

# Ectopic Varices in the Proximal Jejunum Associated with Recurrent Bleeding in a Patient without Cirrhosis of the Liver

Mauricio Melo Peñaloza, MD,<sup>1</sup> María Teresa Galiano de Sánchez, MD.<sup>2</sup>

<sup>1</sup> Gastroenterologist at the Clínica Martha in Villavicencio, Meta, Colombia

<sup>2</sup> Gastroenterologist at the Clínica de Marly in Bogotá, Colombia

Received: 03-02-14

Accepted: 05-11-14

## Abstract

Ectopic varices (EV) in the jejunum are a rare vascular disorder which is associated with portal hypertension (5%). It is even rarer when it occurs without associated portal hypertension.

We report a case of a patient without portal hypertension who had had chronic intestinal bleeding from varices located in the proximal jejunum for several years. We report the patient's clinical development, elements used for diagnosis and the surgical treatment.

## Keywords

Portal hypertension, jejunal varices, occult and obscure intestinal bleeding.

## INTRODUCTION

Obscure intestinal bleeding is defined as bleeding that persists or recurs without any etiology obvious through diagnostic colonoscopy and upper endoscopy. It can be obvious when the patient and the clinician see evidence of bleeding, or it can be hidden and unnoticed by both the clinician and the patient until laboratory test results show that it is present (1, 15).

Lower intestinal bleeding primarily affects people over the age of 65. The annual incidence in the third decade of life is 1 per 100,000, but it can reach 200 per 100,000 people in the ninth decade. Some studies show that 70% of all patients have at least one coexisting illness (3, 9, 14).

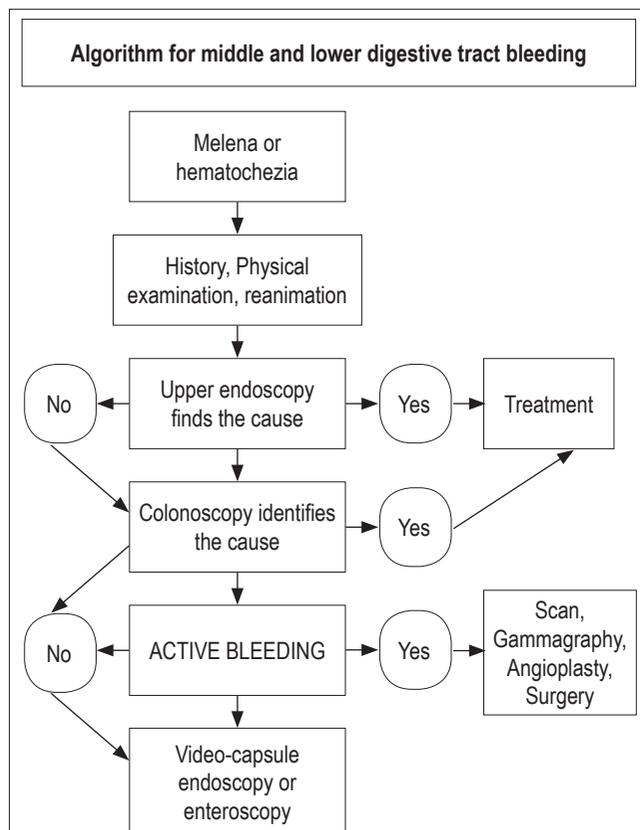
One laboratory test that can help diagnose bleeding is a blood urea nitrogen (BUN) test which can show whether there is any bleeding and the reason for the bleeding. When the test shows a creatinine ratio greater than 33 in patients with no history of chronic or acute renal disease, it indicates that the location of the bleeding is high or in the small intestine but is not in the colon (9, 10).

Approximately 5% of intestinal bleeding occurs between the ligament of Treitz and the ileocecal valve. Vascular lesions account for 40% of the causes of bleeding and of these angiectasis and angiodysplasias these are the most common causes in elderly patients. Less frequent causes include aortoenteric vascular fistulas, hemobilia, pancreatic hemosuccus and varicose veins in the small intestine. Other causes include damage due to NSAIDs and tumors (1, 2, 4, 6-8, 14, 15).

With the advent of new techniques such as capsule endoscopy and enteroscopy, the tendency is to redefine the general intestinal bleeding and obscure intestinal bleeding into three categories: upper, middle and lower bleeding instead of the two traditional high and low bleeding.

Bleeding originating above the ampulla of Vater is upper bleeding. Bleeding originating between the ampulla of vater and the ileum is defined as middle bleeding. It is best investigated by capsule endoscopy or double-balloon push-and-pull enteroscopy. Bleeding originating in the colon is defined as lower bleeding and is evaluated by colonoscopy (1, 2).

If lesions cannot be identified, but there is active bleeding, radionuclide angiography or surgery can be used. If no lesions are found and there is no apparent bleeding, the next step is to use diagnostic capsule video endoscopy or enteroscopy (See Figure 1) (3, 6-8, 12).



**Figure 1.** Algorithm for middle and lower digestive tract bleeding. Adapted from reference 6

Generally, there are two methods of enteroscopy currently in use: push stereoscopy and double balloon assisted enteroscopy. The difference between the two methods is the length of the small intestine that can be examined during one procedure and therefore the number of procedures required to reach a diagnosis. Push enteroscopy reaches a length of 80 cm in the jejunum, but double balloon assisted enteroscopy can reach 230 cm which allows it to find a greater number of lesions (11, 12).

Intraoperative enteroscopy is considered to be the last resort when other methods have failed to clarify the cause of bleeding. Although it makes a diagnosis in 79% of the cases, it has been associated with post-procedural complications including adhesions, perforations, infections and hernias in 5% to 20% of the cases, especially in patients with comorbidities (6, 13).

## CASE REPORT

The patient was a 52 year old black woman who was hypertensive and diabetic. She first came to the clinic for this problem on January 15, 2009. She stated that she had had several occurrences of diarrhea and that the stools had contained mucus. Diarrhea was associated with abdominal cramping and pain. Symptoms had been managed symptomatically. She brought a colonoscopy report from 2003 that showed that her ascending colon was normal.

In September 2009 she returned with symptoms of chest pain and anemia (Hb 4.2 gr/dl). She received a transfusion of red blood cells. Coronary heart disease was discarded but no gastroenterological study was done.

One month later she returned after multiple occurrences of melena. She was treated with transfusions of red blood cells and released.

The next year two outpatient check-ups showed her Hb at 9.1 gr/dl and BUN values of 60 and 110 mg/dl. (Normal range 6 to 20 mg/dl).

In mid-2010 her Hb was 7.2 gr/dl and she again received a transfusion of red blood cells. An upper endoscopy reported antral gastritis, and a colonoscopy found that her colon was normal.

In late 2010, new tests including hematology showed PT 14.1 seconds (Normal range: 11-13 seconds) PTT 18.9 seconds (Normal range: 25-35 seconds), Total bilirubin: 0.26 mg/dl (Normal range: 0.2 to 1.0 mg/dl), Direct bilirubin: 0.16 mg/dl (Normal range: 0.1 to 0.3 mg/dl), Ferritin 5.9 ng/dl (Normal range: 4.63 to 204ng/dl), serum iron: 6 ug/dl (Normal range: 25-156 ug/dl), Hb 6.6 g/dl (Normal female range: 12.1 to 15), Folic acid: 6.30 ng/dl (Normal range: 2.7 to 17 ng/ml), Vitamin B12: 1,053 pg/ml (Normal range: 200 to 900 pg/ml). It was decided to treat the patient for iron deficiency anemia due to an unidentified gastrointestinal loss of blood.

In 2011, after a packed red blood cell simple showed Hb of 6.6 gr/dl, the patient received another transfusion of red blood cells. An abdominal CT scan showed an inflammatory process in the loops of the small intestinal leading from the jejunum with lymphadenopathy in the mesogastric region. Crohn's disease was suspected.

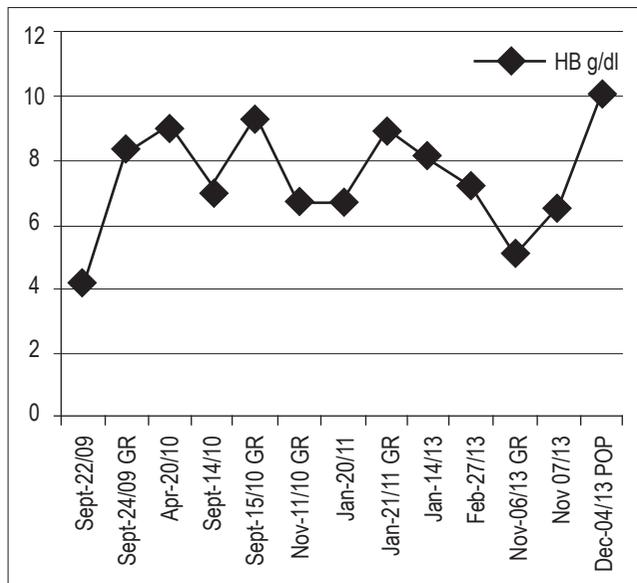
In May 2012, the gastroenterologist study performed capsule endoscopy which found varicose veins in the distal duodenum and proximal jejunum and thickened villi of undetermined nature. Lymphadenopathy and the hookworms were found.

In June 2012, a new episode of melena occurred which was treated with fluids and red blood cell transfusions.

The gastroenterology department considered the possibility of surgery in late 2012 but was unable to perform

it due to administrative problems with the surgical board. Doppler echography of the spleen and portal region had normal results.

The patient returned with a new episode of melena (Hb: 5.1 gr/dl). Given her continued bleeding the patient was again admitted to the hospital and treated with high iron and anti-parasite medication. She was discharged and began treatment as an outpatient again in the first week of November 2013 (See Figure 2).



**Figure 2.** Diagram of middle and lower digestive track bleeding. GR = Transfusion of red blood cells

On November 26, 2013 the patient was readmitted for melena (Hb 6.6 W/dl) and was examined by gastroenterologists and general surgeons. It was decided to perform a laparotomy which found a normal liver but encountered a venous vascular malformation 15 cm from the angle of Treitz. It compromised the entire wall and divided it into two segments about 4 cm in length. The compromised part of the jejunum was resected and rebuilt with a lateral-lateral anastomosis (Figures 3 and 4).

### PATHOPHYSIOLOGY OF ECTOPIC VARICES (EV)

The appearance of dilated jejunal veins or ectopic varices (EV) has been explained in several ways:

1. It has been suggested that EV without the presence of portal hypertension is related to intestinal surgery in which the anastomoses connect the systemic drainage structures to portal drainage structures. This type of procedure may facilitate the appearance of ectopic varices. Examples of such procedures are pancreaticodu-

denectomies with resection of portal veins, colectomies in patients with primary sclerosing cholangitis who suffer from ulcerative colitis, the development of varices of ileostomies, and construction of bilio-entero-gastrostomies (17). At sites of tissue adhesion or surgical stenoses, arterial-venous fistulas secondary to trauma are also thought to be factors that facilitate the development of EV (27, 33, 35).

The risk of EV is higher if the patient's surgical history involves portal circulation or stenosis of the stoma, and it is also higher among patients with a history of surgery who subsequently develop cirrhosis and portal hypertension (17, 35, 29).

It has been found that the greater the size of the EV, the greater the chance of bleeding (16).

2. If the patient does not have portal hypertension or a history of surgery, congenital anomalies of the venous system such as lymphoid nodular hyperplasia, hepatocellular carcinoma and idiopathic anomalies have been suggested as possible causes (25, 27, 34).
3. The presence of EV is most often described in connection with patients who have cirrhosis associated with portal hypertension or portal vein thrombosis.



**Figure 3.** Ectopic varices (EV) in the proximal jejunum



**Figure 4.** Peritoneal ectopic varices

Ectopic varices (EV) related to portosystemic collateral veins can appear anywhere except in the gastroesophageal region (23). Ectopic varices include isolated type II gastric varices located in the antrum or corpus around the pylorus, in the abdominal wall, or in the peritoneal space. It is estimated that up to 8% of patients with portal hypertension may have ectopic varices (17). EV occur most frequently in the duodenum followed by the jejunum ileum, colon, rectum, biliary tree, ovarian circulation system and the peritoneum. Ectopic varices have also been described in those patients with cavernous degeneration or thrombosis of the portal vein (16, 17, 28, 30, 32, 33, 34).

They can develop in any part of the intestinal or biliary circulatory system as the result of short circuits in the portal system due to high blood pressure. Congestion in upper splanchnic circulation increases susceptibility to lesions due to impairment of oxygenation and ischemia (16, 21, 29).

De Palma has defined these changes as enteropathy associated with portal hypertension which may present as inflammatory lesions (erythema, granular lesions, and friable lesions) and vascular lesions (redness, lesions that appear to be telangiectasia, angiodysplasia or varicose veins). Patients with portal hypertension with Child C classification, large esophageal varices and superficial changes in the mucosa of stomach lining develop EV with a frequency between 5.5% and 11% (20).

EV associated with previous histories of ligation or sclerotherapy for esophageal varices has also been encountered (24).

Ectopic varices have been divided into luminal and non-luminal varices. The first are easily detectable with endoscopy, and the second are those that are found anywhere in the abdominal cavity or pelvis (16).

A patient with duodenal varices may present hematemesis or massive lower intestinal bleeding. Varicose veins located distal to the duodenum present as melena or hematochezia. Ectopic varices (EV) should be considered in all patients with portal hypertension in which bleeding is not located by upper or lower endoscopy.

Eventually, ectopic varices in patients with acute abdominal pain during laparotomy. They may be diagnosed when a patient goes into shock if they are in areas such as the intestinal wall, falciform ligament, diaphragm, splenic ligament, or the area behind the bladder. Ectopic varices in these locations can explain bleeding into the peritoneal cavity but often can be fatal (16).

In other cases ectopic varices are diagnosed when patients with chronic anemia are studied and found to have intestinal bleeding or when they test positive for occult bleeding (16).

## TREATMENT OF ECTOPIC VARICOSE VEINS (EV)

There are six types of treatment for EV depending on whether or not they are related to portal hypertension: endoluminal, conventional angioplasty to create a thrombus, balloon angioplasty, angioplasty to treat sclerosis, angioplasty through collateral vessels, transjugular intrahepatic portosystemic shunts (TIPS) and surgery.

The endoluminal treatment to control bleeding uses nylon miniloops to tie off the varices. Cyanoacrylate has also been applied directly to varices to temporarily control bleeding (37, 38).

Treatment with balloon angioplasty involves using a balloon to occlude drainage through the ectopic veins followed by application of haptoglobin to prevent kidney damage and then application of a sclerosing agent (ethanolamine oleate) to achieve sclerosis of the varices (41).

Other methods use direct embolization of varices with coils (coil embolization) access varices through dilated superficial veins (35, 36).

A study of seven hundred and fifty procedures to place TIPS in patients with portal hypertension was found in the literature. Of these, twenty-eight were placed in patients with associated ectopic varices. Twelve were rectal, eight were related to a stoma, four were duodenal, and four were placed in unidentified locations. TIPS were placed after the failure of endoluminal therapies to control bleeding. TIPS placement controlled bleeding in 60% of cases, with a 22 percent recurrence rate for bleeding. In some cases the recurrence was due to shunt dysfunction. The status of liver function markedly influenced results as the Child C category patients did not respond as well to this therapy (40).

Surgical treatment by enterectomy of the area affected by can also be used in situations in which there is hypertension and thrombosis of the portal vein but access for angioplasty is limited (34).

Treatments for EV related to portal hypertension are most frequently mentioned in the literature because this combination is found most often in experience since EV without portal hypertension only occurs in isolated case reports and no studies of a series of such cases exists.

## DISCUSSION

Ectopic varices (EV) in the proximal intestine that are not associated with portal hypertension are a rare entity. Reports of this condition are isolated and there are no series that reveal its pathophysiology.

There are changes in the mucosal surface associated with portal hypertension due to cirrhosis which are different from what are commonly described as esophageal varices. Most of these alterations are nonvascular as evidenced by a recent study in which 55 patients diagnosed with cirrhosis and portal hypertension were included. Video capsule endoscopy was used to study them. It found that 67% suffered from gastrointestinal abnormalities: 32 from erythema 32 (53%), 10 from erosion (17%), nine from angiectasia (15%), and four from varices (7%), and four from villous edema (7%). The majority of the lesions were located in the proximal and middle jejunum. The most significant association found between these lesions and physical examination was the presence of ascites (21).

Ectopic varices were identified in 7% of these patients. Although this is a small percentage, we have to consider this diagnosis in patients with cirrhosis where bleeding cannot be attributed to the persistence esophageal varices.

A recent review in PubMed looked at cases of EV in the small bowel that occurred between 1951 and 2003. The average patient age was 52.9 years. The study found an association with previous abdominal surgery in 84.2% of the cases. The treatment used in 30 of the 57 cases (52%) was enterectomy. Of these 30 cases, 26 (86%) had portal hypertension. There is no information in the study about whether the other patients had portal hypertension (34).

Shiv and Kumar discuss a series of 1,128 cases in which EV was found in the jejunum and ileum: 4.6% of these patients were found to have portal hypertension (30).

Based on this data some authors recommend suspecting EV whenever a patient with a history of previous abdominal surgery and portal hypertension presents hematochezia without hematemesis (36).

EV without portal hypertension, as in the case described above, is even rarer. There are very few reports in the literature. Those that have been published attribute EV without portal hypertension to inherited vascular disorders or even to idiopathic causes (33).

Developing techniques such as capsule endoscopic and enteroscopy may identify these lesions more frequently. In this case the varices were identified with endoscopic capsule (Figures 5, 6 and 7).

Because of the very low frequency of occurrence of these lesions, whether or not there is portal hypertension doctors do not easily take them into consideration when making a differential clinical diagnosis.

## CONCLUSIONS

1. Bleeding EV without portal hypertension is rare and without a satisfactory pathogenesis.



Figure 5. Capsule Endoscopy Images 1

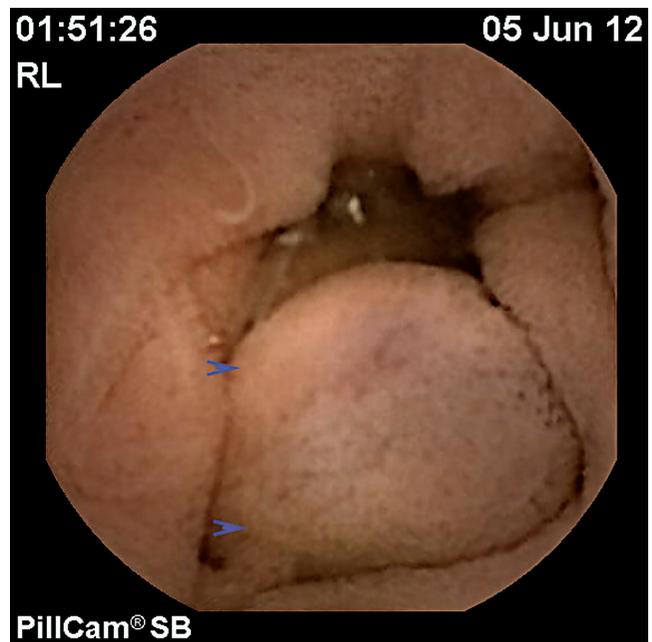


Figure 6. Capsule Endoscopy Images 2

2. A BUN/creatinine ratio greater than 33 may be useful for diagnosing the presence and location of suspected obscure gastrointestinal bleeding.
3. Upper gastrointestinal bleeding in patients with portal hypertension can be caused by ectopic varices (EV).



Figure 7. Capsule Endoscopy Images 3

4. Bleeding EV should be suspected if there is melena without hematemesis in patients with a history of portal hypertension and/or abdominal surgery.
5. Developing new methods such as video-capsule endoscopy and enteroscopy are important for the diagnosis of EV.
6. Endoscopic therapeutic methods for treating EV are similar to those for treatment of esophageal varices but differ in size, location of lesions (highly variable and less than 5% in the duodenum and proximal jejunum), and the need for experience in implementation. All of this makes it difficult to predict the outcome. Therapeutic radiological methods require highly trained staff.
7. In our opinion, surgery is a viable alternative that should be analyzed in depth by clinicians and surgeons.

## REFERENCES

1. Raju G, Gerson L, Lewis B, American Gastroenterological Association (AGA) Institute Technical. Review on obscure gastrointestinal bleeding. *Gastroenterology* 2007; 133: 1697-1717.
2. Rondonotti E, Villa F, Mulder C, Maarten J, de Franchis R, Small Bowel capsule endoscopy in 2007 Indications, risk an limitations. *World J Gastroenterol* 2007; 13 (46):6140-6149.
3. Farrel J, Friedman L, Review article: The management of lower gastrointestinal bleeding. *Aliment Pharmacol Ther* 2005; 21: 1281-1298.
4. ASGE. The role of endoscopy in the management of obscure GI bleeding *Gastrointestinal Endosc* 2010; 72(3): 471-479.
5. Barnert J, Messman H. Diagnosis and management of lower gastrointestinal bleeding. *Nat Rev Gastroenterol and Hepatol* 2009; 6: 637-646.
6. Mitchell S, Schaefer C. A New View of Occult and obscure gastrointestinal bleeding. *Am Fam Physician* 2004; 69: 975-881.
7. Rockey D. Gastrointestinal Bleeding. En *Sleisenger and Fordtrand's. Gastrointestinal and liver disease*. 8<sup>th</sup> edition. Saunders: Elsevier; 2006. p. 255-299.
8. Thomas O, Kovacs G, Jensen D. Lower gastrointestinal bleeding. En *Hawkey C, Bosh J, Richter J, Garcia-Tasao G. Text book of Clinical Gastroenterology and Hepatology*. Wiley Black Well; 2012. p. 132-138.
9. Lisa L, Lower GI. Bleeding: Epidemiology and Diagnosis. *Gastroenterol Clin N Am* 2005; 34: 643-664
10. Chalasani N, Clark W, Wilcox CM. Blood Urea Nitrogen to creatinine concentration in gastrointestinal bleeding: A reappraisal. *Am J Gastroenterol* 1997; 92: 1796.
11. May A, Nachbar L, Schneider M, Christian E. Prospective comparison of push enteroscopy and push- and -pull enteroscopy in patients with suspected small-Bowel bleeding. *Am J Gastroenterol* 2006; 101: 2016-2024.
12. Arakawa D, Ohmiya N, Nakamura M, Honda W, Shirai O, Itoh A, Hirooka Y, Niwa Y, Maeda O, Ando T. Outcome after enteroscopy for patients with obscure GI bleeding: diagnostic comparison between double-balloon endoscopy and videocapsule endoscopy. *Gastrointest Endosc* 2009; 69; 4: 866-74.
13. Monsanto P, Almeida N, Lerias C, Figueredo P, Gouveia H, Sofia C. Is there still a role for Intraoperative enteroscopy in patient with obscure gastrointestinal bleeding? *Rev Esp Enferm Dig* 2012; 104: 190-6.
14. Shiro O, Aoyama T, Imagawa H, Shishido T, Kasuaki C. Effectiveness of polaprezinc for low-dose aspirin-induced small-bowel mucosal injuries as evaluated by capsule endoscopy: a pilot randomized controlled study. *Gastroenterology* 2013; 13: 108.
15. Galiano M, Cepeda R, García F. Angiodisplasias de intestino delgado, presentación de dos casos. *Rev Colomb Gastroenterol* 2004; 19: 269-276.
16. Ahmed H, Khalid Al, Kahtani Al, Fadda M. Updates in the pathogenesis, diagnosis and management of ectopic varices. *Hepatol Int* 2008; 2: 322-334.
17. Brechman T, Wolf S, Volkmar N, Markus R. Gastrointestinal bleeding 30 years after complicated cholecistectomy. *World J Gastroenterol* 2010; 16(37): 4747-4750.
18. Saeki Y, Ide K, Kakisawa H, Ishikawa M, Tashiro H, Ohda H. Controlling the bleeding of jejunal varices formed at the site of choledochojejunostomy: report of two cases and a review of literature. *Surg Today* 2013; 43 (5): 550-5.
19. Watanabe N, Toyonaga A, Seichiro K, Takashimizu S, Kazuhiko O, Kokubo S, et al. Current status of ectopic varices in Japan: Results of a survey by the Japan Society for Portal Hypertension. *Hepatol Res* 2010; 40: 763-776.

20. De Palma G, Rega M, Masone S, Persico F, Siciliano S, Patrone F, Matantuono L, Persico G. Mucosal abnormalities of the small bowel in patients with cirrhosis and portal hypertension: a capsule endoscopy study. *Gastrointest Endosc* 2005; 4: 529-34.
21. Aoyama T, Oka S, Aikata H, Nakano M, Watari I, Neshiro N, et al. Small Bowel abnormalities in patients with compensated liver cirrhosis. *Dig Dis Sci* 2013; 58: 1390-1396.
22. Sandeep K, Dennis A. Occult massive Hemorrhage in a patient with cirrhosis. *Ann Am Thorac Soc* 2013; 10: 160-162.
23. Woong C, Kim S, Woong H, Yun L, Sung J, Sup H, Kim A, et al. A case of variceal bleeding from jejunum in liver cirrhosis. *Clin and Mol Hepatol* 2013; 19: 78-81.
24. Ohtani T, Kajiwara E, Suzuki N, Kawasaki A, Sadoshima S, Sakata H, Sasaguri Y, Onoyama K. Ileal varices associated with recurrent bleeding in a patient with liver Cirrhosis. *J Gastroenterol* 1999; 34(2): 264-8.
25. Yamada A, Watanabe H, Shuntaro O, Sugimoto T, Kondo S, Ohta M, Togo G. Surveillance of small intestinal abnormalities in patients with hepatocellular carcinoma: A prospective capsule endoscopy study. *Digest Endosc* 2011; 23: 124-129.
26. Kastanakis M, Anyfantakis D, Katsougris N, Bobulakis E, Masive gastrointestinal bleeding due to isolated jejunal varices in a patient without portal hypertension. *Int J Surg* 2013; 4(5): 439-441
27. Bhagwat S, Borwankar S, Ramadwar R, Naik A, Gajaree E. Isolated jejunal varices. *J Postgrad Med* 1995; 41: 43-4.
28. Joo Y, Kim S, Choi S, Rew J, Kim H. Massive gastrointestinal bleeding from jejunal varices. *J Gastroenterol* 2000; 35(10): 775-8.
29. Ambiru S, Nakamura S, Mandai Y, Sato T, Kuwahara T, Yokosuka O. Ectopic ileal varices associated with recurrent bleeding: report of case. *Surg Today* 2011; 41(3): 448-52.
30. Shiv S, Chandan K, Kumar N. Ectopic varices. *Clin Liv Dis* 2012; 5: 167-172.
31. Ostrow B, Balnchard R, Bledding small-bowel varices. *Can J Surg* 1984; 27(1): 88-9
32. Yuki N, Kubo M, Kasahara A, Hayashi N, Ito T, Kamada T. Jejunal varices as cause of massive gastrointestinal bleeding. *Am J Gastroenterol* 1992; 87(4): 514-7.
33. Naofumi E, Shigeaki A, Masao H, Takajashi M, Masatoshi T, Atsushi T. Jejunal varices as cause of massive Gastrointestinal bleeding a case report. *Kur Med Journal* 1998; 45 (2): 227-230.
34. Ueda J, Yoshida H, Mamada Y, Mizuguchi Y, Shimizu T, Matzumoto S, Ishikawa Y, Kakinuma D, et al. Successful emergency enterectomy for bleeding ileal varices in a patient with liver cirrhosis. *J Niponn Med Sch* 2006; 73(4): 221-5.
35. Koo S, Soung J, Jae J, Tae L, Seong R, Kim H, Kim J, Kim Y. Jejunal Variceal Bleeding Successfully treated with percutaneous coil embolization. *J Korean Med Sci* 2012; 27: 321-324.
36. Lee-Guam L, Yin-Mei L, Lenny T, Chang S, Sen-Gee L. Percutaneous paraumbilical embolization as an unconventional and successful treatment for bleeding jejunal varices. *World J Gastroenterol* 2009; 15(30): 3823-3826.
37. Ghindrim G, Mishim I, Zastavitsky G. Ruptured duodenal varices successfully treated by mini-loop Ligation: report a case. *Chirurgia* 2010; 104: 625-629.
38. Nakata M, Nakata W, Isoda N, Yoshizawa M, Sugimoto H. Percutaneous retrograde sclerotherapy for refractory bleeding of jejunal varices: direct injection via superficial epigastric vein. *Cadivasc Intervent Radiol* 2012; 35: 203-6.
39. Koushi H, Kunihiro Y, Toshio D, Takahashi T, Sato M. Ruptured duodenal varices Successfully treated with Balloon-Occluded Retrograde Transvenous Obliteration: Usefulness of Microcatheters. *ARJ* 2003; 181: 725-727.
40. Kochar N, Tripathi D, Mcavoy C, Ireland D, Redhead N, Hayes P. Bleeding ectopic varices in cirrhosis: role of transjugular portosystemic stent shunts. *Aliment Pharmacol Ther* 2008; 28: 294-303.