CASE REPORT

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Extramammary Paget's disease in an HIV-positive patient

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Abstract

Extramammary Paget's disease (EMPD) is an uncommon intraepithelial carcinoma usually found as an irregular, pruritic plaque on the apocrine-rich anogenital skin. Diagnosis of EMPD is challenging due to the rarity of the disease and the uncharacteristic clinical aspect and requires histopathological confirmation. We report the case of a 62-year-old human immunodeficiency virus (HIV)-positive male, which presents with a lesion of the left part of pubic area with clinical and dermatoscopic appearance suggestive for Bowen's disease but with histopathological diagnosis of EMPD. We present pathological and immunohistochemical data to confirm the diagnosis.

Keywords: extramammary Paget's disease, dermatoscopy, immunohistochemistry.

Introduction

Extramammary Paget's disease (EMPD) is an uncommon intraepithelial adenocarcinoma, which typically involves the apocrine gland-bearing skin [1–7].

Even if was first described in a male patient [8], in Caucasians EMPD is very rare in men, usually developing in women. It predominantly affects elderly patients and the predilection sites of development are the vulva in women and the perianal region in men [4, 6, 7, 9]. Other common locations are scrotum, perineum, penis, pubic area and the axillary skin whereas EMPD rarely develops on the trunk, face and extremities [2, 4, 6, 7, 10–12].

In most cases EMPD develops as a primary epidermal neoplasm but it also may arise as a cutaneous spreading of an underlying adnexal, rectal, prostatic or urinary tract malignancy [1, 5, 13–19]. Therefore, a thorough systemic evaluation for an underlying neoplasm must be performed.

EMPD usually presents as a well delineated thickened, erythematous plaque, with irregular borders, frequently covered with white scales, sometimes with ulcerations and areas of hyper or hypopigmentation. Local itching or burning sensations are often associated [2, 6, 11, 12].

EMPD resembles clinical features of other inflammatory, infectious or malignant skin diseases, such as eczema, seborrheic dermatitis, lichen simplex chronicus, lichen sclerosus, lichen planus, psoriasis, fungal infections, Bowen's disease, superficial basal cell carcinoma, pagetoid reticulosis or melanoma [2–6, 11–13, 20–23].

Often, the diagnosis of EMPD is a challenge and recent studies suggested that modern *in vivo* skin imaging techniques may improve diagnostic accuracy of EMPD. Dermatoscopy may facilitate the identification of distinctive features of EMPD. Another non-invasive diagnostic technique is reflectance confocal microscopy (RCM), which allows a high-resolution investigation of skin lesions [24–29] and may facilitate earlier diagnosis of EMPD and a better evaluation of tumor margins [3, 5].

Nevertheless, due to the rarity of the disease, its relatively non-specific features and the various clinical presentations histopathological examination is required to confirm the clinical diagnosis [3, 5, 7, 30].

Here we describe the case of a 62-year-old human immunodeficiency virus (HIV)-positive male, which presents with a lesion of the left pubic area with clinical and dermatoscopic appearance suggestive for Bowen's disease but with histopathological diagnosis of EMPD. We present pathological and immunohistochemical data to confirm the diagnosis.

Case presentation

We present the case of a 62-year-old male, which has been identified HIV positive since October 2011. The diagnosis was established by enzyme-linked immunosorbent assay (ELISA) test and confirmed by Western blot. At the time of HIV infection detection, the level of cluster of differentiation (CD) 4+ lymphocytes was 540 cells/mm^3 and viral load (VL) 99.828 copies/mL; all the other laboratory findings were within the normal range. Antiretroviral treatment with lamivudine and zidovudine (Combivir) plus raltegravir (Isentress) was initiated; the patient has favorable clinical and biological evolution; to date (July 2017), the level of CD4+ lymphocytes is 679 cells/mm^3, VL being undetectable.

He presented for a routine check-up in September 2013, accusing the development of a pinkish slightly demarcated asymptomatic maculo-papular lesion in the

left part of pubic area, which has been evolving for six months (Figure 1). Dermatoscopic examination was performed; dermatoscopic images were acquired using a digital video-dermatoscope (FotoFinder, Teachscreen, Germany). The dermatoscopic image showed a non-pigmented tumor with coma-like vessels (Figure 2), hence the initial suspicion of a Bowen's disease in a HIV-positive patient and an initial biopsy of the lesion was performed.

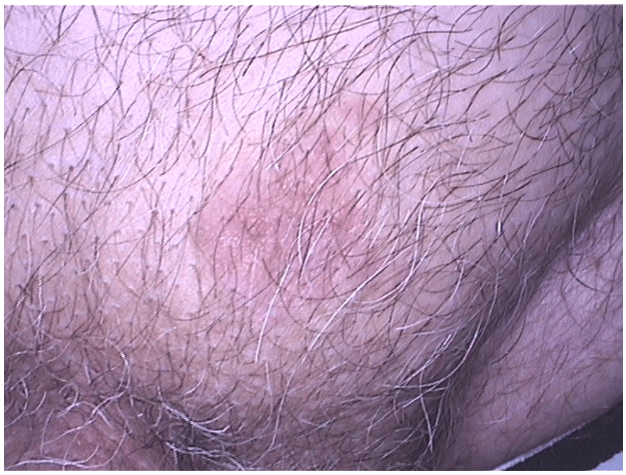

Figure 1 – P*inkish erythematous macular and papular lesion in the left pubic area.*

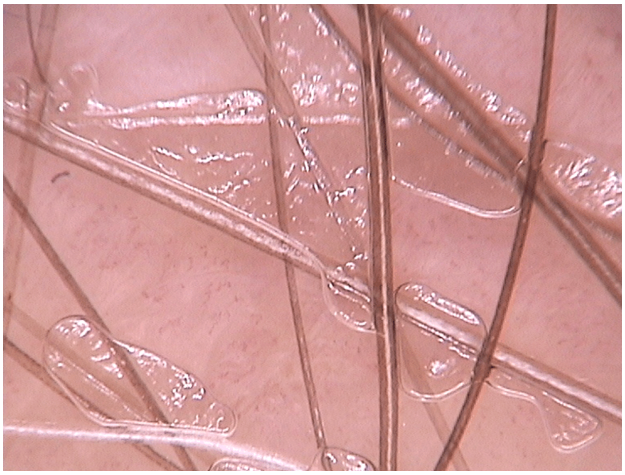

Figure 2 – ***Dermatoscopy shows coma-like vessels suspicious of a Bowen's disease.***

After resection, the cutaneous biopsy was immersed in 10% buffered formalin for 24 hours; afterwards, the tissue was washed in running tap water for 1.5 hours and submitted for routine automatic histopathological processing on a Leica ASP200S tissue processor (ethanol 70^0 for 90 minutes at 40^0C, ethanol 80^0 for 105 minutes at 40^0C, ethanol 96^0 for 105 minutes at 40^0C, ethanol 100^0 for 60 minutes at 40^0C, ethanol 100^0 for 90 minutes at 40^0C, ethanol 100^0 for 90 minutes at 40^0C, three baths of xylene two hours at 52^0C, paraffin 58^0C one hour, paraffin 58^0C two hours, paraffin 58^0C three hours). The tissue fragments were embedded in paraffin blocks using Thermo Fisher Microm EC 1150 H embedding station; 3 µm thick sections were cut using a Leica RM 2265 rotary microtome; the slides were stained with Hematoxylin and Eosin (HE), Periodic Acid–Schiff (PAS) and van Gieson stainings. Immunohistochemical (IHC) tests were performed using several primary antibodies: cytokeratin (CK) 8/18 [mouse monoclonal, clone 5D3, Leica, Nussloch, Germany, trypsin digestion of paraffin section 37^0C for 10 minutes, 1:100 dilution, incubation period 60 minutes], CK7 [mouse monoclonal, clone OV-TL12/30, Leica, Nussloch, Germany, high temperature antigen retrieval using 0.01 M citrate retrieval solution pH 6 for 15 minutes, 1:100 dilution, incubation period 60 minutes], p63 [mouse monoclonal, clone 7 JUL, Leica, Nussloch, Germany, high temperature antigen retrieval using ethylenediaminetetra-acetic acid (EDTA) retrieval solution pH 8 for 15 minutes, 1:100 dilution, incubation period 30 minutes], S100 protein [rabbit polyclonal, Leica, Nussloch, Germany, no antigen retrieval, 1:400 dilution, incubation period 60 minutes], human melanoma black (HMB)-45 [mouse monoclonal, clone HMB45, Leica, Nussloch, Germany, proteinase K digestion of paraffin section 37^0C for 10 minutes, 1:200 dilution, incubation period 30 minutes], melan A [mouse monoclonal, clone A103, Leica, Nussloch, Germany, high temperature antigen retrieval using 0.01 M citrate retrieval solution pH 6 for 15 minutes, 1:200 dilution, incubation period 30 minutes], epithelial membrane antigen (EMA) [mouse monoclonal, clone GP1.4, Leica, Nussloch, Germany, no antigen retrieval, 1:400 dilution, incubation period 60 minutes] and the Novolink™ Max DAB (3,3'-diaminobenzidine) (Polymer, Leica, Nussloch, Germany). Light microscopy examination of slides was performed using a Nikon Eclipse 80i microscope, and pictures were acquired using a digital camera attached to a computer.

Histopathological examination of the biopsy specimens from the lesion revealed the presence of large pale cells with prominent nuclei within the epidermis; the tumor cells presented prominent pagetoid spread (Figure 3). The lesion was CK7 positive (Figure 4). A diagnosis of extra-mammary Paget's disease was established.

The lesion was completely excised (complete excision within macroscopically normal tissues with subsequent *per primam* suture). The specimen consisted in a cutaneous fragment of 4/3 cm in diameters, 1 cm in thickness, with a centrally located slightly elevated tumor of 2.5/2 cm in diameters; the tumor was gray-whitish with irregular surface, uneven contour and firm consistency after fixation. The resection margins were painted with black tissue marking dyes; the specimen was trimmed into six parallel sections; the tumor was present in sections two to five; the specimen was embedded *in toto*. Histopathological processing of the tissue fragments followed the same procedure as cutaneous biopsy (see above). Histopatho-logical examination of the excision specimen showed a similar picture with tumor nests of Paget's cells invading the epidermis, with pagetoid spreading (Figure 5).

Notably, the cells formed prominent duct-like nests in the basal or suprabasal layers. The tumor cells showed nuclear atypia, and the decapitation secretion into the lumina was partly seen in the inner cells of ductal structures. No tumor invasion was found in the dermis. The tumor cells had focal positivity for PAS (Figure 6). Immunohistochemically, the tumor cells were positive for CK8/18 (Figure 7, A and B) and CK7 (Figure 8) and negative for p63 (Figure 9) and HMB-45 (Figure 10), supporting the diagnosis of EMPD. Few apocrine

sudoriferous glands (ectopic glands considering the location of the lesion) were also identified in couple of sections (Figure 11).

A thorough cutaneous and lymph node examination was performed and no involvement of the other organs was detected on various examinations (abdominal ultrasound, computed tomography, chest X-ray, and upper and lower endoscopic analyses). At that moment, the level of CD4 T-lymphocytes was 850 cells/mm^3.

The patient is free of disease after 47 months and is monitored every three months to assess possible local recurrences.

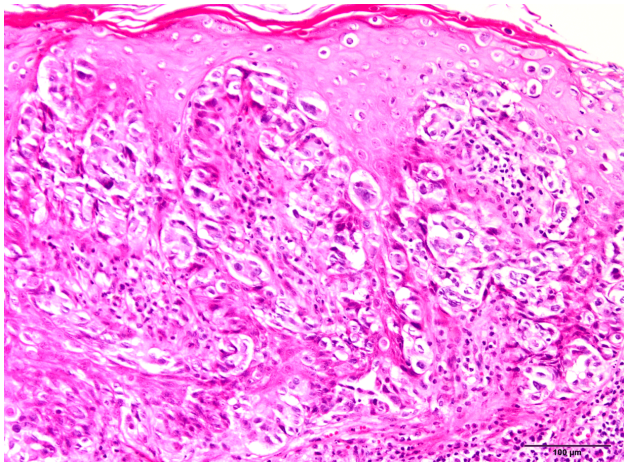

Figure 3 – ***Epidermis with heavy tumor infiltration by nests and isolated polygonal cells with pale cytoplasms and vesicular nuclei; prominent pagetoid spreading. HE staining, ×200. Scale bar: 100 µm.***

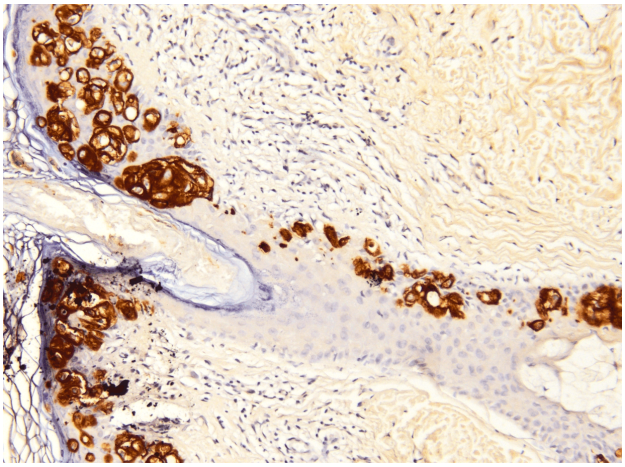

Figure 4 – ***Numerous tumor cells positive for CK7 arranged in small nests or as isolated cells with prominent pagetoid spread and extension along skin adnexa. CK7 immunostaining, ×200.***

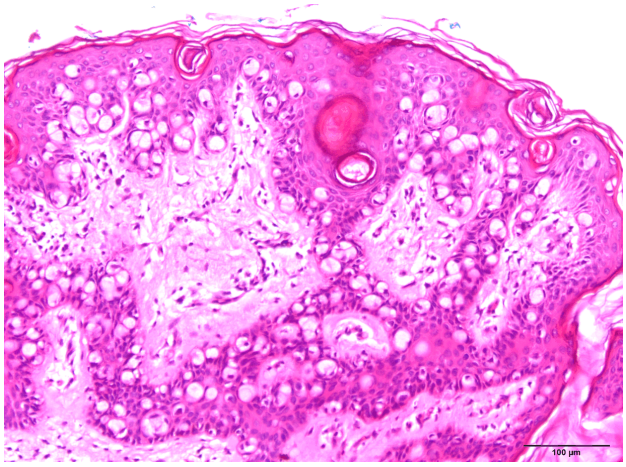

Figure 5 – ***Numerous large tumor cells with pale cytoplasm; most cells are arranged within basal layer but quite numerous cells have pagetoid growth within epidermis. HE staining, ×200. Scale bar: 100 µm.***

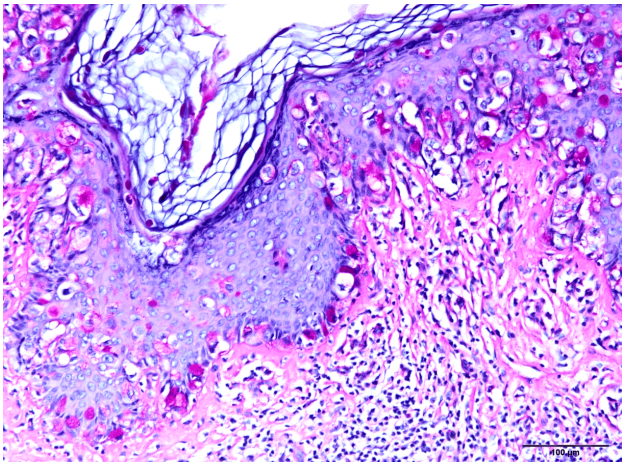

Figure 6 – ***Focal PAS positivity consistent for mucin secretion in the cytoplasm of several tumor cells. PAS staining, ×200. Scale bar: 100 µm.***

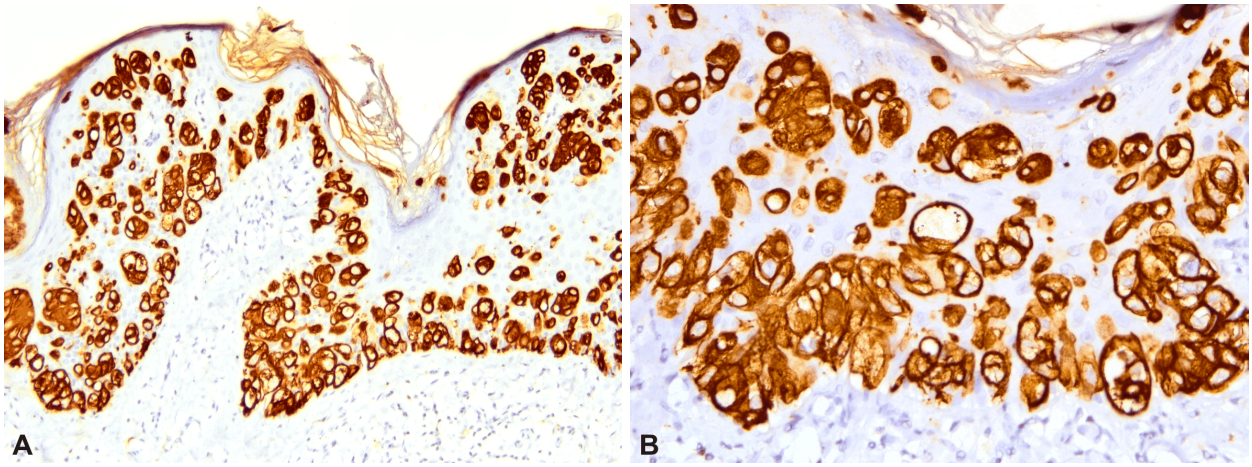

Figure 7 – ***Intense positivity of the tumor cells for CK8/18. Immunohistochemical staining reveals prominent pagetoid growth of the tumor cells: (A) ×200; (B) ×400.***

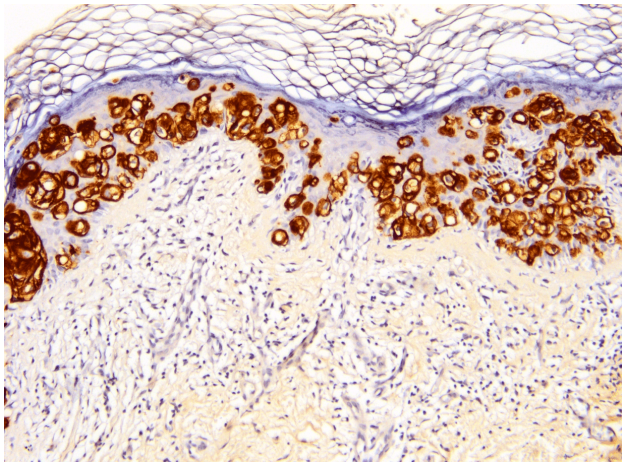

Figure 8 – ***Intense diffuse positivity with prominent pagetoid of the tumor cells for CK7. CK7 immunostaining, ×400.***

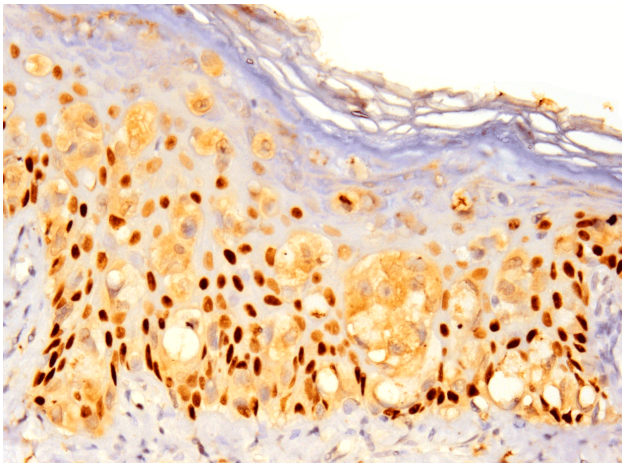

Figure 9 – ***p63 positive in keratinocytes (nuclear staining). Tumor cells are negative. p63 immunostaining, ×400.***

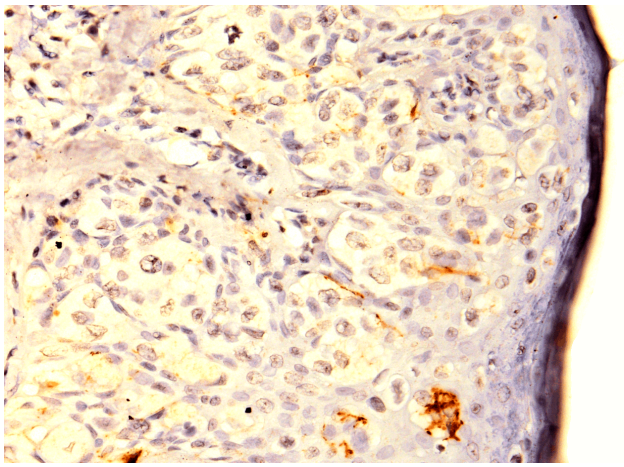

Figure 10 – ***Tumor cells are negative for HMB-45. Few melanocytes are positive (internal control). HMB-45 immunostaining, ×200.***

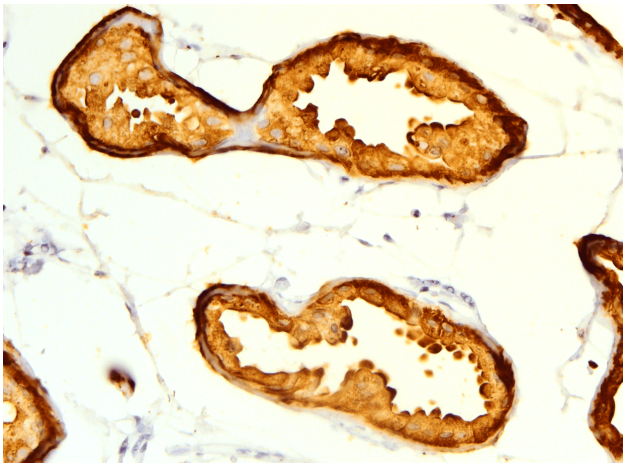

Figure 11 – ***Few apocrine sudoriferous glands present beneath the epidermis with tumor infiltration. Decapitated secretion visible in CK7 staining. CK7 immunostaining, ×400.***

Discussion

EMPD is an uncommon intraepithelial carcinoma, very rare in men, usually found as an irregular, pruritic plaque on the apocrine-rich anogenital skin [31].

EMPD in context of HIV infection raises several categories of problems. Acquired immunodeficiency syndrome (AIDS) is the most severe form of HIV infection, being clinically defined by the presence of defective illnesses (opportunistic infections and tumors) but also by the presence of a marked immunodeficiency syndrome manifested by a low CD4 count [32]. There are several neoplasms considered to be AIDS defining, their presence in the HIV patient exhibiting important staging conditions: Kaposi's sarcoma, non-Hodgkin's lymphoma, and invasive cervical carcinoma. Also, there are several non-AIDS neoplasms described; they have a rising incidence in the HIV-infected patient compared to the general population, especially in the absence of specific antiretroviral therapy but their presence does not automatically change the stage of a HIV-positive patient into AIDS [33]. The list of these malignancies (malignancies in association with HIV infection but non-AIDS-defining) includes various lesions such as Hodgkin's lymphoma, multiple myeloma, melanoma, leukemia, and various carcinomas – anorectal, hepatic, pancreatic, splenic, pulmonary, cerebral, oral and testicular [34]. Moreover, there is a direct proportional increase in both AIDS-defining tumors and the others with the degree of immunodeficiency of the patient and inversely proportional to the level of viral load [32, 33].

Paget's disease does not have a higher incidence in HIV-infected patients, but in the case of severe immunodeficiency (AIDS) it can be associated with a rapidly unfavorable development. Also, extra-mammary manifestations of Paget's disease are not described as more common in the HIV/AIDS patient, but associated immunodepression has an important role in the prognosis and progression of the disease [32].

Diagnosis of EMPD is challenging due to the rarity of the disease and the uncharacteristic clinical aspect. Since clinical features in EMPD include presence of pigmented or hypopigmented plaque with local itching and burning sensation, most often the clinical assumption of an eczema or intertrigo is made. However, the slightly elevated sharp margins and the lack of response to topical anti-inflammatory ointments should raise suspicions and further investigations. Most often, the clinical differential

diagnosis includes leukoplakia, Bowen's disease and even superficial spreading melanoma (especially in hyperpigmented lesions). Hypopigmented lesions prone to confusion with lichen sclerosus and vitiligo. Considering the vast spectrum of diseases mimicked by EMPD, the diagnosis is established by histopathological examination [14, 35].

Dermatoscopy allows identification of several distinctive features of EMPD such as erythematous background coloration, surface scales, dotted, glomerular or polymorphous vessels, ulcerations, pigmentary structures or white areas and lines. Yet, in our case report, dermatoscopic examination has not provided specific aspects of the lesion.

The histological features of EMPD include the presence in the epidermis of clusters or single large atypical cells, with prominent nuclei and mucin-rich vacuolated cytoplasm. Obviously, inflammatory conditions such as spongiotic dermatitis, lichen sclerosus or superficial mycoses are easily excluded. The clinical features (itching and eczematous appearance) may be related to the inflammatory infiltrate commonly found in the upper dermis of EMPD. The inflammatory infiltrate is composed of lymphocytes, histiocytes, neutrophils and eosinophils [13, 31]. It has also been highlighted the presence of mast cells in the perilesional dermis, very numerous in some cases [36, 37]. Thus, considering the role of mast cells in the inflammatory processes of the skin and their close connections with the nerve structures [38–43], one can speculate a link between the perilesional mast cells and the local pruritus that is often described.

Tumor conditions are differentiated based on morphologic, histochemical and immunophenotypical characteristics. The cells of EMPD are positive for PAS staining; keratinocytes have also cytoplasmic positivity for PAS but in more diffuse pattern of staining while EMPD cells usually show intracytoplasmic PAS+ vacuoles containing mucin. EMPD cells may also contain intracytoplasmic melanin granules rendering the histopathological differential diagnosis more difficult [2, 4, 6]. Formation of glandular structures in the epidermis was described as an important feature of EMPD, feature that does not occur in Bowen's disease, leukoplakia, squamous cell carcinoma or melanoma [36].

Immunohistochemistry is helpful for confirmation of the diagnosis and the distinction between the primary and the secondary form of EMPD. It is very useful for the differential diagnosis with other malignancies, such as pagetoid melanoma or pagetoid Bowen's disease [4, 44]. EMPD cells show positive immunoreactivity for CK7, which is a sensitive marker for confirmation of the diagnosis. Other markers are CK8/18, gross cystic disease fluid protein (GCDFP)-15 and carcinoembryonic antigen (CEA) [44, 45].

Another helpful immunohistochemical marker is p63. It can be used to exclude pagetoid Bowen's disease, which is positive for p63 but typically negative for CK7 [46]. It was also used to distinguish between primary EMPD and EMPD secondary to urothelial carcinoma [47]. EMPD cells are typically negative for S100 and HMB-45 and these markers can be useful in differentiating EMPD from pagetoid melanoma [4, 48].

Moreover, recent studies have suggested that various tumor-related biomarkers can be used for the diagnosis or monitoring therapeutic efficacy for cutaneous neoplasms [49–53]. In EMPD, serum CEA has been reported as a possible biomarker, especially in more advanced stages of the disease [54, 55]. More recently, expression of another tumor-associated antigen – receptor-binding cancer antigen expressed on SiSo cells (RCAS1) has been reported in EMPD. The serum level of RCAS1 is increased in patients with invasive lesions, and decreases after therapy, suggesting that it might be a potential biomarker useful for staging of the disease and monitoring the treatment efficiency [56, 57].

EMPD is typically a slow expanding malignancy, which has a good prognosis with adequate therapy. However, in this context of profound economic and social changes in which the healthcare systems and the pharmaceutical industry are facing major challenges [58], the early diagnosis and the correct treatment are crucial in reduction of the healthcare and social costs. If the diagnosis is delayed it may become invasive and metastases can occur, leading to a less favorable outcome [7].

Often, the tumor has subclinical extensions or indistinct borders and wide local excision or Mohs micrographic surgery are effective therapeutic options. Alternative treatment modalities include photodynamic therapy, radiotherapy, topical imiquimod or 5-fluorouracil [7, 59–65]. Considering the normal count of CD4 lymphocytes in our patient, no specific therapeutic modalities are recommended, since his immune response is within normal limits; however, considering the possible risks of progression towards AIDS, complete surgical excisions (confirmed in our case by histopathological examination of the whole specimen) is the therapeutic method of choice. In cases of secondary EMPD, the affected skin area should be excised together with the appropriate therapy for the underlying neoplasm, the prognosis being related to the associated malignancy. Local recurrence of EMPD is very frequent, hence long-term follow-up and careful monitoring of the patients is recommended [66, 67].

Conclusions

Our case is an unusual presentation of EMPD in a Caucasian patient with concomitant HIV infection, in which immunosuppression cannot be considered a triggering factor. These findings made us speculate that association between HIV and EMPD in this patient was a random one. There are no other reports in the literature to associate these two conditions, definitely because of the rare incidence of EMPD.

Conflict of interests

The authors declare that they have no conflict of interests.

Author contribution

Constantin Căruntu and Gheorghiță Jugulete equally contributed to this work.

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