A Review of Paraneoplastic Syndromes in Gastrointestinal Tumors

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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, renal, neurological and other manifestations. (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)
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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) The pathogenesis of CAC is multifactorial, but the inflammatory cytokines induced or produced by the tumor play a fundamental role. (7) Among these tumor cytokines, 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)

**Acanthosis Nigricans (AN)**

Acanthosis nigricans consists of velvety plaques with hyperpigmented symmetrical areas of relief located in intertriginous sites such as axillae, 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)

**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.

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

**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-Trelat 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)

Acanthosis nigricans, palmoplantar keratoderma (also known as velvet palms or tripe palms) and the Leser-Trelat 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-Trelat 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-Trelat 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-Trelat 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%
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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 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, peripheral edema, 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 erythematosus 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. Erythema 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)

**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)

**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)
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.

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 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 gastrointestinal 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-
Raynaud’s phenomenon 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).

**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...

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.

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<td>Stiff person syndrome (SPS)</td>
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<td>Polymyositis¹</td>
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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.

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<td>Malignant hypercalcemia</td>
<td>Esophageal squamous cell carcinoma</td>
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<tr>
<td>Cushing’s syndrome</td>
<td>Neuroendocrine, stomach, and esophageal tumors</td>
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<tr>
<td>Carcinoid syndrome</td>
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<tr>
<td>Carcinomatous polyarthritis</td>
<td>Colon, stomach, and esophageal and pancreas</td>
</tr>
<tr>
<td>Palmar fasciitis and arthritis</td>
<td>Gastric, pancreatic, and colorectal cancer</td>
</tr>
<tr>
<td>Multicentric histiocytosis</td>
<td>Gastric and colon</td>
</tr>
<tr>
<td>RS3PE</td>
<td>Stomach, pancreatic, and rectal</td>
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<td>Hypertrophic osteoarthropathy</td>
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<td>Colon neoplasias</td>
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<tr>
<td>Raynaud’s syndrome</td>
<td>Gastric cancer</td>
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<td>Gastric, esophageal, and colorectal cancer</td>
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<tr>
<td>Paraneoplastic gastrointestinal syndromes</td>
<td>Gastric, pancreatic, gallbladder, and esophagean and carcinoid tumors</td>
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