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Review Article

A brief review of perianal paget disease

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Abstract: Paget's disease (PD) is a kind of malignant tumor that is usually localized within the epidermis. PD can be divided into mammary PD (MPD) and extramammary PD (EMPD). EMPD is rare, but the actual incidence is not known. Perianal PD (PPD) refers to EMPD that is located within 6 cm of the anal orifice and below the pectinate line. In this study, we summarize the pathogenesis, clinical characteristics, diagnosis, and treatment of PPD. Pubmed and Web of Science data-bases were used to search for the relevant studies, and the key words were "EMPD" and "PPD". The symptoms of PPD are similar to those of other benign skin diseases, and so the diagnosis of PPD is always delayed. Histopathology is necessary for the diagnosis of PPD. Many treatment methods have been used for PPD, but surgical resection remains the treatment of choice. The rarity of PPD has hampered further research.

Keywords: PD, EMPD, PPD, histopathology, surgery

Introduction

Paget's disease (PD) is a rare type of cancer that arises in the epidermis. It is classified as mammary PD (MPD) and extramammary PD (EMPD). MPD arises in the epidermis of the nipple or the areola of the breast [1], and was first reported by James Paget in 1874 [2]. In 1889, Radcliffe Crocker described EMPD in a male patient in whom the disease presented with eczema-like lesions on the skin of the penis and scrotum [3]. EMPD can occur at any site where apocrine glands are present, *e.g.*, the vulva, perineum, and perianal region [4]. Perianal PD (PPD), which was first described by Darier and Coulillaud [5, 6], refers to lesions which are located below the pectinate line and within 6 cm of the anal orifice. Patients with PPD present with well-defined erythematous lesions and invariably complain of itching [7]. Because the symptoms of PPD are similar to those of many benign skin diseases, the diagnosis of PPD is always delayed [8].

The precise incidence and prevalence of EMPD are unknown. PD accounts for about 4% of all breast cancers, while EMPD accounts for about 6.5% of all skin diseases [9, 10]. The most common site for EMPD is the vulva, followed by the perianal area, penis, scrotum, and groin area [11]. The incidence of PPD is hard to estimate, but it is believed that PPD accounts for about 20% of EMPD and 6% of PD [12]. PPD is often accompanied by other cancers, such as ovarian and colorectal cancers [13].

In this study, we summarize the pathogenesis, clinical characteristics, diagnosis, and treatment of PPD. This information will be helpful for early diagnosis and proper treatment of PPD.

Pathogenesis of PPD

EMPD may originate from three different cell types [8]: 1) Derived from the apocrine adenocarcinoma or exocrine adenocarcinoma, especially the sweat gland; 2) Originated from the adenocarcinoma in the epidermis, which is also called intraepithelial neoplasia; 3) Derived from adenocarcinoma of other organs spread to the epidermis.

PPD can be divided into two types: primary cutaneous PPD and secondary dermal-derived PPD [14]. Primary cutaneous PPD is a type of epithelial adenocarcinoma and always presents with intraepithelial infiltration. Its precursor cells appear to be the undifferentiated pluripotent cells of the epidermis or skin appendages. Epidermal cells are also considered to be precursors of Paget cells. Primary cutaneous PPD is rarely invasive, and so metastasis is

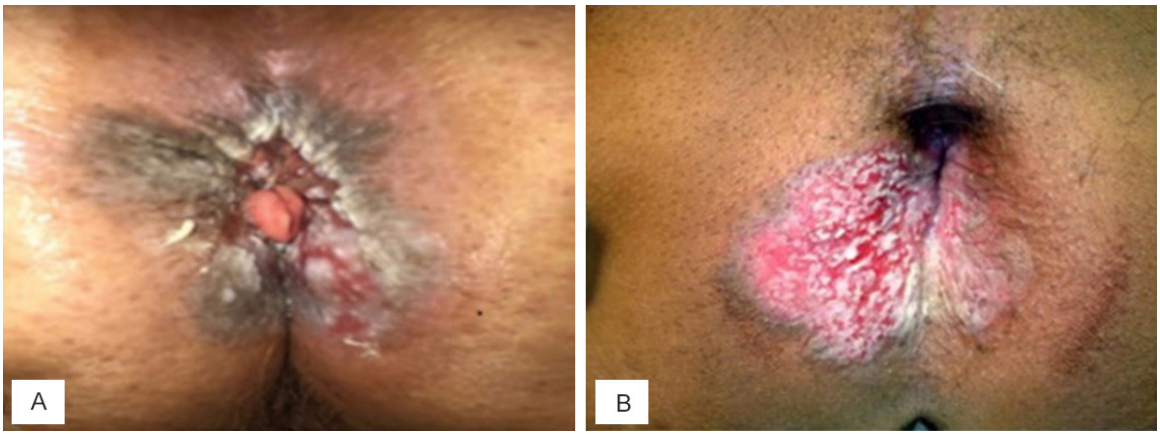

Figure 1. Different presentations of perianal Paget disease: A. Erythematous skin lesion in the perianal area with surrounding lichenification [15]. B. A thickened plaque like area in the perineal region [16].

uncommon [14]. Secondary dermal-derived PPD originates from the adenocarcinoma tissues of other organs. For example, rectal adenocarcinoma and urinary tract cancer cells may spread to the perianal epidermis and lead to secondary dermal-derived PPD. When secondary dermal-derived PPD is diagnosed, further examination must be conducted to identify the primary malignancy [14].

Clinical characteristics

Because EMPD is a slow-growing intraepithelial tumor, its clinical manifestations are often nonspecific. PPD patients invariably have rash, accompanied by itching and pain in the affected area. In addition, some patients complain about hematochezia, perianal swelling, and change in bowel habits. The skin color in the affected area can vary from pink to dark red, and large lesions may present with multiple colors. There may be scales, exudates, patchy erosions, or white spots on the surface of the lesions. Severe lesions may be irregular, with unclear boundaries. Due to centrifugal growth, large lesions may completely involve the anal and genital area, leading to the formation of polygonal boundaries [9]. Zeng *et al.* reported a rare case of PPD that presented as an erythematous skin lesion in the perianal area with surrounding lichenification (**Figure 1A**) [15]. The patient complained about pruritus, but had no pain or bleeding. Another patient presented with a butterfly-shaped thickened plaque in the perineal region, with sparing of the anal opening (**Figure 1B**) [16]. This patient had pruritus and mild pain in the perianal area and also complained about a "leathery" feel of the affected skin.

Diagnosis of PPD

The diagnosis of PPD is based on histopathological and immunohistochemical analysis [9]. There are differences between primary cutaneous PPD and secondary dermal-derived PPD in the histopathological and immunohistochemical features [17]. It is important to distinguish between the two types of PPD because the surgical methods and prognosis are different. Secondary dermal-derived PPD mostly originates from anal cancer or low rectal cancer and carries a worse prognosis. Under the microscope, primary cutaneous PPD typically shows uniformly distributed tumor cells, with only occasional glandular cavities. Whereas secondary dermal-derived PPD is characterized by irregularly arranged tumor cells and a relatively greater number of glandular cavities [18]. Immunohistochemistry of cytokeratin (CK)-7, CK-20, and gross cystic disease fluid protein (GCDFP-15) can help in differentiating different types of EMPDs. EMPD tissues originating from urothelial carcinoma will be positive for CK7 and CK20 and negative for GCDFP-15. EMPD derived from the urinary tract is commonly positive for GCDFP-15 [19]. PPD derived from rectal and anal cancer is usually positive for CK-20 and negative for CK7 [20], although some cases may be positive for CK7 and negative for CK20 [21]. Pandey *et al.* reported a case of histopathology-confirmed primary cutaneous PPD that was positive for CK7 and GCDFP-15 (**Figure 2**) [16].

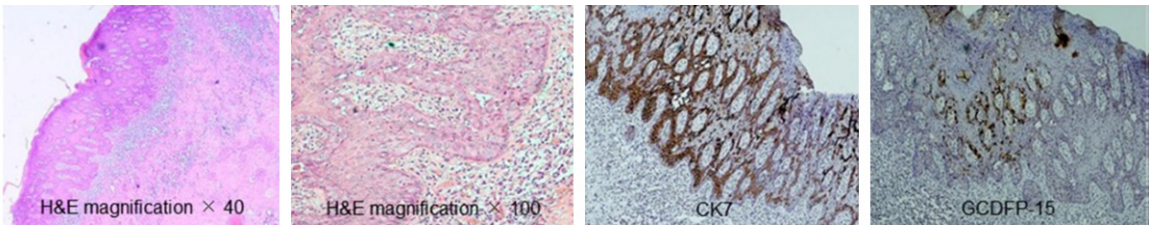

Figure 2. Histological features of primary cutaneous perianal Paget disease [16].

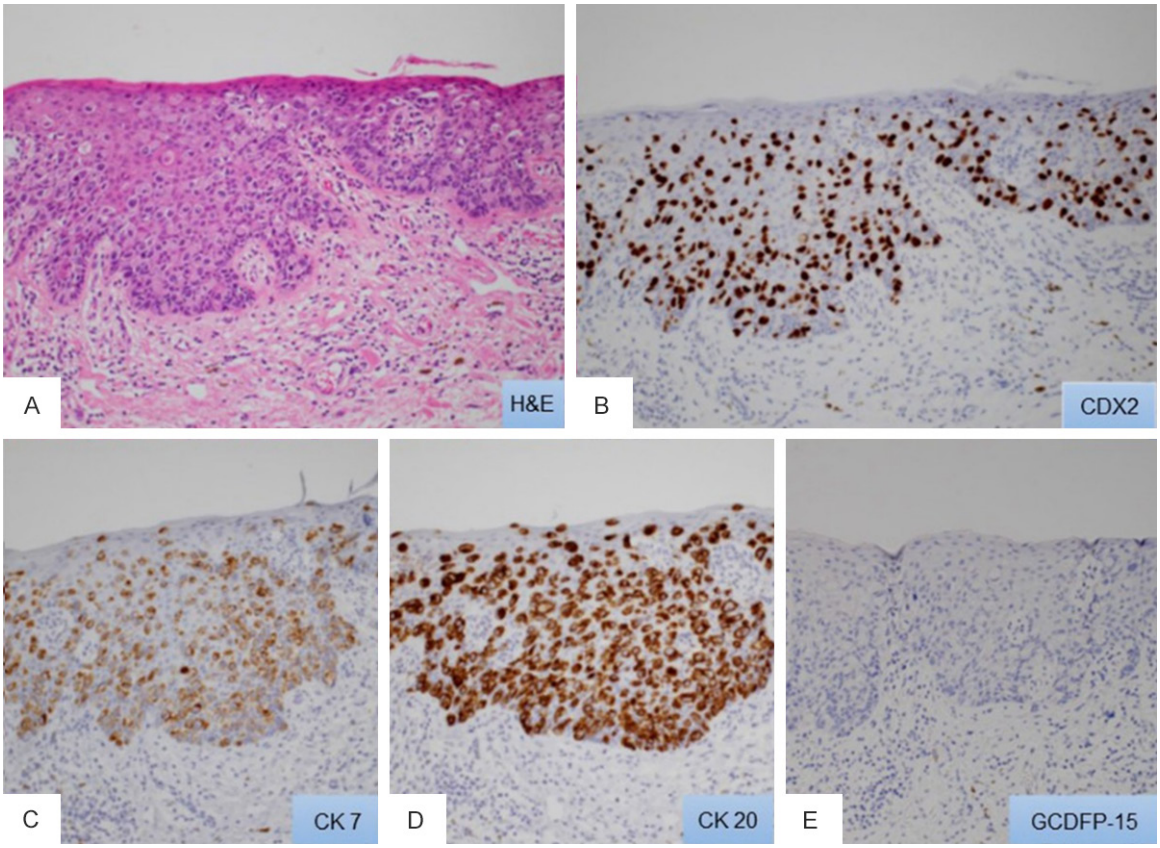

Figure 3. Histological findings of perianal Paget disease [26]. (A) Paget cells with clear cytoplasm and large pleomorphic nuclei (hematoxylin-eosin; magnification × 20). (B-D) Positive immunohistochemical staining for CDX2 (B), CK7 (C), and CK20 (D), and negative staining for GCDFP-15 (E) (magnification × 20).

Carcinoembryonic antigen (CEA) is also a useful marker of urothelium-derived PPD. However, some cases of rectal and anal cancer-derived PPD may also be negative for CEA. Therefore, as with CK7 and CK20, CEA staining alone is insufficient for definite diagnosis of urothelium-derived EMPD.

Caudal-related homeobox gene nuclear transcription factor-2 (CDX2) is a gene involved in the regulation of the proliferation/differentiation of intestinal cells. Positive staining for CDX2 is common in both primary and metastatic rectal cancer [22-24]. Nisi *et al.* found primary EMPD to be positive for CK7 and negative for CK20 and CDX2, and secondary EMPD to be positive for CDX2 [25]. CDX2 is therefore considered a sensitive marker for rectal- and anal-derived EMPD. In one report of anal gland carcinoma *in situ* with pagetoid spread [26], histological examination showed Paget cells with clear cytoplasm, and immunohistochemistry was positive for CK7, CK20, and CDX2 and negative for GCDFP-15 (**Figure 3**).

Recently, mucin staining has been proposed as a sensitive method for diagnosis of EMPD. Mucin is a high-molecular-weight glycoprotein with nine subtypes (MUC1-9) which are differentially expressed in different types of tissues [27]. MUC1 is often found on the apical surface of the glandular epithelium and has recently been shown to be a very sensitive marker of EMPD [28, 29]. Some researchers have reported the typical patterns of mucin staining in EMPD. Kuan *et al*. reported three cases of rectal adenocarcinoma–derived PPD that stained positive for MUC2 [30]. Kondo *et al.* found diffusely positive MUC2 staining in two of three patients with primary PPD [27]. Liegl *et al.* reported 23 patients with EMPD who had positive MUC1 staining [29]. Yoshii *et al.* reported 36 patients with EMPD, 2 of whom had PPD [28]. Both PPD patients showed negative staining for MUC2 and no underlying adenocarcinoma was found in the PPD tissues. Some researchers have reported MUC5AC in some EMPD tissues [28, 30].

It is necessary to differentiate PPD from Bowen disease, contact dermatitis, mossy lesions, psoriasis, melanoma, perianal Crohn disease, mycosis fungoides, squamous cell carcinoma, and femoral hernia. In Bowen disease, the lesion presents as irregular erythema with a clear boundary and varying degrees of scabing, desquamation, and even erosion and exudation. Histopathology shows atypical hyperplasia with pleomorphic nuclei. Some lesions can progress to invasive cancer. Bowen disease may be related to chronic sun damage, immune abnormalities, chronic irritation, human papilloma virus infection, and trauma [31, 32]. Matsumoto *et al.* reported that whereas Paget cells were positive for CEA, CK7, and CK8, the atypical keratinocytes of Bowen disease were negative for CEA but positive for CK7 and CK8 [33]. Thus, CEA could be used to distinguish EMPD from Bowen disease. Pigment present in the cytoplasm of some EMPD tumor cells could lead to suspicion of malignant melanoma. However, the tumor cells of Paget-like malignant melanoma are atypical or clustered and are rich in melanin. On immunohistochemistry, malignant melanoma cells are positive for S-100, HMB-45, melan-A, and MART-1, whereas Paget cells are negative for all of them. Differentiation of EMPD from other diseases may require direct mycological examination and mycological culture in addition to histopathological analysis.

Treatment of PPD

Treatment methods for PPD include surgery, photodynamic treatment, 5% imiquimod cream application, CO_2 laser ablation, radiotherapy, and chemotherapy.

Surgical treatment is applicable for epidermal/intradermal PPD in the perineum, scrotum, or vulva [3, 34, 35]. Most researchers believe that wide local excision of the visible lesion is adequate for PPD treatment. However, excision results in large tissue defects. In most cases, primary suture or skin grafting will not be appropriate, and flap reconstruction surgery will be required. Importantly, the reconstruction of the perianal defect has to ensure the preservation of anal function and satisfactory cosmetic results. Good results have been reported with bilateral musculocutaneous flaps from the gluteal or thigh regions and with “V-Y” island flaps [36, 37]. Kishi *et al.* reconstructed anal and perianal areas using a posterior thigh trilobed flap and reported good results [38]. Shen *et al.* reported a female PPD patient who underwent wide local excision of the lesion followed by posterior thigh reconstruction [39]. There were no complications and the patient achieved satisfactory bowel control (**Figure 4**). The posterior thigh flap has certain advantages for reconstruction of perianal defects. The donor site is close to the defect and flap transfer is easy. In addition, the flap has good blood supply, which significantly increases the survival rate [40]. In severe PPD, colostomy may be required before extensive local excision. Some researchers recommend that colostomy should be performed when more than half of the perianal area needs to be removed, or when the resection radius is >3 cm [36].

Literature review shows that the recurrence rate of primary EMPD after standard extensive local resection is as high as 60% [41]. Recurrence may be local, in the lymph nodes, or at a distant location [42]. The determination of the resection margin during surgery is a major challenge. Intraoperative frozen section analysis can help to a certain extent. However, because of the multicentric nature of PPD and the limited time for intraoperative analysis, the false negative rate of frozen section analysis is

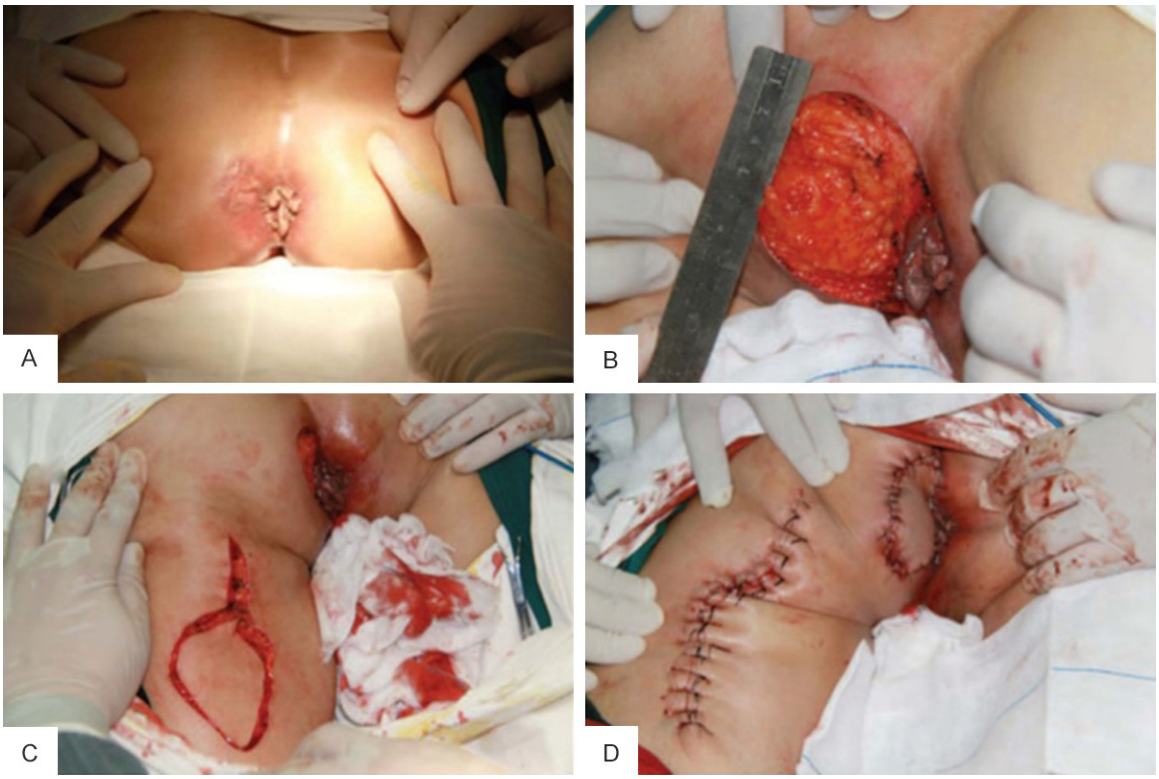

Figure 4. Surgical treatment of perianal Paget disease [39]. A. The lesion in the left perianal area measures 3 × 3 cm and shows surrounding lichenification. B. The defect is 7 × 6 cm in size. C. Posterior thigh flap is designed according to the defect in the perianal region. D. The defect after flap reconstruction.

about 40% [43]. To address this problem, Mecker developed a method for resection of PPD in stages [44]. In stage 1 (contoured margin excision), the margin of the lesion is first marked. Then an outline is drawn 1-2 cm away from the marked margin and the direction is determined. Under local or general anesthesia, 2-3 mm of tissue at the incision site is removed and sent for pathological analysis. The wound is sutured and the patient is discharged from hospital. If the pathology report indicates a positive margin, the patient is readmitted and the affected edge is resected. The first stage can be repeated as needed. Stage 2 (central resection and reconstruction) is undertaken once the margin is confirmed to be negative. The wound is reconstructed by plastic surgery. The Mecker method not only guarantees complete tumor resection, but also provides a clear boundary. It is a convenient method to avoid excessive resection and consequent loss of function.

Although EMPD progresses slowly, local and distant metastasis can occur through direct dermal invasion and lymphatic spread. Treatment delay may cause serious harm. Standard surgical resection may not be sufficient because PPD is invasive and prone to recur. Because visual examination cannot identify the extent of invasion, it is difficult to determine the optimal surgical resection range. Mohs microsurgery (MMS) may be useful. MMS is a tissue-retaining surgery used for treatment of recurrent, invasive, high-risk skin cancers. In MMS, the surgeon can directly observe the edge of the lesion through a microscope, which makes optimal resection more likely and thus reduces the risk of local recurrence. A retrospective study has suggested that MMS may be better than standard local extensive resection, with a recurrence rate as low as 16% [41].

Photodynamic therapy (PDT) has also been applied for the treatment of EMPD. PDT is based on a photochemical reaction caused by the combination of a pro-neutral photosensitizer and light [45, 46]. A topical photosensitizer is selectively localized to the tumor and then activated by light, resulting in destruction of the

tumor tissue without damaging healthy tissue. Aminolevulinic acid (ALA) or its methyl ester (M-ALA) are the most commonly used photosensitizers. Recent studies have shown good response rates and symptom control with PDT [47-49]. A phase II prospective clinical trial found that although M-ALA-based PDT does not cure PPD, it does help improve life quality and is better than surgical resection [50].

Imiquimod (5%) cream has been used alone and in combination with other methods for treatment of PPD. Imiquimod 5% cream is an immune response modifier and stimulator that is approved for the treatment of genital and perianal fistulas [51]. Zempognoa *et al.* reported two cases of PPD who were successfully treated with imiquimod 5% cream [52]. In another study, topical imiquimod treatment of PPD in a patient without primary gastrointestinal neoplasia resulted in complete regression of the lesion, and no recurrence was noted over a 12-month follow-up period [53]. The most common side effects of imiquimod 5% cream are local skin irritation, erythema, and erosion, which may occur at 4-6 weeks after the initiation of imiquimod treatment [51]. These side effects are dose-dependent and can be alleviated by decreasing the frequency of topical application or with the withdrawal time prolonged [51].

Carbon dioxide (CO_2) laser ablation has been used to treat PPD in the vulva as it can preserve vulvar anatomy. However, the treatment is painful and local recurrence rates are very high [54]. In one study, the recurrence rates of PPD after local surgery, CO_2 laser ablation, and extensive local excision were 56%, 33%, and 23%, respectively [55].

Radiation therapy is another method for treatment of EMPD. It has been used as the definitive treatment for PPD and also for prevention of postoperative local recurrence. There are several reports on the effectiveness of radiation therapy in noninvasive PPD [56-58]. Yanagi *et. al.* used skin biopsy before and after radiotherapy to confirm the effectiveness of radiation therapy [59]. The recommended radiation dose is 40-50 Gy and lower doses are associated with higher risk of disease recurrence [60]. The main side effects after radiation therapy are local telangiectasia and fibrosis.

Systemic chemotherapy for EMPD has been minimally advanced. Various chemotherapy regimens have been reported for the treatment of EMPD, including low-dose 5-fluorouracil (5-FU) and cisplatin [61], vinorelbine and cisplatin [62], 5-FU and leucovorin [63], and a combination of mitomycin C, etoposide, and cisplatin [64]. Hallak *et. al.* reported good results in patients with PPD treated with oxaliplatin-assisted chemotherapy after extensive local excision and abdominoperineal resection [65]. The combination of 5-FU local chemotherapy and local surgery has also been used for treatment of EMPD [66]. Systemic chemotherapy can be used as monotherapy or in combination with other methods for EMPD patients with distant organ metastases.

Prognosis of PPD

The depth of tumor invasion and the number of metastatic lymph nodes are closely related to the prognosis of PPD [67]. Metastasis is rare in EMPD, but when it does occur, the most common sites are lymph nodes and bones. PPD may be more aggressive than genital and perineal EMPD. One study showed significantly lower disease-specific survival in PPD associated with rectal/anal cancer than in PPD not associated with rectal/anal cancer [68]. However, this finding was not confirmed in multivariate analysis [68].

Conclusions

Because of the rarity of PPD, all studies so far have had small sample sizes. Most of the researchers recommend surgical resection as the primary treatment method. The effectiveness of chemotherapy and radiation therapy is uncertain. PPD is more common among Asians, and Chinese clinicians need to be alerted to the possibility of PPD when a patient presents with abnormal perianal skin. Perianal skin biopsy should be considered for perianal rashes not responding to the usual treatments. Moreover, as PPD can be asymptomatic, all anorectal biopsies should be examined histologically. Because of the risk of invasive anal/perineal cancer in patients with PPD, close follow-up is required after resection, regardless of the margin status. Physicians should be aware of the risks of PPD-related cancer and should not exclude these risks during treatment.

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Disclosure of conflict of interest

None.

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