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Acanthosis Nigricans – a Clinical Manifestation of a Gastric Cancer

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Abstract: Diffuse cutaneous hyperpigmentation may have various causes: endocrine, metabolic, autoimmune, melanosis secondary to metastatic melanoma, drug or heavy metal poisoning. A cause to remember is acanthosis nigricans, which, in the form of paraneoplastic syndrome may be the first or even the only clinical manifestation of a cancer. The most common cause of malignant acanthosis nigricans is the gastric adenocarcinoma. This report presents a case, on those the histopathological diagnosis of acanthosis nigricans was not recognized, but which was suspected clinically. Investigation that followed found an aggressive gastric neoplasm, which has could benefit from surgery and chemotherapy. There are discussed the pathogenesis of this paraneopastic syndrome and the clinical manifestations of its association with the gastric cancer.
Keywords: Acanthosis nigricans, Cutaneous hiperpigmentation, Fibroblast growth factor receptor 2, Gastric cancer, Paraneopastic syndrome, Smoking

INTRODUCTION

The diffuse cutaneous hyperpigmentation requires thorough investigation to establish the etiology. It must be excluded the most common causes: endocrine (Addison's disease - in which there is overproduction of the melanotrop hormone and the patients have fatigue, weight loss, hypotension, and gastrointestinal disorders), metabolic (hemochromatosis - in which the intestinal absorption of dietary iron increases, responsible also of hepatomegaly, diabetes, heart and gonadal failure; porphyria cutanea tarda - with hyperpigmentation, especially in sun-exposed areas, with clear or hemorrhagic fluid bubbles, followed by erosions covered with scars and scabs, Whipple's disease - 50% of patients have diffuse hyperpigmentation, which is associated to diarrhea, weight loss, arthritis, lymph nodes), autoimmune (scleroderma – in which hyperpigmentation of the face, trunk and extremities can occur; primary biliary cirrhosis - where the disorder of the melanotrop hormone production is responsible for hyperpigmentation of areas exposed to light, plus itching, jaundice and xantomas), melanosis secondary to metastatic melanoma (with black-blue or gray tint), medicines or heavy metal poisoning (ACTH, amiodarone, busulfan, cyclophosphamide, chlorpromazine, or silver poisoning or long-term treatment with gold salts) [1].

CASE REPORT

Such a generalized skin hyperpigmentation more pronounced in the cervical region, chest and in the folds of flexion, occurred in a patient of 69 years, smoker (20 cigarettes a day for 20 years), who worked 25 years as a driver, exposed to contact with organic solvents and aromatic hydrocarbons. He ignored it. In the next four months came also skin itching, loss of appetite and weight loss (6 kg), which led him to contact the family doctor, who sent him for investigation in dermatology and endocrinology services. There it have been excluded: hemochromatosis (blood glucose, sideremia, and liver biochemistry were normal and skin biopsy slides colored Perls without iron deposits), cutaneous amyloidosis (without amyloid deposits on Congo red colored slides), lichen pigment (skin biopsy), adrenal insufficiency (normal blood pressure, serum and urine electrolytes - normal, ACTH and cortisolemia - normal), ACTH-secreting pituitary adenoma (ACTH and normal cranial MRI - slight pituitary atrophy). Mycological examination of the skin isolated Malassezia furfur and skin biopsy was interpreted as confluent and reticulated papillomatosis Gougerot - Carteaud.

Because under antifungal (terbinafine hydrochloride 250 mg 1 tablet/day and Sabouraud solution), and antihistaminic therapy (loratadine 10 mg 1 tablet/day) the clinical manifestations persisted, he came to the internal medicine service, where it was suspected that skin hyperpigmentation may be the expression of a paraneoplastic syndrome. On the clinical examination the hyperpigmentation was diffuse, included the upper half of the body, including the

cephalic extremity and was pruritic; multiple hyperkeratotic papules were present, with tendency to junction in plaques with irregular edges, well demarcated, brown dirty. Blood counts and usual biochemical tests were normal. Abdominal ultrasound examination revealed the presence of gallbladder gallstones and a left adrenal tumor of 62/31 mm, confirmed by abdominal computertomography, which has seen small perigastric and celiaco-mesenteric lymph nodes. Upper gastrointestinal endoscopy described a large ulcerative-infiltrating area, located subcardial on the large gastric curvature, to the posterior wall. In two of the three biopsy fragments was observed a poorly differentiated adenocarcinoma with areas of necrosis and ulceration of the mucosa, infiltrating.

The patient having gastric adenocarcinoma with retroperitoneal and left adrenal metastases was treated surgically (total gastrectomy with Roux-en-Y esophagojejunostomy, perigastric lymphadenectomy and direct cholecystectomy). Subsequently, for the left adrenal metastasis it has been opted for chemotherapy with capecitabine (900 mg/day). Eight months after the onset of skin pigmentation he has been in good clinical condition and has continued the chemotherapy.

DISCUSSION

On the skin biopsy reevaluation, the same pathologist found the presence of squamous epithelium with mild hyperkeratosis and acanthosis. If on these we add the skin hyperpigmentation and the papillomatous lesions there are present the diagnosis criteria of acanthosis nigricans [2]. Only the dermatologist appreciation that the skin lesions would be willing rhomboidal and the presence of hyphae and fungal spores in the stratum corneum were initially inclined to confluent and reticulated papillomatosis Gougerot – Carteaud, usually present in adolescents, as hyperkeratotic papules, initially erythematous, which later become brown and have a reticular distribution [3].

In the U.S., acanthosis nigricans is relatively common, especially among Native Americans. It is less common in African Americans and Hispanics. In the Caucasian it is the most rare [4]. In the pathogenesis of non-paraneoplastic form of acanthosis nigricans is involved insulin, which can promote growth by its setting on insulin-like growth factor 1 receptors and by the augmentation of the serum levels of free insulin growth factor 1, which is involved in the stimulation of cell growth and differentiation. In paraneoplastic form of acanthosis nigricans, which is more rare, there are occurring mutations which confer hyperfunction or variations of fibroblast growth factor receptor 2, observed in the diffuse type of gastric cancer [5]. In the gastric tumor of a patient with acanthosis nigricans it was highlighted an amplification of the epidermal growth factor receptor, which is the ligand of transforming growth factor alpha, which has mitogenic effect on keratinocytes in vitro [4, 6]. Another opinion is that some tumor gastric cells of patients with malignant acanthosis nigricans may result from endocrine cells [7].

The most common cause of malignant acanthosis nigicans is adenocarcinoma of gastrointestinal tract and especially of the stomach [8]. On the other hand, in gastrointestinal carcinoma there may be various skin manifestations, including acanthosis nigricans [9]. In addition to skin lesions, in acanthosis nigricans may occur lesions also on angles of the mouth, oral and esophageal mucosa [2], and conjunctival mucosa may also occur[6]. Some patients may have ascites [8]. It was cited a case of meningeal carcinomatosis appeared 2 months after the gastric resection in a patient with gastric cancer and acanthosis nigricans, which responded well to intrathecal therapy with cytarabine, methotrexate and hydrocortisone [10]. It was published a case of cutaneous hyperpigmentation in a patient with hereditary hemochromatosis and who developed acanthosis nigricans as a paraneoplastic manifestation of gastric adenocarcinoma [11]. Some gastric cancers manifest themselves only by skin lesions [9]. "Tripe palms" is characterized by thick and velvety-white palm skin with hypertrophy of the dermatoglyphics [12] and is associated in 77% of cases with a gastric cancer if the patients have acanthosis nigricans [13].

Most gastric adenocarcinoma of patients with paraneoplastic skin manifestations, including acanthosis nigricans, are found in advanced stages [9, 14], fact which explains the small survivals (often less than 1 year). There are also exceptions: a woman survived 8 years and 6 months after surgery, and her acanthosis nigricans lesions disappeared completely [14].

CONCLUSION

Although malignant acanthosis nigricans is not frequent, it have to be noted as cause of skin hyperpigmentation. Recently appeared skin hyperpigmentation should be suspected also as an expression of a paraneoplastic syndrome and patients should be investigated in this regard. The most common cause of malignant acanthosis nigricans is gastric adenocarcinoma, and prognosis of these patients is poor because the tumor is found frequently in advanced stages. In our opinion, it is recommended that patients with cutaneous hyperpigmentation to be directed to internal medicine services to be investigated, because the internist doctor has a large overview on the pathology and can develop an investigation plan which may conduct rapidly at diagnosis. Thinking, clinical experience, and the guidelines have to guide the investigation of patients. Any analysis that involves a

degree of subjectivity is better to be done by more experts.

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