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Re: Extramammary Paget disease - diagnostic and therapeutic challenges

Dear Sir,

Pegalajar-García MD *et al*. reported in this Journal the case study of a 70-year-old man, who had the diagnosis of extramammary Paget's disease (EMPD).[1] At first, the main clinical hypothesis considered for differential diagnosis included Langerhans cell histiocytosis, Bowen's disease, amelanotic melanoma, besides mycosis fungoides. But a dermoscopy evaluation revealed whitish and dotted vessels suggestive of the EMPD diagnosis, which was further confirmed by the gross cystic disease fluid protein 15 (GCDFP-15), mammaglobin and CK7 positive, and HMB 45 and S-100 protein negative. Imaging and complementary laboratory determinations discarded concomitant malignancies, a major prognostic factor, which can occur in contiguous (23%) or distant (8%-46% locations. He underwent the excision of the plaque, but non-surgical procedures include the management utilizing imiquimod, photodynamic therapy, or radiotherapy. The authors emphasized the common genital or perianal and rare axillary sites; the prevalence from 35 to 80 years of age; the high recurrence rate, and the long follow-up.[1] Considering the importance of this case report to increase the suspicion index of non-specialists about the EMPD, which may evolve unsuspected or misdiagnosed, the objective is present a short review of additional literature data from 2022 and 2023.[2-8] Besides, the classical dermoscopic patterns of EMPD, as the milky-red and white structureless areas, polymorphous vascular patterns and glomerular vessel patterns, surface scales, ulcers, shiny white lines, and pigmentary structures must be highlighted;[1,3] this resource is useful to assess and detect recurrent EMPD, and improve the outcomes.[3]

Caruso G, *et al*. reviewed 96 studies (5 prospectives, 24 retrospectives, 30 case series, and 37 case reports) about the vaginal Paget's disease (VPD); the 5617 patients were aged between 29 and 100 years, with the average of 71 years at their diagnoses.[2] The majority

of VPD lesions were erythematous, eczematoid, and pruriginous; the median follow-up varied from one month to 9 years, with 23% to 73% of recurrences that were managed by new surgical excision or imiquimod, 5-fluorouracil, or radiotherapy.[2] The authors stressed the need of databases to better understand this challenging disease. Fang WC, *et al*. reported the use of dermoscopy to monitor recurrences of EMPD in four patients with histopathological diagnosis of EMPD in the axilla (n = 1) and in genital area (n = 3); 3 patients had wide excision with clear surgical margins and one completed the treatment with photodynamic therapy (PDT) followed by topical use of imiquimod.[3] Interestingly, typical vascular patterns were found in the lesions of scrotum but not in those of axilla, possibly due to the axillary papillomatous epidermis and thicker dermis.[3] Navajas Hernández P, *et al*. reported a 85-year-old man with two decades of diagnosed ulcerative colitis (UC), who had the diagnosis of recent perianal primary Paget's disease and evolved to death before the radiotherapy management to control the invasive lesions.[4] The authors commented on the rarity of perianal PD (1.3% of all PD), the prevalence among 60-70 year-old women, besides the CK7 and 34ßE12 positive tumor markers; and the lack of literature data establishing a relationship between the UC and perianal PD.[4] Pérez JC, *et al*. performed a review on the diagnosis and treatment of EMPD localized or metastatic, and called attention about the low incidence of this entity, the lack of randomized clinical trials, and the role of publishing retrospective studies or case reports.[5] They also reported the case study of a 75-year-old woman with the diagnosis of vulvar PD, and inguinal lymph node implants of a poorly differentiated adenocarcinoma.[5] The CK7, EMA, androgen receptors, and CEA positivity; besides CK20, estrogen and progesterone receptors, and GCDFP 15 negative, confirmed metastases of vulvar origin.[5] She started chemotherapy (carboplatin AUC-4 plus paclitaxel) with a lymph node partial response, followed by the consolidation radiotherapy on the vulvar area plus pelvic and inguinal lymph node chains; as she had hepatic implants and the HER2 was positive 3+, the schedule was changed by trastuzumab and paclitaxel (suspended after neurotoxicity).[5] She was treated with only trastuzumab till moved to another state, with loss to follow-up. The authors commented on the few reported cases of anti HER2 treatment and androgen and/or estrogen blockade with favorable outcomes, which may justify the routine evaluation of the HER2, androgen, and estrogen receptors overexpression in vulvar PDs.[5] Sohn BS, *et al*. performed a retrospective study to evaluate the treatment outcomes among 37 patients with advanced and metastatic EMPD; 6 had locoregional and 31 had systemic chemotherapy as first-line treatments (22 platinum-based had an objective response rate

(ORR) of 45.5%, and 8 taxane-based had 62.5%, while the systemic chemotherapy combined with anti-HER2 antibody had an ORR of 100%.[5] They stressed the lack of standard treatment for advanced or metastatic EMPD, but trastuzumab plus taxane can propitiate longer survival than monotherapy or platinum- or taxane-based chemotherapy.[5]

Early diagnosis of EMPD often constitutes a challenging task for non-specialists, and due to rarity, the advanced or metastatic have no established standard treatment. Classical dermoscopic patterns are useful to detect EMPD and improve the prognosis.

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Response from Authors

Dear Sir,

Thank you for your interesting comment to our research. EMPD is considered an infrequent entity, even more outside genital location. As you have emphasized, dermoscopy is an essential tool for the suspicion of this entity, but also for detection of recurrences[1], which are very common in this disease. It is remarkable that Fang et al[1] mention in their article the lack of vascular patterns in the axillary lesion, as in our case. They try to explain this finding based on axilla's histology, with papillomatous epidermis and thicker dermis. The presence of papillomatous structures we describe in our report may be consistent with this fact. This characteristic could rise the suspicion of this tumour, in addition to the rest of the mentioned findings[2].

Although the important role of non-specialists and dermatologists in recognizing this entity through clinical and dermoscopics findings, we should point out that histology is the gold standard for EMPD's diagnosis. Biopsy should be performed in all this cases in order to stablish a proper diagnosis, but also because it helps to distinguish between primary or secondary disease[3].

We agree with the affirmation that strong evidence based on clinical trials and consensus guides about its management and treatment is mandatory, both in local EMPD disease but even more in advanced and metastatic EMPD.

In conclusion, EMPD is a rare cutaneous tumour where dermoscopy can be essential for early diagnosis, both of initial lesion or recurrences during the following, and robust scientific investigation is needed to improve the clinical attendance for these patients.

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