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Case Report

Malignant acanthosis nigricans as a paraneoplastic manifestation of metastatic breast cancer☆,☆☆

Javier Arellano [a,b], Pamela Iglesias [a], Claudia Suarez [a], Yamile Corredoira [c,d], Katty Schnettler [d]

[a] Department of Dermatology, University of Chile, Santiago, Chile
[b] Department of Dermatology, Hospital Clínico San Borja, Arriarán, Chile
[c] Department of Pathology, University of Chile, Santiago, Chile
[d] Department of Pathology, Hospital Clínico San Borja, Arriarán, Chile

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ABSTRACT

Malignant acanthosis nigricans is a rare paraneoplastic syndrome, usually associated with a gastric adenocarcinoma and less frequently with other neoplasms. In general, its appearance indicates a poor prognosis with a survival of <2 years. We describe the case of a 40-year-old patient who presented with generalized cutaneous thickening that had a velvety appearance, was rapidly progressing, and involved right axillary adenopathy. Skin and nipple biopsy yielded results consistent with acanthosis nigricans, and palpable adenopathy biopsy results were compatible with mammary adenocarcinoma (human epidermal growth factor receptor 2 positive and estrogen and progesterone receptor negative) without a detectable primary tumor. This case of malignant acanthosis nigricans is presented because of the importance of its early recognition as a paraneoplastic syndrome and its relation with mammary adenocarcinoma, an association infrequently reported in the literature.

Introduction

Cutaneous manifestations are often reflections of internal diseases, with the skin as the only indication in some cases (Vora et al., 2016). The cutaneous manifestations of internal malignant tumors could be due to direct effects (i.e., invasion of the skin by a tumor or its metastasis) or indirect effects that trigger cutaneous signs or symptoms that are part of the paraneoplastic syndromes (Yuste-Chaves and Unamuno-Pérez, 2013).

Skin disease can sometimes provide the first clue in the diagnosis of internal malignancy (Vora et al., 2016). The first dermatosis associated with a malignant process was malignant acanthosis nigricans (MAN; one of the most studied associations), which may precede, occur simultaneously with, or be found after a diagnosis of cancer (Ehst et al., 2010; Thiers et al., 2009). Its most frequent association is with abdominal, mainly gastric, tumors (Thiers et al., 2009), which are important to rule out in cases of suspected MAN. We present the case of a woman with MAN in whom metastatic breast adenocarcinoma was diagnosed, an association scarcely reported in the literature.

Clinical Case

A 40-year-old female patient with a history of arterial hypertension, under treatment with losartan and nifedipine, was seen in dermatology for xerosis of sudden and rapidly progressive onset of 2 months' evolution, associated with the appearance of a right axillary nodule and estimated weight loss of 2 kg. Physical examination revealed a generalized thickening of the skin, with a velvety appearance, accentuated in the eyelids, lips, neck, nipples, axillae, palms, groin, and knees. No alterations were observed in the oral mucosa. Hyperpigmentation was also observed in the axillae and groin. The diagnosis of MAN was suggested (Fig. 1) Skin biopsies were performed and showed hyperkeratosis, papillomatosis, mild acanthosis, and minimal superficial lymphocyte perivascular infiltrate consistent with the diagnosis (Fig. 2)

Concomitantly, a systemic study was conducted and highlighted erythrocyte sedimentation rate (ESR) 45 mm/h with the rest of the laboratory parameters as normal. With regard to the breast imaging study, bilateral mammography showed no suspicious signs of malignancy (Breast Imaging Reporting and Data System (BIRADS) 2), and

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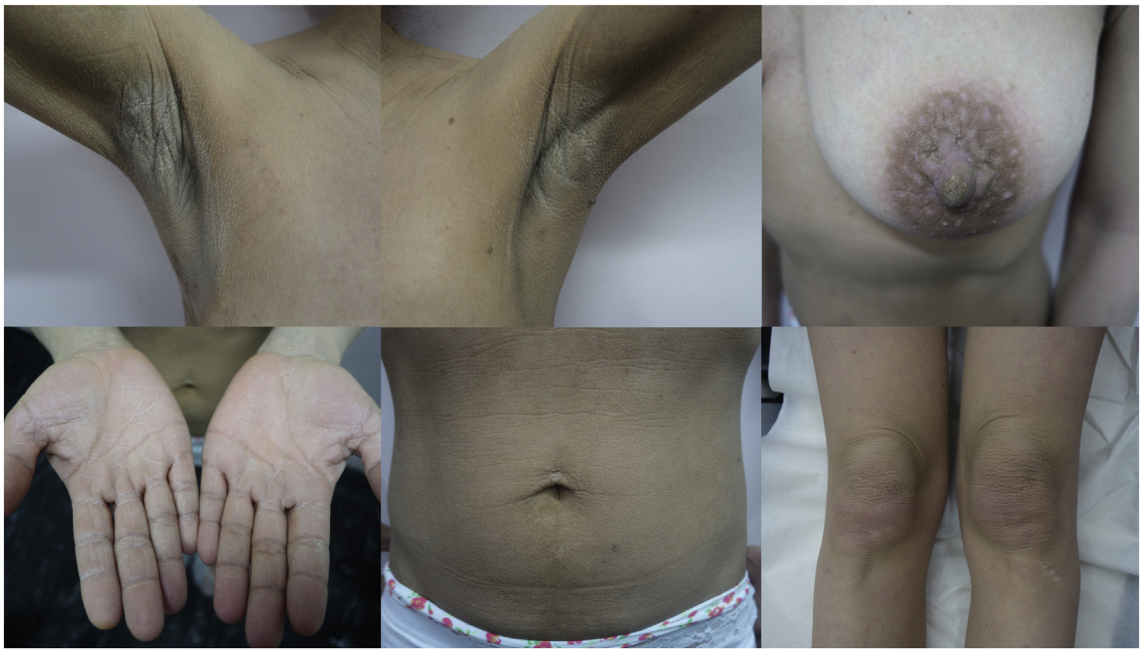

Fig. 1. Generalized thickening of the skin, especially evident in the areolae, lips, and hands.

bilateral mammary ultrasound revealed only markedly dense breasts. A percutaneous biopsy of the palpable right axillary adenopathy was performed, and the results were consistent with breast adenocarcinoma metastasis. In the absence of a detectable primary breast tumor, a regional axillary lymphadenectomy was performed. Adenocarcinoma metastasis was found in 2 of the 20 lymph nodes resected, with positive immunohistochemical study for total cytokeratins (CK; AE1/AE3), GATA-3, CK 7, mammaglobin, and HER2 and negative for estrogen receptors (Clone EP1), progesterone receptors (Clone 636), CK-20, CK5/6, p63, S100 protein, TTF-1, GCDFP-15, napsin, PAX-8, CEA, and CDX-2. HER2 + status was confirmed with the fluorescent in situ hybridization technique (Fig. 3).

Ultrasound-guided core biopsies were taken from nodules of benign appearance in the left and right breast with nonspecific architectural distortion, with no cytological atypia in the examined tissues. The study of chest, abdomen, and pelvis by computed tomography with contrast showed no compromise of the internal organs, and there were no osteoblastic lesions by bone scintigraphy. Upper digestive endoscopy was performed and revealed active chronic antral gastritis without signs of gastric neoplasm. Given the described findings, a TxN2M0 metastatic breast adenocarcinoma was diagnosed. Treatment with chemotherapy, trastuzumab, and localized radiation therapy in the right breast and ipsilateral axilla were indicated.

Discussion and review

Acanthosis nigricans is a skin condition characterized by papillomatous, velvety, and hyperpigmented plaques that tend to affect intertriginous and flexor areas symmetrically, although it can compromise any part of the body. Acanthosis nigricans can be classified

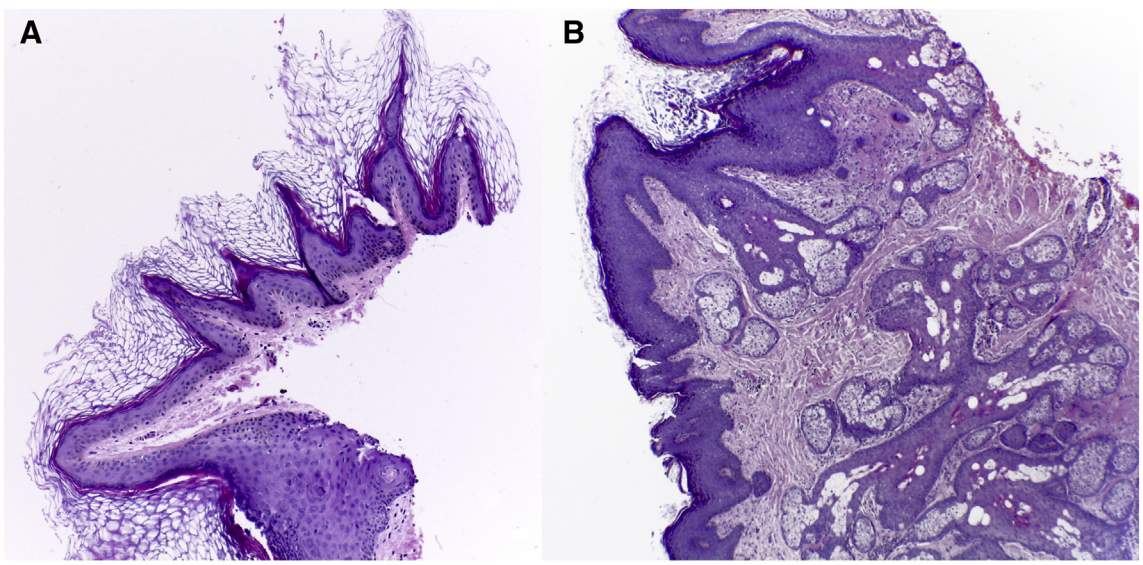

Fig. 2. (A) Skin showing hyperortokeratosis, marked papillomatosis, mild acanthosis, and discrete melanic hyperpigmentation of the epidermal basal layer. (B) Areola skin with hyperortokeratosis, papillomatosis, and acanthosis.

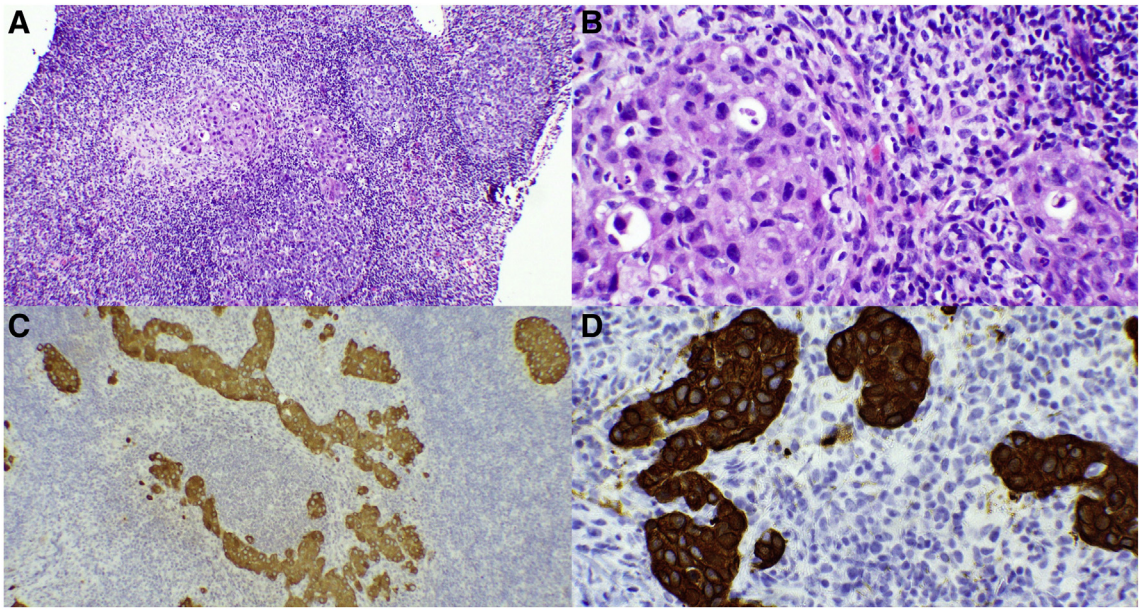

Fig. 3. (A,B) Lymph node showing metastasis of adenocarcinoma (hematoxylin and eosin). (C) Mammaglobin stain diffusely positive in tumor cells. (D) Total cytokeratins (AE1/AE3) positive in cytoplasm of tumor cells.

as benign or malignant. Benign acanthosis nigricans is associated with endocrinopathies, such as obesity, insulin resistance, diabetes mellitus 2, acromegaly, Cushing syndrome, and hypothyroidism, and with congenital abnormalities and drug use (Schwartz and Janniger, 2011). On the other hand, MAN is considered a paraneoplastic dermatosis (i.e., related to internal neoplasms but not, in itself, a malignant condition).

MAN was first described in 1890 by Pollitzer (1891) and Janowsky (1891), who each reported a case of acanthosis nigricans in the same volume of the *International Atlas of Rare Skin Diseases* (1891). Later, Darier pointed out the association of this condition with internal malignancies, emphasizing the concept of MAN as a paraneoplastic syndrome (Darier and Pollitzer, 1920). Its exact prevalence is unknown. Acanthosis nigricans is more frequent in patients aged >40 years and does not present differences by sex (Curth, 1955; Kubicka-Wolkowska et al., 2014).

MAN is characterized by sudden onset, extensive condition, and progressive course. It can be generalized, with cutaneous and mucosal involvement, in some cases being associated with the development of acrochordons, oral papillomatosis, multiple seborrheic keratosis (Leser-Trélat sign), and acanthosis nigricans palmoplantar (Mekhail and Markman, 2002; Sedano and Gorlin, 1987). MAN can appear before (17.4%), during (61.1%), or after (21.5%) the diagnosis of neoplasia (Curth, 1955), and skin lesions tend to improve with tumor resection. MAN can reappear before recurrences (Curth, 1955; Yu et al., 2017). In general, the occurrence of MAN has been associated with a poor cancer prognosis; the average survival of patients after diagnosis is <2 years (Sedano and Gorlin, 1987).

The pathogenesis of this condition is unknown. Currently, it is proposed that certain cytokines produced by the tumor, such as transforming growth factor alpha, insulin-like growth factor 1, and fibroblast growth factor, participate in the development of the lesions in acanthosis nigricans through the stimulation of keratinocytes, melanocytes, and fibroblasts (Kubicka-Wolkowska et al., 2014). Transforming growth factor alpha plays a primordial role through its action on the epidermal growth factor receptors, according to reports in several publications (Ellis et al., 1987; Koyama et al., 1997; Torley et al., 2002; Wilgenbus et al., 1992).

The histological characteristics of MAN are not specific; it is characterized by hyperkeratosis and papillomatosis, with a certain degree of acanthosis and thickening of the spinous layer (Pipkin and Lio, 2008). The dark coloration observed in acanthosis nigricans is due to hyperkeratosis and not to an increase in melanocytes (Thiers et al., 2009).

MAN is most frequently associated with intra-abdominal carcinomas (73.2%), and only 26.8% of cases have extra-abdominal tumors (Rigel and Jacobs, 1980). From a histologic point of view, the tumors are mainly adenocarcinomas (Ehst et al., 2010), with gastric adenocarcinoma detected most frequently (56%-61%) and tumors in the liver, uterus/cervix, breast, lung, pancreas, and colon/rectum, among others, detected less frequently (Rigel and Jacobs, 1980).

Reported cases of breast cancer are scarce. In an analysis by Curth (1943), 9 cases were presented; in 1980, 5 more cases were added in another study (Rigel and Jacobs, 1980). From that date until today, no new cases have been reported that associate breast cancer with MAN.

Conclusions

We describe the case of a woman who presented with sudden, generalized acanthosis nigricans, in whom metastatic breast cancer adenocarcinoma (TxN2M0 HER2) was diagnosed synchronously. There are few reported cases in the literature of MAN in the context of breast cancer (Rigel and Jacobs, 1980). This case of MAN presented with a rapidly progressive and concomitantly diagnosed cancer, as occurs in most cases. In addition, the cancer showed aggressive behavior, with regional lymph node metastases, which is consistent with the ominous prognosis associated with this paraneoplastic syndrome.

This case is presented because it indicates the importance for the medical community, especially dermatology, to recognize MAN and its associations early. Early detection can change the prognosis and treatment of patients. Of note, although MAN is present mainly in the context of intra-abdominal neoplasms (mostly gastric), other tumors can develop MAN as a paraneoplastic skin manifestation, as evidenced in this reported case.

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