Case Report
Olgu Sunumu

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Extramammary Paget's disease: Report of two cases located on the vulva and penis

Ekstramamaryan Paget hastalığı: Vulva ve penis yerleşimli iki olgu sunumu

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Abstract

Extramammary Paget's disease (EMPD) is a rare intraepithelial adenocarcinoma involving the epidermis and sometimes extends into the dermis. EMPD is most commonly seen in the intraepidermal primary form and rarely it occurs as a secondary form associated with malignancies. EMPD mostly occurs in areas such as vulva, penis, scrotum, perineum and axilla where apocrine glands are located. The most common site of involvement is vulva (65%). EMPD of male genital organs is less common, it accounts for 14% of cases. EMPD is a rare entity with very limited data in the literature and EMPD may occur in association with an underlying malignancy in adjacent organs. The diagnosis of EMPD is often delayed because of its non-specific features, its rarity, as well as the use of various treatments for dermatitis. The diagnosis and clinical management of EMPD is difficult. Biopsy should be taken from genital lesions unresponsive to treatment and histopathological examination, which is the basis of the diagnosis, should be performed. A detailed examination is necessary to detect an associated malignancy after diagnosis. Long-term follow-up of patients for regional lymphadenopathy, distant metastasis, local recurrence and development of internal malignancy form the basis of clinical management.
Keywords: Extramammary, genital, paget, penis, vulva

Öz

Ekstramamaryan Paget hastalığı (EMPH) epidermisi tutan ancak bazen dermise de uzanım gösterebilen nadir bir intraepitelyal adenokarsinomdur. EMPH en yaygın olarak intraepidermal primer form şeklinde bulunur. Daha az sıklıkla malignitelerle ilişkili olarak ortaya çıkar. EMPH çoğunlukla apokrin bezlerin bulunduğu vulva, penis, skrotum, perine ve aksillada gelişir. EMPH'de %65 oran ile en sık tutulum bölgesi vulvadır. Erkek genital organlarının EMPH'si daha az yaygın görülüyor olup olgularının %14'ünü oluşturur. EMPH literatürde çok sınırlı sayıda veriye sahip nadir bir antite olup komşu organlarda altta yatan bir malignite ile ilişkili olabilmektedir. Spesifik olmayan özellikleri, nadir olması ve çeşitli dermatitlere yönelik tadaviler nedeniyle EMPH tanısı çoğunlukla gecikir. EMPH'nin hem tanısı hem de tanı sonrası klinik yönetimi zordur. Tedaviye yanıt vermeyen genital bölge lezyonlarına mutlaka biyopsi alınmalı ve tanının temelini oluşturan histopatolojik inceleme yapılmalıdır. Tanıyı takiben hastalara ilişkili bir maligniteyi saptayabilmek açısından kapsamlı bir inceleme gereklidir. Lokal rekürrens, internal malignite gelişimi, bölgesel lenfadenopati ve uzak metastaz açısından hastaların uzun süreli izlenmesi klinik yönetimin temelini oluşturur.
Anahtar Kelimeler: Ekstramamaryan, genital, paget, penis, vulva

Introduction

Extramammary Paget's disease (EMPD) is a rare intraepithelial adenocarcinoma involving the epidermis and sometimes extends into the dermis[1]. EMPD is most commonly seen in the intraepidermal primary form and rarely it occurs as a secondary form associated with malignancies[1-3]. EMPD mostly occurs in areas such as the vulva, penis, scrotum, perineum, and axilla where apocrine glands are located[1]. The most common site of involvement is the vulva (%65)[4,5].

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EMPD of male genital organs is less common, it accounts for 14% of cases[3].

EMPD is a rare entity with very limited data in the literature and EMPD may occur in association with an underlying malignancy in adjacent organs. The diagnosis of EMPD is often delayed because of its non-specific features, its rarity, as well as the use of various treatments for dermatitis. The diagnosis and clinical management of EMPD is difficult. Biopsy should be taken from genital lesions unresponsive to treatment and histopathological examination, which is the basis of the diagnosis, should be performed. A detailed examination is necessary to detect an associated malignancy after diagnosis. Long-term follow-up of patients for regional lymphadenopathy, distant metastasis, local recurrence, and development of internal malignancy form the basis of clinical management.

Case Reports

Case 1

A 78-year-old female patient was admitted to the obstetrics and gynecology clinic with vulvar pain, itching, burning, swelling, and ulceration. On examination, a lesion with a size of about 3x2 cm in the form of white papules and plaques with an irregular appearance, localized on the labium majus, labium minus, and clitoris, was observed. First, an incisional biopsy, and then an excisional biopsy sampling was performed. In both biopsy samples, a group of tumor cells with large nuclei, prominent nucleoli, and with large pale cytoplasm, were observed in the epidermis (Figure 1,2). Tumor cells were positive for CK7, EMA, GCDFP15, HER2, and mucicarmine (Figure 3-5). Tumor cells were negative for CK20, HMB45, melan A, S100, ER, and PR. Based on the morphological and immunohistochemical findings, the case was reported as vulvar EMPD (Figure 6). Clinical-radiological correlation of the patient was recommended in terms of internal malignancies, especially urogynecological and colorectal malignancies. Imaging examinations for cancer screening revealed a 1.6 cm diameter microlobulated, irregular, hypoechoic, solid, BI-RADS5 mass in the upper inner quadrant of the right breast. In the right lumpectomy material, a 1.8x1.2x1 cm grayish-white, solid, radially spreading lesion was detected. Ten months after the diagnosis of vulvar EMPD, the lesion detected in the breast was diagnosed as invasive ductal carcinoma.

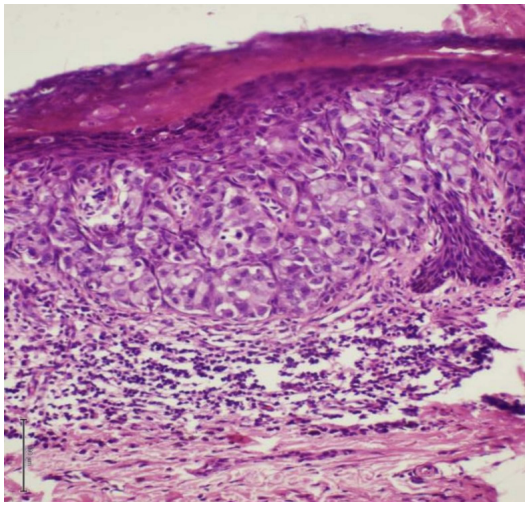

Figure 1. Paget cells with vesicular nuclei, prominent nucleoli, and abundant pale cytoplasm form nests in the epidermis (hematoxylin-eosin, x100)

Case 2

A 44-year-old male patient was admitted to the dermatology clinic with the complaint of ulceration and burning on the penile skin which had been present for 20 months. Physical examination revealed an erythematous eroded lesion, 1x1 cm in size, on the ventral side of the penis (Figure 7). A macular, hypopigmented, white-colored, irregularly circumscribed lesion was observed in the skin biopsy specimen. On microscopic examination, tumor cell nests were observed in the epidermis. Tumor cell nests consisted of large cells with atypical large nuclei and abundant pale cytoplasm. Immunohistochemically atypical cell groups were positive with CK7, EMA, GCDFP15, no staining was observed with CK20. The case was diagnosed as penile EMPD. Malignancy screening program could not be performed as the patient lost to follow-up. Informed consent was obtained.

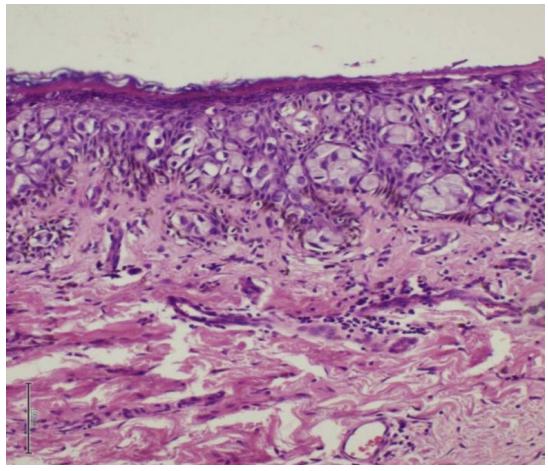

Figure 2. Paget cells are arranged as single cells along the epidermis (hematoxylin-eosin, x100)

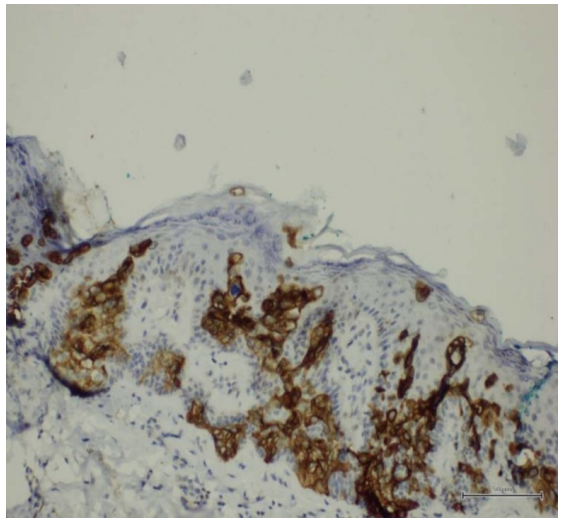

Figure 3. CK7 positivity in Paget cells (hematoxylin-eosin, x50)

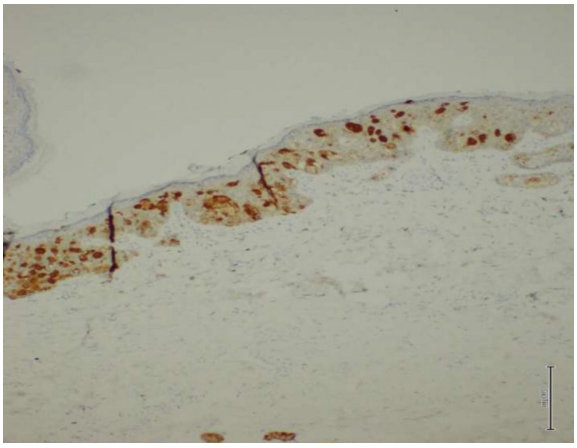

Figure 4. GCDFP15 positivity in Paget cells (hematoxylin-eosin, x50)

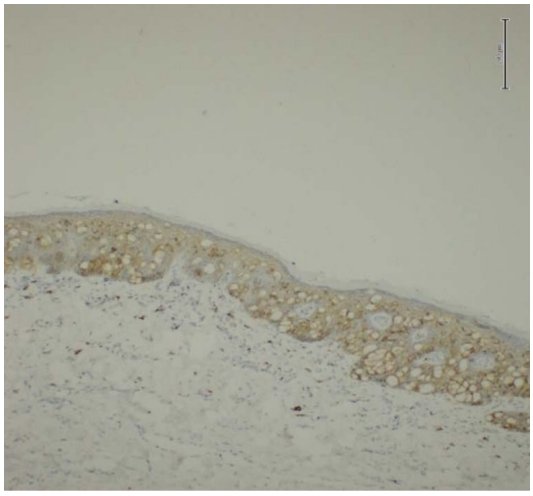

Figure 5. HER2 positivity in Paget cells (hematoxylin-eosin, x50)

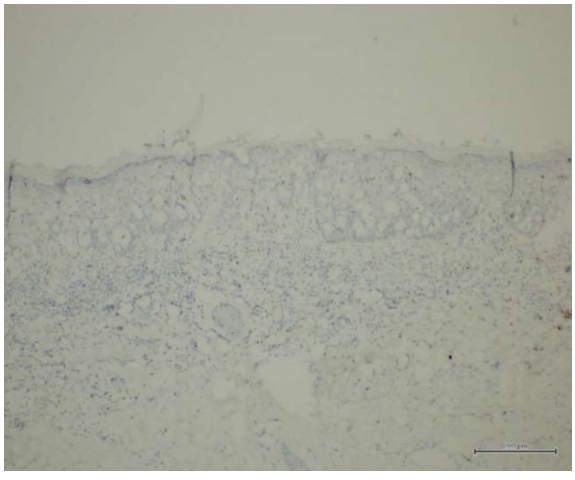

Figure 6. CK20 is negative in Paget cells (hematoxylin-eosin, x50)

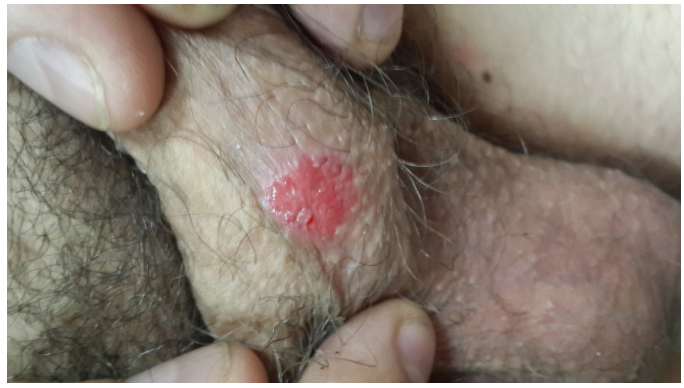

Figure 7. Erythematous eroded lesion 1x1 cm in size on the ventral side of the penis

Discussion

EMPD localized to the scrotum and penis was first described by Crocker[6] in 1889, and vulvar EMPD by Dubreuilh[7] in 1901. EMPD has similar histological features with Paget's disease (EMPD) of the breast. EMPD is a rare intraepithelial adenocarcinoma that affects anatomical regions with a large number of apocrine sweat glands[1]. The most common site of involvement of EMPD is the vulva and shows vulvar localization in 65% of cases. The labia majora are the most common sites of vulvar EMPD[2,3]. In the first case, the lesion was localized on the vulva, which is consistent with the literature. EMPD can also occur in the perineal, perianal region, scrotum, and penis[4,8]. EMPD of the male genitalia is less common, accounting for only 14% of EMPD cases[5]. Penoscrotal EMPD most often occurs in the scrotum in 86% of cases, and more rarely on the penile shaft, pubic region, inguinal folds, and glans penis[9]. In the second case, the lesion was localized on the penis, which is defined as a very rare localization in the literature. Perianal EMPD accounts for 20% of cases and often occurs close to the anus. Perianal EMPD lesions may spread to the perineum, genital area, gluteal region, and rarely to the anal canal[3]. Less commonly, it may arise on the axillae, umbilicus, eyelid, external auditory meatus, head and neck, and extremities[2,10-12]. Although the exact incidence is unknown, EMPD constitutes 6.5% of all cutaneous Paget's diseases. It mainly affects individuals between the ages of 50-80, but the highest incidence is observed at the age of 65. In the first case, the age of the patient was within the age range described in the literature, but the second case was younger than the age range in which the disease frequently occurs. EMPD occurs most frequently in females and Caucasians but is more common in males in Asian populations[8,13]. EMPD typically occurs in areas with a large number of apocrine sweat glands. It presents as a slow-growing, well-circumscribed, asymmetrical, erythematous, white-scaly plaque that is often painful or itchy. Large lesions in more advanced stages may appear irregular and poorly circumscribed and may present as hypopigmented or hyperpigmented macular lesions, and then the lesions may become erosive, ulcerative, bleeding, and crusted. EMPD may rarely present as nodules, vegetative lesions, or with regional lymphadenopathy. The most common symptom is itching, but there may also be burning, pain, swelling, and tenderness[3,14-16].

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In both cases, we presented an eroded, irregularly circumscribed, white-colored hypopigmented lesion causing non-specific symptoms such as itching and burning. Approximately 10% of patients with EMPD are asymptomatic[6]. Because of non-specific clinical symptoms, EMPD is often misdiagnosed as inflammatory or infectious conditions. Therefore, if itchy eczematous lesions in areas with apocrine sweat glands do not respond to standard topical treatment for 4-6 weeks, a skin biopsy is recommended[3]. Due to its rarity, EMPD is diagnosed late in many cases, especially when localized on the scrotum and penis. A biopsy is necessary for penile and scrotal non-specific eczematous skin lesions that do not respond to treatment[17]. It is reported that there is a delay of approximately two years in diagnosing EPMD because the lesions are non-specific and multiple topical treatments are usually tried before the diagnosis[8]. As noted here, the second case with penile lesion first received topical treatment. A biopsy was performed because there was no regression in the lesion. EMPD most commonly occurs as an intraepidermal primary form of glandular origin, originating from the epidermis or skin appendages. Less frequently, EMPD presents as intraepidermal spread of malignant cells, usually associated with sweat gland carcinoma or underlying malignancy of the lower gastrointestinal or urinary tract[1-3]. It is reported that there is an additional malignancy occurring before, simultaneously with, or after the development of EMPD in 4-58% of the cases, and it is called secondary EMPD. Additional malignancies accompanying EMPD may include extragenital skin cancers, and distant visceral malignancies such as carcinomas of the rectum, stomach, bladder, urethra, prostate, cervix, and breast[1,2]. In secondary EMPD cases, the EMPD site is usually associated with the site of the underlying malignancy[1,8]. Despite the high rate of vulvar involvement, EMPD accounts for only 1-2% of all vulvar malignancies. 4-17% of vulvar EMPDs are associated with underlying cutaneous appendageal carcinoma, 11-20% with carcinoma of the colon, rectum, and urogynecological structures. The incidence of underlying associated malignancy is highest in perianal EPMD[8,16,18]. Some 33-86% of perianal EMPDs are associated with the lower gastrointestinal tract and tuboovarian malignancies; 11% of penoscrotal EMPDs are associated with urinary system malignancies such as prostate, bladder, and testis[1,18]. Distant visceral malignancies reported in association with EMPD include carcinomas of the breast, ovary, bile duct, lung, stomach, and pancreas, as well as hepatocellular carcinoma and renal cell carcinoma[1]. In Chanda's review, 29% of patients had an associated visceral malignancy. In the same review, Chanda et al.[4] reported that of 109 cases with vulvar EPMD, 11 had breast cancer, 9 had uterine carcinoma, 3 had vaginal cancer, and 1 had ovarian cancer. It was reported that anorectal carcinoma was found simultaneously in 6 of 24 patients with perianal EMPD[2]. In a series of 100 cases, Fanning et al.[19] reported that 26 of the patients had associated visceral cancer; 6 of these were reported as breast cancer, 4 as endometrial cancer, 3 as pancreatic cancer, 3 as lung cancer, 3 as stomach cancer, and 6 as thyroid cancer[19]. In our second case with penile EMPD, no accompanying malignancy was detected. In our first case, after the diagnosis of vulvar EMPD, a second primary carcinoma was detected in the same year, and it was diagnosed as invasive ductal carcinoma of the breast. EMPD is characterized by intraepidermal proliferation of Paget cells (PC), which are malignant glandular epithelial cells[3,15]. There are two types of PCs: the classic type (type A) and the signet ring type (type B). Classic type PCs are cells with vesicular nuclei, prominent nucleoli, and abundant pale cytoplasm, whereas signet ring type PCs are characterized by eccentrically located nuclei and large cytoplasmic mucin droplets[3]. PCs are arranged as single cells or in nests along the the epidermis and form lumen or gland-like structures (Figure 1,2). Reactive changes such as acanthosis, papillomatosis, hyperkeratosis, parakeratosis in the epidermis and lichenoid type inflammatory infiltration in the papillary dermis may be seen[8,13,15,20]. Mitotic activity is variable[8]. Differential diagnoses include diseases with similar histopathological appearance such as malignant melanoma, Bowen's disease, Langerhans cell histiocytosis, mycosis fungoides, sebaceous carcinoma, and Merkel cell carcinoma due to the pagetoid spreading pattern of PCs[13]. Because of their similar clinical and histopathological appearances, it is sometimes difficult to distinguish primary and secondary EMPD, but making this distinction is of great importance as there is a great difference between their treatment and prognosis[21]. Immunohistochemical staining is helpful in distinguishing between primary and secondary EMPD and distinguishing EMPD from other pathological processes[15]. Low molecular weight cytokeratins such as CK7 and CK20, CEA and GCDFP15 immunohistochemical stains are used to categorize EMPD and to investigate whether there is an underlying malignancy[13,18]. CK7 sensitivity is high (86-100%) in distinguishing PCs, but CK20 is more specific for EMPD[15,18]. CK20 and GCDFP15 are the most useful markers in distinguishing between primary and secondary EMPD. GCDFP15 expression is reported in approximately 90% of primary EMPDs, while CK20 expression is reported in approximately 95% of secondary EMPDs[15]. Plaza et al.[22] reported HER2 positivity in more than 30% of EMPD cases[22]. The immunoprofile of primary EMPD shows CK7+/CK20−/GCDFP15+[3]. The immunoprofile of secondary EMPD varies depending on the underlying carcinoma[15]. The immunoprofile of colorectal carcinoma and urothelial carcinoma, which are the most common internal malignancies associated with EMPD, are CK7-/CK20+/GCDFP15- and CK7+/CK20+/GCDFP15-, respectively[3]. Most primary vulvar EMPDs, 67% of urothelial carcinomas, and more than 90% of colorectal carcinomas show CEA immunoreactivity, so CEA is of little use in distinguishing between primary and secondary EMPD[18]. PCs show androgen receptor expression, but no estrogen receptor or progesterone receptor expression[20]. MUC5AC expression is particularly common in vulvar EMPD and EMPDs in the male genitalia. MUC5AC expression may be lost in invasive disease. PCs contain intracytoplasmic mucin, so positive staining with periodic acid-Schiff, Mucicarmine and Alcian blue help with diagnosis[2,13]. Both of our cases showed CK7+/CK20-/EMA+/GCDFP15+ immunohistochemically and were diagnosed as primary EMPD. Our first case diagnosed as vulvar EMPD also showed HER2 expression.

The standardized approach for the treatment of EMPD is surgical excision. Resection margins are often positive and local recurrences are common, as the tumor is multifocal, irregular in shape, and has indistinct borders[1,8]. More radical surgical procedures are associated with lower recurrence rates; the recurrence rate is 15% in radical vulvectomy, 20% in radical hemivulvectomy, and 43% in wide local excision[8,21]. Wide local excision is the traditionally used standardized surgical approach[2,16,21]. However, Mohs micrographic surgery (MMS) minimizes tissue loss and morbidity and is supported because it is associated with lower recurrence rates following excision[1,2,16].

EMPD is a rare malignancy, therefore the effectiveness of MMS in the management of EMPD is under investigation[18]. If the disease is limited and surgical intervention is contraindicated, there are various alternative treatment methods such as topical imiquimod 5% cream, topical 5-Fluorouracil, photodynamic therapy, carbon dioxide laser vaporization, topical-systemic chemotherapy, and radiotherapy (RT)[1,15]. In addition, it is reported that the use of Trastuzumab in EMPD cases with HER2 overexpression has successful clinical results[15,18].

The presence of dermal invasion, increased serum CEA levels, the presence of nodular areas in the primary lesion, and bilateral lymph node metastasis are associated with an increased risk of death[23]. Dermal invasion is the most important part of disease management and should be carefully evaluated[21]. Invasion is graded into three groups by Hatta et al.[23]: Intraepidermal invasion, minimal invasion into the papillary dermis, and deep invasion into the reticular dermis or subcutaneous tissues[23]. Depth of invasion is associated with lymph node metastasis, distant organ metastasis, higher recurrence rate, shorter recurrence time, and reduced survival[2]. In both cases we presented, the tumor was limited to the epidermis, and no dermal invasion was observed. The prognosis of primary EMPD confined to the epidermis is very good in patients who receive appropriate treatment and have follow up care[21]. The prognosis is poor in an invasive primary EMPD, especially if lymphovascular invasion is present[8]. Invasive tumor size and depth of dermal invasion are associated with decreased overall survival[21]. Minimally (microscopic) invasive lesions with a depth of dermal invasion less than 1 mm have a better prognosis than lesions with deeper dermal invasion[8]. Lymph node metastasis has been reported in patients with minimally invasive tumors, and lymph node metastasis is associated with a poor prognosis[15,21]. Secondary EMPD has a worse prognosis than primary intraepithelial EMPD[4]. In the presence of an additional malignancy in adjacent organs, the prognosis of secondary EMPD depends on the prognosis of the primary tumor[16]. Chanda et al.[4] reported that seconder EMPD mortality is 46%.

Patients diagnosed with EMPD are reported to have a higher risk of developing a second primary cancer, especially the first year after diagnosis[20]. After the diagnosis of EMPD is confirmed histopathologically, investigations to exclude underlying associated malignancies are of great importance. Detailed examination of organ systems and diagnostic imaging tests should be performed in all patients. Clear screening guidelines for patients diagnosed with EMPD are lacking but there is a recently proposed algorithm for malignancy screening[1,2]. According to the algorithm, all patients require detailed immunohistopathological examination, urine cytology, colonoscopy; prostate-specific antigen, and digital rectal examination in men; women need Pap smears and mammograms; in addition to clinical history, physical examination, and standard cancer screening tests. This algorithm also recommends lymph node examination in the presence of invasive EMPD or EMPD-related internal malignancy[24]. Long-term and close follow-up of these patients is necessary in terms of local recurrence, internal malignancy, regional lymphadenopathy, and distant metastasis. Local recurrence, internal malignancy, regional lymphadenopathy, and distant metastasis may occur in these patients; therefore, long-term and close follow-up is necessary[2,18].

Conclusion

Both of these cases presented here are of great importance and rare and we aim to contribute to the literature. As in the penile EMPD case we presented, genital area lesions that do not regress over time can be confused with many inflammatory and infectious entities; therefore, although it is rare, EMPD should be kept in mind and biopsy sampling should be performed. It should be remembered that, as in our first case with vulvar EMPD, these patients are predisposed to develop a second primary malignancy, and in these patients, EMPD may develop due to another underlying malignancy. Most importantly, we aimed to emphasize the importance and necessity of cancer screening after the diagnosis of EMPD, as its importance has been emphasized in the literature.

Ethics

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.O., C.T., E.Ş., Concept: S.O., C.T., E.Ş., Design: S.O., C.T., E.Ş., Data Collection or Processing: S.O., C.T., E.Ş., Literature Search: S.O., C.T., E.Ş., Writing: S.O., C.T., E.Ş.

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