A Review of Paraneoplastic Syndromes in Gastrointestinal Tumors

Laura Rodríguez P.[1], James Yurgaky S.[2], William Otero R.[3], Michel Faizal[4]

1 Intern in the Faculty of Medicine at the National University of Colombia in Bogotá, Colombia
2 Internist, Endocrinologist and Gastroenterology Fellow at the National University of Colombia and the National University of Colombia Hospital in Bogotá, Colombia
3 Professor of Medicine in the Gastroenterology Unit of the National University of Colombia and the National University of Colombia Hospital and Gastroenterologist at the Foundations Clinic in Bogotá, Colombia. Email: waoteror@gmail.com
4 Professor of Medicine in the Dermatology Unit at the National University of Colombia and the National University of Colombia Hospital in Bogotá, Colombia

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Abstract
Paraneoplastic syndromes produce tumors at sites distant from themselves and are not physically related to those tumors or to their metastases. Various gastrointestinal tumors may present syndromes or systemic, dermatological, hematological, renal, neurological and other manifestations. This study reviews these manifestations.

Keywords
Paraneoplastic syndrome, gastrointestinal, tumors.

INTRODUCTION

Paraneoplastic syndromes (PNS) are a heterogeneous group of clinical manifestations that occur when a tumor causes damage to a distant organ or system and that are not physically related to the tumor or its metastases. (1) These alterations are independent of the local effect of the tumor, invasion of other organs, nutritional deficits and consequences of antineoplastic treatment. (1, 2) These widely varying clinical manifestations are secondary to substances released by malignant neoplastic cells. (2) These substances include hormones, hormone-like peptides, growth factors and cytokines. (1, 2, 3) In addition, immune responses are also involved. They are initially directed against the new substances or tumor antigens (oncoantigens) but through cross reaction end up injuring normal tissues and finally result in accumulation of immune complexes. (3, 4, 5) The various PNS are classified according to the organ or system they affect as endocrine and metabolic, dermatological, hematological, rheumatological and neurological. (3) This review describes PNS produced by gastrointestinal (GI) tumors.

CACHEXIA ASSOCIATED WITH CANCER (CAC)

Cachexia associated with cancer (CAC) are the most frequently occurring and best-known PNS. They increase morbidity and mortality rates and result in progressive loss of skeletal muscle mass with or without loss of adipose tissue. (6, 7) The main criterion for diagnosis is involuntary loss of more than 5% of a person's usual weight within six months (Figure 1). (7)

CAC occurs in 50% of all cancer patients and increases progressively as the disease advances. (6, 8, 9) In the last two weeks of life, it is found in more than 86% of patients with cancer. (6) It is more frequent in patients with gastrointestinal and pancreatic adenocarcinoma where its incidence is 87% to 90%. (7, 10) Per se, death occurs in 20% of cases. (6, 8, 9, 10) The pathogenesis of CAC is multifactorial, but the inflammatory cytokines induced or produced by the tumor play a fundamental role. (7) Among these tumorkines, the tumor necrosis factor alpha (TNF-α), IL-1, IL-6 and interferon stand out. (6, 7, 8) These substances produce systemic inflammation, (6, 7, 8, 9, 10) anorexia, (6, 9, 8, 10, 11, 12) increases of brown adipose tissue, (9) and alterations of lipid, protein and carbohydrate metabolism. (8) In addition, they produce increased energy expenditure. (6) Other mediators that have been found include muscle uncoupling protein (UCP3) in humans and IL-6 in animal models. (6, 10)

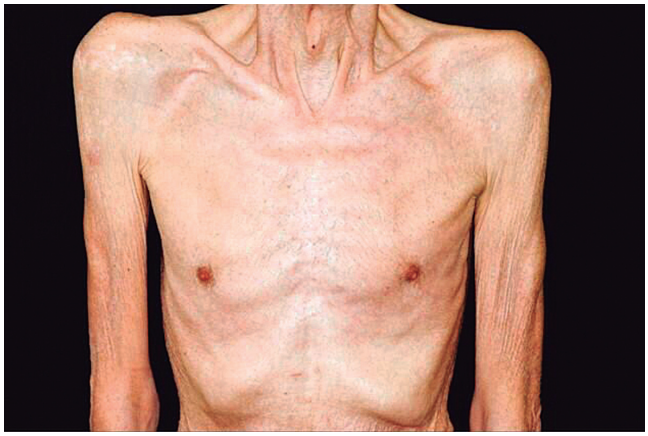

Figure 1. Cachexia. Taken from: http://tomasalud.com/archivos/743

DERMATOLOGICAL PARANEOPLASTIC SYNDROMES

Dermatological paraneoplastic syndromes are the second most frequent type of paraneoplastic syndrome after the endocrine syndrome. (13) They act as markers for GI tumors which in many cases allow timely detection. (14) The Curth criteria must be met for diagnosis of the syndrome: absence of direct infiltration of malignant cells, simultaneous initiation with the tumor, parallel development, and exclusion of genetic syndromes. (13, 15) The most important dermatological alterations are acanthosis nigricans (AN), paraneoplastic acrokeratosis, acquired hypertrichosis lanuginosa, paraneoplastic pemphigus, paraneoplastic dermatomyositis, erythema gyratum repens, cutaneous leukocytoclastic vasculitis, Sweet's Syndrome, pityriasis rotunda, and erythroderma.

Acanthosis Nigricans (AN)

Acanthosis nigricans consists of velvety plaques with hyperpigmented symmetrical areas of relief located in intertriginous sites such as armpits, the neck, the anal-genital area, and below the breasts (Figure 2). (14, 15, 16) In some cases, pedunculated skin projections called acrochordons and hypopigmented papillomatous lesions membranes are found on mucous membranes. (17) In 35% to 50% of cases, the oral mucosa is compromised, (1, 18) although other mucous membranes may also be compromised. (14, 15) In 41% of cases, it is associated with pruritus. (19)

Prevalence ranges from 7% to 74% depending on the population. (16) This alteration can be classified as benign, associated with obesity, syndromic, malignant, acral, unilateral, drug-induced and mixed. (16, 17) The malignant form accounts for 20% of cases and occurs in two out of 12,000 patients with cancer. (20, 21) Unlike the benign form, it usually appears in people older than 40 years of age without family associations. (13, 17) It starts spontaneously, is extensive and progresses rapidly. (14, 15) In addition, it follows a course parallel to the cancer and is an indicator of recurrence. (17)

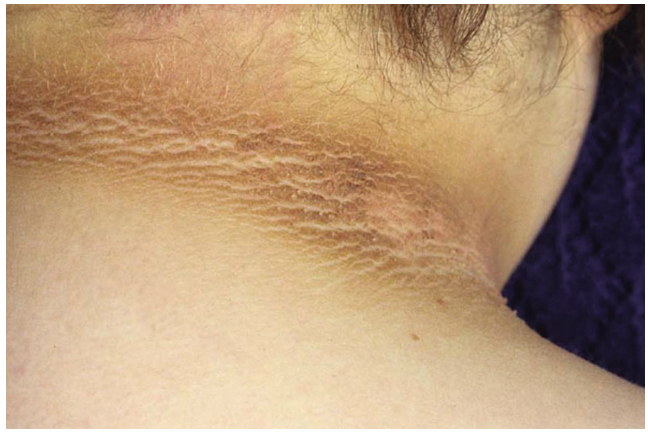

Figure 2. Acanthosis nigricans. Taken from: http://www.sanar.org/cuidado-de-la-piel/acantosis-nigricans

Ninety percent of malignant AN cases are associated with abdominal neoplasms, 70% to 90% of which are which are gastrointestinal. (13, 22) Gastric adenocarcinoma, the most frequent, accounts for 55% to 61% of these cases but accounts for 73% in China. (1, 13, 22, 23) Other neoplasms that are also associated with this alteration occur in the esophagus, the pancreas, the liver and the bile duct. (13) The alteration is detected simultaneously with the tumor in 30% and 60% of cases, but it can be found before neoplasia in 17% and 33% of cases. (16, 22) Therefore, the

detection of this lesion warrants a thorough investigation, and even more so in patients older than 40 years of age who have another paraneoplastic sign such as tripe palm (Figure 3) or the Leser-Trélat sign (Figure 4) and who do not have any benign pathology that might explain the lesions such as obesity or other endocrinopathies. (13, 14, 16, 22)

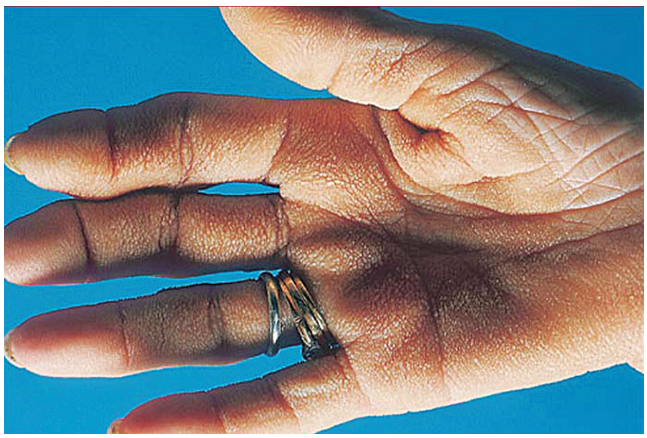

Figure 3. Tripe palms. Taken from: http://www.handresearch.com/news/hands-on-cancer-hand-palm-cancers.htm

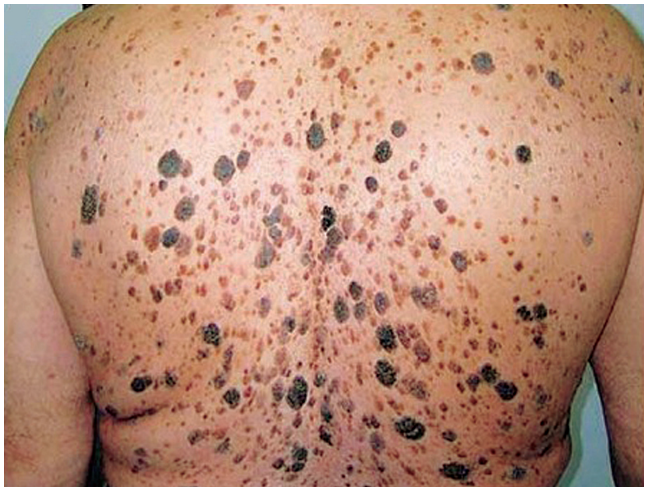

Figure 4. Sign of Leser-Trélat. Taken from: https://quizlet.com/69755928/medi-tqs-flash-cards/

Acanthosis nigricans, palmoplantar keratoderma (also known as velvet palms or tripe palms) and the Leser-Trélat sign have been frequently related to each other. Although their etiologies are unknown, they are considered to have the same pathophysiological mechanism through the production of growth factors by the tumor that interact with the epidermal growth factor (EGF) or its receptor. (13, 14, 15, 22) Tripe palm consists of rough epidermal thickening on the palms with prominent dermatoglyphs (pachydermatoglyphia) (15). It is associated with malignancy in 90% of cases, and the most frequent tumor is gastric adenocarcinoma. (16) Onset is simultaneous in 80% of cases, prior to appearance of tumor in 12%, and after tumor development in 8%. (23)

The sign of Leser-Trélat is sudden onset or sudden increase in size and/or number of multiple seborrheic keratoses. (24) When it is associated with malignancy, it is known as the Leser-Trélat syndrome. (24) Among the elderly, seborrheic keratoses are found frequently, so their association with tumors is controversial. (15) In addition, the size and numbers of gastrointestinal tumors also increase with age and may be independent coincidental alterations in this age. (15) There is no dispute, however, that they are causally associated in young people for whom this is a true paraneoplastic syndrome. (13) The most frequent tumor is gastric adenocarcinoma (45%). (25) Other tumors associated with the Leser-Trélat sign are those of the colon and rectum. (13) This sign is unusual in tumors of the esophagus, duodenum, pancreas, gallbladder, and liver, as well as in extra-digestive neoplasms such as those of the lung, prostate, bladder, kidney, ovary and melanoma and lymphoproliferative neoplasms. (13, 14) When present, the patient's prognosis is poor. (15) Itching develops in 26% to 51% of the patients with this syndrome. (19, 26)

Paraneoplastic Acrokeratosis (Bazex Syndrome) (Figure 5)

Bazex Syndrome is a rare symmetric acral psoriasiform dermatosis characterized by purplish, peeling skin lesions with well-defined edges that compromise the nasal and malar surfaces, hands, feet, ears (1, 13, 15, 27) and the nail region (paronychia, onychorhexis and onycholysis). (17) Locations of the lesions are different than those of psoriasis. (17) Bazex syndrome is divided into three clinical stages: asymptomatic neoplasm in which lesions only affect the most distal regions; neoplasm has local symptoms and prolonged lesions; and advanced neoplasms and lesions which may compromise the trunk. (17) It has been associated with malignancy in every case described. (27) In 80% of the cases, the underlying tumors are squamous cell carcinomas of the upper digestive tract and pulmonary airway. (1, 13, 15, 27) These tumors have had the following distribution: oropharynx and larynx (48%), lung (17%), esophagus (10%) and unknown location (16%). (13, 14) In addition, other associated tumors such as gastric adenocarcinoma, colon cancer and hepatobiliary cancer have been reported. (14) Bazex Syndrome is most common among men over the age of 40. (14) Occasionally, it is associated with itching (18%). (28) Although it is related to a poor prognosis (27), it has been found that it precedes the tumor in 65% of cases by an average time of one year. (13, 29, 30) With the treatment of the tumor, this lesion improves in 90%

to 95% of the cases and may reappear if the tumor recurs. Recurrence is a marker for relapse into malignancy. (15)

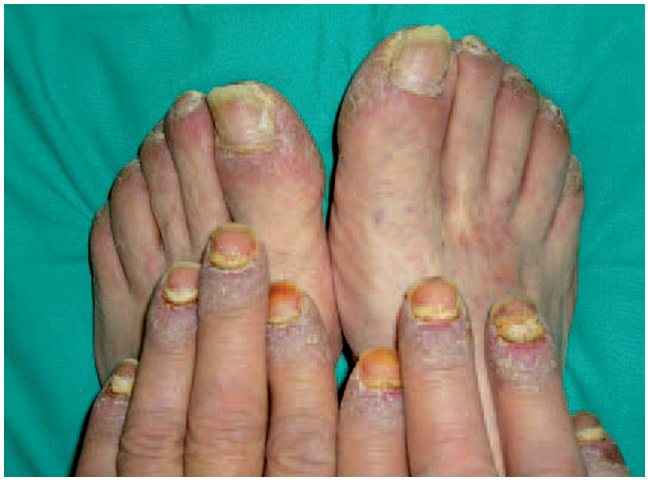

Figure 5. Paraneoplastic acrokeratosis or Bazex syndrome. Taken from: http://apps.elsevier.es/watermark/ctl_servlet?_f=10&pident_articulo=13136503&pident_usuario=0&pcontactid=&pident_revista=103&ty=112&accion=L&origen=zonadelectura&web=www.elsevier.es&lan=es&fichero=103v100n04a13136503pdf001.pdf

Acquired hypertrichosis lanuginosa

Acquired hypertrichosis lanuginosa consists of rapid development of long, fine unpigmented hair especially on the face (Figure 6). (13) It occurs most frequently in women and is considered to result from stimulation of hair follicles by cytokines or growth factors secreted by the tumor. (13, 14) The principal underlying digestive tumors are located in the colon and rectum although lung carcinoma is the most frequent cause. (31, 32) The condition develops as much as two and a half years prior to diagnosis, (13) so by the time of diagnosis the tumor has already metastasized. This is the reason it is considered to indicate poor prognosis. (14) It can coexist with malignant AN and with CAC. (13, 14) Other tumors that cause acquired hypertrichosis lanuginosa include cancer of the pancreas, gallbladder and breast. (13, 32)

Paraneoplastic Pemphigus (Figure 7)

Paraneoplastic pemphigus is a mucocutaneous acantholytic bullous disease. (15) The paraneoplastic form most often compromises the mucous membranes and affects the eyes with pseudomembranous conjunctivitis in 70% of cases. (18) It can involve the trunk, limbs, palms, soles, oral mucosa, esophagus and genitals. (14, 15) It is believed to be the result of a cross-reaction between antibodies and desmosomes and hemidesmosomes. (33) There is no known neoplasia in one third of these patients, (33) but the majority occur in cases of hematologic malignancies. (84%) However, in 10% of these cases it is associated with adenocarcinoma of the colon or pancreas. (15, 18)

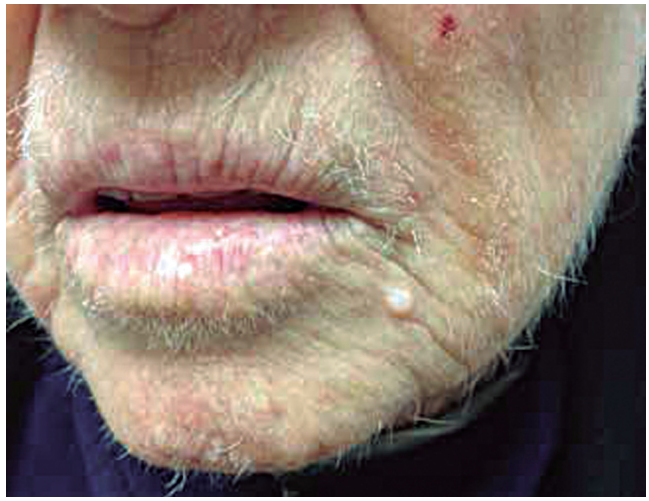

Figure 6. Paraneoplastic hyperthyroidism lanuginosa. Taken from: http://www.medigraphic.com/pdfs/cosmetica/dcm-2015/dcm153f.pdf

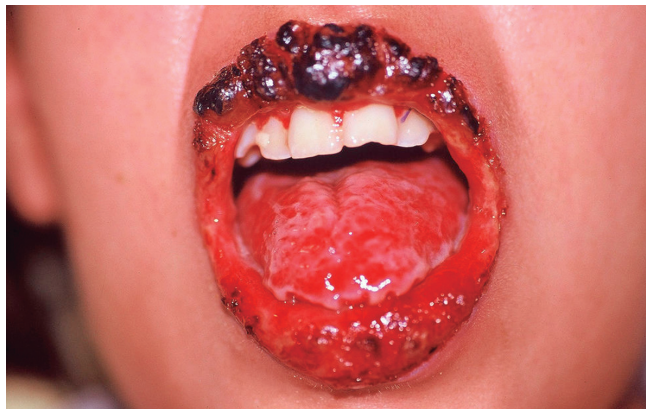

Figure 7. Paraneoplastic pemphigus. Taken from: http://actasdermo.org/en/pnfigo-paraneoplsico-sndrome-multiorgnico-autoinmune-paraneoplsico-/articulo/S0001731010003339/

Paraneoplastic Dermatomyositis

Paraneoplastic dermatomyositis is similar to classical dermatomyositis (DM), an idiopathic inflammatory myopathy which has an incidence of 5 to 10 cases per 100 000 inhabitants. (34) When it appears in people over 40 years of age, it is associated with malignant neoplasms, including gastrointestinal neoplasms, in 15% to 40% of cases. (15, 35) Clinically, there is proximal muscle weakness, periorbital heliotrope, reddish to purplish Gottron's papules on knuckles and phalangeal joints, the shawl sign of violet areas with telangiectasias in areas exposed to the sun (poi-

kilodermatous photosensitivity), and hyperkeratosis on the palms. (14, 17) Also, alterations such as thickening of the cuticle of the nails, periungual telangiectasias, ragged cuticles (Samitz sign) are sometimes seen. (17) Dysphagia occurs in 10% to 20% of patients. (34) The diagnostic criteria include skin and muscle alterations, electromyography, muscle biopsies and muscle enzymes. (17) Figure 8 shows a patient with symmetrical violet erythema on the upper eyelids which is known as a heliotrope rash. In addition, the patient has facial erythema and the shawl sign of violet erythema in the upper region of the thorax and arms.

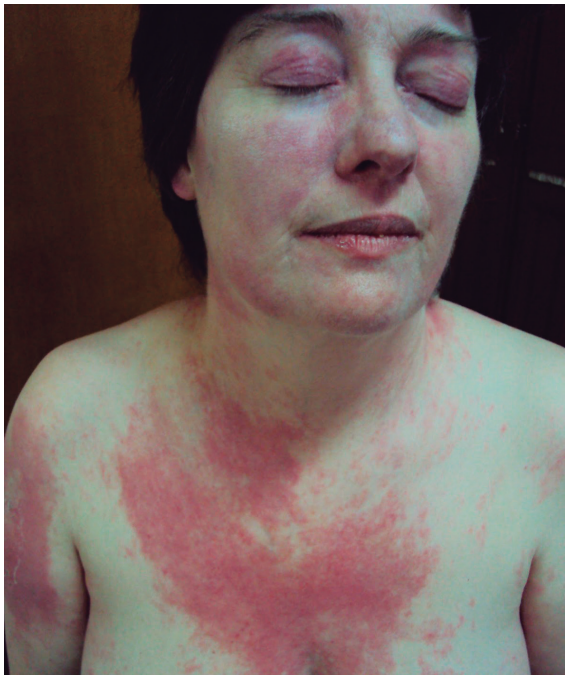

Figure 8. Dermatomyositis. Taken from: http://www.elrincondelamedicinainterna.com/2010/11/exacerbacion-cutanea-de-dermatomiositis.html

Considering the strong association of paraneoplastic dermatomyositis with tumor pathologies, an exhaustive in search for tumors over three to five years following its diagnosis has been recommended for these patients. (36). The most frequent tumors are colorectal adenocarcinomas (5%) and lung adenocarcinomas (15%). (14) In Japan, gastric cancer is found in up to 25% of patients. (14) Other neoplasms that have been associated with paraneoplastic dermatomyositis are tumors of the pancreas, (37) breast, ovaries, nose and pharynx, and non-Hodgkin's lymphoma. (15, 38, 39) Only two cases of associated esophageal tumors have been reported. (40, 41) Predictive factors for malignant neoplasms include patient age over 50 years, male gender, ulcers, skin necrosis, dysphagia, increased erythrocyte sedimentation rates (ESR), increased amounts of C-reactive protein (CRP), (14) anti-155/140 antibodies, (42) and elevated serum creatine phosphokinase, (which has the highest specificity). (14, 17)

Autoantibodies against Jo-1, Mi-2 and/or SRP are characteristic of DM that does not present with malignant neoplasms, so their absence predicts a hidden malignancy. (14, 15, 39).

Erythema Gyratum Repens

Erythema gyratum repens consists of erythematous stripes with symmetrical wavy edges of peeling itchy skin that forms concentric rings (Figure 9). (13, 17, 25) It grows rapidly at about one cm per day. The diagnosis is confirmed when lesions are associated with eosinophilia. (17) Eighty percent of these patients have malignant tumors, so it is of great importance for all cases to be investigated for neoplasms. The most frequent are lung cancer (32%) followed by cancer of the esophagus (8%) and breast cancer (6%). Cancers of the colon, stomach, rectum and pancreas have also been observed. In 80% of patients, this lesion is found four to nine months before diagnosis of the tumor. (13, 25)

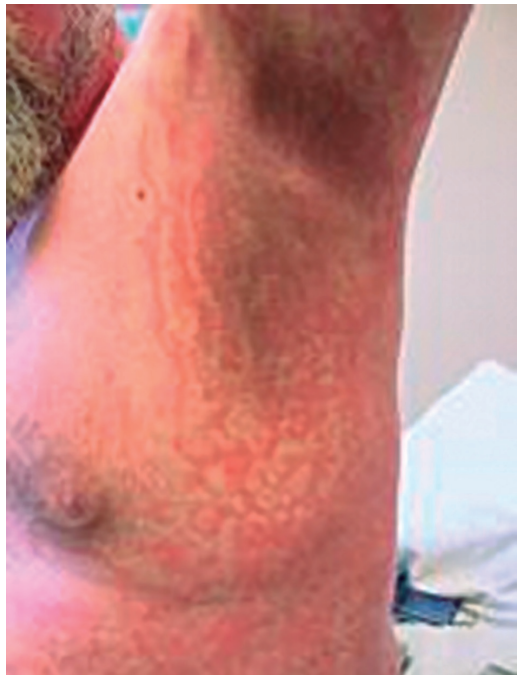

Figure 9. Eritema gyratum repens. Taken from: https://www.onlinedermclinic.com/archive/erythema-gyratum-repens

Cutaneous Leukocytoclastic Vasculitis

Cutaneous leukocytoclastic vasculitis, also known as allergic vasculitis, has been associated with neoplasms more often than other forms of vasculitis. It is generated

by infiltration of small blood vessels by accumulations of antitumor immune complexes or by cross-reaction. (1, 3) Clinically, palpable purpura or red wine-colored papules are present. They progress to violaceous color and finally to hyperpigmentation (Figure 10). They are associated with pain and pruritus and are located predominantly in the lower limbs. (1) Although a skin biopsy is the gold standard, clinical and paraclinical histories should be evaluated, and searches should be done for only the most frequent tumors according to the patient's age. (3, 17) The most frequent malignant tumors are hematological neoplasms and carcinomas of the urinary and gastrointestinal tracts and the bronchial tubes (20% -26%). (1, 3)

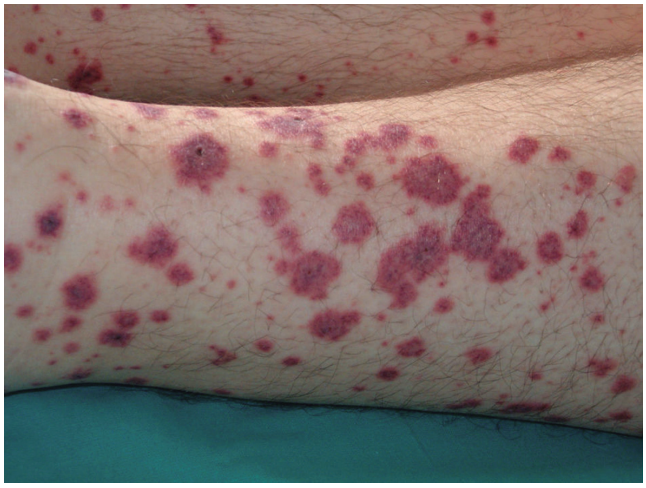

Figure 10. Cutaneous leukocytoclastic vasculitis. Taken from: http://www.actasdermo.org/es/alertas-cutaneas-malignidades-sistemicas-parte/articulo/S000173101200186X/

Sweet's Syndrome

Sweet's syndrome is a rare acute febrile reactive dermatosis associated with neutrophilia that manifests itself with the sudden appearance of painful bright erythematous plaques, nodules, papules, pustules or vesicles located on the face, neck or upper limbs (Figure 11). (13) The paraneoplastic form is more severe, can affect the trunk and lower limbs, presents with fever or low-grade fever, migraine arthralgia of large joints, leukocytosis, neutrophilia and high ESR which improves with systemic corticosteroids. (17, 18) Most causes are benign and include autoimmune diseases, infections and medications, (17) but 10% to 20% of cases are associated with hematological neoplasms. Testicular, colon, rectum, lung, ovarian and prostate tumors have also been found in association with this syndrome. (18)

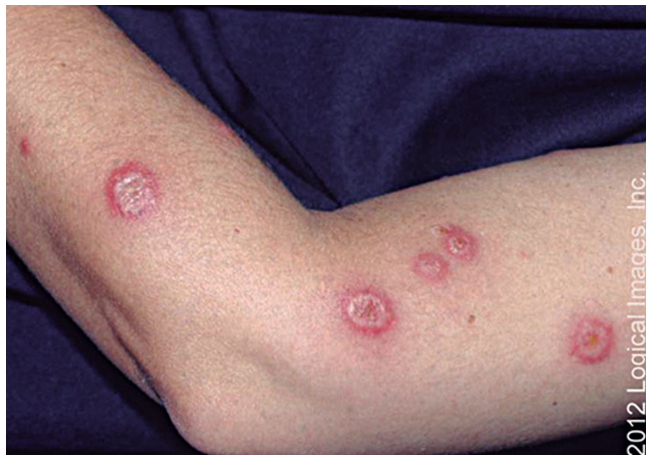

Figure 11. Sweet's syndrome. Taken from: http: //www.elrincondelamedicinainterna.com/2013/03/dermatosis-neutrofilicas.html

Pityriasis Rotunda

Pityriasis rotunda is a rare disease that is characterized by multiple, well-defined, circular, squamous plaques on the trunk. It can be asymptomatic without inflammatory changes but may be hyperpigmented or hypopigmented (Figure 12). (13) It appears in people from 25 to 45 years of age and is associated with chronic diseases such as malnutrition; infections, such as tuberculosis; and neoplasms including hepatocellular, gastric, esophageal, prostate, chronic lymphocytic leukemia, and multiple myeloma. (13, 43)

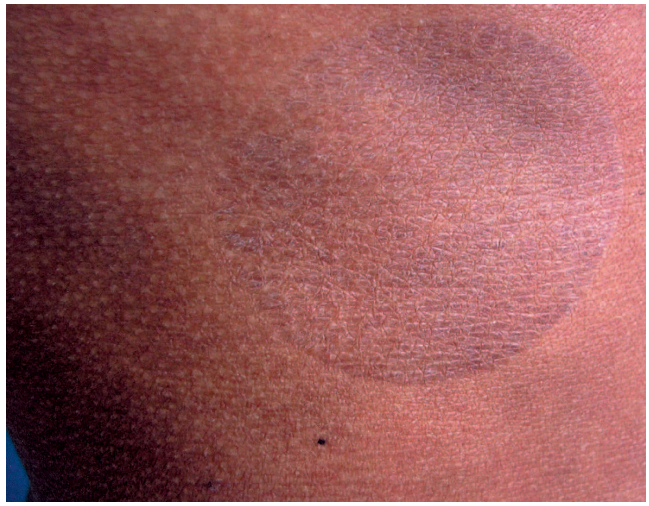

Figure 12. Pityriasis rotunda. Taken from: http://www.scielo.br/pdf/abd/v82n3/v82n03a12.pdf

Erythroderma

Erythroderma is an erythematous skin rash that affects more than 70% of the body surface with impaired blood flow, hemodynamic alterations and loss of proteins and other components. (17) This reactive dermatosis is caused by previous skin conditions, medications, idiopathies and neoplasms. (17) Associated neoplasms include leukemia, lymphoma and gastrointestinal tumors including colorectal, gastric, esophageal and gallbladder cancer. (3) A typical case of erythroderma is shown in Figure 13.

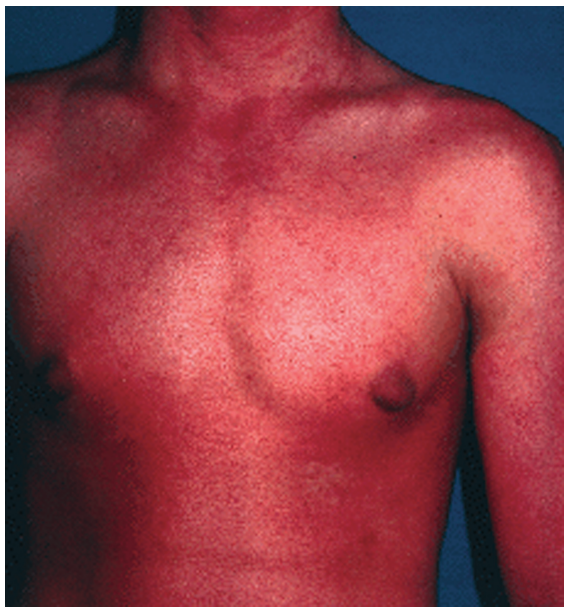

Figure 13. Erythroderma. Taken from: http://www.actasdermo.org/es/eritroqueratodermia-simetrica-progresiva-generalizada/articulo/13014775/

HEMATOLOGICAL PARANEOPLASTIC SYNDROMES

Thrombotic and hemorrhagic complications are the second most common cause of death in patients with cancer. (44) Cancer produces a state of hypercoagulability so that people who suffer from it have double the risk of venous thromboembolism during their lives than do people without malignancies. (45, 46) Pathogenesis involves production of procoagulant substances such as the procoagulant factor of cancer and proinflammatory cytokines by the tumor. (45, 46) Tumors most frequently associated are mucinous carcinoma of the pancreas, lung tumors and gastrointestinal tumors such as gastric tumors. (45).

Ninety-two percent of patients with gastric cancer present hemostatic alterations in laboratory analyses. Of these, 26.8% have clinical manifestations especially in advanced and metastatic stages. (44, 45) Nevertheless, there is a great deal of controversy as to whether a hidden tumor should be sought in patients with a thrombotic event without any associated risk factors. In the first two years following an episode of venous thromboembolism (VTE), between 2.2% and 12% of these patients are diagnosed with a hidden tumor. (47)

The three most common diagnoses of cancer after idiopathic VTE are lung, liver and colorectal cancer (18.3%, 12.3% and 10.9%, respectively). (46) A study published more than 10 years ago found VTE in 15% of patients with cancer. Distribution of cancer types was as follows: pancreas 28%, lung 27%, gastric 13% and colon 3%. (45)

At present, a thorough investigation of coagulation disorders is not recommended even though there have no studies of the usefulness of these studies. (47, 48) Sensitivity in the first two years of routine evaluation is 89% (95% CI: 67% to 99%). (47) These is zero prevalence for people under 40 years of age. (45) Nevertheless, these patients have worse prognoses, and about 44% have metastases. (47, 48) Patients with VTE who benefit most from a search for a tumor are those who do not have other risk factors for thrombosis, (47, 48) those over 40 years of age, (45) those with long life expectancies, those whose VTE is recurrent, and those who have bilateral DVT. (47) The most cost-effective tests are abdominal-pelvic CT scans and mammography. In the SOMIT study, the difference was not statistically significant. (49)

Trousseau Sign or Migratory Thrombophlebitis

Migratory thrombophlebitis is a rare alteration that presents as superficial migratory venous thrombosis affecting the thorax and the upper limbs. (45) It is a warning sign of advanced malignancy, particularly of pancreatic and pulmonary tumors. (50) A few cases of gastric, colon and rectal cancers have been reported. (50, 51)

Paraneoplastic Eosinophilia

Generally, paraneoplastic eosinophilia is asymptomatic.(2, 3) The neoplasms most commonly associated with it are lymphomas and leukemia, but it can also be seen in association with lung, gastrointestinal and gynecological tumors as well as colorectal and stomach cancer, and other alterations such as hemolytic anemia. (3, 52) In squamous cell carcinoma of the esophagus, an acquired inhibitor of factor V of coagulation may appear. (53) This alteration may be asymptomatic or cause life-threatening hemorrhaging. (53) It should be suspected when there is an excessive increase in coagulation times which does not improve when plasma is administered. (53) In other gastrointestinal cancers, leukocytosis has been found, (54, 55) although it is debated whether it really represents a paraneoplastic syndrome.

RENAL PARANEOPLASTIC SYNDROMES

Nephrotic syndrome is reportedly be found in 11% to 22% of patients with cancer. (5, 56) The most frequent are gastric cancer (25% of cases), lung cancer (15% of cases), and lymphoma (10% of cases). (56). Among all patients with cancer, 50% of cases of paraneoplastic nephrotic syndrome are associated with lung and gastro-intestinal cancer. (57, 58) The main underlying renal lesion is membranous glomerulonephritis. (57, 58) Surgical resection of the tumor improves this condition in up to 78% of patients, so it is indicated even if the patient's condition is poor. (56)

Another important pathology is membranous nephropathy, which represents 6% to 22% of cases of renal compromise. The tumors most frequently associated with it are gastrointestinal, lung and prostate cancers. (5) Verification of its paraneoplastic origin requires the following three criteria: improvement with resection, relapse with recurrence and a pathophysiological link. (5) Some characteristics such as the absence of anti-PLA2R1 antibodies, the predominance of IgG1/IgG2 deposits, and the presence of more than 8 inflammatory cells per glomerulus make a hidden neoplasm more likely. (5) When there is proteinuria, the prognosis is poor. (59) Other nephropathies that have been described include immunoglobulin A nephropathy in gastric and esophageal adenocarcinoma. (60) Membranoproliferative glomerulonephritis has also been found together with this tumor along with rapid progression. (61) In colon cancer, the disease has been documented with minimal changes. (61)

ENDOCRINE PARANEOPLASTIC SYNDROMES

The most common paraneoplastic syndromes occur in the endocrine system although they are rare in most gastrointestinal tumors. (13) The most frequent are described below.

Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)

Paraneoplastic syndrome of inappropriate antidiuretic hormone secretion occurs in between 1% and 2% of patients with cancer. Malignant cells secrete antidiuretic hormone (ADH). (3) The syndrome is characterized by hyponatremia (plasma sodium less than 135 mEq/L, serum osmolarity less than 275 mmol/L) and normal blood volume. (3, 62) Generally, it is asymptomatic or presents with mild symptoms such as nausea, weakness and headaches. In some cases, it can cause severe deterioration of consciousness and seizures. (3, 63) Symptoms suggestive of SIADH are urinary sodium higher than 40 mmol/L and/or urinary osmolality over 100 mOsm/kg of water with normal thyroid function and normal serum cortisol. (3, 62) This syndrome has most frequently been linked with small cell lung cancer, but it has also been found in tumors of the gastrointestinal tract. (62, 64-66)

Hypercalcemia of Malignancy

Hypercalcemia of malignancy, found in 20% to 30% of patients with cancer, is one of the most frequent paraneoplastic syndromes. (67) It is an ominous alteration since 50% of patients who develop this condition die within 30 days. (67) Eighty percent of the cases are due to tumor secretion of the peptide related to the parathyroid hormone. (3, 67) It should be suspected in patients with reduced levels of serum parathyroid hormone (less than 20 pg/mL) in the absence of ionized calcium but with a serum calcium level higher than 10.5 mg/dL. This should be corrected with albumin. (62, 67) The symptoms of this syndrome are fatigue, nausea, vomiting, mental alterations, renal failure, hypertension and bradycardia. (3) The syndrome is rarely associated with gastrointestinal tumors, although it has been found in 1.3% of esophageal tumors, especially squamous cell carcinoma. (68)

Cushing's Syndrome

Five to ten percent of the cases of Cushing's syndrome are of paraneoplastic origin while the rest are of non-paraneoplastic origin. (3) When it is of paraneoplastic origin, overproduction of adrenocorticotropic hormone (ACTH) or corticotropin-releasing hormone (CRH) comes from tumor cells. (3) The most important manifestations are arterial hypertension, hypokalemia, hyperglycemia, proximal muscular atrophy, generalized cutaneous atrophy, violaceous stretch marks and reduction of bone mineral density. (3) These patients tend to be thin, unlike those affected by non-paraneoplastic Cushing's syndrome most of whom develop obesity (up to 90% of cases). (3) Extra-pituitary neoplasia should be suspected when ACTH-dependent hypercortisolism is not suppressed with dexamethasone and when hypo-pituitary lesions are not identified in imaging tests. (3, 69) The most frequently associated tumors are pancreatic, small cell lung cancer, bronchial tumors and gastrointestinal neuroendocrine tumors. (70) Other cases have been associated with stomach metastases, squamous cell carcinoma, and esophageal adenocarcinoma (69).

Carcinoid Syndrome

The clinical picture of carcinoid syndrome is characterized by episodes of flushing of the face, neck and upper trunk that lasting one to two minutes; (15) diarrhea, which occurs in 85% of patients with facial flushing; (71) difficult breathing and bronchospasms, (15) and heart valve disease. (70) This syn-

drome occurs in 8% to 10% of patients with neuroendocrine tumors of the midgut derived from enterochromaffin cells. (15) Although tumors occur most frequently in the appendix (50%), the syndrome is found mainly in association with tumors of the jejunum and ileum. When this syndrome is present, the tumor has usually metastasized, especially to the liver. (31) Serotonin is primarily responsible for the clinical picture. (15, 71) Diagnosis is based on detection of 5-hydroxyindolacetic acid in a 24-hour urine test. Sensitivity and specificity are both 80%. (71) Serum chromogranin is also useful, but it is not specific for this syndrome, and the large number of false positives reduces its diagnostic utility. (71)

Another endocrine syndrome associated with gastrointestinal tumors is acromegaly which occurs due to elevation of growth hormone and insulin-like growth factor (IGF-1). (72). Gastric and pulmonary tumors are most frequently associated with acromegaly. (63) Ectopic prolactin production has been found in women with colon cancer. This causes galactorrhea and amenorrhea. When ectopic prolactin production occurs in men, it produces gynecomastia and hypogonadism. (63) Hypoglycemia has been found in association with gastrointestinal stromal tumors (GIST). (72).

PARANEOPLASTIC RHEUMATIC SYNDROMES

Paraneoplastic rheumatic syndromes are infrequently occurring syndromes. The best documented are shown in Table 1.

Table 1. Paraneoplastic rheumatic syndromes

Entities	Associated tumors
Carcinomatous polyarthritis	Neoplasms of the colon, (73) stomach, esophagus and pancreas (37)
Palmar fasciitis and arthritis	Ovarian cancer, gastric cancer, (37), pancreatic, lung and colon cancer (73)
Multicentric reticulohistiocytosis[1]	Lung, gastric, breast, cervix, colon and ovarian cancer (73)
Remitting seronegative symmetrical synovitis with pitting edema (RS3PE)	Adenocarcinoma of the stomach, prostate, pancreas, endometrium, (74) cancer of the rectum (37)
Hypertrophic osteoarthropathy (Bamberger–Marie syndrome)[2]	Intrathoracic tumors: bronchial, pleural and esophageal (77)
Polymyalgia rheumatica[3]	Neoplasms of the colon (3)
Raynaud's phenomenon[4] (Figure 14)	Stomach, lung and ovarian neoplasms; lymphoproliferative disorders (73)

[1] Paraneoplastic in 25% to 31% of cases (73)
[2] Characterized by digital clubbing (Figure 15), acropachy, polyarthralgia and periosteal proliferation (75, 76)
[3] Generally with atypical manifestations (37, 73)
[4] In patients older than 50 years. Clinically, it is asymmetrical and with digital necrosis and appears from 7 to 9 months prior to the diagnosis of the tumor. (73)

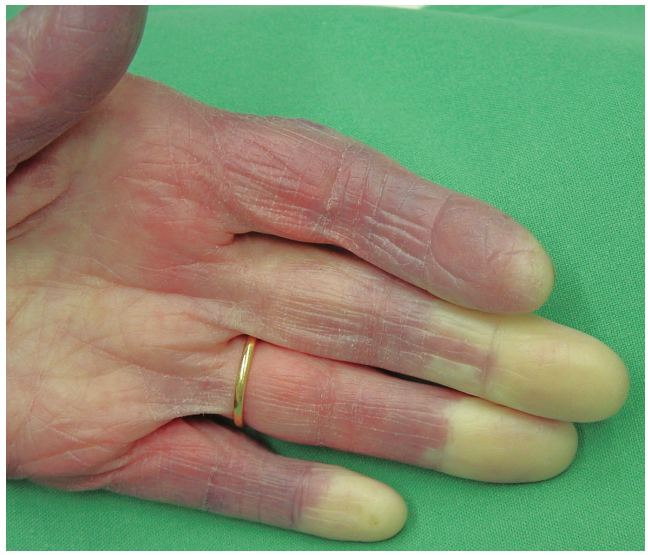

Figure 14. Raynaud's phenomenon consists of transient discoloration of the fingers and toes secondary to vasomotor disorders. Classically, it has three phases. It begins with vasoconstriction which causes pallor, followed by cyanosis secondary to hypoxia of the compromised area, and finally redness when the vasoconstriction ceases and the blood flow returns. Taken from: http://angiogrup.es/patologias/arterioaptias/sindrome-de-raynaoud/

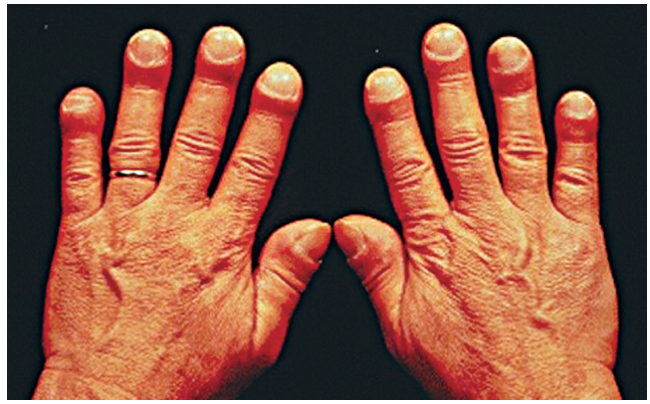

Figure 15. Acropachy. Taken from: http://www.oncoprof.net/Generale2000/g04_Diagnostic/Symptomes/Index/gb04-symp-ix-01.html

NEUROLOGICAL PARANEOPLASTIC SYNDROMES

Neurological paraneoplastic syndromes occur very rarely and affect only 0.01% to 1% of patients with cancer. (35) Pathogenesis is related to the presence of onconeural antigens in the nervous system and in the tumor. (4, 35) In 60% to 70% of cases, neurological alterations are identified before the tumor is found. (4, 78) They can be classified as classical and non-classical syndromes. (78) Classical syndromes include encephalomyelitis, limbic encephalitis, subacute cerebellar degeneration, opsoclonus-myoclonus

syndrome, subacute sensory neuropathy, chronic intestinal pseudo-obstruction, Lambert-Eaton myasthenic syndrome, and dermatomyositis. (35) Associated neoplasms include small cell lung cancer, thymomas, breast cancer and gynecologic tumors, Hodgkin's lymphoma, multiple myeloma, and colon cancer. (79)

Although they are not frequently associated with GI tumors, multiple cases of neuroendocrine tumors of the gastrointestinal tract have been reported. These include neuromyelitis optica (small intestine), (80) gastric tumors, (81) cancer-associated retinopathy (CAR) (small intestine), (82) and brainstem encephalitis (rectum). (83)

Numerous case reports of neurological paraneoplastic syndromes related to gastrointestinal tumors have been made. They can be divided according to whether they affect the central nervous system (Table 2) or the peripheral nervous system (Table 3).

GASTROINTESTINAL PARANEOPLASTIC SYNDROMES

Gastrointestinal paraneoplastic syndromes are extensions of neurological paraneoplastic syndromes produced by visceral neuropathy due to damage of the myenteric plexus neurons. (35) This manifests as pseudoachalasia (102), gastroparesis and intestinal pseudo-obstruction. (38, 103, 104) Gastroparesis is most common while paraneoplastic pseudoachalasia is very rare (1 person in every 750 000). (105, 106) About 30% of patients have impaired motility and manifest severe constipation, abdominal distension, dysphagia, nausea, vomiting and abdominal pain. (35, 78, 107) If anti-Hu or anti-CV2 antibodies are detected, a search for metastasis should be initiated. (35) The most frequent tumors are small cell lung cancer, thymomas and breast cancer, (35, 78) they have also been related to gastric, pancreatic, gallbladder and esophageal cancer as well as to carcinoid tumors. (103, 108)

CONCLUSIONS

Tumors of the gastrointestinal tract can produce almost any paraneoplastic syndrome as summarized in Table 4, but at different magnitudes. This has been discussed in detail in this article. Taking this into account, a basic search should be performed, signs of alarm and risk of malignancy should be detected, and then a more specific search should be done for the most frequent paraneoplastic syndromes such as CAC and malignant acanthosis nigricans.

Table 2. Paraneoplastic syndromes of the central nervous system.

Entities	Associated tumors
Paraneoplastic cerebellar degeneration syndrome	Esophageal adenocarcinoma (84, 85); gastric, colon, (35) and diffuse gastric lymphoma of large B lymphocyte (86, 87)
Encephalitis	Esophageal carcinoma (68, 88)
Limbic encephalitis	Small cell carcinoma and adenocarcinoma of the esophagus (89, 90, 91) and colorectal adenocarcinoma (92, 93)
Opsoclonus-myoclonus syndrome	Squamous cell carcinoma of the esophagus (94) and gastric adenocarcinoma (95)
Optic neuropathy and retinopathy	Colon adenocarcinoma (96, 97)
Necrotizing myelopathy	Esophageal cancer (98)

Table 3. Paraneoplastic neurological syndromes of the peripheral nervous system

Entities	Associated tumors
Sensory-motor polyneuropathy	Cancer of the stomach and esophagus (99)
Lambert-Eaton myasthenic syndrome	Rectal cancer (100)
Stiff person syndrome (SPS)	Colon cancer (35)
Polymyositis[1]	Non-Hodgkin's lymphoma, lung cancer, bladder cancer. (38) Less frequently, gastrointestinal tumors (101)

[1] This is one of the most frequent neurological paraneoplastic syndromes. From 15% to 20% of cases are paraneoplastic, occurs mostly in those over 50 years of age (38)

Table 4. Paraneoplastic syndromes associated with gastrointestinal tumors.

Paraneoplastic syndromes	Tumors that produce syndromes
Cachexia	Gastrointestinal or pancreatic adenocarcinoma
Acanthosis nigricans	Gastric, esophageal, pancreatic, liver and bile duct adenocarcinoma
Tripe palms	Gastric adenocarcinoma
Leser-Trélat syndrome	Gastric adenocarcinoma of the colon, rectum, esophagus, duodenum, pancreas and gallbladder and liver
Bazex syndrome	Esophageal, colon, gastric and hepatobiliary cancer
Paraneoplastic hypertrichosis lanuginosa	Colon, rectal, pancreatic and gallbladder cancer
Paraneoplastic pemphigus	Adenocarcinoma of the colon and pancreas
Paraneoplastic dermatomyositis	Colorectal, gastric, pancreatic and esophageal cancer
Erythema gyratum repens	Gastric, esophageal, colon, rectal and pancreatic cancer
Cutaneous leukocytoclastic vasculitis	Gastrointestinal tube
Sweet's syndrome	Colon and rectum
Pityriasis rotunda	Hepatocellular, gastric and esophageal carcinoma
Erythroderma	Colorectal, gastric, esophageal and gallbladder
VTE	Gastric, hepatic, colorectal and pancreatic
Trousseau's Sign	Gastric, pancreatic, colon and rectal
Paraneoplastic eosinophilia	Gastrointestinal tumors
Hemolytic anemia	Colorectal and stomach cancer
Acquired coagulation factor V inhibitor	Esophageal squamous cell carcinoma
Membranous glomerulonephritis	Gastric cancer
Immunoglobulin A nephropathy	Gastric and esophageal adenocarcinoma
SIADH	Gastric, esophageal, pancreatic, duodenal, colon and rectal cancer
Malignant hypercalcemia	Esophageal squamous cell carcinoma
Cushing's syndrome	Neuroendocrine, stomach and esophageal tumors
Carcinoid syndrome	Neuroendocrine tumors
Carcinomatous polyarthritis	Colon, stomach, esophagus and pancreas
Palmar fasciitis and arthritis	Gastric, pancreatic and colon cancer
Multicentric histiocytosis	Gastric and colon
RS3PE	Stomach, pancreatic and rectal
Hypertrophic osteoarthropathy	Esophageal cancer
Rheumatic polymyalgia	Colon neoplasias
Raynaud's syndrome	Gastric cancer
Paraneoplastic neurological syndromes	Gastric, esophageal and colon cancer, and neuroendocrine tumors
Paraneoplastic gastrointestinal syndromes	Gastric, pancreatic, gallbladder, esophageal and carcinoid tumors

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