Florid cutaneous papillomatosis and acanthosis nigricans maligna revealing gastric adenocarcinoma *

Papilomatose cutânea florida e acantose nigricante maligna reveladoras de neoplasia gástrica

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Abstract: This paper reports the case of a 57-year-old, previously healthy male with no systemic symptoms who over a short period of time developed multiple wart-like lesions on his trunk, limbs and face, typical lesions of acanthosis nigricans in the major body folds and tripe palms. Diagnostic tests revealed a metastatic gastric adenocarcinoma. Despite the implementation of therapy, which had a transient effect on the tumor and skin lesions, the patient died in 14 months. The association of these three paraneoplastic dermatoses (florid cutaneous papillomatosis, acanthosis nigricans maligna and tripe palms) in the same patient, apparently with a common pathogenic mechanism, is noteworthy.
Keywords: Acanthosis nigricans, paraneoplastic syndromes; Stomach neoplasms

Resumo: Apresenta-se o caso clínico de um doente de 57 anos, previamente saudável, sem sintomatologia sistêmica, que, num curto intervalo de tempo, desenvolve múltiplas lesões semelhantes a verrugas virais no tronco, membros e face, lesões típicas de acantose nigricante nas grandes pregas e uma queratodermia difusa palmar com paquidermatoglifia. Os exames complementares de diagnóstico revelaram uma neoplasia gástrica metastizada. Apesar da instituição da terapêutica, com efeito transitório na neoplasia e nas lesões cutâneas, o doente viria a falecer em 14 meses. Salientamos a associação destas três dermatoses paraneoplásicas num mesmo paciente: papilomatose cutânea florida, acantose nigricante maligna e tripe palms que parecem ter um mecanismo patogênico comum.
Palavras-chave: Acantose nigricans; Neoplasias gástricas; Síndromes paraneoplásicas

INTRODUCTION

Florid cutaneous papillomatosis (FCP) is characterized by the rapid appearance of numerous papulous lesions that are clinically indistinguishable from viral warts on the trunk, limbs and face. The condition has been described in association with acanthosis nigricans maligna (ANM) and internal neoplasia and does indeed appear to represent an obligate paraneoplastic dermatosis, since it is always associated with an internal, generally intraabdominal malignancy, which tends to progress in parallel with the dermatosis.

CASE REPORT

A 57-year old, white, previously healthy, male patient sought medical care for a dermatosis that had appeared around three and a half months previously. The condition was becoming progressively worse; however there was no accompanying systemic or local symptomatology. He had various types of skin lesions: 1) poorly delineated, symmetrical brownish keratotic plaques with a velvety surface in the axillae and lateral and posterior surfaces of the neck, typical of acanthosis nigricans; 2) purplish plaques with a

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mammillated, verrucous surface in the inguinal regions (Figure 1); 3) diffuse palmoplantar keratoderma and tripe palms (Figures 2 and 3); 4) millimetric, keratotic papular lesions located on the face, predominantly in the periocular and peribuccal regions (Figure 4); 5) hyperkeratotic papillomatosis of the nipples and mammary areolae (Figure 5); and 6) multiple papular, keratotic lesions measuring between 3 and 6 mm, scattered over the skin, predominantly on the upper limbs and trunk. No further abnormalities such as weight loss, palpable peripheral adenopathy or hepatosplenomegaly were found at clinical examination. A clinical diagnosis of florid cutaneous papillomatosis and acanthosis nigricans was made (confirmed by histopathology that showed irregular papillomatosis with orthokeratotic hyperkeratosis; Figure 6). A decision was made to hospitalize the patient. The analytical study failed to show any significant alterations other than an increase in tumor markers: CEA = 22.0 ng/ml (normal levels <5.4) and CA 19.9 = 64.0 U/ml (normal levels <37). Upper gastrointestinal endoscopy showed multiple papillomatous lesions in the esophageal mucosae; however, no abnormalities were found in the gastric or duodenal mucosae. Computed tomography of the chest, abdomen and pelvis showed three lesions suggestive of lung metastases, each measuring < 15 mm, and multiple intraabdominal adenopathies. In view of the strong suspicion of gastrointestinal malignancy and despite the results of endoscopy, esophageal, gastric and duodenal transit was performed, the report stating that "in the corpus–antrum transition zone, an area of convergence of folds, apparently surrounding a mass measuring 2.5 cm in diameter, with central ulceration, suggestive of a gastric tumor". Upper gastrointestinal endoscopy was then repeated, the report stating that "on the posterior side of the corpus-antrum transition zone, in an area of difficult access, a small, slightly irregular, cicatrizing ulcer, in which cytology and biopsies were performed". Anatomopathology revealed a diffuse gastric adenocarcinoma. The decision was taken to initiate neoadjuvant chemotherapy with 5-fluorouracil and cisplatin. After the second cycle of chemotherapy, the lung metastases disappeared and there was a considerable reduction in the number and dimensions of the intraabdominal adenopathies, as well as a significant improvement in the skin lesions. However, by the end of the third cycle, the patient's general condition and that of the skin lesions had once again deteriorated and new adenopathies had appeared in the mediastinum and peritoneal cavity. Chemotherapy was changed to 5-fluorouracil and irinotecan, and the patient's clinical condition improved, albeit transitorily. From the third cycle onwards, the patient's condition deteriorated once

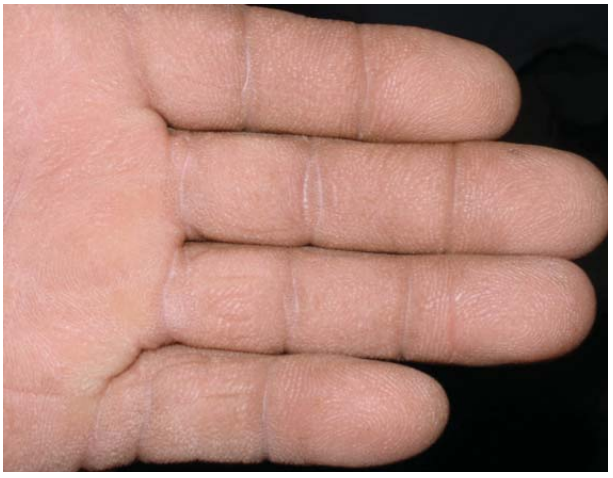

Figure 2: Tripe palms

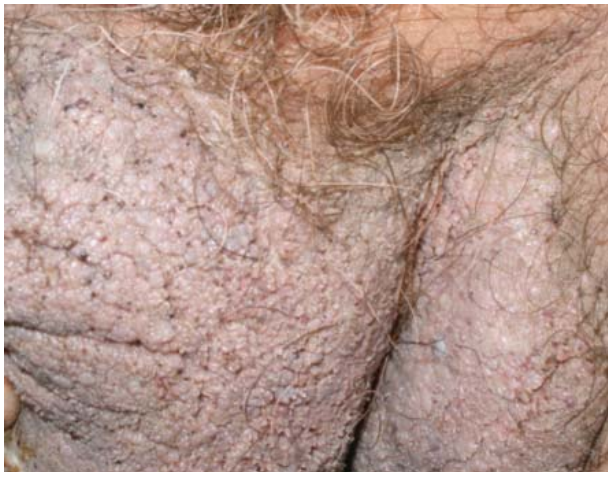

Figure 1: Purplish plaques located in the inguinal regions

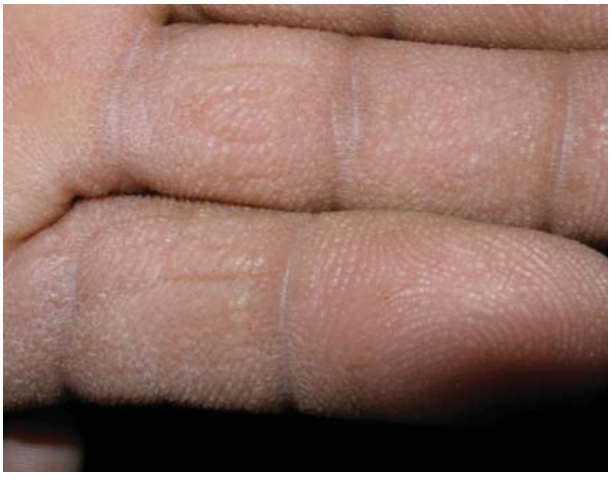

Figure 3: Tripe palms

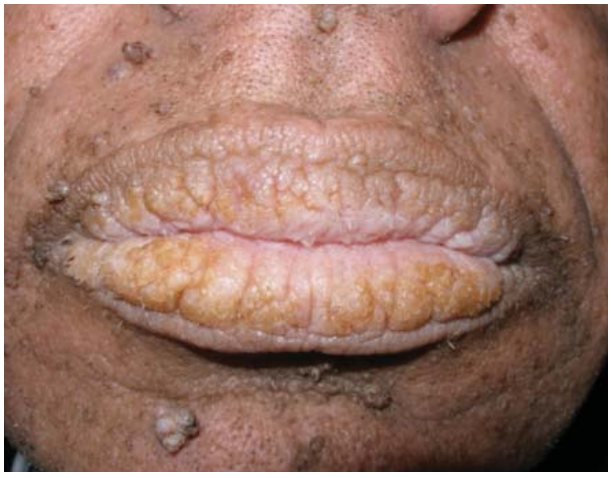

Figure 4: Peribuccal involvement

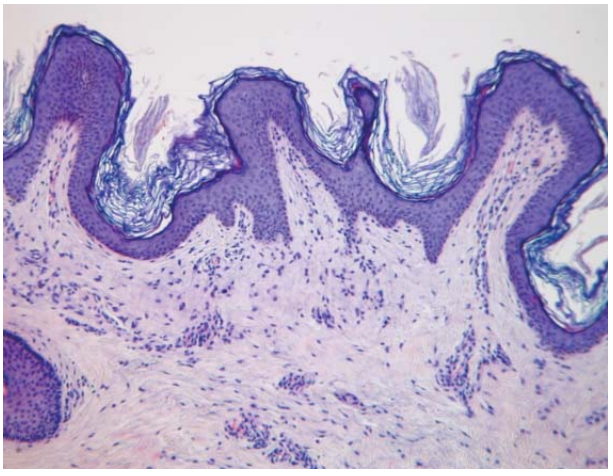

Figure 6: Irregular papillomatosis with orthokeratotic hyperkeratosis

again and chemotherapy was suspended after the fifth cycle due to lack of response. The patient died 14 months after diagnosis.

DISCUSSION

Acanthosis nigricans (AN) is clinically characterized by the appearance of thick velvety skin with hyperpigmentation located symmetrically in intertriginous areas. The condition is histologically characterized by hyperkeratosis and papillomatosis with mild acanthosis. Eight types of AN have been described: acral, benign, malignant, drug-induced, mixed, associated with obesity, syndromic and unilateral. Benign AN may be associated with obesity, polycystic ovary syndrome, diabetes mellitus, adrenal insufficiency and other insulin-resistant conditions. AN may also occur secondary to the use of drugs such as nicotinic acid, insulin, systemic corticosteroids and diethylstilbestrol, and, less commonly, with oral contraceptives, fusidic acid and methyltestosterone. Discontinuation of the drug leads to improvement or even disappearance of the AN lesions. Acanthosis nigricans maligna (ANM) is a well-known paraneoplastic dermatosis that was first described in 1890. [1] The exact incidence of the condition has never been established; however, it was reported in 2 out of 12,000 patients with cancer over a 10-year period. [2,3] There is extensive mucocutaneous involvement and rapid progression in association with systemic neoplasia, usually a gastric adenocarcinoma. Rigel and Jacobs [4] reported the association of ANM with carcinomas of the ovary, endometrium, cervix, breast, testicle, lung, kidney, pancreas, liver, esophagus, prostate, thyroid and pharynx, among others. The underlying malignancies tend to be very aggressive. Mean survival following diagnosis has been reported to range from 8.7 to 11.9 months.

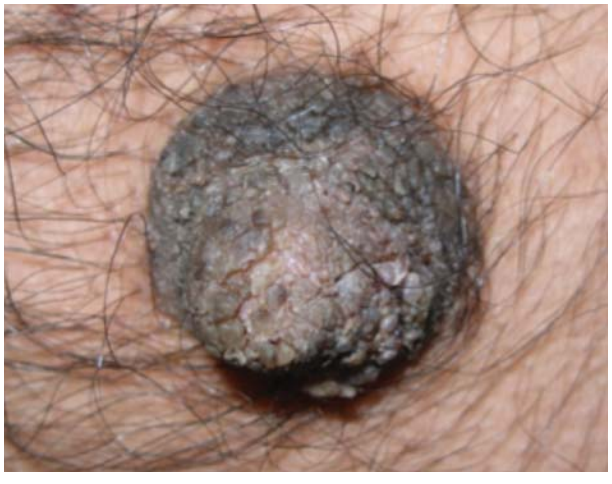

Figure 5: Hyperkeratosis of the nipple and mammary areola

Florid cutaneous papillomatosis (FCP) is a rare paraneoplasia first described by Pollitzer in 1891[5] and named by Schwartz and Burgess in 1978. [6] In 1991, Gheeraert identified 23 cases in a literature review. [7] Of the underlying tumors present in these patients, the most common was gastric adenocarcinoma (15/23). The condition is characterized by the rapid appearance of multiple verrucous lesions that are clinically indistinguishable from common warts. The lesions begin on the limbs, particularly on the backs of the hands and wrists, but may affect the trunk and the face. As in the present case, they may affect the ocular and oral mucosae, as well as the nipples and mammary areolae. Pruritus may be limited to the areas affected by the skin lesions or may be generalized. The histology of these lesions shows hyperkeratosis, irregular acanthosis and papillomatosis, with no epidermal vacuolization, parakeratosis or

eosinophilic inclusions suggestive of common warts. The underlying malignancy is generally intraabdominal (most commonly gastric) and progresses concomitantly with FCP. A significant improvement in the skin lesions of FCP is found in one-third of cases following chemotherapy or surgical intervention directed at the primary tumor,[6] while, on the other hand, FCP lesions become worse following dissemination and metastasis of the tumor, [8,9] as seen in the present case.

Hyperkeratosis of the nipple and areola (HNA) is characterized by hyperpigmented, verrucous or filiform keratotic thickening. It is further classified into three types: type 1: associated with an epidermal nevus, generally unilateral; type 2: associated with a more disseminated dermatosis, namely AN,[10,11] Darier disease, chronic eczema such as atopic eczema and cutaneous T-cell lymphoma; it is generally bilateral, reflecting the disseminated or systemic nature of the underlying pathology; and type 3: nevoid or idiopathic HNA, which is unassociated with any other pathology and is an isolated finding. It may occur unilaterally, but is often bilateral. HNA has also been described in association with sorafenib, [12] an inhibitor of various intracellular kinases involved in cell growth. The association between ANM and FCP is common, as is the association between these two dermatoses and Leser-Trélat (LT) sign, which is characterized by the sudden onset of multiple seborrheic keratoses that are often pruriginous and distributed over the trunk in a Christmas tree-like pattern.

Tripe palms (TP) were first described by Clarke [13] and later by Breathnach and Wells,[14] who classified them as a form of palmar acanthosis. The condition is characterized by diffuse, yellowish palmar hyperkeratosis, with enhancement of the epidermal ridges on the hands (dermatoglyphics), resembling intestinal villosities. Cohen[15] reported the association of TP with internal neoplasia in 69/77 cases (90%). Andreev [2] referred to TP and LT sign as clinical variants of ANM; however, cases of both conditions have been reported in which ANM was not present.[15] These paraneoplastic dermatoses may be found prior to or at the time of diagnosis of the primary malignancy or, in rare cases, later. Usually, progression accompanies evolution of the tumor. [4,7,11] The etiopathogenesis of ANM, as well as FCP, TP and LT sign, remains to be fully clarified. These conditions are thought to be directly induced by the primary neoplasia, probably triggered by a growth factor produced by the tumor. The role of insulin resistance in the benign forms of AN, although complex, has already been established. Insulin resistance leads to compensatory hyperinsulinemia. In turn, increased serum insulin levels interact with insulin-like growth factor 1 (IGF-1) receptors in peripheral tissues, leading to the proliferation of keratinocytes and fibroblasts. In ANM, increased serum levels of growth factors, particularly transforming growth factor (TGF)-alpha, act through the epidermal growth factor receptors (EGFR). Hida et al. also reported the possible role of fibroblast growth factor receptor 3 (FGFR3) in the etiopathogenesis of ANM. [16] The case reported here, with typical lesions of acanthosis nigricans maligna, florid cutaneous papillomatosis and tripe palms occurred in the absence of any gastrointestinal complaint. Since gastric adenocarcinoma is the most common neoplasia associated with these paraneoplastic dermatoses, supplementary diagnostic tests were performed and a malignant gastric tumor was confirmed, already with distant lung metastases and regional lymph node metastasis. Chemotherapy successfully reduced the number and size of the intraabdominal adenopathies and resulted in regression of the three pulmonary lesions. A significant improvement was seen in the paraneoplastic skin lesions. Nevertheless, with the progression of the primary neoplasia, a progressive deterioration occurred in the patient's general state of health, with a further deterioration in the skin lesions, as has also been reported in the literature. This case shows the importance of FCP, ANM and TP as neoplastic markers and emphasizes the need to perform an exhaustive study as soon as possible when attempting to diagnose the underlying neoplasia so as to provide the patient with the most appropriate treatment. ❑

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