Original Article

Perianal Paget's Disease: Presentation of Twelve Cases and a Literature Review

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Key Words
Extramammary Paget's disease;
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Radiotherapy;
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Purpose. Perianal Paget's disease (PPD) is a rare intraepithelial adenocarcinoma. To date, ~200 cases have been reported, representing ~20% of all extramammary Paget's disease cases. The standard treatment is wide local excision, although PPD has a high recurrence rate. Here, we review our management for PPD and review the currently recommended treatment approaches.
Methods. In this study, we reviewed 12 patients diagnosed with PPD between 1995 and 2014. Clinical data including age, sex, symptoms, symptom duration, histopathology, treatment modality, recurrence, follow-up duration, and survival outcome were evaluated. We also reviewed the published literature from 1990 to 2014 to identify the treatment strategies used in 213 cases of PPD.
Results. Twelve patients with in situ disease with a median age of 70.8 (65-76) years, including 3 female patients (25%), were diagnosed with PPD. Eleven patients underwent surgery. The mean follow-up time was 92.1 (36-200) months. One patient died from liver cancer and bone metastasis, and the remaining patients are alive; 10 are disease-free and 1 experienced postsurgical local recurrence. This patient refused extensive radical excision, so radiotherapy (32 Gy in 16 fractions) was administered and the patient remains disease-free after 4 years.
Conclusion. Surgery is the mainstay treatment for PPD. Nonsurgical modalities could be considered an alternative to surgery for those with noninvasive PPD who refuse radical surgery or who are medically unfit for surgery. Further research and follow-up are needed to compare the effectiveness of surgical and nonsurgical therapeutic modalities for PPD.
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The most common sites of extramammary Paget's disease (EMPD) are the scrotum, penis, and perianal region, but the etiology of EMPD is unknown.[1] Perianal Paget's disease (PPD) is a rare intraepithelial adenocarcinoma first described in 1893 by Darier and Coulillaud as arising from the dermal apocrine sweat glands.[2] PPD accounts for ~20% of all EMPD cases. Experience of PPD is limited and most of the ~200 published observations are single case reports.[3-6]

PPD is characterized by a slowly expanding erythematous plaque that can be crusted, eczematous, or ulcerated.[7] The most common symptoms are pruritus and pain, sometimes concomitant with a burning sensation or bleeding. A diagnosis of PPD is confirmed

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histologically and immunohistochemically.[8] The associated malignancy rate of PPD has been reported as 30-85%,[9] with a high prevalence of colorectal and tubo-ovarian cancers.[10]

To our knowledge, there are no definitive guidelines on the management of PPD, and treatment decisions are usually made according to physician's preference.[1] In most cases, surgery, such as wide local excision, is considered the first-line treatment.[1,10,11] However, because of incomplete surgical excision, the local recurrence rate can be high.[12,13]

To further understanding of PPD, we report on 12 cases of PPD treated at our hospital over a 20-year period. In addition, we review the published PPD-associated literature.

Materials and Methods

Patients

In Chang-Hua Christian Hospital records, each pathologic diagnosis has a code. According to the coding system, we searched for cases of PPD treated between January 1995 and August 2014, using the ICD9 codes 173, 184, and 230.5. We reviewed the data retrospectively for clinicopathological characteristics including age, sex, symptoms, symptom duration, histopathology, treatment, recurrence, follow-up duration, and survival outcome. We also reviewed the published literature from 1990 to 2014 for current treatment strategies, identifying 213 cases of PPD.

Results

Data from 12 patients, including 9 males and 3 females, with a median age of 70.8 years (range, 65-76 years) were reviewed. Patient demographics, diagnoses, and clinical courses are shown in Table 1. The most common symptoms were a perianal patch with an eczematous surface and well-defined borders with reddish scaling located on the perianal skin and extending to the anal canal margin (Fig. 1). The median duration of symptoms prior to diagnosis was 2 years (range, 1-3 years). The mean follow-up time was 92.1 months (range, 36-200 months). In 10 patients with no evidence of recurrence, radical resection (R0) with ≥ 10 mm margins was performed.

Histopathological examinations revealed specific tumor cells (Paget's cells) with clear cytoplasm and round hyperchromatic nuclei that were confined to the epidermis. In 3 patients, immunohistochemical analysis was performed for a definitive diagnosis. In one case, the Paget's cells were cytokeratin (CK)7-positive and CK20-negative, and a primary cutaneous intraepithelial neoplasia was suspected. The other two cases were CK7-positive, CK20-positive, and gross cystic disease fluid protein-15-negative. All biopsies confirmed a diagnosis of non-invasive PPD (Fig. 2).

Eleven patients were evaluated for concomitant gynecological, urological, breast, and gastrointestinal malignancies, with the work-up including colonoscopy, but associated carcinomas were not detected. The remaining patient (case 5) did not consent for further investigation, but returned to the clinic 7 years later because of jaundice caused by liver cancer and bone metastasis. Radiotherapy was arranged for his untreatment PPD, but the patient died from liver cancer 3 months later, which was before the completion of radiotherapy.

Treatment modalities are shown in Table 1. Wide local excision with microscopically clear margins was performed in 10 cases. One patient (case 10) experienced local recurrence, despite having clear margins postoperatively (Fig. 3). This patient refused extensive radical excision, so radiotherapy (32 Gy in 16 fractions) was administered and the patient remains disease-free after 4 years.

Discussion

PPD is rare,[14] mostly affecting postmenopausal Caucasian females with a peak of incidence in the sixth and seventh decades of life.[15] Interestingly, in our series only 3 patients were female, which might indicate a different sex bias in Asian populations. However, an accumulation of further cases would be needed to confirm this hypothesis.

Because the symptoms of PPD are non-specific,

Table 1. Patients' characteristics, treatment and clinical course

Patient no/ Sex	Age (years)	Symptom duration (months)	Initial therapy	Recurrence (months)	Additional therapy	Follow-up (months)	Status
1 M	76	14	WLE + skin graft	No	No	48	Alive No recurrence
2 M	67	25	WLE + house flaps	No	No	120	Alive No recurrence
3 M	67	18	WLE + local flap	No	No	120	Alive No recurrence
4 F	71	36	Bilateral simple vulvectomy	No	No	200	Alive No recurrence
5 M	70	28	No		No	84	Died from liver cancer
6 M	72	23	WLE + FTSG	No	No	160	Alive No recurrence
7 M	71	24	WLE + FTSG	No	No	140	Alive No recurrence
8 F	70	24	WLE + FTSG	No	No	72	Alive No recurrence
9 M	65	22	WLE + skin graft	No	No	36	Alive No recurrence
10 M	71	18	WLE + FTSG	Yes (3)	Yes (Radiotherapy)	48	Alive No recurrence
11 M	70	16	WLE + FTSG	No	No	36	Alive No recurrence
12 F	71	14	WLE + FTSG	No	No	42	Alive No recurrence

M, male; F, female; WLE, wide local excision; FTSG, Full-thickness skin grafts.

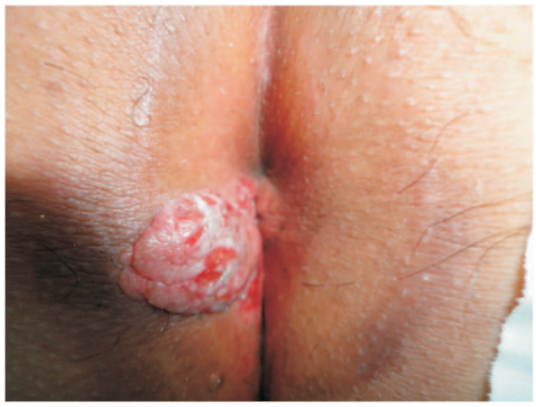

Fig. 1. The clinical appearance of perianal Paget's disease.

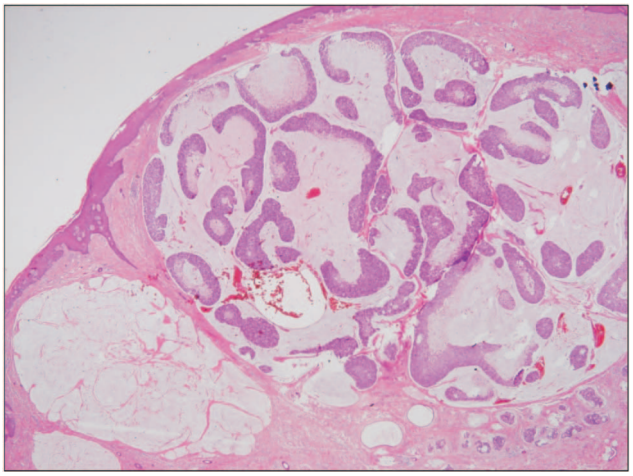

Fig. 2. The pathologic appearance of perianal Paget's disease. Pale and large cells within the basal and parabasal layers, accompanied by isolated cells in the upper epithelium (hematoxylin and eosin, x100).

symptom duration prior to diagnosis can be considerably long and most lesions are at first treated as benign dermatologic conditions.[16] This was the case for all of the patients in the present study with symptoms being present for ~1 year before a definitive diagnosis was made. Differential diagnoses for PPD included contact dermatitis, psoriasis, intraepithelial neoplasia, fungal infections, and melanoma. Therefore, if treated

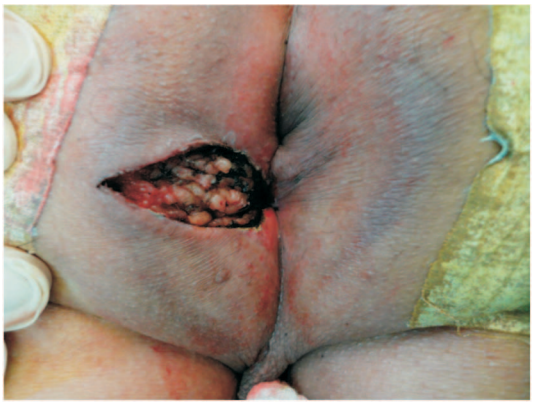

Fig. 3. The clinical appearance of a case of perianal Paget's disease recurrence after the first surgical resection in a patient with surgical margins that were not clear microscopically.

perianal lesions have not healed after some months, then a biopsy should be performed to prevent the misdiagnosis of PPD. EMPD is associated with an underlying neoplasm in ~25% of cases.[17] The most common cancers that coexist with EMPD are gastrointestinal,[18] genitourinary, and breast cancers. In one of our cases, liver cancer and bone metastasis were diagnosed 7 years after PPD.

Intraoperative frozen sections are obtained to ensure adequate surgical excision because of the high positive margin rate in EMPD. Besa et al.[19] noted a positive surgical margin rate of 53% in patients with perineal EMPD, and Pierie et al.[20] noted microscopically positive margins in 56% of their patients. Overall, the local recurrence rate has been reported as 31-61%,[17,18,20] and a second surgery may be necessary. In the present study, the rate of recurrence was much lower than that previously suggested (9.1%), and only 1 patient demonstrated recurrence. In this patient, the PPD lesion involved the left side of the perianal area. Because of the limited margin potential (1-cm margin) and because intraoperative frozen section analyses were not performed, this patient showed inadequate microscopic margins after excision. Minicozzi et al.[4] and Kyriazanos et al.[21] suggested that if the surgical margin was 1 cm away from clinically normal skin then the procedure would be safe, but Hendi et al.[22] suggested that if micrographic surgery cannot be performed then a 5 cm margin of normal skin should be considered. However, increasing the extent of surgery can result in significant morbidity, such as tissue loss, scaring, and strictures, and most defects should be covered with local flaps or skin grafts.[8,19] In addition, poor wound healing has been observed in some patients with comorbid diseases, such as diabetes mellitus, who undergo extensive resection.[19]

Several nonsurgical modalities, such as radiotherapy or photodynamic therapy (PDT) could be viable alternatives to surgery, especially in those who refuse radical surgery, in those who are medically unfit for surgery, or in those who present with concomitant multifocal widespread disease. The advantages of PDT are that it is minimally invasive, it has a low functional deficit rate, and the results are cosmetically appealing. Shieh et al. reviewed 5 patients with PPD who were treated with 5-aminolevulinic acid PDT and noted a 50% complete remission rate at a 6-month follow-up.[23] The disadvantages of PDT include local recurrence, but more importantly, the likelihood of developing of PDT-associated cancer is uncertain because of the lack of cases and inadequate follow-up durations.[3]

Radiotherapy has been used as a monotherapy and in the postexcisional setting to prevent local recurrence, especially in cases of anogenital EMPD. Dilme-Carreras et al.[24] reported that in patients with anogenital EMPD treated by irradiation with a total dose of 60 Gy, there were no local recurrences or internal malignancies at a 2-year follow-up. In a retrospective study by Luk et al.[25] of 6 patients with EMPD who underwent radiotherapy to control local recurrence after excision, 4 were alive and disease-free after 2-14.8 years of follow-up, 1 required salvage surgery, and 2 died because of distant metastasis 14 months after radiotherapy. Overall, they suggested that a dose range of 40-70.2 Gy resulted in a disease-free period ranging from 5 months to 13 years. One of the patients in the present study underwent radiotherapy after local recurrence with a dose of 32 Gy administered in 16 fractions. To date this patient remains disease-free with no evidence of distant metastasis. A number of small series reports and cases reports suggested that radiotherapy might play an important role in the future management of EMPD in patients who refuse surgical treatment (Table 2).

Table 2. Radiotherapy case report for perianal Paget's disease

Reference	Age (years)	Sex	History	Treatment type	Dose/fractions	Follow-up	Status
Thirlby et al. 1990 [26]	69	Male	Incomplete resection	Primary	50 Gy/25	14 months	No recurrence
Brierley & Stockdale 1991 [27]	76	Female	Not available	Primary	54 Gy/12	13 months	No recurrence
	84	Female	Not available	Primary	50 Gy/25	31 months	No recurrence
Besa et al. 1992 [19]	72	Female	PPD 4 × 5 cm	Primary	56 Gy/28	21 months	No recurrence
Goldman et al. 1992 [28]	75	Male	PPD 3 × 3.5 cm incomplete excision	Adjuvant	66 Gy/33	16 months	No recurrence
Amin 1999 [29]	71	Male	ppd 13 × 12 cm with recurrence after surgery	Recurrence	50 Gy/10	10 years	No recurrence
Velenik et al. 2008 [30]	80	Female	ppd 8 × 5 cm	Primary	45 Gy/15	28 months	No recurrence
Yasar et al. 2015 [31]	65	Female	ppd, refused surgery	Primary	54 Gy/32	5 years	No recurrence

RT: radiotherapy.

Conclusion

Nonsurgical modalities could be an alternative option to surgery in patients with noninvasive PPD who refuse radical surgery, those who are medically unfit for surgery, or those with concomitant multifocal widespread disease. However, additional data from longer-term follow-up studies is required to determine recurrence rates and the rate of development of associated cancers following nonsurgical treatments.

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原　著

肛門周圍之乳房外柏哲德氏症之系列案例分析及文獻回顧

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目的　肛門周圍柏哲德氏症，是一種罕見皮膚的惡性腫瘤，約佔乳房外柏哲德氏症20%，目前有提出論文討論的病例數 200 例左右，手術治療為主要方法，但復發率在統計上仍偏高。因此，我們收集彰化基督教醫院案例進行分析，並回顧相關文獻。

方法　本研究回溯本院 1995 年至 2014 年間，診斷為「肛門周圍柏哲德氏症」之 12 位患者。我們記錄並分析其年紀、性別、臨床表現、確診時間、病理報告、術前診斷、手術方法與復發及死亡與否，另搜尋 1990-2014 可得論文共針對 213 例患者治療文獻做回顧及討論。

結果　12 位患者中平均年齡為 70.8 歲 (65-76 歲)。其中三位 (25%) 是女性。其中十一位接受手術切除。平均追蹤時間為 92.1 個月。只有一位患者死於肝癌，其餘患者皆存活。接受手術切除的患者中只有一位有復發情形，此病人拒絕再次接受廣泛性切除，因此安排放射治療 (32 Gy/16 fractions)，追蹤四年後，無復發情況發生。

結論　手術切除是目前認為最主要的治療方法，但非手術的治療方式，對於不希望手術或不適合手術，且病理上為非侵犯性的肛門周圍之乳房外柏哲德氏症之病人，或許是可行的方法，因病例數不多，未來仍需更多的研究來證明此論點。

關鍵詞　肛門周圍柏哲德氏症、乳房外柏哲德氏症、放射治療、光照治療。