Paraneoplastic cutaneous manifestations: concepts and updates *

Manifestações cutâneas paraneoplásicas: conceitos e atualizações

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Abstract: The skin often signals systemic changes. Some neoplastic diseases that affect internal organs may trigger several cutaneous manifestations. Although these dermatoses are relatively unusual, the recognition of some typical paraneoplastic dermatoses may lead to the early diagnosis of a neoplasm and determine a better prognosis. In this review article, we discuss the paraneoplastic cutaneous manifestations strongly associated with neoplasms, which include acanthosis nigricans maligna, tripe palms, erythema gyratum repens, Bazex syndrome, acquired hypertrichosis lanuginosa, necrolytic migratory erythema, Leser-Trélat sign and paraneoplastic pemphigus. We also review the clinical manifestations of each condition and include updated knowledge on disease pathogenesis.

Keywords: Neoplasms; Paraneoplastic syndromes; Skin manifestations

Resumo: A pele é, muitas vezes, reflexo de manifestações sistêmicas. Doenças neoplásicas que afetam órgãos internos podem exibir manifestações cutâneas diversas. Apesar de relativamente incomuns, o reconhecimento de dermatoses paraneoplásicas pode levar ao diagnóstico precoce da neoplasia e, consequentemente, determinar melhor prognóstico. Nesta revisão serão discutidas as manifestações cutâneas paraneoplásicas com maior força de associação a neoplasias, que incluem acantose nigricante maligna, paquidermatoglifia adquirida, erythema gyratum repens, síndrome de Bazex, hipertricose lanuginosa adquirida, eritema necrolítico migratório, sinal de Leser-Trélat e pênfigo paraneoplásico. Para cada condição serão revisadas e atualizadas as manifestações clínicas, principais neoplasias associadas e etiopatogenia.

Palavras-chave: Manifestações cutâneas; Neoplasias; Síndromes paraneoplásicas

INTRODUCTION

Paraneoplastic diseases may be defined as hormonal, neurological or hematological disturbances and as clinical and biochemical imbalances associated with the presence of malignancies without direct association with primary tumor invasion or metastasis. The skin may provide the doctor with signs that are suggestive of systemic diseases, thus contributing to the diagnosis of many diseases, including malignancies.¹² In 1868, Hebra was the first to suggest that skin pigmentation could indicate the presence of visceral cancer.³ Since then, more than 50 dermatological conditions have been reported as potential markers of malignancy.¹ The skin may be directly or indirectly involved in malignancies. Direct involvement implies...
the presence of tumor cells in the skin caused by direct tumor extension or metastasis. Indirect involvement, in turn, is caused by a variety of factors (inflammatory, proliferative or metabolic factors) related to the neoplasia, such as polypeptides, hormones, cytokines, antibodies or growth factors that act as mediators, interfering with cell communication and, consequently, with its activity. In this case, there is no presence of neoplastic cells in the skin, and this involvement is considered a dermatological paraneoplastic syndrome.3,6

Paraneoplastic dermatoses are a heterogeneous group of clinical manifestations that may have a benign appearance. They are the second most common paraneoplastic syndrome, only behind endocrine syndromes. It is not always easy to determine the correlation between a dermatologic finding and an internal neoplasm or even to define the frequency of this association in the general population.1,5 Curth, in his studies of acanthosis nigricans maligna, proposed some criteria to assess the causal relationship between dermatological change and potential underlying malignancy (Chart 1).2,4,6 Given the wide scope of the subject, we will discuss the dermatoses that are highly correlated with malignancy, whose recognition implies a mandatory investigation of internal malignancy. Since cutaneous paraneoplastic syndromes commonly precede or follow visceral cancer, their recognition may result in earlier diagnosis and better prognosis for the patient (Chart 2).7,8

**ACANTHOSIS NIGRICANS MALIGNA**

Acanthosis nigricans can be classified as benign or malignant. The benign form (80%) is relatively common and may be associated with obesity, insulin resistance, diabetes mellitus and drug use, contrary to the malignant form, which is rare.3,5,9-12

Acanthosis nigricans maligna (ANM) was the first dermatosis truly associated with malignant processes, being perhaps the best known among all associations.6 It occurs equally in both sexes without racial predilection or familial association.19 The disease has a sudden onset with extensive and severe lesions that develop quickly. It affects adults with an average age of 40 years. In contrast, the benign form usually manifests earlier in life and develops slowly.5,9,10

**Clinical manifestations.** It begins with symmetrical hyperpigmentation in intertriginous areas such as the axilla, cubital fossa, submammary, inguinal and posterior cervical regions, although any part of the body can be affected (Figure 1).5,8-10 Lesions then become slightly infiltrated, with velvety hyperkeratotic plaques, commonly surrounded by acrochordons.5,9 There may be an association with generalized pruritus and involvement of mucosal surfaces, which present a verrucous aspect in severe cases.6,9,11 Approximately 25% of patients present concomitant involvement of the palmoplantar region in a pattern known as *tripe palms* (acquired pachydermatoglyphia). It may also be associated with the sudden onset of multiple lesions of seborrheic keratosis (Leser-Trélat sign).5 Both associations are described below.

**Associated malignancies** ANM can precede, occur simultaneously or occur after the diagnosis of cancer.6,9 In a review study, this dermatological finding was observed in 58% of patients before tumor diagnosis.7 ANM is associated with 90% of all abdominal cancers; 55-61% are of gastric origin, and adenocarcinoma is found in 70-90% of cases (Figure 2).3,5,9,11,12 Other less associated malignant conditions include uterine, liver, intestine, pancreas, thyroid, ovary, kidney, breast, lung, bladder and gallbladder cancers, mostly consisting of adenocarcinomas.5,11 An association with lymphomas and mycosis fungoides has also been reported.1

ANM tends to evolve simultaneously with the underlying neoplasia and it aggravates as the condition worsens.12 It improves with treatment or relapses in the occurrence of metastasis, often serving as a standard measure of progression or recurrence of malignancy (Figure 2).7 Despite the presence of acanthosis nigricans in benign and non-neoplastic conditions, such as drug use and insulin resistance, a detailed medical history should be taken from patients diagnosed with this dermatosis. The diagnosis of ANM should be strongly considered in adults over 40 years of age, without endocrinological changes or genetically determined diseases with fast-

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**Chart 1:** Curth’s criteria for the diagnosis of cutaneous paraneoplastic syndromes

1) Both conditions began simultaneously (neoplasia and paraneoplasia)
2) Development of a parallel course *
3) The skin lesion is not associated with a genetic syndrome
4) There is a specific type of neoplasia that occurs with paraneoplasia
5) The dermatosis is rare in the general population
6) There is a high frequency of association between both conditions

* Treatment of the neoplasia results in regression of the skin lesion; recurrence of the neoplasia implies recurrence of the skin lesion.
growing skin lesions. In these individuals, an extensive gastrointestinal evaluation is mandatory.\(^6,11\) Prognosis, however, is poor. Underlying tumors present in patients with ANM tend to have an aggressive behavior, which leads to a mean survival of 2 years after the diagnosis of ANM.\(^3,11,13\)

**Histopathology.** Histologically, ANM shows hyperkeratosis, papillomatosis and some degree of acanthosis with thickening of the spinous layer of the epidermis.\(^2,12\) The dark color is more related to hyperkeratosis than to the presence of melanin; therefore, the term “acanthosis nigricans” is merely descriptive, as there is no proliferation of melanocytes.\(^2,6\)

**Pathophysiology.** The exact pathophysiological mechanism of ANM is not well defined.\(^7\) It is believed that cytokines produced by neoplastic cells are involved, such as transforming growth factor alpha (TGF-\(\alpha\)), insulin growth factor-like (IGF-1), fibroblast growth factor (FGF) and melanocyte-stimulating hormone (MSH-\(\alpha\)). TGF-\(\alpha\) would be structurally similar to the epidermal growth factor (EGF-\(\alpha\)), interacting with this receptor present in the surface of epidermal cells.\(^2,3,11,13\) So far, no factor has been conclusively identified.\(^6\)

**ACQUIRED PACHYDERMATOGlyphIA**

Also referred to as *tripe palms* or acanthosis palmaris, acquired pachydermatoglyphia (AP) is a term that was introduced in the medical literature in 1970 by Clark. It is a skin condition that is usually associated with Leser-Trélat sign and ANM, being considered by some authors much more a variant of ANM than actually a new disease. It predominantly affects adults, with a predilection for males (63% of cases).\(^2,9,12\)

**Clinical manifestations.** It presents with yellowish, velvety, diffuse palmar hyperkeratosis, with accentuated dermatoglyphic patterns, leading to a rough appearance that resembles the intestinal villosities, which explains the term *tripe palms* (Figure 3).\(^13,14\)
Associated malignancies. Neoplastic processes have been reported in 90% of cases of AP. Gastric and lung cancer account for 50% of tumors. In the absence of an association with ANM, lung cancer becomes more prevalent, being found in more than 50% of cases. Other neoplasms have been correlated with AP, such as breast and genitourinary tract cancers.

Histopathology. Histological examination reveals acanthosis and hyperkeratosis, and perivascular deposition of mucin in the dermis may be observed.

Pathophysiology. Physiologically, it is believed that EGF-α and TGF-α released by neoplastic cells are involved. Histologically and physiologically, AP is very similar to ANM, which suggests a possible connection between them.

ERYTHEMA GYRATUM REPENS

Erythema gyratum repens (EGR) is a rare dermatosis. It was first described in 1952 by Gammel in a patient nine months before the appearance of a breast adenocarcinoma. Lesions usually recede some weeks after removal of the tumor, and the clinical manifestations are considered typical of a paraneoplastic dermatosis. The average age of onset is 63 years, and the disease affects twice as many men than women.

Clinical manifestations. It presents as a widespread, serpiginous, polycyclic and pruriginous erythema which is desquamative around the edges and fast-
growing, about 1 cm/day, producing concentric figures that resemble a wood surface (Figure 4).\textsuperscript{9,10,15} Hands and feet are often spared. Other manifestations include palmoplantar keratosis, ichthyosis and onychodystrophy in the sacral region.\textsuperscript{1,2}

Patients with this dermatosis should be considered as having malignancy and should be mandatorily evaluated. The evolution of EGR often accompanies an underlying neoplastic disease.\textsuperscript{2} Successful treatment of the neoplasia often leads to complete resolution of the lesions.\textsuperscript{16}

**Associated malignancies.** Malignant neoplasms are found in 82% of the patients with EGR. Lung cancer is the most common (32%), followed by cancer of the esophagus (8%) and breast (6%).\textsuperscript{2,9} Other malignancies have been associated with EGR, such as colon, stomach, bladder, prostate, uterine, rectal and pancreatic cancer and multiple myeloma.\textsuperscript{9,10,17} The diagnosis of EGR precedes the diagnosis of the neoplasia in approximately 80% of patients, on average from four to nine months.\textsuperscript{9,15,17} Non-neoplastic conditions may be rarely associated with EGR, such as tuberculosis, pregnancy, calcinosis, esophageal dysmotility, sclerodactyly, Sjögren’s syndrome and CREST syndrome.\textsuperscript{1,2}

**Histopathology.** Histopathology is nonspecific, showing mild hyperkeratosis, parakeratosis, acanthosis and spongiosis with a perivascular mononuclear inflammatory infiltrate in the dermis.\textsuperscript{1,2}

**Pathophysiology.** Its pathophysiology is unknown. Immune mechanisms are probably involved since immunosuppression accompanies the resolution of EGR. The immunological explanation is supported by the presence of immune deposits (C3) in the sublamina densa seen by direct immunofluorescence (DIF).\textsuperscript{16,17} In some cases, anti-basement membrane antibodies were detected by DIF. The theory states that antibodies to tumor antigens may react against skin antigens, which justifies the deposition of immune complexes in this tissue.\textsuperscript{9,16}

**ACROKERATOSIS PARANEOPLASTICA** (Bazex syndrome)

In 1965, Bazex described the first patient with this syndrome. This paraneoplastic process predominates in men with an average age of 40 years.\textsuperscript{1,8}

**Clinical manifestations.** Erythematous lesions with a psoriasiform aspect that manifest as symmetrical erythematous-violaceous scaly patches on the bridge of the nose, helix, and distal ends of the extremities are initially found.\textsuperscript{5,6,9} As the disease progresses, desquamation affects the dorsal and palmar regions producing a violaceous keratoderma. The nails may also be affected from the onset, with subungual hyperkeratosis, onycholysis and dystrophy (Figure 5).\textsuperscript{2,9,10} Eventually, additional areas may be
affected such as the knees, legs, arms and scalp, with centripetal distribution of the lesions. Bullous lesions, mainly in the hands and feet, have been described. Although lesions show a psoriasiform aspect, their distribution is not typical of psoriasis, helping with differential diagnosis.

Lesions are resistant to targeted therapy (steroids or keratolytic drugs). In about 90% of cases, the dermatosis follows the neoplastic course with improvement after effective treatment of the neoplasia and recurrence when the tumor returns. Nail changes, however, slowly improve and may be persistent.

**Associated malignancies.** All the cases cited in the literature were associated with malignancy. Skin manifestations often precede the diagnosis of cancer in approximately 2-6 months in 65-70% of patients; less often, they occur simultaneously (10-15%) or after tumor diagnosis (15-25%). About 80% of cases are associated with tumors of the upper aerodigestive tract (oral cavity, larynx, pharynx, trachea, esophagus and lung), commonly squamous cell carcinoma. Metastasis to cervical lymph nodes appears to be common in patients with Bazex syndrome. In a retrospective study, 48.6% of cancers involved the oropharynx and larynx, followed by the lung (17%) and esophagus (10.6%). Isolated cases associated with ductal breast cancer, cholangiocarcinoma, colon adenocarcinoma and Hodgkin’s disease have been reported.

**Histopathology.** Its histopathology is nonspecific, with findings of hyperkeratosis, acanthosis, parakeratosis, vacuolar degeneration, pigmentary incontinence and perivascular lymphocytic infiltrate. DIF shows local deposits of immunoglobulins, complement (C3) or fibrin in the basement membrane.

**Pathophysiology.** Its pathophysiology remains unknown. Immunological factors with antibodies directed against the tumor in a cross-reaction with the epidermis or basement membrane have been considered. Another possibility is the secretion of growth factors by the tumor leading to the growth and differentiation of epidermal cells. In many cases, the presence of the same type of human leukocyte antigen (A3 and B8) suggests a genetic susceptibility to this dermatosis.

**ACQUIRED HYPERTRICHOSIS LANUGINOSA**

It is a rare paraneoplastic dermatosis that was first described in 1865 by Turner in a female patient with breast cancer. It is characterized by the sudden onset of thin and soft hair, lanugo-like, initially on the face. Acquired hypertrichosis lanuginosa (AHL) must be differentiated from hypertrichosis associated with endocrine or metabolic alterations (porphyria cutanea tarda and hyperthyroidism), and use of medication (cyclosporine, penicillamine, glucocorticoids, interferon, minoxidil, phenytoin, spironolactone and cetuximab). Women are three times more affected than men, with an average age of 40-70 years.

**Clinical manifestations.** It presents with long, thin, soft, non-pigmented hair that affects the face and ears (Figure 6). It may involve the thorax and extremities, spreading in a craniocaudal manner. Manifestations such as painful glossitis, angular cheilitis, hypertrophic fungiform papillae and altered taste and smell can be present. Complaints of weight...
loss, lymphadenopathy and diarrhea are also common. This dermatosis may be associated with ANM.

The report of lanugo-like hair growth in areas that were previously hair free should be seen as an important indicator of the possibility of internal malignancy. In the evaluation of patients with AHL, an extensive clinical history and physical examination are necessary, in conjunction with laboratory screening, chest radiography, colonoscopy and, in women, mammography. Successful treatment of the tumor usually leads to regression of pathological hair growth.

**Associated malignancies.** AHL often precedes tumor diagnosis in about two and a half years. In the presence of this dermatosis, however, metastasis is common, which is why prognosis is poor, with mean survival of less than three years after diagnosis. Among women, colorectal cancer is the most frequent association, followed by lung and breast cancer. Men show greater association with lung cancer, followed by colorectal cancer. Associations with lymphomas, leukemias, and kidney, pancreatic, uterine and ovarian cancer have been reported.

**Histopathology.** Histologically, hairs are described as being horizontal or parallel to the epidermis, which contrasts with the vertical position of normal hair.

**Pathophysiology.** So far no biochemical abnormality has been identified in the pathophysiology of the disease, neither has the involvement of virilizing hormones. It is believed that growth factors secreted by tumor cells are involved; various fibroblast growth factors (FGF) are known to regulate hair growth. Secretion of FGF has been reported in lung cancer, as well as production of other factors that participate in hair follicle growth, such as Wingless proteins and β-Catenin; the latter is able to start new hair growth in vitro. The recent observation that treatment of AHL with EGF-α receptor antagonist may result in hypertrichosis is also intriguing.

**NECROLYTIC MIGRATORY ERYTHEMA**

Necrolytic migratory erythema (NME) is often associated with glucagonoma syndrome and consists of the triad NME, glucose intolerance and hyperglucagonemia, whose levels greater than 1000 pg/mL are highly suggestive of glucagonoma. NME is more common in women after 45 years of age, with an average age of onset of 52 years. The recognition of this dermatosis may lead to early diagnosis with potential cure of the neoplasia, since NME can be its first manifestation.

**Clinical manifestations.** Initially, a pinkish, maculopapular rash with irregular edges and a standard arcuate or polycyclic pattern, prominent in areas of trauma, is observed, often affecting the knees and intertriginous areas. Sometimes there is formation of flaccid bullae that rupture easily forming crusts, while new vesicles continue to develop along the edges (Figure 7). NME is often complicated by infection with *Candida albicans* or *Staphylococcus aureus*. This is why some patients are misdiagnosed as having chronic candidiasis. These patients often report prior treatment with antibiotics and antifungal agents without improvement before a conclusive diagnosis is reached. Pressure or trauma can initiate or aggravate the lesions, which may present a pattern similar to that of staphylococcal scalded skin syndrome. Lesions may be pruritic and painful and are associated with glossitis, angular cheilitis, normocytic anemia, weight loss, diabetes, abdominal pain, dyspepsia, diarrhea, venous thrombosis, alopecia, steatorrhea and neuropsychiatric symptoms. There is a high risk of thromboembolism, which occurs in about 24% of patients. It leads to pulmonary embolism in 11% of cases. NME and weight loss are the most prevalent symptoms of glucagonoma, which can occur in about 65 -70% of patients.
Associated malignancies. Glucagonoma is a rare endocrine tumor of pancreatic alpha cells. It is less common than gastrinoma and insulinoma. A CT scan may be useful in the diagnosis. In addition, 95% of glucagonomas are positive in somatostatin receptor scintigraphic. Somatostatin positivity may be useful in the treatment of the symptoms and signs of glucagonoma, since that hormone inhibits glucagon secretion and improves the clinical symptoms without, however, inhibiting tumor growth. Rare cases of association between NME and non-glucagon-secreting tumors have been reported, leading to pseudoglucagonoma syndrome, such as small-cell lung cancer, liver cancer, insulin-secreting tumors and duodenal neoplasms.

Glucagonoma is often slow-growing, which is why there is a delay of three years on average in the diagnosis, when about 50% of patients already have metastasis to liver, vertebrae, ovary and peritoneum, often resistant to chemotherapy. Resolution of the dermatosis is obtained by tumor resection in the absence of metastasis, and residual hyperpigmentation at the sites previously affected is common. Cases of complete remission of NME within 48 hours after surgery have been reported.

Histopathology. Histological findings are non-specific and show different changes depending on the degree of involvement. It may present edema and irregular acanthosis with basal cell hyperplasia, moderate perivascular inflammatory infiltrate with predominance of lymphocytes, and parakeratosis with vacuolated epidermal cells associated with superficial necrosis; the latter is an important histological finding for diagnosis.

Pathophysiology. It has been suggested that, in the presence of cancer, zinc and amino acids needed for the formation of albumin (the main carrier of zinc) may be reduced due to the catabolic state consequent to glucagon. Reduced levels of serum amino acids would lead to increased production of arachidonic acid, thus leading to inflammation of the skin. This theory would explain the dermatological findings of ENM in diseases without any evidence of glucagonoma, such as malabsorption syndromes, liver failure, inflammatory bowel disease and celiac disease, in which there is also loss of amino acids and minerals. Another theory points to decreased niacin, a biomolecule that is necessary for epidermal growth and renewal, as the primary responsible for NME. Disorders involving niacin, such as pellagra, result in dermatitis, diarrhea and neurological alterations. Diarrhea and neurological alterations are also reported in patients with glucagonoma.

LESER-TRÉLAT SIGN
Leser-Trélat sign (LTS) is attributed to Edmund Leser and Ulysse Trélat, who associated the appearance of angiomas (and not seborrheic keratoses) with neoplasms. In 1900, Holander was the first to associate the appearance of numerous seborrheic keratoses with a possible internal malignancy, but the eponym remained for Leser and Trélat. LTS primarily affects individuals with an average age of 61 years, without gender or racial predilection. The association with malignancy has remained controversial because seborrheic keratosis is a common condition in the elderly, which is the most affected age range. The presence of LTS in a 20-year-old woman with osteogenic sarcoma and in a 22-year-old man with germinoma of the pineal body, both unlikely to have multiple seborrheic keratoses, shows the validity of this sign.

Clinical manifestations. It presents as a sudden increase in the size and number of seborrheic keratoses. These are papular, verrucous, usually well-defined lesions of varying colors (brown, black or tan) which primarily affect the thorax and dorsum, followed by the extremities, face, abdomen, neck and axilla (Figure 8). Pruritus and inflammation are frequent findings. Approximately two thirds of patients have another paraneoplastic syndrome, of which ANM is the most common, occurring in one third of cases. LTS is usually ignored by both doctors and patients, leading to a delay in the diagnosis of diseases that could be potentially curable. All patients with LTS should be screened for neoplasms. Medical history and physical examination associated with complete blood count (CBC), serum biochemistry, chest
radiography, mammography, Pap smear, PSA screening, upper digestive endoscopy and colonoscopy are required during this investigation.2

**Associated malignancies.** Approximately half of all cancers associated with LTS are adenocarcinomas, present in the gastrointestinal tract in 32% of cases; gastric carcinoma is the most common, followed by colon and rectal cancer.6,8,7 Lymphoproliferative abnormalities are associated in 21% of cases. There are reports of LTS in transitional cell carcinoma of the bladder, kidney tumors, prostate, lung, ovary and kidney cancer, and melanoma,9,10 as well as lymphoproliferative neoplasias.29,33 Non-malignant conditions such as pregnancy and benign tumors may be rarely associated with LTS.1

**Histopathology.** The histopathological pattern of the lesions does not differ when compared to that of patients without malignancy.8

**Pathophysiology.** The exact pathophysiology of the disease remains unknown. Neoplastic cells may secrete factors similar to EGF-α, stimulating keratinocyte growth.7 Higher levels of EGF-α and IGF-1 are found in patients with LTS.7 Also, higher levels of TGF-α have been found in the urine of a patient with LTS and melanoma; in this case, TGF-α levels became undetectable after removal of the tumor.31

**PARANEOPLASTIC PEMPHIGUS**

Since 1990, when paraneoplastic pemphigus (PNP) was first described by Anhalt et al. as a distinct entity, more than 200 cases of the disease have been described. There is no gender predominance and two thirds of patients have a recognized neoplasia at the onset of PNP. The diagnostic criteria (revised by Helm and Camissa) suggested for PNP can be divided into major criteria (polymorphous skin eruption, concurrent internal neoplasia, antibodies with an immunoprecipitation specific standard) and minor criteria (histological evidence of intraepithelial acantholysis, DIF showing a linear pattern in an area of the basement membrane with IgG and C3 deposition, and indirect immunofluorescence using rat bladder epithelium as a substrate). Three major criteria or two major and one minor are needed. Contrary to pemphigus vulgaris, in which DIF shows only intercellular deposition in epithelial cells, the basement membrane is also affected in PNP.2,8,9,34

**Clinical manifestations.** Oral involvement with painful stomatitis is seen in almost all cases and can often be the first symptom, being generally the least responsive to treatment (Figure 9). Oral lesions may be severe, diffuse and affect the hypopharynx and esophagus; they may also involve the conjunctival and anorectal mucosa. Skin manifestations range from papules and plaques similar to erythema multiforme, vesicles and blisters that resemble pemphigus vulgaris or even pruritic plaques similar to lichen planus. Contrary to pemphigus vulgaris, there may be acral and paronychial involvement. Some patients have respiratory complications such as bronchiolitis obliterans, with the potential risk of respiratory failure. PNP is associated with high mortality rate secondary to sepsis, bleeding and respiratory failure.2,8,34,35

**Figure 8: Leser-Trélat Sign. Multiple seborrheic keratoses of rapid onset and evolution in the dorsum.**

**Figure 9: Oral lesions in paraneoplastic pemphigus.** Reprinted from: Ehst BD, et al. 2010. Copyright 2010. Used with permission from Elsevier, Inc.
Associated malignancies. Most associated malignancies develop in patients who are between 45 and 70 years old. Approximately 80% are of hematological origin (B-cell lymphoproliferative disorders), such as non-Hodgkin lymphoma (42%), chronic lymphocytic leukemia (29%), Castleman’s disease, thymoma, Waldenström’s macroglobulinemia and follicular dendritic cell sarcoma. In children and adolescents, association with Castleman’s disease is the most frequent. Minimal laboratory workout includes CBC, protein electrophoresis, chest, abdomen and pelvis CT scan.

Histopathology. Suprabasal acantholysis and necrosis of keratinocytes are observed. In DIF, there is deposit of IgG (with or without C3) in the intercellular spaces of the epidermis and/or basement membrane. IIF shows antibodies of the IgG type.

Pathophysiology. The exact etiology of the disease is unknown. It is believed that an immunological deregulation in antitumor antibodies leads to the production of autoantibodies that bind to epidermal proteins (plakin family) present in desmosomes and hemidesmosomes responsible for cell adhesion, thereby causing skin displacement. The search for malignancy should be conducted through a comprehensive physical examination targeting the liver, spleen and lymph nodes.

OTHER PARANEOPlastic DERMATOSES
Some other skin diseases are often associated with neoplasia, but with less associative strength than the paraneoplastic syndromes previously described. We briefly describe the main syndromes below. Upon finding such dermatoses, the doctor should investigate possible cancers.

Pityriasis rotunda. It is a rare disease characterized by multiple, well-defined circular macules that can be hyper or hypopigmented and that are typically found in the trunk. One third of patients have an underlying disease, including tuberculosis, lepromy, liver and lung diseases. Associated neoplasms include hepatocellular, gastric and esophageal carcinoma, prostate cancer, chronic lymphocytic leukemia and multiple myeloma.

Dermatomyositis. It is an idiopathic inflammatory disease that affects the skin and muscles. Classical clinical findings include heliotrope and Gottron’s sign, malar erythema and poikiloderma in a “V” photodistribution on the thorax (with no history of sun exposure) - known as shawl sign - associated with symmetric proximal paresis. Approximately 10% to 25% of cases are paraneoplastic. Incidence is even higher in adults over 45 years, since dermatomyositis in children is not associated with malignancies. Clinical manifestations are the same in the absence or presence of an underlying neoplasm. Ovarian, pulmonary (bronchogenic carcinoma), gastric (adenocarcinoma) and genital carcinomas are the most often correlated.

Palmoplantar keratoderma. It is a disease characterized by alterations in keratinization, which may be inherited or acquired. Different associations with malignancy have been described. The prototype of the inherited disease is Howell-Evan’s Syndrome, which has a 36-fold higher risk of development of oral or esophageal carcinoma. Skin lesions usually begin in childhood, although neoplastic involvement occurs on average at 61 years of age. The pathogenesis of the syndrome has been linked to chromosome 17q24, a site of keratin.

Pyoderma gangrenosum. It is a neutrophilic dermatosis that manifests as painful nodules and pustules with erythematous edges and rapid evolution to deep ulcerations with undermined edges, whose debridement or surgical intervention may lead to worsening of the lesion due to pathergy. The pretibial area is the most affected. About 70% of cases are associated with an underlying condition, such as inflammatory bowel disease and rheumatoid arthritis. Seven percent (7%) are associated with neoplasms, and malignant and premalignant hematological diseases, such as myelodysplastic syndrome, myeloma, paraproteinemia (IgA) and leukemias, are the most often reported.

Sweet Syndrome (acute febrile neutrophilic dermatosis). It is a process of systemic neutrophilic reactivation characterized by painful, edematous, shiny erythematous nodules or plaques which usually occur in the head, neck and upper limbs. It is described in three associations: classical or idiopathic form - associated with inflammatory bowel disease, infection of the upper respiratory tract and pregnancy; post-drug; associated with malignancy (20%). Most neoplastic associations involve hematologic neoplasms, and acute myelogenous leukemia and myelodysplastic syndrome are the main ones.

Other diseases classified as paraneoplastic syndromes are acquired ichthyosis, necrobiotic xanthogranuloma, multicentric reticulo-histiocytosis, primary systemic amyloidosis, scleromyxedema and diseases included in the group of genodermatoses.
CONCLUSION

Numerous systemic diseases can be diagnosed through the skin, among them are changes suggestive of internal malignancies. Cutaneous paraneoplastic syndromes are important clinical markers that may precede (most commonly), occur simultaneously or after the diagnosis of a given neoplasm. More than 50 dermatoses have been correlated with underlying neoplastic processes, many of which correlate with specific neoplasms, thus being an important diagnostic aid. Recognition of the major cutaneous paraneoplastic syndromes allows the doctor to establish an early diagnosis and treatment, which could lead to a higher chance of cure and better prognosis for the patient.

REFERENCES

1. Ramos-E-Silva M, Carvalho JC, Carneiro SC. Cutaneous paraneoplasia. Clin Dermatol. 2011;29:541-7.
2. Pipkin CA, Lio PA. Cutaneous manifestations of internal malignancies: an overview. Dermatol Clin. 2008;26:1-15.
3. Sneddon IB. Cutaneous manifestations of visceral malignancy. Postgrad Med J. 1970;46:678-85.
4. Poole S, Fenske NA. Cutaneous markers of internal malignancy. I. Malignant involvement of the skin and the genodermatoses. J Am Acad Dermatol. 1993;28:1-13.
5. Ortega-Loayza AG, Ramos W, Gutierrez EL, Paz PC, Bobbio L, Galarza C. Cutaneous manifestations of internal malignancies in a tertiary health care hospital of a developing country. An Bras Dermatol. 2010;85:736-42.
6. Thiers BH, Sahn RE, Callen JP. Cutaneous manifestations of internal malignancy. CA Cancer J Clin. 2009;59:73-98.
7. Azulay RD, Azulay DR, Abulafia LA. Sinais malignos na pele versus síndromes paraneoplásicas cutâneas: revisão. An Bras Dermatol. 2000;75:621-30.
8. Dourmishev LA, Dragarov PV. Paraneoplastic dermatological manifestation of gastrointestinal malignancies. World J Gastroenterol. 2009;15:4372-3.
9. Ehrst BD, Minzer-Conzetti K, Swerdlin A, Devere TS. Cutaneous manifestations of internal malignancy. Curr Probl Surg. 2010;47:384-445.
10. McLean DI. Cutaneous manifestations of internal malignant disease. Can Fam Physician. 1987;33:2357-65.
11. Krawczyk M, Mykala-Ciesla J, Kolodziej-Jaskula A. Acanthosis nigricans as a paraneoplastic syndrome. Case reports and review of literature. Pol Arch Med Wewn. 2009;119:180-3.
12. Costa MC, Martinez NS, Belicha MG, Leal F. Acanthosis nigricans and “tripe palm” as paraneoplastic manifestations of metastatic tumor. An Bras Dermatol. 2012;87:498-500.
13. Brinca A, Cardoso JC, Brites MM, Tellechea O, Figueiredo A. Florid cutaneous papillomatosis and acanthosis nigricans maligna revealing gastric adenocarcinoma. An Bras Dermatol. 2011;86:573-7.
14. Ribas J, Peixoto LF, Almeida MF, Lima WC. Dermatologia comparativa: paquidermatogíia adquirida associada a carcinoma gástrico avançado. An Bras Dermatol. 2007;82:582-3.
15. De La Torre-Lugo EM, Sanchez JL. Erythema gyratum repens. J Am Acad Dermatol. 2011;64:e89-90.
16. Bakos N, Krasznai G, Bélgény Á. Erythema Gyratum Repens An Immunological Paraneoplastic Dermatosis. Pathol Oncol Res. 1997;3:59-61.
17. Serrão V, Martins A, Ponte P, Baptista J, Apetato M, Felo AB. Erythema gyratum repens as the initial manifestation of lung cancer. Eur J Dermatol. 2008;18:197-8.
18. Ljubenovic MS, Ljubenovic DB, Rinic II, Jankovic AS, Jovanovic DL. Acrokeratosis paraneoplastica (Bazex syndrome). Indian J Dermatol Venereol Leprol. 2009;75:329.
19. Rio Ramirez MT, Casado Lopez ME, Peirón Poyal MJ, Peñas Herrero JM. Pulmonary adenocarcinoma and Bazex syndrome (paraneoplastic acrokeratosis). Arch Bronconeumol. 2007;43:46-8.
20. Lee A. Skin manifestations of systemic disease. Aust Fam Physician. 2009;38:498-505.
21. Sla PH, van der Waal RI, Schagen van Leeuwen JH, Tupker RA, Thimme R, Seldenrijk CA et al. Paraneoplastic hypertrichosis lanuginosa acquisita: uncommon or overlooked? Br J Dermatol. 2007;157:1087-92.
22. Hovenden AL. Hypertrichosis lanuginosa acquisita associated with malignancy. Clin Dermatol. 1993;11:99-106.
23. Jabbour SA. Skin manifestations of hormone-secreting tumors. Dermatol Ther. 2010;23:643-50.
24. Mendoza-Guil F, Hernández-Jurado I, Burkhardt P, Linares J, Naranjo R. Necrolytic migratory erythema associated with glucagonoma. Actas Dermosifiliogr. 2005;96:175-8.
25. Teixeira RC, Nico MM, Ghidei AC. Necrolytic migratory erythema associated with glucagonoma: a report of 2 cases. Clinics (São Paulo). 2008;63:267-70.
26. Qadan M, Visser B, Kim J, Pai R, Triadallopoulos G. Abdominal Mass, Anemia, Diabetes Mellitus, and Necrolytic Migratory Erythema. Dig Dis Sci. 2012;57:1465-8.
27. Dal Coleto CC, de Mello AP, Piquero-Casals J, Lima RR, Vilela MA, Festa-Neto C et al. Necrolytic migratory erythema associated with glucagonoma syndrome: a case report. Rev Hosp Clin Fac Med São Paulo. 2001;56:183-8.
28. Echenique-Elizondo M, Martinez de Lizarduy I. Glucagonoma and necrolytic migratory erythema. Rev Esp Enferm Dig. 2005;97(6):455-7.
29. Bártholo RM, Bártholo TP, Florião RA. Leser-Trelat: Um sinal clinico revisitado. Pulm RJ. 2009;18:3-56.
30. Kluger N, Guillot B. Sign of Leser-Trelat with an adenocarcinoma of the prostate: a case report. Cases J. 2009;2:8868.

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1. More than 50 dermatologic conditions have been reported as potential markers of malignancy. It is correct to state the following about cutaneous paraneoplastic manifestations:
   a) They are easily recognized, especially when associated with histological examination, given the peculiar cell features resulting from cell growth factors released by the tumor.
   b) When they precede the onset of malignancy, their evolution is not related to the patient’s response to cancer therapy.
   c) Paraneoplastic manifestations comprise a heterogeneous group of dermatoses that can occur directly (tumor invasion) or indirectly (distant interaction of the skin with substances released by the tumor).
   d) Due to their parallel course with the underlying neoplasm, they serve as a standard for the evaluation of progress or recurrence of malignancy.

2. Curth’s criteria are used in the recognition of cutaneous paraneoplastic syndromes. These criteria include all of the following, except:
   a) Parallel course of the neoplasm and cutaneous manifestation
   b) Lack of association between cutaneous manifestation and genetic syndrome
   c) Presence of tumor cells in skin lesions
   d) High frequency of association between the neoplasm and cutaneous manifestation

3. Acanthosis nigricans maligna:
   a) It is closely associated with diabetic nephropathy.
   b) It is a condition commonly found in insulin-dependent diabetes with poor control of the disease.
   c) It has a sudden onset and is predominantly associated with abdominal carcinomas.
   d) The underlying neoplasms tend to have an indolent course, which leads to long-term survival of patients.

4. Which of the following exams should be first requested of a patient with acanthosis nigricans malignant?
   a) Thyroid ultrasound with Doppler
   b) Upper digestive tract endoscopy
   c) Mammography
   d) Chest x-ray

5. Which of the following are NOT characteristics of acquired dermatoglyphia?
   a) It predominantly affects children with diseases of the lymphoid-hematopoietic tissue.
   b) It gives the palms a velvety yellowish aspect.
   c) It is often associated with Acanthosis Nigricans Malignant.
   d) Lung and gastric carcinoma should be investigated.

6. Widespread, serpiginous, polycyclic and pruriginous erythema which is desquamative around the edges and fast-growing, often associated with lung cancer. This description corresponds to:
   a) Erythema gyratum repens
   b) Erythema migrans necrolytic
   c) Erythema annulare centrifugum
   d) Disseminated granuloma annulare

7. Male patient, 45 years old, smoker, presenting with erythematous scaly patches on the nose, helix, and extremities for six months. He was being treated with topical corticosteroids and keratolytic drugs, without improvement of his condition. He also presented with subungual hyperkeratosis, onycholysis, and nail dystrophy. He was diagnosed with squamous cell carcinoma of the larynx. These dermatological symptoms probably correspond to:
   a) Seborrheic dermatitis and onychomycosis
   b) Psoriasis Vulgaris
   c) Bazex Syndrome
   d) Palmoplantar keratoderma of Unna-Thost

8. Female patient, 42 years old, had been undergoing laser hair removal treatment for 6 months with a non-dermatologist due to excessive hair growth on her face. She came to see the doctor due to treatment ineffectiveness. On examination, thin, soft and non-pigmented hair was observed on her face and ears. Complementary examination was normal. Based on this description, which of the following is the most prudent course of action?
   a) Regular monitoring with periodic examinations, since the condition can precede the onset of cancer.
   b) Referral to an endocrinologist for serial assessment of hormonal profile.
   c) Maintenance of laser hair removal treatment, changing the parameters of the device.
   d) Prescription of oral contraceptives with an antiandrojen profile.

9. It is correct to state the following about acquired hypertrichosis lanuginosa associated with malignancies:
   a) Its pathogenesis is well established with overproduction of virilizing hormones.
   b) It is more common in men and usually spares the face.
   c) In addition to a detailed clinical history, laboratory screening includes chest x-ray, colonoscopy and, in women, mammography.
   d) Metastasis is unusual and the patient usually has good prognosis.

10. Which of the following findings should be primarily considered and investigated in a patient with erythema migrans necrolytic?
    a) Pancreatic nodule seen on computed tomography.
    b) Type IV Bosniak cysts on computed tomography.
    c) BI-RADS III findings on digital mammography.
    d) Chammas III thyroid nodule on ecodoppler.

11. Early diagnosis and treatment of glucagonoma increase the potential for cure of cancer. Surgical resection is the treatment of choice, since the tumor is often resistant to chemotherapy. Which of the following options make up the triad of glucagonoma: glucose intolerance, hyperglucagonemia and:
    a) Erythema gyratum repens
    b) Erythema migrans necrolytic
    c) Halstead-Cullen Sign
    d) Erythema chronicum migrans
12. Patient, 70 years old, uncommunicative, accompanied by a caregiver in a nursing home. The caregiver noted the recent onset of numerous brownish papules and plaques, with a verrucous and waxy surface in the dorsum. The patient also presented significant weight loss and frequent nausea. The presumptive diagnosis of the underlying disease is:
   a) Squamous cell carcinoma of the larynx.
   b) Gastric Adenocarcinoma.
   c) Prostate Adenocarcinoma.
   d) Malignant Melanoma.

13. It is incorrect to state the following about the Leser-Trelat sign:
   a) It primarily affects the chest and dorsum.
   b) Pruritic and eczematous lesions are frequent findings.
   c) Association with paraneoplastic syndrome is common, especially with ANM.
   d) Histopathology of skin lesions is essential for diagnostic confirmation of the Leser-Trelat sign.

14) 68-year-old patient presenting with night sweats, weight loss and Pel-Ebstein fever. Extremely painful oral erosions develop. The probable diagnosis is:
   a) Pyostomatitis vegetans.
   b) Bullous pemphigoid.
   c) Behcet’s Disease.
   d) Paraneoplastic pemphigus.

15) Which of the following options characterizes paraneoplastic pemphigus:
   a) Preferential involvement of the skin of the trunk when compared to oral and conjunctival mucosae.
   b) Positive indirect immunofluorescence with rat bladder substrate.
   c) Low mortality rate.
   d) The autoantibodies produced by the tumor exclusively affect the skin and mucosae.

16. Female patient, 62 years old, presenting with periorbital erythema and edema, violaceous papules on interphalangeal joints with periungual erythema and telangiectasias. Which of the following is the most adequate initial management:
   a) Oral corticosteroids and observation, since it is an idiopathic disease.
   b) Alendronate and diltiazem, given its frequent association with calcinosis in this age group.
   c) Transvaginal ultrasound and chest X-ray, due to the known association with lung and ovarian carcinoma.
   d) Interruption of drug use, as clinical manifestations probably correspond to a drug-induced skin rash.

17. Which of the following alternatives is the correct association between a paraneoplastic manifestation and a neoplasia:
   a) Acanthosis nigricans malignant - Lymphoproliferative Disorders.
   b) Tripe palms - Medullary Thyroid Carcinoma.
   c) Bazex paraneoplastic acrokeratosis - aerodigestive tract.
   d) Erythema migrans necrolytic - Pancreatic adenocarcinoma.

18) Acute febrile neutrophilic dermatosis, also known as Sweet syndrome, has several causes. The following should be primarily investigated, except:
   a) Infection of the upper respiratory tract.
   b) Prior use of drugs.
   c) Hematological Malignancies.
   d) Rheumatoid Arthritis.

19. Patient with a deep ulceration with undermined edges in the pretilial region resulting from local trauma. Biopsy of the border of the ulcer showed neutrophilic inflammation with abscesses and necrosis. It is correct to state the following:
   a) Most cases are idiopathic.
   b) Nikolsky’s sign is typical of this condition.
   c) Inflammatory bowel diseases and neoplasms should be investigated.
   d) Pentavalent antimony, despite its adverse effects, remains the treatment of choice.

20. Male patient, 67 years old, diagnosed with bronchogenic carcinoma. T3N1M0 (stage IIIA), undergoing chemotherapy with cisplatin and etoposide. One week after the second treatment cycle, he developed pruritus and erythema on waxy brownish pre-existing papules and plaques on the upper limbs and bosom, as well as hyperpigmentation in the dorsal surface of extremities and nails. Which of the following is the most likely hypothesis for the clinical manifestations described:
   a) It is Bazex paraneoplastic acrokeratosis, often occurring in association with carcinomas of the upper aerodigestive tract and indicating poor prognosis.
   b) The clinical manifestations correspond to the Leser-Trelat sign and indicate metastases screening.
   c) The clinical manifestations refer to skin reactions to the antineoplastic drugs used and do not require interruption of treatment.
   d) The clinical manifestations refer to photosensitivity due to the use of alkylating agents and indicate substitution of the chemotherapy regimen, due to the risk of serious drug eruptions in case of reexposure.

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**Answer key**

Mycosis fungoides and Sézary syndrome: clinical, histopathological and immunohistochemical review and update2012;87(6):817-30.

| 1.  | 6.  | 11. | 16. |
|-----|-----|-----|-----|
| d   | d   | c   | a   |
| b   | b   | d   | b   |
| d   | c   | d   | b   |
| b   | b   | c   | a   |
| b   | b   | b   | d   |

**Papers**

Information for all members: The EMC-D questionnaire is now available at the homepage of the Brazilian Annals of Dermatology: www.anaisdedermatologia.org.br. The deadline for completing the questionnaire is 30 days from the date of online publication.