722 cases of GBH they studied. (10)

To establish the diagnosis of this entity, upper endoscopy within a biopsy is the first choice. Given the submucosal nature of these glands, histological specimens obtained by conventional biopsy are often negative or inconclusive. This makes deeper biopsy methods such as polypectomy biopsies necessary. They have higher diagnostic yields but are also associated with increased risk of complications such as bleeding and perforation. (9)

When histology is inconclusive, echoendoscopy is the technique of choice for characterizing GBH. It allows determination of their origin and study of their vascularization. (1, 3) Finally, some authors propose the use of contrast CT scans to establish both the extent and differential diagnosis with other entities such as adenomatous polyps, lipoma, leiomyoma, and gastrointestinal stromal tumors (GIST). These tools make it possible to plan an appropriate therapeutic approach that avoid sexcessively aggressive treatments of these lesions with low potential of malignancy. (2, 3)

There are no clinical guidelines for treatment or quality studies in this area. It is accepted that these lesions should be resected when they are larger than 2 cm and when they produce symptoms. (2) Treatment can be endoscopic or surgical, and each case must be individualized according to the characteristics of the patient, the lesion, and the experience of the medical center. So far there is no evidence of recurrence after removal by either method. In recent years there has been a strong tendency to use endoscopic treatment due to technical advances that have resulted in lower morbidity and mortality rates. Endoscopic techniques include resection with either a traditional polypectomy loop or an endoloop and submucosal endoscopic dissection. (2) Surgical techniques range from transduodenal polypectomy to pancreaticoduodenectomy.

CONCLUSION

The diagnosis of duodenal lesions such as BGH is usually made after histological study of biopsies obtained during endoscopy. This procedure has potential complications such as gastrointestinal bleeding due to the abundant vascular irrigation of BGH. When necessary, endoscopic or surgical treatment should be decided on an individual basis.

Conflicts of Interests

The authors declare that they have no conflicts of interest.

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A special combination of pregnancy and inflammatory bowel disease: case report and literature review

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Abstract

Inflammatory bowel disease (IBD) comprises a spectrum of chronic immune-mediated diseases that affect the gastrointestinal tract. Onset typical occurs in adulthood. Its incidence is increasing everywhere, the highest incidence of Crohn's disease of 20.2 per 100,000 people/year is in North America while the incidence of ulcerative colitis is 24.3 per 100,000 people/year in Europe. Since it is not curable, the remission is the main objective of management. Many women are affected by IBD at different stages of their lives, including during reproductive life, pregnancy and menopause, so the way the disease is managed in reproductive age women can affect IBD's course. Treatment and maintenance strategies are very relevant. For patients with a desire to have children, disease remission is very important from conception through pregnancy to birth to ensure adequate results for both mother and fetus. It is well known that active disease during conception and pregnancy is associated with adverse outcomes of pregnancy. In addition, active perianal disease is an indication for cesarean delivery which entails increased risk of bowel surgery and complications in the postoperative period. We present a case of IBD during pregnancy.

Keywords

Inflammatory bowel disease, Crohn's disease, ulcerative colitis, pregnancy.

The patient was a 32-year-old woman with chronic diarrhea containing mucus and blood that was associated with intermittent colic. She had shown some improvement after treatment with multiple antibiotics. Two years prior to onset, a pregnancy had ended at 26 weeks with a stillbirth. Following the miscarriage, her gastrointestinal symptoms worsened. Fetal malformations found included overgrowth of limbs, hemifacial microsomy and hydrops. A colonoscopy found severe ulcerative colitis (UC) compromising the left colon. I inflammatory bowel disease (IBD) was diagnosed. Oral administration of 40 mg/day of steroids and 4 g/day of mesalazine was begun. The patient's clinical condition improved, but she continued to lactate. Her condition was determined to be a corticodependent disease and biological therapy with infliximab and 2.5 mg/kg/day of azathioprine was begun.

The patient developed a severe infectious process which required suspension of biological therapy. Management with azathioprine and mesalazine continued. At the age of 37 years, she was hospitalized again with severe exacerbation of both clinical and endoscopic disease triggered by poor adherence to the established treatment. She again required steroids, but due to corticosteroid criteria it was decided to restart infliximab and to continue azathioprine and mesalazine. Good control of the disease was achieved. The patient then consulted with a pregnancy of 5 weeks. She was told to continue biological therapy, but thiopurine was suspended. Despite medical advice, the patient decided to suspend all types of medication. The pregnancy proceeded normally, without any complications. She delivered a live fetus with low birth weight but without other complications by caesarean section. During the first ten

days postpartum, the patient' intestinal disease worsened. Mesalazine was begun again but she decided not to restart biological therapy despite the medical recommendation.

This case demonstrates the impact of IBD on gestation and postpartum health. In clinical practice, the management of this type of patient is a challenge for the gastroenterologist and gynecologist. Multiple questions arise when these two entities are both present. We will try to answer these questions below.

WHAT IS THE NORMAL IMMUNOLOGICAL RESPONSE DURING PREGNANCY?

Naïve T helper cells ($CD4^+$) differentiate into Th1 and Th2 depending on the type of cytokines most prevalent in the environment in which they are produced. If IL-12 and TNF prevail, differentiation to Th1 is favored, but if IL-4 predominates differentiation to Th2 is favored. Th1 cells induce various cytotoxic and inflammatory actions mediated by the action of IL-2, IL-12, INFγ, and TNFα, and are responsible for inflammatory reactions of cellular immunity, delayed hypersensitivity, and tissue damage in infectious diseases. and autoimmune. Th2 cells produce IL4, IL5, IL6 and IL10 and are associated with a humoral-type responses which favor the appearance of antibodies. (1)

In addition, there are cytokines that do not match the typical Th1 and Th2 responses but which are important for maintaining pregnancy. They include IL-11 and IL-18 which are present at specific times of pregnancy suggesting regulatory functions. (1) A prevalence of Th1 response over Th2 response has been found to be associated with higher rates of fetal resorption, implantation failure, INFγ production, and lower resistance to infection. (2) Direct cytotoxic action of Th1 response on embryos has been demonstrated to cause trophoblastic cell lesions. Both TNFα and INFγ inhibit trophoblastic growth in vitro, and cytokines associated with Th2 responses contribute to embryo implantation, development of the placenta and survival of the fetus until the end of gestation. (3)

Different cytokines are produced in different amounts depending on the time during gestation at which they are assessed as well as on their receptors. Both inflammatory and anti-inflammatory cytokines are expressed in maternal peripheral blood. They include IL-2, IL-4, IL-10, and INFγ, so appears that the maternal immune system is not compromised during pregnancy as had been thought previously. (4)

Production at the maternal-fetal interface depends not only on the relatively few CD4 T lymphocytes, but also on other cytokine-producing cells in maternal and fetal territories. Thus, the trophoblast, macrophages within the villous trophoblast, NK cells, and macrophages and stromal cells in the decidua contribute to maintaining the Th2 environment which develops during the first trimester of gestation. Towards the end of the third trimester as the mother's body prepares for labor, a shift to Th1 predominance occurs. This has led some authors to see these immunological phenomena as elements in the mechanisms that initiate labor.

Although data is not conclusive, hormones, especially estradiol, progesterone, the placental pregnancy-specific protein (SP-1), and plasma protein associated with pregnancy (PAPP-A), appear to have roles in immunomodulation during pregnancy. SP-1 stimulates the production of Th2 cytokines by monocytes, PAPP-A inhibits in in vitro T-cell proliferation while secretion of IL-2 contributes to maternal tolerance by promoting the Th2 response over Th1.

Leukocyte inhibitory factor (LIF) is synthesized and secreted by the maternal endometrium and stromal cells. Its receptor is necessary for implantation, differentiation and growth of the trophoblast. (1) Among the substances that activate LIF are progesterone, IL-4 and IL-1. INFγ and IL-12 inhibit it.

Progesterone production by the corpus luteum, necessary for maintenance of pregnancy, is stimulated by IL-6 and IL-4. The lymphocytes of pregnant women are especially sensitive to progesterone. Pregnancy increases the number of progesterone receptors that are exposed in peripheral blood lymphocytes. This makes them more susceptible to progesterone inhibitory mechanisms. In their presence, lymphocytes secrete a protein that directly inhibits the cytolytic effect of NK. Progesterone concentrations only suppress the immune system locally within the uterus and placenta. (1)

Progesterone in the syncytiotrophoblast favors production of Th2 cytokines. Progesterone, catecholamines, prostaglandins and human chorionic gonadotropin induce the production of IL-10. Estrogens cause the endometrium to produce chemotactic interleukins and macrophages which are attracted to the maternal-fetal interface. (5) Taking all of this into account, a Th2-type immune response predominates in pregnancy and could be related to the type of response to IBD.

A study evaluating the types of cytokines in the different kinds of IBD has shown that ulcerative colitis tends to have higher levels of IL5 production which leads to a predominance of Th2 response. This could exacerbate the disease during the establishment of pregnancy.

WHAT IS THE EFFECT OF INFLAMMATORY BOWEL DISEASE ON FERTILITY?

Inflammatory bowel diseases occur between the ages of 33.4 and 45 years, and it is vitally important to understand that infertility rates in women with inflammatory bowel

disease without activity are similar to those of the general population (8% to 10%). (6) Remission of the disease not only improves fertility rates, but most studies have also shown that it leads to more favorable pregnancy outcomes. Active disease reduces fertility, probably in response to the inflammatory process and adhesions that develop in the fallopian tubes and/or ovaries.

Similarly, patients who have previously had surgery such as a proctocolectomy or ileal anastomosis with an anal reservoir have 3 to 4 times greater risks of infertility. This is due to the pelvic adhesions that tend to form and which affect the permeability of the fallopian tubes leading to obstructions. (7) Therefore, the recommended time for conception is 3 to 6 months following remission of the disease.

There is no evidence that inactive ulcerative colitis or Crohn's disease (CD) affects fertility, but decreased fertility among patients with ileal bags has been documented.

WHAT IS THE EFFECT OF INFLAMMATORY BOWEL DISEASE ON PREGNANCY?

Patients with CD or UC have worse pregnancy outcomes than do healthy women. Studies have also shown that the odds of worse pregnancy outcomes are greater in patients with Crohn's disease than in patients with ulcerative colitis.

A 1998 review by Subhani et al. found that Crohn's disease, especially when active, is associated with decreased birth weight, premature delivery, and cesarean sections. (8) Furthermore, patients with IBD have labor induced more frequently than women who do not have IBD (32% vs. 24%, $p = 0.002$), undergo caesarean sections more frequently (32% vs. 22%), and develop chorioamnionitis more frequently (7% vs. 3%, $p = 0.04$). Rates of occurrence of neonatal complications including low birth weights, intrauterine growth restrictions, Apgar scores and congenital anomalies were found to be similar in populations with and without IBD. (9) There are no studies reporting greater probability of fetal malformation in these patients which makes this case striking. Although there may be multiple factors associated with fetal malformation, it is noteworthy that fetal death ending the first pregnancy was related to the onset of the inflammatory disease and presentation of the morphological alterations described. This invites reflection on this topic. Despite the absence of clear evidence in this regard, prenatal follow-up of these patients should be especially detailed and strict.

Another study of 461 pregnant patients with IBD showed that patients with IBD were at increased risk of miscarriage, eclampsia, preeclampsia, placenta previa, premature placental abruption, and premature rupturing of membranes. That study did not find that active disease was associated with worse outcomes, but did find that diagnosis of IBD, a history of IBD bowel surgery, and not being white were independent predictors of worse outcomes. (10) These results support current treatment guidelines which indicate that maintaining remission during pregnancy is of vital importance. It is important to understand that the risks faced by this type of patient can be reduced to those of the general population if disease is controlled at the beginning of gestation.

WHAT IS THE EFFECT OF PREGNANCY ON INFLAMMATORY BOWEL DISEASE?

Approximately 80% of women with IBD who become pregnant when the disease is in remission tend to remain in remission throughout pregnancy and the postpartum period. About 66% of patients who have active disease at conception continue to have active disease or worsening disease during pregnancy. (11) Ulcerative colitis worsens during the pregnancies of up to 45% of patients who have diagnoses of active ulcerative colitis when they conceive. Crohn's disease worsens in 30% of the patients who conceive while their disease is active. (12)

A prospective study has found that the disease exacerbation rate in pregnant of pregnant Crohn's disease patients in remission were similar to the disease exacerbation rate in Crohn's disease patients who were not pregnant. (3) On the other hand, relapse rates were higher among women with Crohn's disease who conceived while their disease was active than among non-pregnant patients with Crohn's disease (50% vs. 33%, respectively). Pregnant patients with ulcerative colitis had a higher risk of exacerbation of the disease during pregnancy and in the postpartum period than did controls. Exacerbation of the disease was most frequent in the first six months of pregnancy and in the first three months of the postpartum period. (13) This should make it clear that active disease at the time of conception helps predict the course of the disease during pregnancy. Ideally, women should be in remission at the time of conception.

HOW DO MEDICINES USED TO MANAGE INFLAMMATORY BOWEL DISEASE AFFECT FERTILITY?

Although there are no data on the effects of IBD medications on female fertility, it is clear that immunosuppressants such as methotrexate have clear associations with teratogenicity and are totally contraindicated in patients who have a desire to conceive.

The use of sulfasalazine has been reported to condition reversible reduction of sperm motility, an effect related to drug dosage. (14) Methotrexate favors oligospermia which

may improve over time when use of the drug is stopped. (15) Infliximab appears to affect semen quality by reducing sperm motility. (16) Azathioprine has not been found to influence sperm quality. (17)

WHAT SIDE EFFECTS DO MEDICINES HAVE FOR THE MANAGEMENT OF INFLAMMATORY BOWEL DISEASE IN PREGNANCY?

IBD management guidelines recommend that pregnant women who need pharmacological treatment to maintain remission of the disease should continue to use those medications during pregnancy. However, methotrexate must be discontinued prior to conception and during pregnancy. In addition, any exacerbation of disease during pregnancy should be treated aggressively.

Although the FDA's risk category classification for pregnancy is no longer widely used we have used them in the descriptions below of medications that are frequently used in pregnant patients with IBD.

Aminosalicylates and sulfasalazine (class B)

In general aminosalicylates and sulfasalazine (class B) are considered to be insurance. A cohort study conducted in Denmark found increased risk of preterm birth and stillbirth in women who received aminosalicylates during pregnancy. However, that study made no distinction between the effects of disease activity and the use of aminosalicylates. (18) Other studies have not found any significant association between aminosalicylates and adverse effects during pregnancy. (19)

Women who use sulfasalazine, which is known to inhibit synthesis of folates, must take folic acid supplements to reduce adverse effects on the neural tube. (20)

In summary, aminosalicylates and sulfasalazine can be used without limitation during pregnancy and are not associated with significant adverse outcomes.

Thiopurine (azathioprine) (class D)

It has been shown that fetal serum levels of thiopurine can reach levels as high as 5% of the maternal drug level. Results of human studies regarding the safety of using azathioprine during pregnancy have been discordant, but it is recommended that this drug be continued during pregnancy in order to maintain the disease in remission. Recent studies have shown that the use of azathioprine does not favor increased risk for the fetus and that it is safe to continue the medication during pregnancy considering that tradeoff between the negative impact of active disease and the uncertain effects of the medication. (21)

Methotrexate (class X)

It is well known that methotrexate has teratogenic and abortifacient effects, so it is contraindicated during conception and pregnancy. The use of methotrexate between the sixth and eighth week of pregnancy can favor congenital anomalies while use in the second and third trimester favors miscarriages. In addition, methotrexate should be suspended three to six months before attempting conception since it actively persists in body tissues. (20)

Corticosteroids (class C)

Glucocorticoids are known to cross the placenta and can reach the fetus, but enzymes of the placenta convert corticosteroids into less active metabolites. These types of medications are frequently used to treat episodes of inflammatory bowel disease activity. Contradictory results are found in pregnancy, but there are reports of increased numbers of orofacial fissures in newborns when they are used in the first trimester of pregnancy. (22)

There are few data regarding the exact dosages of corticosteroids that induces toxicity in either the mother or the fetus. They should be administered with caution and at the discretion of the treating physician. Studies of in other autoimmune diseases have been extrapolated to show that corticosteroids favor preterm deliveries and low birth weights.

Antibiotics

Metronidazole (class B) and ciprofloxacin (class C) are frequently used to treat abscesses and fistulas in IBD patients. They are detectable drugs in breast milk at low levels. A study of women with IBD who required metronidazole during pregnancy has found it to be safe in all trimesters, but recommended avoidance of its use in the first trimester. (23) Studies of ciprofloxacin have not reported any significant increases in major congenital abnormalities including musculoskeletal problems, but it is recommended that it not be used during pregnancy given the risk of congenital arthropathy. (24)

Penicillins have not been shown to condition fetal malformations or adverse pregnancy outcomes and are considered to be first line therapy in pregnancy.

Cyclosporine (class C)

Cyclosporine crosses the placenta but does not cause teratogenicity in animal models. Studies conducted with this drug have been related to kidney transplantation, so an association with low birth weight and preterm delivery is suggested. Similarly, in severe relapses of ulcerative coli-

tis during pregnancy, cyclosporine has been used with favorable responses because it has reduced the need for colectomies without significant adverse effects. The most frequently reported side effect is hypertrichosis in the mother. Other adverse effects that have been described include nephrotoxicity and hepatotoxicity. (25) The use of cyclosporine can be considered in patients with fulminant ulcerative colitis during pregnancy.

Biological agents (class B)

Anti-TNFs such as infliximab, adalimumab, certolizumab, and golimumab are biological agents that are used to manage moderate to severe inflammatory bowel disease and fistulizing-stenosing Crohn's disease. Since TNF is mainly produced by the placenta, levels increase during pregnancy. TNF is important in the early stages of pregnancy and is also important for the development of the fetal immune system.

Observational studies and systematic reviews have shown their safety during pregnancy, but both infliximab and adalimumab are IgG1 monoclonal antibodies that cross the placenta while Certolizumab is a Fab fragment of IgG1 which does not cross the placenta. (26) For this reason, infliximab and adalimumab are not recommended from the second trimester of pregnancy. (27) Other groups have recommended continuation of biological therapy throughout pregnancy, especially in high-risk patients with active disease activity. They only recommend suspension when requested by the pregnant woman. (28) When suspension of biological therapy to decrease fetal exposure is considered, it is recommended that administration cease between the 22nd and 26th week of gestation.

Increased rates of miscarriage, stillbirth, birth defects, and preterm births have not been observed among pregnant women who have been exposed to adalimumab or golimumab. Also, anti-TNFs do not have higher risks of complications during pregnancy than does thiopurine or suspension of all medications. (29)

Levels of infliximab and adalimumab have been detected in infants up to 12 months after delivery, but no increases in infections or allergic reactions have been detected nor have decreased responses to vaccines been found. Nevertheless, it has been observed that infants exposed to the combination of immunomodulators and biological agents have more infections than other infants between 9 and 12 months of age. (30)

Anti-integrin (class C)

Anti-integrin is a humanized monoclonal IgG4 antibody that acts against the α4-integrin adhesion molecule. Data are scarce regarding its use during pregnancy. A review of the natalizumab global safety database did not find increased rates of birth defects among children whose mothers were exposed to natalizumab during pregnancy. It is possible to extrapolate to other diseases from the results of the pregnancies of 35 multiple sclerosis patients who accidentally became pregnant while being treated with natalizumab. Of these patients, 29 had viable pregnancies, 28 had unchanged children, and 1 child was born with hexadactyly. Of the remaining six patients, one decided to undergo an abortion and the other five miscarried. (31)

WHAT IS LABOR LIKE IN WOMEN WITH INFLAMMATORY BOWEL DISEASE?

In the context of pregnancy and IBD, labor should be managed by a multidisciplinary team including an obstetrician, a gastroenterologist and a coloproctologist. Cesarean delivery is indicated when the patient has active perianal disease, rectovaginal compromise, or a surgical history of ileoanal reservoir or ileorectal anastomosis secondary to IBD. Vaginal delivery with episiotomy has been shown to be related to increased risk of perianal damage. (32) Vaginal delivery with all of its benefits for a newborn is indicated for IBD patients who have no perianal compromises. Studies suggest that cesarean delivery is a risk factor for the development and exacerbation of IBD.

WHAT SHOULD WE TAKE INTO ACCOUNT DURING BREASTFEEDING?

Breastfeeding may be associated with increased inflammation since prolactin is associated with increased production of tumor necrosis factor. Nevertheless, one study found that the rates of disease relapse in the first postpartum year were similar among women who breastfed (26%) and those who did not (29.4%). (33)

The following guidelines regarding the use of medications during lactation should be taken into account:

- Aminosalicylates and sulfasalazine can be continued during lactation, bearing in mind that aminosalicylates can favor osmotic diarrhea and sulfasalazine can cause jaundice. Nevertheless, drug concentrations in breast milk are low.
- Azathioprine can be continued during lactation. It is detected in low concentrations in breast milk, although higher concentrations of the drug are found during the first 4 hours after consumption of the drug. It is recommended that milk obtained during these hours be discarded.
- Methotrexate is contraindicated during lactation because of its teratogenic potential.

- Corticosteroids are found in low concentrations in breast milk, with moderately high levels being found in the first 4 hours after taking the drug. It is recommended that milk obtained during these hours be discarded.
- Biological agents can be continued during pregnancy. Minimal concentrations of infliximab and adalimumab are found in breast milk and no significant adverse events have been reported in infants. Detectable levels in newborns are related to placental transfer.. In addition, no association has been found between breastfeeding and the risk of infection in newborns exposed to biological agents. (34)

Vaccination with non-living viruses in newborns exposed to anti-TNF in the womb does not differ from unexposed babies, so they have adequate responses to vaccination. Vaccines with live viruses such as rotavirus, oral polio and BCG should be provided only when anti-TNF levels are no longer detectable. Babies should not receive live vaccines during the first 6 months of life, and anti-TNF should be suspended at week 33 of pregnancy although some other authors suggest it should be suspended at week 26. Suspension allows delivery to occur with undetectable levels of it thus eliminating its involvement in the newborn's vaccination schedule.

CONCLUSION

The medical team for patients with IBD must clearly understand how to face manage preconception, conception and postpartum for these patients since multiple factors must be taken into account. These include disease control during fertility, pregnancy management, and clarity about the use of medications during the various stages of a woman's pregnancy and postpartum period. This will provide peace of mind for both the treating doctor and the patient. Appropriate education and awareness increases the probability that physicians will follow best practice guidelines for management of pregnant patients with IBD.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Endoscopic diagnosis of Uncinariasis, presentation of a case with severe iron deficiency anemia

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Abstract

We present the clinical case of a young man from a rural area who required transfusion of blood products due to severe iron deficiency anemia although there was no obvious bleeding. Multiple tests ruled out hemolytic, autoimmune causes and chronic disease as the cause of his anemia. Endoscopy found massive ancylostomiasis, a potentially curable cause of anemia in our environment. In this article we describe the clinical case, discuss differential diagnoses of iron deficiency anemia, and review the literature.

Keywords

Anemia, ancylostomiasis, parasitic diseases, endoscopy, differential diagnosis.

INTRODUCTION

Hookworm infections (also known as ancylostomiasis or hookworm infections) are caused by Necator americanus or Ancylostoma duodenale nematodes. They are transmitted by direct contact with soils containing these parasites. In humans, they primarily manifest in the digestive tract, and their most frequently found symptoms are chronic blood losses, secondary iron deficiency anemia and protein-losing enteropathy with secondary hypoalbuminemia.

Although hookworm infections are common in Colombia, they are usually underdiagnosed or underestimated in cases of severe anemia. (1, 2) Hookworm infections are endemic especially where physical and sociocultural environment favors fecal-oral contamination. Preschool and school children are most susceptible to infection, but the disease also occurs in adults. (2, 3) Several studies published in Latin America and Africa have confirmed the causal relationships of hookworm infections with poverty, poor environmental sanitation, and residence in rural areas. (4-6) Diagnosis is usually made by identifying the parasite or its eggs in fecal matter.

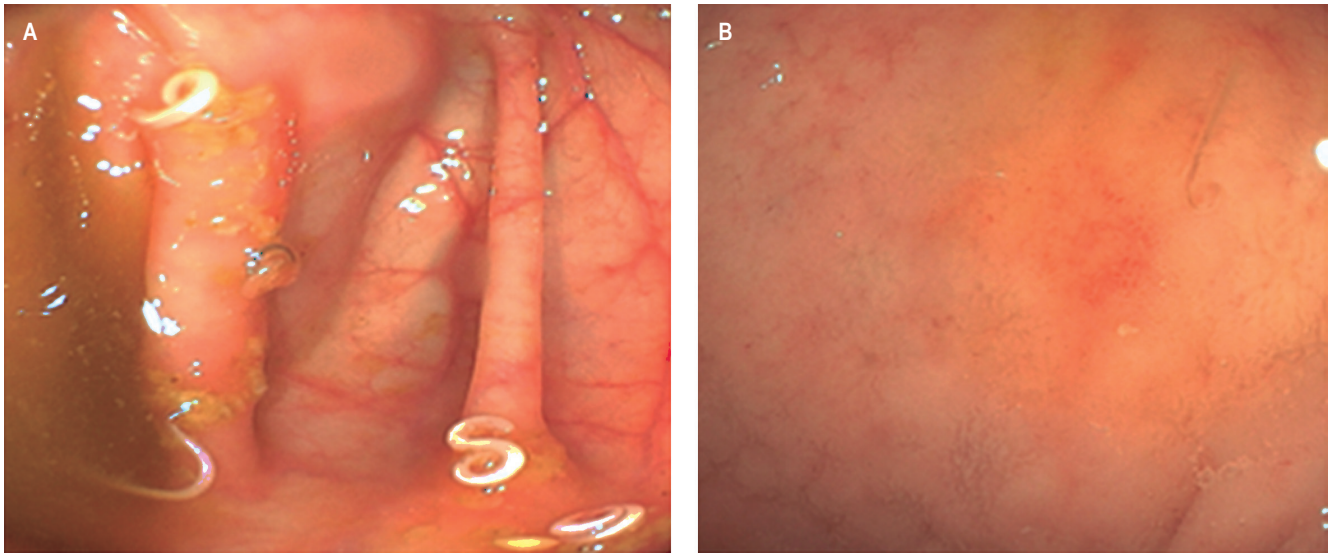
CLINICAL CASE

A 20-year-old farmer from a reservation of indigenous people in Cauca was evaluated at the municipal health center in February 2017. He had been suffering unquantified intermittent fevers, feelings of weakness, fatigue and diaphoresis. On physical examination, his overall physical condition was found to be poor. He had marked cutaneous and mucosal paleness and a fever of 38.5° C. Blood tests showed severe anemia with a hemoglobin (Hb) count of 3.6 g/dL. A thick smear was positive for malaria (P. falciparum with 1520 asexual forms). Treatment was initiated with 4 tablets of Coartem® (20 mg of artemether and 120 mg of lumefantrine) every 12 hours for 6 doses in total. He was referred to our medical center, where additional blood tests of ferrokinetics, hemolysis and other infections were performed (Table 1). In addition, the thick smear was repeated and found a significant decrease of parasitemia. He was treated for anemia with 3 units of packed red blood cells and antimalarial treatment continued. His fever disappeared and his Hb count increased to 7.8 g/dL, so he was discharged.

The was readmitted on October 5, 2017 due to marked asthenia, adynamia, fatigue, itching and pulsatile headache. He said he had not suffered any manifest gastrointestinal bleeding or jaundice. At admission, he required a blood transfusion due to severe anemia (hemoglobin: 4.9 g/dL). Upper digestive endoscopy found evidence of inflammatory changes and erosion in the duodenum where moving parasites were identified (Figure 1A). Colonoscopy identified at least 15 elongated whitish worms that were moving within the right colon and cecum (Figure 1B). Daily oral doses of iron salts for 6 months plus treatment with 10 mg/kg of pyrantel pamoate for 3 days every 6 months for 3 years was recommended for the patient and his close relatives. In addition, he was offered health education on basic hygiene. In telephone follow-up calls at 6 and 9 months, he reported complete improvement of his symptoms.

Table 1. Hospital blood test results

	First hospital stay
Blood chemistry	ALT 14, AST 21 Total bilirubin: 0.93, Direct bilirubin: 0.39, Alkaline phosphatase: 69, C-reactive protein: 0.93, Creatinine: 0.83, Blood urine nitrogen: 9.5, Na: 137, Cl: 104.5, Ca: 8.2, K: 4.21
Infectious diseases	Hemoparasites: 16 gametocytes of plasmodium falciparum per mm^3 HIV: Non-reactive
CBC Anemia study	Hb 3.7; Hematocrit 12.9; Mean corpuscular volume 68; Mean corpuscular hemoglobin 19.5, Red blood cell distribution width 20, leukocytes: 6,200, neutrophils: 3,700, eosinophils, 1,300, lymphocytes: 1400, platelets 222,000, Iron: 24, Transferrin: 330, Total iron binding capacity: 412, transferrin saturation: 6%, ferritin: 13 pmol/L
	Second hospital stay
Blood chemistry	ALT: 19, AST: 32, Creatinine: 0.81, Blood urine nitrogen: 8.5, Na: 139, Cl: 104.9, K: 4.86, Ca: 9.4, INR: 1.11, PT: 11.9 (10.79), PTT: 29.9 (30.6)
Infectious diseases	Hemoparasites: Negative HIV: Non-reactive
CBC Anemia study	Hb: 4.9, Hematocrit: 17.8, Mean corpuscular volume: 57, Mean corpuscular hemoglobin: 15.7, leukocytes: 6,200, Neutrophils: 2,542, Lymphocytes: 1,860, Eosinophils: 1,364 L 1,860, Platelets: 362,000, Reticulocytes: 31,000 (index 0.4 percentage 1.0), LDH: 212, Iron: 20, Ferritin 3.6 pmol/L



Multiple hookworms in right colon

Hookworm in duodenum with evidence of local erosion

Figure 1. Diagnostic images. Endoscopic evidence of hookworms in the duodenum and colon

DISCUSSION

Iron deficiency anemia, the world's most common nutritional disorder, is a global public health problem. It affects more than 2 billion people with approximate prevalences of 40% in preschool children, 30% in women of childbearing age and up to 38% in pregnant women. (7) It is responsible for almost half of all cases of anemia in low and middle income countries. (8) In developing countries it usually results from poor nutrition or gastrointestinal blood loss due to intestinal parasites. (7)

The symptoms of anemia vary greatly and are nonspecific. Classic symptoms include fatigue, dyspnea related to exercise, itching, headache and impaired concentration (which can manifest as the result of iron deficiency without associated anemia). Some obvious signs are cutaneous and mucosa paleness, tachycardia and orthostatic hypotension. Other less frequent, and perhaps more subtle, symptoms include glossitis, angular stomatitis and koilonychias. (9)

There is a broad spectrum of possible causes of iron deficiency anemia (Table 2), not least of which is gastrointestinal bleeding (manifest or occult). (10) Parasitosis should be considered in the initial diagnosis of patients with iron deficiency anemia due to digestive losses. Late diagnosis can generate use of unnecessary diagnostic aids and expose patients to risks of possible complications such as neurodevelopmental delay, heart failure, miscarriages, and morbidity in pregnant women. (2, 7)

The most serious cases of anemia produced by parasites are observed in hookworm infections, malaria, trichuriasis and diphyllobothriasis. Parasitosis can cause anemia secondary to chronic malnutrition through various pathophysiological mechanisms. These include malabsorption and anorexia resulting from inadequate diet; hemolytic anemia, as in cases of malaria and babesiosis; and gastrointestinal bleeding due to lesions in the gastrointestinal mucosa such as those that occur in infections by protozoans such as Entamoeba histolytica, Balantidium coli or infections by helminths such as Ancylostoma duodenale, Necator americanus, Strongyloides stercoralis and Trichuris trichiura. (10)

The etiology of anemia in this case was initially attributed to more than one factor since the initial diagnosis was P. falciparum malaria. However, hemolysis markers were not documented nor did the patient's hemoglobin levels improve noticeably successful completion of treatment with artemether/lumefantrine (Coartem®). In addition, eosinophilia is rare in cases of malaria.

Hookworm infection is a parasitic disease caused by Necator americanus or Ancylostoma duodenale, two species of blood-borne nematodes of the Ancylostomatidae family. These infections cause digestive disorders and hypochromic microcytic anemia which is more intense in massive infections. Infection in humans is caused by penetration of the skin by filariform larvae which are found in contaminated soils. In early stages of maturation, they are called rhabditiform larvae. In the migration phase, the larvae reach the lungs and penetrate the alveolar sacs. The intestinal phase begins with swallowing which results in erosions or ulceration of the gastrointestinal mucosa. The correlation between clinical severity and the intensity of parasitism varies according to nutritional status and any preexisting anemia in these patients. (2)

Clinically, hookworm infections are considered to be mild when the fecal egg count is below 2,000 eggs per gram. Moderate infections have 2,000 to 4000 eggs per gram, and severe infections have counts greater than 4,000 eggs per

Table 2. Causes of iron deficiency anemia

Cause	Condition	Mechanism
Increased requirements	Children and adolescents Pregnancy	Rapid growth Increase red cell mass
Inadequate diet	Poor nutrition, vegetarians	Dietary iron deficiency
Diminished absorption	Gastrectomy, duodenal bypass, bariatric surgery, celiac disease, inflammatory bowel disease, atrophic gastritis, Helicobacter pylori infection, proton pump inhibitor, Chronic renal insufficiency	Decreased absorption surface and/or increased gastric pH and/or hepcidin
Chronic bleeding	Gastrointestinal lesions, steroids, NSAIDs, uterine bleeding, intravascular hemolysis, coagulation defects	Increased blood loss due to conditions that perpetuate bleeding
Mechanisms associated with inflammation	Chronic renal insufficiency inflammatory bowel disease, obesity and heart failure	Increased hepcidin
Acute blood losses	Major surgery	Postoperative anemia

Adapted from C. Camaschella Blood. 2017; 31 (4): 225-33.

gram. (2) For necator americanus, the approximate number of adult worms is obtained by dividing the number of eggs per gram of fecal matter by 80. Cases of severe infestation are estimated to have 50 adult parasites in the intestine. It has been shown that Necator americanus generates a daily blood loss of at least 0.04 mL per parasite while for Ancylostoma duodenale daily blood loss is estimated to be 0.20 mL per parasite. Transient bleeding results when a worm detaches itself from the mucosa to move to another site. After a few months of infection, the result is microcytic and hypochromic iron deficiency anemia. (2) Other manifestations include pruritic dermatitis and nonspecific neurological and pulmonary symptoms such as pulsatile headache and drowsiness. In cases of early childhood infections, retardation of growth and neurodevelopment may occur. (2)

A diagnosis is confirmed when worm eggs are found in feces or when adult parasites are seen. Useful methods include direct examination, the Willis-Faust concentration method, and the quantitative techniques of Stoll and Kato-Katz which indicate the number of eggs per gram of feces. (10) Fecal culture by the Harada-Mori method allows differentiation between Ancylostoma duodenale and Necator americanus species according to the morphologies of their filariform larvae. (10)

In the case presented, the diagnosis was made from the sum of clinical, laboratory and endoscopic data. Although the endoscopic studies in this case played an important role in the diagnosis, we believe that expensive and invasive examinations can be avoided with a more rational approach.

Treatment consists of administration of anthelmintics, especially benzimidazole and pyrantel pamoate, plus treatment of anemia. In Colombia, the most commonly recommended and most frequently used anthelmintics are mebendazole, albendazole and pyrantel pamoate. Their cure rates vary (Table 3). (1, 2) The authors' preference is pyrantel pamoate because it inhibits the cholinesterase enzyme and causes depolarization of the muscle plaque. This causes spastic paralysis of the nematodes which has a beneficial effect on massive parasitosis by minimizing the risk of larval migrations. (2). These schemes are inexpensive and have few adverse effects, so they can be administered whenever there is suspicion of a hookworm infection even in patients without a confirmed diagnosis who live in areas of high prevalence.

Table 3. Medications used to treat hookworm infections in Colombia

Medication	Dose	Cure rate
Mebendazole	100 mg 2 times a day for 3 days. 500 mg single dose	Healing rate: 22% Reduction of eggs: 82% (in control campaigns)
Albendazole	400 mg/day for 3 days. 500 mg single dose in control campaigns	56% cure rate and 98% egg reduction rate (in control campaigns)
Pyrantel Pamoate	10 mg/kg/day for 3 days	80% cure rate 95% egg reduction rate

Adapted from D. Botero et al. Parasitosis humanas. Corporación para Investigaciones Biológicas. 2012. p. 145-60

Conflicts of Interest

None.

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Metastatic anal canal squamous cell carcinoma in a patient with HIV treated with concomitant radiotherapy chemo. Case report and literature review

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Abstract

Anal canal carcinoma is responsible for up to 4% of all cases of colon, rectum and anus cancer. The most common histological type is squamous cell carcinoma. A non-negligible proportion of patients have metastasized by the time of diagnosis. In these stages the prognosis is poor, and treatment is usually based on palliative chemotherapy with cisplatin and 5-fluorouracil. Five year survival rates do not exceed 30%. Some recent studies have suggested that multidisciplinary chemoradiotherapy (chemotherapy combined with radiation therapy) in earlier stages of the disease could improve survival for a select group of patients.

We present the case of a 54-year-old male patient with squamous cell carcinoma of the anal canal with extensive metastasis who also had HIV. He was treated at an institution specializing in cancer treatment where complete remission of the disease was achieved after treatment with chemoradiotherapy with Mitomycin C and 5-fluorouracil. He remains in remission four years after discontinuation of treatment. We discuss the case and review the literature.

Keywords

Anal canal, neoplasms of the anus, squamous cell carcinoma, HIV, chemoradiotherapy.

INTRODUCTION

Anal canal carcinoma accounts for 2% to 4% of all cases of colon, rectal and anal cancer. (1) Its peak age of presentation is between 58 and 64 years, and its frequency has been increasing. In the United States, incidence rates went from 0.8 cases per 100,000 people/year in 1975 to 1.5 cases per 100,000 per 100,000 people/year in 2011. This could be due to the impact of human immunodeficiency virus infections (HIV). (2) The most common histological type is squamous cell carcinoma which accounts for 85% to 90% of all cases. (2, 3) Half of the patients have localized disease at the time of diagnosis, a third present as regional nodal disease, and 10% to 15% have distant metastases. (4)

There is little information regarding the natural history of metastatic squamous cell carcinoma, especially due to the paucity of prospective studies. (5) The National Comprehensive Cancer Network (NCCN) recommends palliative systemic chemotherapy based on cisplatin and 5-fluorouracil for advanced stages. For some patients, it recommends sequential palliative radiation therapy rather than concomitant radiation therapy. (6) Chemotherapy offers a reasonable response rate but has poor strong outcomes with 5-year survival probability between 15%

and 30%. (7) Recent evidence suggests that for some well-selected patients with metastatic disease, multidisciplinary treatment with concomitant chemoradiation therapy mayd improve survival outcomes. (8)

We present the case of an HIV patient with metastatic anal canal squamous cell carcinoma who was treated at the National Cancer Institute of Colombia. He received concomitant chemoradiation therapy with 5-fluorouracil and mitomycin-C followed by chemotherapy alone with the same protocol for 6 cycles. Sustained complete response over time was achieved, and the patient has been in remission for almost four since discontinuance of treatment. The case is discussed, and the literature is reviewed.

CASE DESCRIPTION

In May 2013, a 54-year-old man came to the institute because of pain and feeling of mass in the rectoanal region. He had a history of HIV infection which had been treated with HAART therapy since December 2012. His CD4 count was 57 cells/μL, and his viral load was 40,612 copies/mL (Log 5.6). Physical examination revealed sarcopenia and multiple lymphadenopathy in left level IV, axillary, and groin area lymph nodes. Examination of the perineal region revealed external edematous hemorrhoids, at least 5 subcutaneous nodules in the gluteal region measuring up to 5 mm in diameter, and a rectal lesion that started above the anal rim on the anterior side of the distal rectoanal canal. The rest of the physical examination was within normal parameters.

A rectosigmoidoscopy found a neoplastic lesion in the rectal ampulla 5 cm from the anal rim. A biopsy reported a moderately differentiated squamous cell carcinoma. An MRI of the pelvis showed neoplastic thickening of the anal canal with an area of anterior focal ulceration in contact with the membranous urethra and apex of the prostate. Magnetic resonance imaging of the abdomen reported metastatic lesions in the right adrenal gland, left paraaortic lymph nodes, and infrarenal, retrocaval, celiac axis and right retrocrural lymph nodes. A CT scan of the chest reported multiple tumor adenopathies in the right axillary, supraclavicular, prevascular, paraesophageal, right retrocrural, and left paraaortic regions. In addition, it showed a cavitating nodular lesion at the base of the left lung and multiple subcentimeter nodules with randomly distributed soft tissue density which led to suspicion of malignancy (Figure 1).

An excisional biopsy of a right axillary node confirmed distant metastatic involvement for squamous cell carcinoma with sarcomatous dedifferentiation of the anal canal. Stage IV T4N2M1 squamous cell carcinoma of the anal canal was diagnosed (American Joint Committee on Cancer, version 7). (9) Despite extensive disease at a distance, given the patient's overall good condition, we decided to provide treatment usually reserved for earlier stages to provide the maximum possible response. We began concomitant chemoradiation therapy with mitomycin C 10 mg/m2 on days 1 and 29 plus continuous infusion of 1,000 mg/m2/day of 5-fluorouracil on days 1 to 4 plus radiation therapy on days 29 to 32. He received this treatment between August 20 and October 5, 2013 without limiting toxicity. A complete clinical response was obtained in the anal canal and a CT scan showed a partial response with more than 30% decrease in the lymph node conglomerate in the left and right axillary IV level, resolution of the mediastinal node component, decreases in the sizes of lung lesions, resolution of some abdominal lymphadenopathy and decreases in the sizes of the right adrenal gland lesions (Figure 2).

Given the good response obtained, it was decided to continue systemic treatment with the same mitomycin C + 5-fluorouracil chemotherapy regimen with close hematological and renal monitoring. The patient completed 6 cycles on October 10, 2014 and has since been followed up. End-of-treatment reevaluation CT scans showed complete pulmonary, axillary nodal, and cervical responses with only a few residual left retrocrural and retroperitoneal adenomegalies remaining and lesion stability in the right adrenal gland. Since then, follow-ups with clinical examinations and imaging have continued. As of the examination of August 2018, the patients lesions are stable and without evidence of disease progression (Figure 2).

DISCUSSION

Most of the literature on the treatment of metastatic anal canal squamous cell carcinoma is limited to case reports and series in which the chemotherapy protocols used for squamous cell carcinomas from other locations such as the lung and cervix have been extrapolated. (10) Although the disease is not yet curable, the most important oncology guidelines advise the use of polychemotherapy with palliative intent while leaving open the option of sequential rather than concomitant pelvic radiation therapy in palliative doses in case of large symptomatic primary tumors. (1, 6) In metastatic stages, median progression-free survival of 5 to 7 months and overall survival of 15 to 22 months has been reported. (7, 8)

Platinum chemotherapy plus 5-fluoruracil (5-FU) has reported partial responses in almost 60% of patients. Median survival time is up to 34.5 months, but there have been no sustained long-term responses. (11, 12) A retrospective series at MD Anderson Cancer Center demonstrated median progression-free survival of 7.2 months and overall survival of 38 months. (13) Other regimens that have been used include the carboplatin/paclitaxel combination which has had overall survival of 12 months. (14) The combination of paclitaxel, carboplatin and 5-FU has been evaluated in a

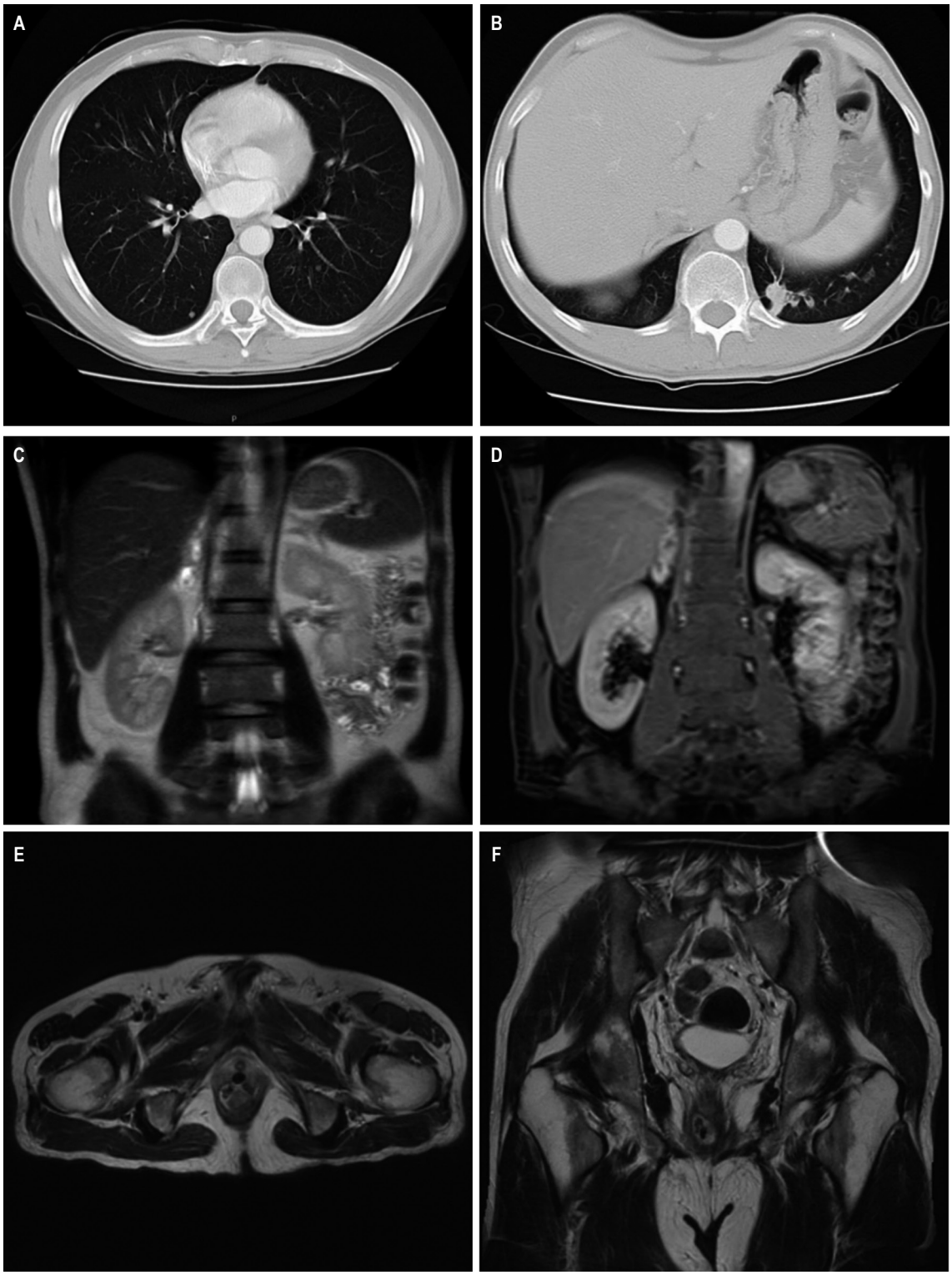

Figure 1. Images of the patient at the time of diagnosis. A and B. Axial projection of CT scan of the chest shows multiple subcentimeter nodules with random soft tissue density and a dominant nodular lesion in the left lung base. C and D. Coronal projection of abdominal MRI shows two focal lesions in the right adrenal gland: one in the 14 x 17 mm medial arm and the other in the body of the 14 x 19 mm gland. The lesion in T2 (C) is hyperintense while the lesion in T1 (D) is hypointense. Neither suppresses signal in out-of-phase sequences, both restrict peripheral diffusion and peripheral enhancement of contrast medium in relation to necrotic metastases (these last two sequences are not illustrated). E and F. Axial and coronal projections in T2 sequence of pelvic MRI shows concentric and neoplastic appearing thickening with an area of anterior ulceration in the anal canal with a thickness of 14 mm. There is moderate enhancement of the contrast medium in contact with the membranous urethra without fistulas to this organ.

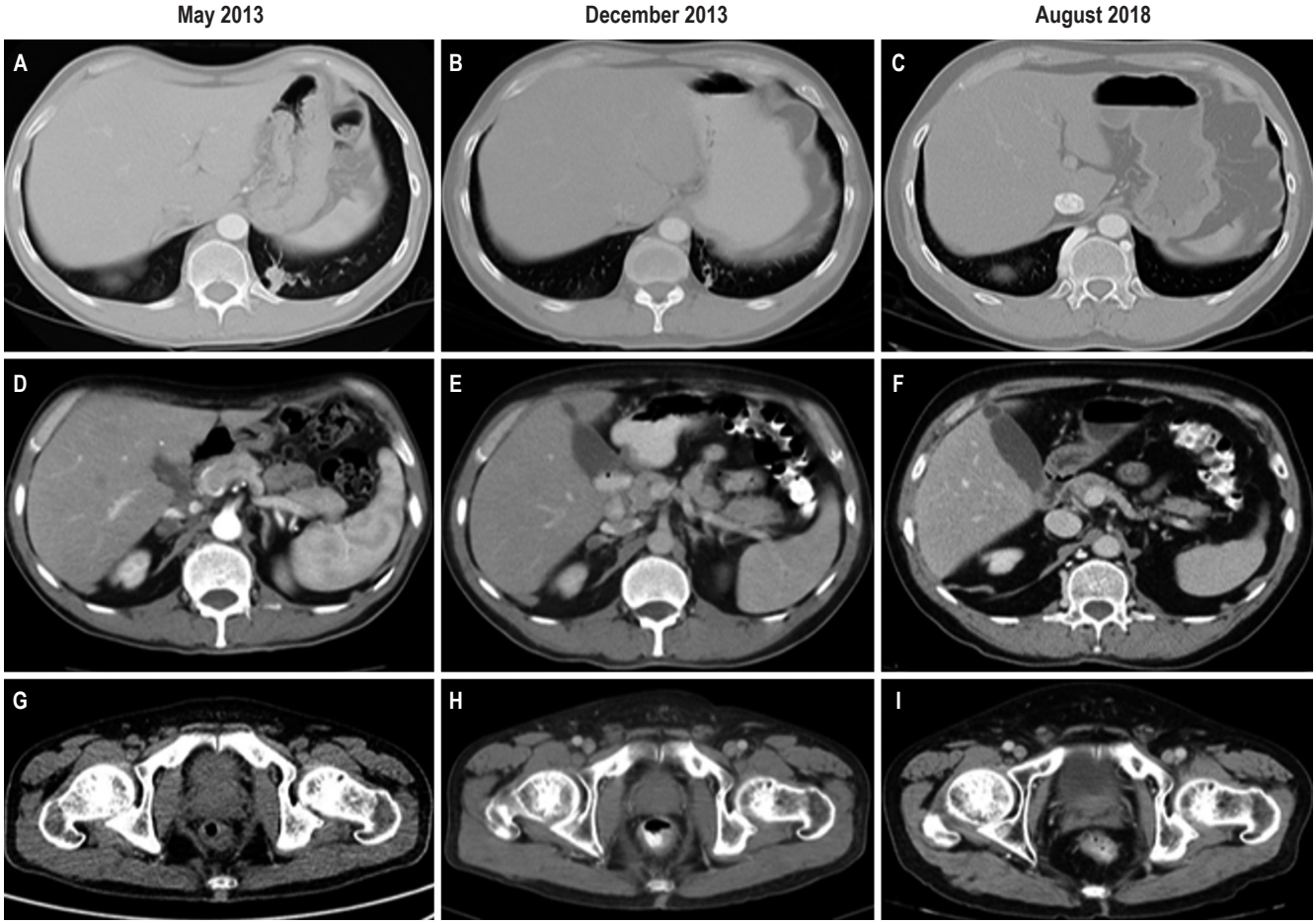

Figure 2. Tomographic monitoring of the patient. A-C. The images show the evolution of the size of the metastatic nodule at the base of the left lung with complete resolution as of the last follow-up. D-F. The evolution of one of the metastatic lesions in the right adrenal gland is evident with complete response in the last study. G-I. The images show partial response in the anal canal with stable disease as of August 2018.

phase II study which tested its efficacy for treating squamous cell carcinoma of several primary sites. It demonstrated overall responses in four of the seven patients with a primary site, but there were considerable side effects including leukopenia (48%), mucositis (28%) and diarrhea (17%). (15) In 2006, Jhawer et al. studied the use of mitomycin C, adriamycin, cisplatin, and bleomycin-CCNU and obtained an overall response rate of 60%, a median progression-free survival of 8 months, and overall survival of 15 months. However, severe toxicity that included leukopenia and thrombocytopenia (10%), vomiting (10%), cramps (5%) and cardiac arrhythmia (5%) developed. (16)

As stated, the prognoses of patients with metastatic disease are very poor. The patient in our case achieved complete local response and partial systemic response with the initial concomitant chemoradiation therapy (standard scheme in non-metastatic disease) and, after 6 cycles of mitomycin C + 5-fluorouracil, the patient achieved complete response which has been maintained for about 4 years.

Sequential chemoradiation therapy in metastatic disease is recommended in international management guidelines, but there is little evidence of the impact that this type of treatment may have nor for the optimal timing for its initiation. Small case series have shown improvement of long-term disease-free survival. (17) Also, optimal duration of therapy for those who achieve adequate responses has not been established although some authors suggest continuing treatment indefinitely to achieve a maximum response in patient who properly tolerated it. (10)

When metastasis is preset, the guidelines suggest using radiation therapy only in combination with 5-FU and a platinum. Here, we present a successful experience using mitomycin C instead of cisplatin, in which an almost complete response and stability of lesions were achieved after four years of

the Nigro scheme. A phase II study comparing the use of cisplatin + 5 FU with weekly administration of carboplatin with paclitaxel for patients with inoperable or locally recurrent metastatic anal canal squamous cell carcinoma is currently underway. The main objective of the study is to evaluate the response rate and secondary outcomes include progression-free survival, overall survival, toxicity, and quality of life. (18)

HIV patients with anal canal carcinoma have worse prognoses than do seronegative patients and may experience greater toxicity with chemotherapy, especially when their CD4 counts are less than 200 cells/μL. They may also require longer rest periods and reduced doses of chemotherapeutic agents. (19, 20) The main toxicities they experience have been hematological, gastrointestinal and dermal. They may also require reduction of the radiation field through intensity modulated radiation therapy (IMRT). (21) Although some authors have found a trend toward improved survival in patents with CD4 counts that are over 200, the evidence is not conclusive and the impact on the immune systems of patients with anal canal squamous cell carcinoma and HIV who undergoing HAART therapy remains to be established. (21, 22) In addition, HIV patients have been excluded from large studies of squamous cell carcinoma of the anal canal such as ACT I, RTOG 98-11 and ACCORD 03. (23) In our case, the patient had an acceptable tolerance of chemoradiation therapy and concomitant antiretroviral therapy, there were no requirements for prolonged rest periods, and all chemotherapy cycles were completed.

In recent years, targeted cancer therapy has become important as demonstrated by the work of doctors Allison and Honjo in cancer immunotherapy for which they were awarded the 2018 Nobel Prize in Physiology or Medicine. (24, 25) The role of human papilloma virus (HPV) in the carcinogenesis of squamous cell carcinoma of the anal canal, especially in immunosuppressed patients, has led to the use of anti-PD-1 antibodies in two recent studies. In 2017, Ott et al. studied the safety and efficacy of pembrolizumab in a cohort of PD-L1 positive patients with locally advanced or metastatic anal canal carcinoma from the phase I KEYNOTE-028 study who had experienced failure of at least one previous attempt with standard therapy. The primary outcomes were safety and overall response rate, and overall outcomes were progression-free survival and duration of response. Twenty-five patients with a median age of 63 years were randomized. Sixty-four percent experienced treatment-related adverse events, with no treatment-related deaths. Four patients had partial responses, the overall survival rate was 17% (95% CI: 5% to 37%), and 42% had stable disease for a median time of 3.6 months. Median progression-free survival was 3 months, and median overall survival time was 9.3 months. The authors concluded that this molecule demonstrated a manageable safety profile and acceptable antitumor activity. (26)

In another phase II study, conducted by Morris et al., the efficacy of nivolumab was assessed in patients who had metastatic anal canal squamous cell carcinoma but had not previously received immunotherapy. A total of 39 patients were randomized. Median age was 56 years. Seven patients (21%) had partial responses, and just over half achieved stable disease, with a disease control rate of 79%. Median progression-free survival time was 4.1 months, and overall survival time was 11.5 months. The most common adverse effects were fatigue, nausea, and rashes. The authors concluded that nivolumab demonstrated potentially significant activity, with adequate tolerance. (27)

Epidermal growth factor receptor (EGFR) inhibitors have also been studied. The use of cetuximab has been described in case reports of patients with wild-type KRAS. Retrospective analyses initially found a possible role for this drug in patients with anal canal squamous cell carcinoma, (28) but safety outcomes found when EGFR inhibitors have been used in patients with locally advanced disease receiving chemoradiation therapy must also be taken into account. Grade 3/4 toxicity rates of up to 90% have been found, and response rates have not been very good. This has led to recommendations that the search for more effective and less toxic therapeutic alternatives continue. Safety and efficacy and safety outcomes for metastatic cases have yet to be verified in randomized clinical trials and prospective studies. (29)

CONCLUSIONS

Our case shows that it is possible to offer concomitant chemoradiation therapy in curative doses, standard for localized disease, in selected patients with distant metastatic disease and to achieve complete and sustained response and control of systemic disease. The MD Anderson Cancer Center case series also supports this approach. This may be the starting point for a change in the oncological paradigm in terms of the prognosis and treatment of this disease. Long-term randomized clinical trials with patient follow-up are required to confirm this hypothesis, and better quality evidence regarding the treatment of stage IV squamous cell carcinoma of the anal canal is still needed.

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Case report of Bouveret syndrome: a strange cause of upper intestinal obstruction

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Abstract

Bouveret syndrome is a rare pathology which is characterized by gastric or duodenal obstruction secondary to a gallstone embedded in the lumen after migrating through a cholecystoduodenal fistula. Its incidence is approximately 1% to 3% of all cases of biliary ileus. The main symptoms consist of vomiting, abdominal pain, hematemesis, weight loss and anorexia. Surgery is required in 91% of cases. This article presents the case of a 50-year-old patient who had suffered from abdominal pain in the epigastrium and mesogastrium, abdominal distension and multiple episodes of emesis for two months. Physical examination indicated obstruction of the intestine. An abdominal CT scan showed that the obstruction was in the first duodenal portion and that Rigler's triad was present. It was diagnosed as Bouveret Syndrome.

Keywords

Biliary fistula, Bouveret syndrome, intestinal obstruction, biliary ileus.

INTRODUCTION

Bouveret syndrome (BS) was first reported in the literature by Beaussier in 1770 and was later named after French physician Leon Bouveret reported two cases in 1896. (1) It is defined by the presence of a bilioenteric fistula which allows one or more gallstones to pass into the duodenum and on to the pylorus where the stone(s) obstruct gastroduodenal drainage. (2, 3) The fistula is the product of chronic inflammation which increases intraluminal pressure leading to wall ischemia, an adhesion system, and subsequent perforation which communicates between the biliary system and the intestine and allows passage of biliary stones. (4, 5)

BS accounts for approximately 1% to 3% of cases of gallstone ileuses and 2% to 3% of all small bowel obstructions. (1, 3) Its prevalence is higher in women than in men, and the average age of presentation is 74 years. In most cases stones measure more than 2.5 cm, or BS is a postoperative alteration. Currently, the mortality rate in these cases is around 12%. (1-4) Imaging shows BS as a foreign body, with or without a calcified capsule, in the duodenal lumen which is associated with pneumobilia and intestinal obstruction with duodenal dilation (Rigler's triad). (6-8)

Only a few cases have been reported in the literature, and diagnosis is difficult due to the low specificity of symptoms and rarity of occurrence. Currently available diagnostic aids have allowed greater certainty of diagnosis and more timely and appropriate management of this pathology.

We report the case of a 50-year-old patient with recurrent upper bowel obstruction secondary to BS that was initially managed with an exploratory laparotomy plus adhesion release. In addition, we review the literature.

CASE PRESENTATION

The patient was a 50-year-old woman who had had an appendectomy two years prior and had undergone exploratory laparotomy plus release of adhesions due to intesti-

nal obstruction secondary to flanges two months before she was referred to us for epigastric/mesogastric colic associated with multiple episodes of vomiting, abdominal distension, and stoppage of defecation and flatulence. Symptoms had worsened in the five days prior to admission.

Upon admission, her vital signs were stable, and there were no signs of systemic inflammatory response. Physical examination showed that her abdomen was distended but not painful on palpation. No masses or irregular enlargements of organs were found, but peristalsis was minimal. Intestinal obstruction was diagnosed and medical management with intravenous hydration, a nasogastric tube with free drainage and electrolyte replacement was initiated. Admission paraclinical tests showed metabolic alkalosis with pH 7.53, hypokalemia of 2.2 mEq/L, but no leukocytosis or neutrophilia (Table 1). Abdominal radiography found no signs of intestinal obstruction, so an abdominal CT scan and upper digestive tract endoscopy were requested.

The abdominal CT scan showed intestinal obstruction as an intraluminal image in the first 4.5 x 3 cm duodenal portion (Figure 1 and 2). It was associated with pneumobilia and contrasted bile duct passage. This meets the criteria of Rigler's triad. In addition, upper digestive tract endoscopy showed dilatation of the gastric chamber secondary to obstruction of the duodenal lumen and an impacted calculus in the duodenal bulb (Figure 3 and 4).

Table 1. Results of paraclinical tests performed at admission

Test	Results
Arterial gases	pH 7.53; HCO_3 32 mmol/L; PCO_2 34.2 mm Hg; PO_2 140
Calcium	8.7 mEq/L
Sodium	136 mEq/L
Potassium	2.2 mEq/L
Complete blood count	Hemoglobin 12.9; hematocrit 36; leukocytes 7,100; neutrophils 62%; lymphocytes 22%; platelets 230,000

HCO_3: bicarbonate; PCO_2: partial pressure of carbon dioxide; PO_2: partial oxygen pressure.

Given the clinical findings, paraclinical findings, and images, Bouveret syndrome was diagnosed, and we performed an exploratory laparotomy with gastrostomy and extraction of the stone impacted in the duodenal bulb followed by gastrorraphy (Figure 5 and 6). During the surgery, inflammation became evident with multiple adhesions on intestinal loops from the omentum to the liver and gallbladder. This made visualization difficult.

Following surgery, the patient remained hospitalized where her evolution was satisfactory. She was assessed in an outpatient follow-up appointment two months after surgery and was found to be without abdominal pain or new obstructive episodes. Her physical examination was within normal limits.

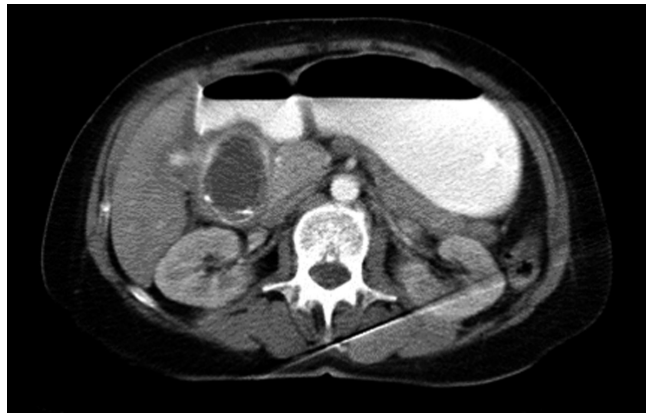

Figure 1. Abdominal CT scan shows a rounded image obstructing the duodenal lumen.

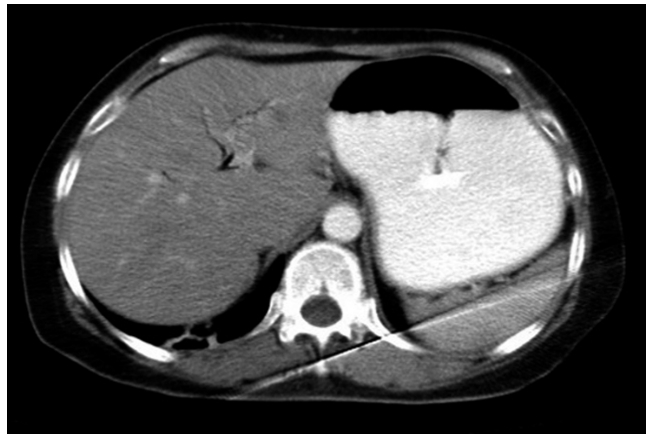

Figure 2. Abdominal CT scan shows pneumobilia and dilation of the gastric chamber.

DISCUSSION

Bouveret syndrome is a rare disease which usually occurs in elderly women who have histories of biliary lithiasis. It is characterized by gastric or duodenal obstruction secondary to an impacted stone in the duodenal lumen which had passed through a cholecystoduodenal fistula. First described in 1896 by Leon Bouveret, it only occurs in 15% of cases in which stones pass into the duodenum. (2, 8, 9) Its clinical presentation is nonspecific clinic but can include vomiting, abdominal pain, hematemesis, weight loss and anorexia. (1) Its incidence is about 1% to 3% of all cases of biliary ileus, so a high index of clinical suspicion is required for diagnosis.

The advent and increasing availability of new diagnostic tools has made adequate pre-surgical diagnosis possible. Computed tomography is the key tool because its diagnostic

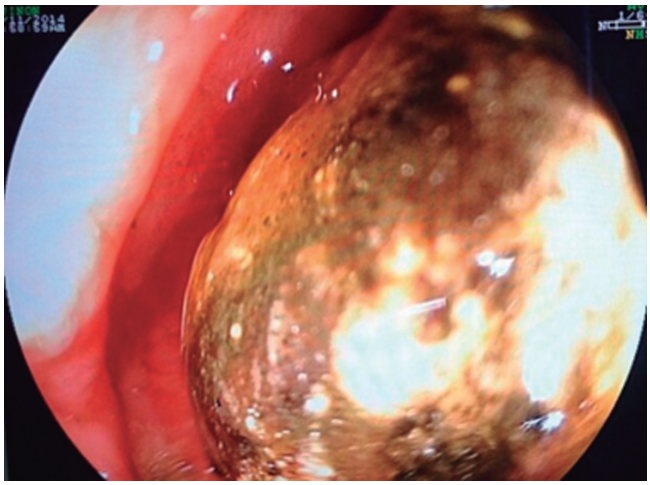

Figure 3. Endoscopic view of stone in the lumen of the duodenal bulb.

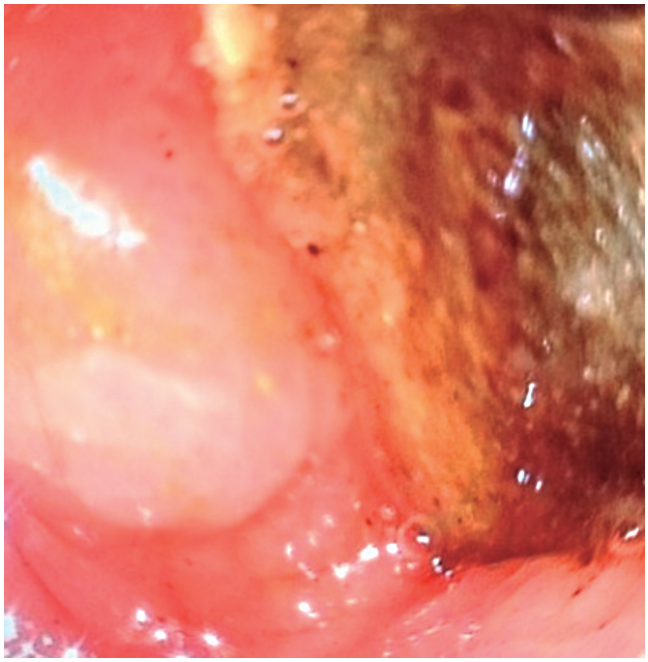

Figure 4. Endoscopic view of stone lodged in the lumen of the duodenal bulb.

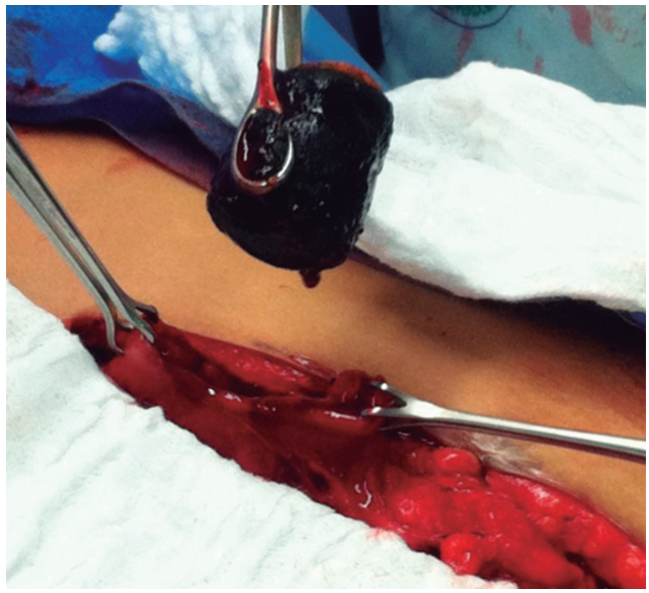

Figure 5. Removal of stone lodged in duodenal lumen through open gastrostomy. The image shows the anterior wall of the open gastric corpus from which the calculus was extracted.

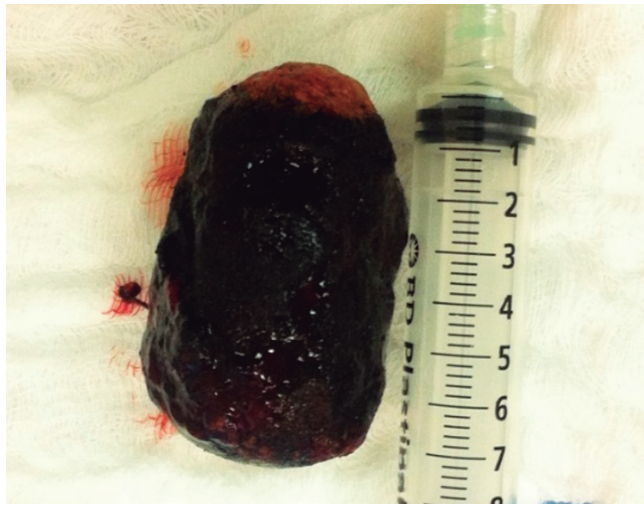

Figure 6. Biliary calculus extracted from duodenal lumen.

sensitivity is 93% while its specificity is 100%. Upper digestive endoscopy is also very useful for diagnosis of this pathology and is considered the reference method for diagnosis. In this case, both of these examinations were performed. Bilioenteric fistulas can be cholecystocolic, cholecystogastric or cholecystoduodenal. The latter is the most frequent and accounts for 60% of all cases. The main imaging characteristics are pneumobilia, a foreign body lodged in the duodenal lumen, intestinal obstruction with duodenal dilation and bilioenteric fistula. Together, these are called Rigler's triad which was present in our patient. (9, 10)

In more than 91% of cases, treatment of Bouveret syndrome requires surgical management. However, treatment can vary. Since most of these patients are elderly people who have comorbidities, endoscopic treatment is the first choice because its morbidity and mortality rates are lower than those of both open and laparoscopic surgery. Surgical management, either open or laparoscopic, can include

enterolithotomy or enterolithotomy with cholecystectomy and correction of the fistula. The latter is ideal because it reduces the risk of recurrences, hemorrhaging, cholecystitis and gallbladder cancer, but it has higher rates of morbidity and mortality. (9, 11-14) This is why the choice of management varies according to the clinical characteristics and comorbidities of each patient. The overall mortality rate is about 12% to 27%. (2) In our case, management with enterolithotomy through a gastrostomy was chosen. This is the most commonly used surgical technique. In our case, the patient's clinical evolution was good two months after surgery. (1)

CONCLUSION

Bouveret syndrome is a rare disease which requires a high index of clinical suspicion for proper diagnosis. Technological advances in diagnostic tests has allowed presurgical diagnosis to become highly sensitive allowing better management of patients according to their individual clinical statuses and comorbidities. Familiarity with Bouveret syndrome's radiological semiology is important. In our case, the patient was managed with enterolithotomy through a gastrostomy which is the most commonly used surgical technique for stone extraction. At two months follow-up, the patient's evolution was satisfactory.

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Letter to the editor
Treatment and outcome in acute pancreatitis

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Dear Editor:

After reading the article written by H. Puerto et al. and published by your magazine, I considered it important to comment. The article is about treatment and outcomes of patients with acute pancreatitis over three years at a university hospital.

I would like to mention that the American Gastroenterology Association recommends starting enteral nutrition early rather than late on the bases of 11 randomized controlled trials. Those trials did not demonstrate decreasing mortality but did demonstrate fewer infectious complications including peripancreatic necrosis, multiple organ failure and surgery to address pancreatic necrosis. (1, 2) The recommended route is oral (with either gastric or post-pyloric catheter) depending on the tolerance of each patient. Similarly, all possible clinical mechanisms for the use of this route such as antiemetics, prokinetic agents, pancreatic enzymes, soluble fiber and antidiarrheal agents should be exhausted if need be. (3)

In severe cases of acute pancreatitis, enteral nutrition may need to be delayed until the patient is stabilized, but it is still the preferred method of feeding. (4) This is so because parenteral nutrition has higher rates of organ failure, infectious and metabolic complications and mortality than does enteral nutrition. (5, 6) The time needed to achieve daily energy and protein requirements can precipitate the use of complementary parenteral nutrition or even total parenteral nutrition in patients without previous malnutrition for whom the daily enteral nutrition volume cannot be increased. According to the 2012 Atlanta classification of acute pancreatitis, neither organ failure, localized complications nor systemic complications should occur after the first 48 hours of mild acute pancreatitis. Thus, most of these patients will tolerate the oral route, and very few will require gastric or post-pyloric feeding tubes. Moderately severe acute pancreatitis leads to reversible organ failure, systemic complications or local complications. Some of these may require parenteral nutrition. Severe acute pancreatitis may require parenteral nutrition more frequently.

Due to the high risk of adverse outcomes, surgery is only recommended when there are infectious complications refractory to intensive antimicrobial treatment, progressive clinical deterioration, severe mechanical complications such as behavioral syndrome refractory to clinical management, obstruction, bleeding or perforation. (4, 7) If surgery is necessary, it should be carried out as late as possible, to allow the necrosis and inflammation of the peripancreatic tissues to be defined as well as possible.

Conflicts of interests

The author has no conflicts of interest.

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Response to the letter to the editor Treatment and outcome in acute pancreatitis

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Mr. Editor:

After carefully reading Dr. Abel Salvador Arroyo-Sánchez's letter responding to "Outcomes of Three Years of Experience Managing Acute Pancreatitis at a Fourth Level Hospital in Huila, Colombia", we would like to make a few comments. (1)

First, we want to thank Dr. Arroyo for his interest in contributing to our knowledge of treatment of this disease. We agree with his assessment of the nutritional schemes recommended for acute pancreatitis by most evidence-based guidelines. (2-4) These guidelines clearly establish the benefits of enteral nutrition in patients with acute pancreatitis. As shown in Table 12, more than 80% of patients in our work received enteral or mixed nutrition. In the specific case of patients with necrosis, 62% received this type of nutrition. (1) It should be noted that the enteral route had been exhausted in patients who received parenteral nutrition.

As can be seen in Figure 2, a high percentage of patients with pancreatic necrosis in our study (62.5%) underwent surgery. These patients had complications refractory to conservative medical treatment or were not candidates for percutaneous or endoscopic management. As shown in Table 13, there were fatal outcomes in three of these cases. All of these patients had Marshall severity scores upon admission that were over four while their average APACHE II score was 16 points. From the outset, their prognoses had shadows cast over them.

Finally, we consider that all contributions of letters to the editor show interest in the article and enrich research.

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