Ectopic extramammary Paget disease in thoracic location

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Abstract

Extramammary Paget disease (EMPD) is a rare skin cancer that affects areas with a high concentration of apocrine glands including genital, axillary, and anal skin. When it affects other locations it is called ectopic extramammary Paget disease (E-EMPD) and is uncommon. To date, there are only 45 case reports to the best of our knowledge. The clinical manifestation is typically a soft, red or bright pink patch or plaque with scattered white islands of hyperkeratosis and erosion. Diagnostic confirmation requires conventional histology with immunohistochemistry. The importance of immunohistochemical staining for the diagnosis of primary neoplasia, without underlying malignancy, is highlighted. We report the first Latin American confirmed case, to our knowledge, of primary E-EMPD in a 55-year-old man with a 1-year history of asymptomatic thoracic plaque.

Keywords: dermatologic oncology, ectopic extramammary Paget disease, thorax, rare disease, skin cancer, rare cancer

Introduction

Extramammary Paget disease is an uncommon adenocarcinoma that affects areas with a high apocrine gland concentration including the genital skin, axillae, and anus [1]. Extramammary Paget disease (EMPD) has been rarely reported to occur in areas either containing smaller concentrations of, or completely devoid of apocrine glands; such cases have been termed ectopic EMPD (E-EMPD), [2]. Classic EMPD and E-EMPD have similar clinical and histological presentation, except for the location of cutaneous lesion [3].

To date, there have been only 45 reported cases of E-EMPD in a wide variety of anatomic locations, which were more common among Asian patients [3]. Herein, we report a case of primary E-EMPD arising on the thorax.

Case Synopsis

A 55-year-old Chilean man with a history of controlled diabetes mellitus presented with a 1-year history of an asymptomatic progressively growing erythematous plaque on the thorax that showed no response to topical treatment with antifungals and corticosteroids. Physical examination revealed a 12mm asymmetric pinkish-brown plaque with a slight scale on the left parasternal area (**Figure 1A**). Dermoscopy revealed an erythematous background with brown clustered dots and irregular brown structures associated with isolated dotted vessels on the periphery and structureless whitish areas and short shiny white lines in the central zone (**Figure 1B**).

Complete excision of the skin lesion was performed. Histopathology showed an epidermis infiltrated by glandular structures and nests of atypical cells, which were large round cells with abundant and clear eosinophilic cytoplasm and pleomorphic large, centrally situated basophilic nuclei. Parakeratosis and invasion of adnexal structures were present, associated with a mild perivascular inflammatory infiltrate of lymphocytes and histiocytes in the upper

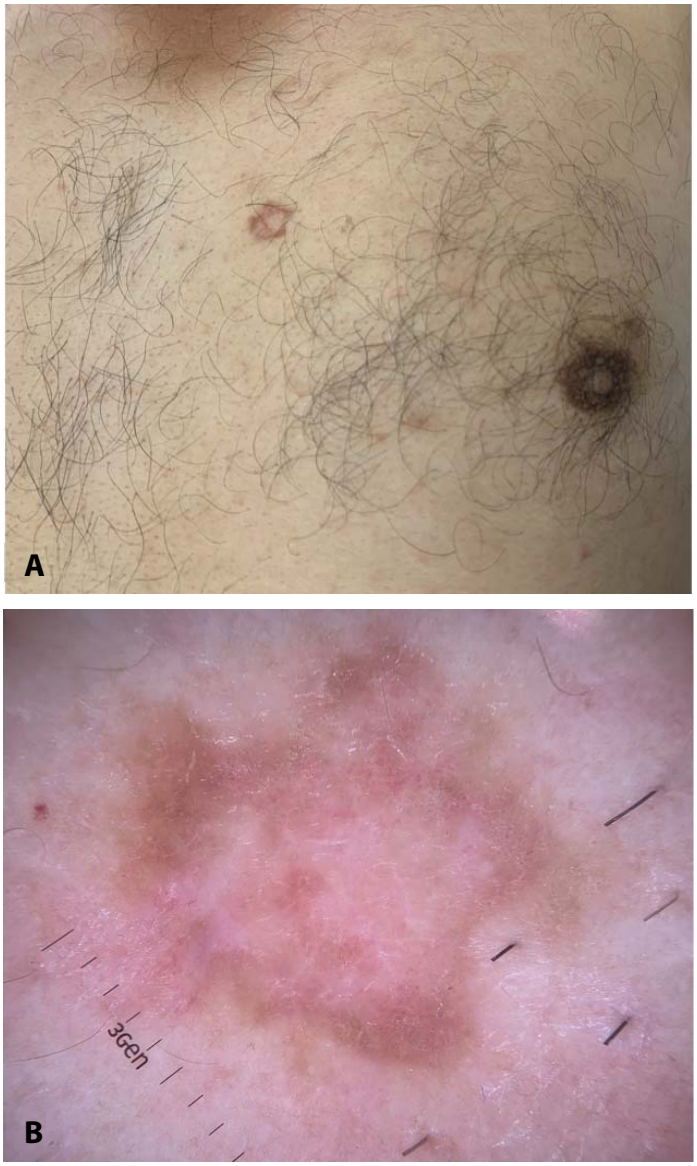

Figure 1. ***A)*** *Clinical image. A 12mm asymmetric pinkish-brown plaque with a slight scale on the left parasternal area.* ***B)*** *Dermoscopic image. An erythematous background with brown clustered dots and irregular brown structures associated with isolated dotted vessels on the periphery and structureless whitish areas with short shiny white lines on the central zone.*

dermis (**Figures 2A-C**). Positive staining with periodic acid-Schiff demonstrated intracytoplasmic sialomucin (**Figure 2D)**. Immunohistochemical study demonstrated expression by the cells of CK7 and GCDFP-15, whereas they failed to express CK20, SOX-10, Melan-A, p63, ER, and PR (estrogen and progesterone receptor). Herceptest was negative.

Imaging tests were performed, and PET-CT showed diverticular disease of the colon without other pathological findings. Colonoscopy revealed diverticulosis of the sigmoid colon and normal upper digestive endoscopy. Other screening laboratory tests were negative including PSA of 0.6ng/ml. Bilateral MRI of the breasts showed no evidence of solid nodules or pathological lymphadenopathy. The diagnosis of primary ectopic extramammary Paget disease was confirmed. Owing to the reported surgical excision with neoplasm-free margins (5mm) without other suspicious skin lesions, he returned to his rural town because of the Covid-19 pandemic without any further treatment. Clinical follow-up of the patient was recommended and at three months of follow-up there was no sign of recurrence.

Case Discussion

Ectopic extramammary Paget disease is a very rare intraepithelial adenocarcinoma and the existence in areas void of apocrine glands could be explained by the theory that Paget cells are derived from pluripotent germinative cells within the epidermis capable of differentiating into either apocrine or eccrine glands after exposure to certain carcinogenic factors [2,3].

Typically the tumor presents as a soft, red or bright pink patch or plaque with scattered white islands of

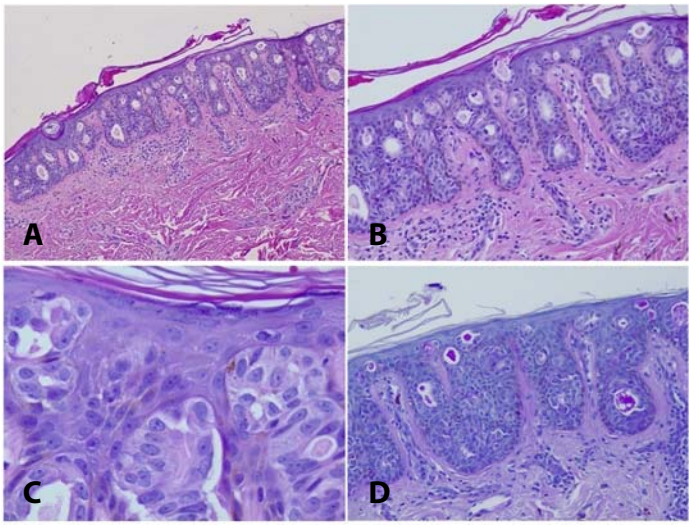

Figure 2. ***A, B)*** *Epidermis infiltrated by glandular structures and nests of atypical cells and a slight inflammatory infiltrate of lymphocytes in the upper dermis. H&E,* ***A)*** *100×,* ***B)*** *200×.* ***C)*** *Atypical large round cells with abundant and clear eosinophilic cytoplasm and pleomorphic large, centrally situated basophilic nuclei. H&E, 1000×.* ***D)*** *The large cytoplasmic vacuoles are caused by abundant mucin, which is easily recognized by histochemical stains such as periodic acid-Schiff/Alcian blue, 200×.*

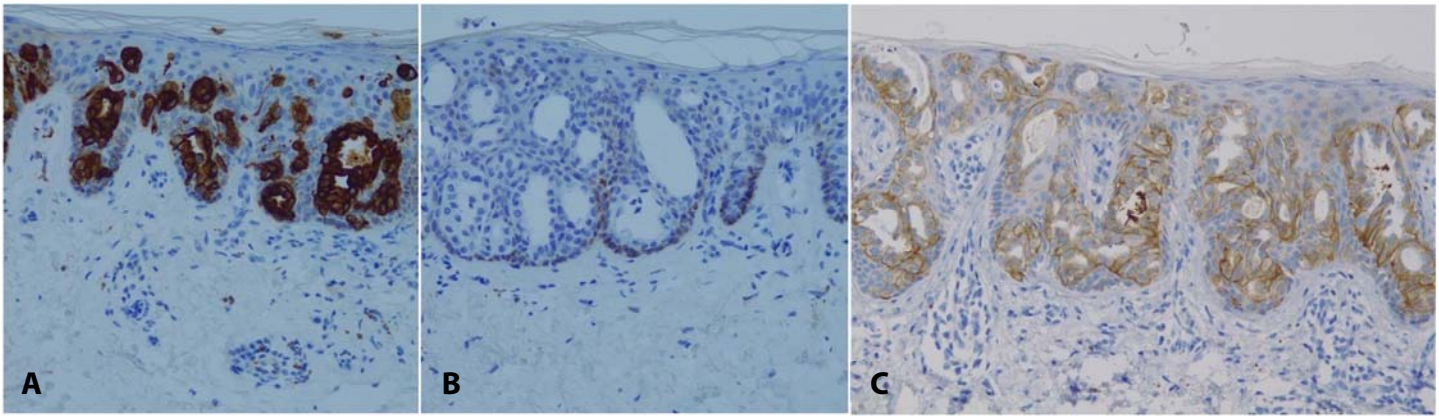

Figure 3. *Immunohistochemical staining of proteins expression in extramammary Paget disease.* ***A)*** *Positive expression of CK7, 200×.* ***B)*** *Negative expression of CK20, 200×.* ***C)*** *Positive expression of GCDFP-15, 200×.*

hyperkeratosis and erosion, often referred to as "strawberries and cream" appearance [3]. It may be asymptomatic or present with a burning sensation and pruritus [4]. The differential diagnosis of E-EMPD includes various dermatitides such as eczema, intertrigo, psoriasis, or cutaneous neoplasms [1]. In relation to the dermoscopic findings described, we must consider Bowen disease and malignant melanoma in the differential diagnosis. Only one dermoscopic sign described here, the irregular brown structures, could be more associated with E-EMPD [5].

Histopathological examination is essential in the diagnosis of EMPD, which must include hematoxylin and eosin staining and immunohistochemical staining. Specific immunohistochemical stains are used to identify Paget cells and also differentiate primary from secondary forms of EMPD [1,2]. Cytokeratin stains such as CK7 and CK20 are used to categorize EMPD and predict whether an underlying malignancy may be present. CK7 has high sensitivity but low specificity as an EMPD marker (**Figure 3**). CK20 is usually present in many carcinomas of the gastrointestinal and urothelial tracts. Therefore, primary EMPD usually stains CK7+ and CK20-, whereas secondary EMPD generally stains CK7+ and CK20+ [2,6]. Furthermore, gross cystic disease fluid protein (GCDFP-15) is strongly expressed in cases of EMPD without underlying malignancy [2,6]. There is little evidence linking E-EMPD with associated malignancies, making it difficult to determine if a specific evaluation is necessary. It is recommended to follow the protocol established for EMPD, which, based on patient characteristics, can include abdomen/pelvis imaging, chest X-ray, positron-emission tomography scan, colonoscopy, cystoscopy, mammography, and/or pelvis imaging examinations [3]. Our case corresponds to a primary E-EMPD because it did not present with an associated underlying malignancy. All this was consistent with the described immunohistochemistry profile (CK7+/CK20-/GCDFP15+) and the extensive imaging study performed.

The treatment modalities described for E-EMPD include conventional surgical excision, Mohs micrographic surgery (MMS), topical immunotherapy, and photodynamic therapy. Although available reports are limited, wide local excision with a two-to-three cm clinically-clear margin or MMS is recommended [3]. Mohs micrographic surgery appears to be superior to wide local excision when considering tissue sparing ability and disease recurrence and has been described for classic EMPD [2]. Nonsurgical interventions have also been investigated with varied results [3]. In our case, the excision was performed with smaller margins than recommended, owing to low diagnostic suspicion of E-EMPD. Follow-up was decided, because of the absence of other suspicious lesions and the current health context (Pandemic covid-19), added to the favorable prognosis of E-EMPD described in the literature. There are no reports of dermal invasion and only one case has been reported with lymph node invasion [3]; there are no cases where distant metastasis were identified in the

literature, suggesting E-EMPD might have a more benign biological activity [3]. Regardless of the treatment performed, long-term follow-up is recommended to observe for local recurrence of the disease.

To date, 45 cases of E-EMPD have been reported [3]. Our patient is case number 46 reported, being the 30th case of E-EMPD arising in the trunk and the first case reported in Latin America. There are racial differences in the incidence, gender, and sites of ectopic EMPD [3]. It is postulated that some apocrine differentiating germ cells may exist particularly in the trunk of the Asian population, which would explain the predominance of cases of E-EMPD in this location and population [3,7].

Conclusion

Ectopic extramammary Paget disease is a rare variant of extramammary Paget disease with, to our knowledge, only 46 cases reported. The clinical manifestation is usually an erythematous or pink plaque asymptomatic or with burning sensation and pruritus, located in areas either containing smaller concentrations of or completely devoid of apocrine glands, unlike extramammary Paget disease. The diagnosis requires conventional histology with immunohistochemistry. The importance of immunohistochemical staining for the diagnosis of primary neoplasia, without underlying malignancy, is highlighted, confirming the immunohistochemical profile (CK7+/CK20-/GCDFP15+) described for primary extrammamary Paget disease. All the same, as in extramammary Paget disease, cases of associated malignancy should be ruled out through study of images or endoscopies, evaluated on a case-by-case basis. The recommended treatment is extrapolated to that for extramammary Paget disease, which consists of surgical excision with 2-3cm clear margins. However, regardless of the treatment carried out, long-term follow-up is recommended.

Potential conflicts of interest

The authors declare no conflicts of interest.

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