Clinical, Cosmetic and Investigational Dermatology

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CASE REPORT

Secondary Perianal Paget's Disease Originating From Adenocarcinoma of the Anorectal Junction: A Case Report

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Abstract: Secondary extramammary Paget's disease (EMPD), originating from the cutaneous dissemination of malignant cells, represents a rare subtype prone to misdiagnosis. This study presents a case of secondary perianal Paget's disease (PPD) associated with adenocarcinoma at the anorectal junction. Preoperative full-thickness mapping biopsy was utilized for the assessment of lesion margins. The patient demonstrated favorable postoperative recovery following a multimodal therapeutic regimen.

Keywords: Extramammary Paget's disease, perianal Paget's disease, anorectal cancer

Introduction

In 1874, James Paget first reported Paget's disease (PD), a rare form of intraepithelial adenocarcinoma predominantly affecting skin regions containing apocrine glands.[1] Based on the primary lesion location of PD, the disease is categorized into two types: mammary Paget's disease (MPD) and extramammary Paget's disease (EMPD).[2] In 1893, perianal Paget's disease (PPD), a subtype of EMPD, was first described by Darier and Couillaud.[3] Owing to the limited number of cases, our understanding of this disease remains incomplete and necessitates further investigation. In this report, we present a case of secondary PPD which is associated with adenocarcinoma of the anorectal junction.

Case Presentation

A 67-year-old Chinese male patient presented with a one-year history of perianal rash. Three months prior to presentation, the patient experienced worsening perianal pruritus accompanied by perianal pain and exudation, hematochezia, and increased stool frequency. In January 2020, the patient sought medical attention at our hospital. His medical history was significant for prostatic hyperplasia, with no documented history of cancer or other malignancy-related conditions. Physical examination revealed symmetrically distributed lichenoid lesions extending from the perianal region into the anal canal, measuring approximately 15 cm in diameter. The well-demarcated erythematous lesion exhibited crusts, scales, and erosions (Figure 1A). A comprehensive diagnostic evaluation was performed. Digital rectal examination and colonoscopy identified a mass involving the anterior side of the anorectal junction (Figure 1B). Abdominopelvic computed tomography (CT) and contrast-enhanced pelvic magnetic resonance imaging (MRI) demonstrated thickening and enhancement of the tissues in the perianal region and the junction of the rectum and anal canal. Biopsies of the perianal skin and anal canal mass confirmed EMPD and adenocarcinoma of the anorectal junction, respectively. Staging investigations, including chest and brain CT scans as well as an abdominal enhanced CT scan, did not reveal any evidence of distant metastasis. Subsequently, the case was reviewed at a multidisciplinary team (MDT) comprising

Received: 12 June 2025
Accepted: 11 September 2025
Published: 20 September 2025

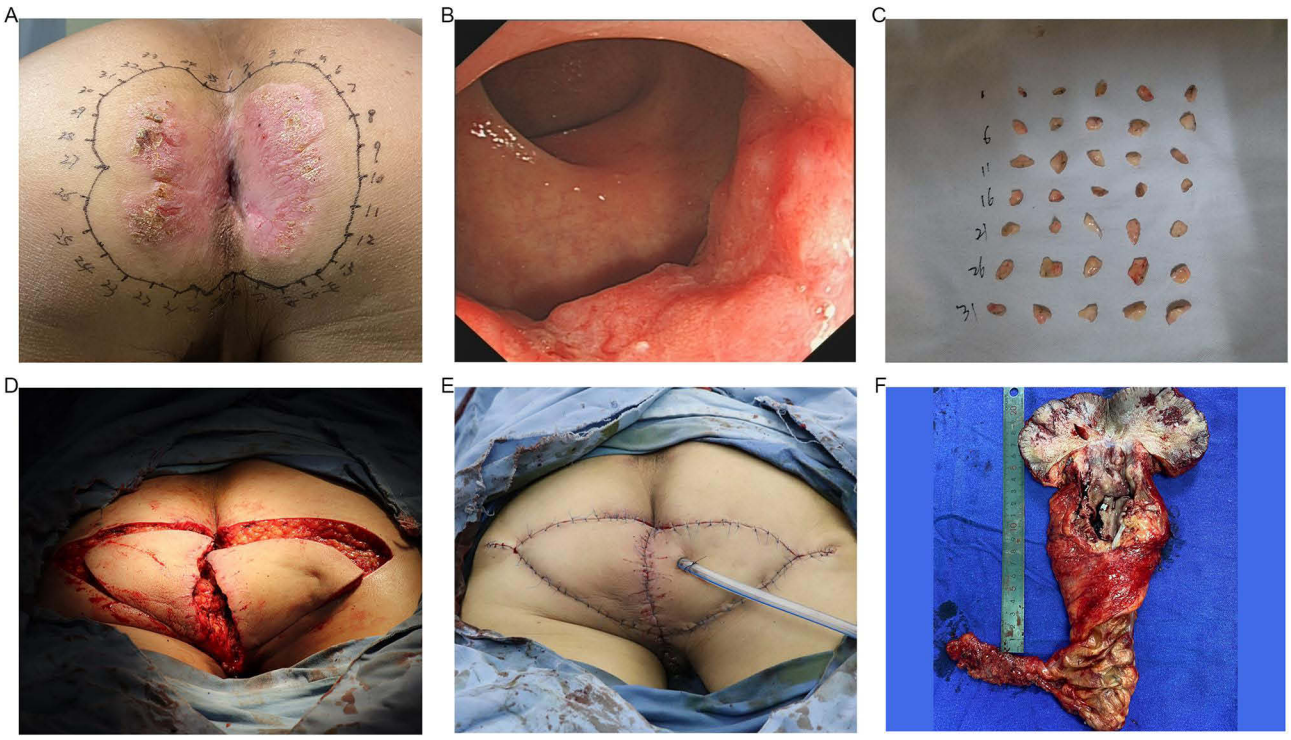

Figure 1 Preoperative and postoperative images of the patient. (**A**) A well-demarcated erythematous lesion with crust, scale, erosion, and mapping biopsy sites is shown; (**B**) A mass in the anterior side of the anorectal junction is depicted; (**C**) Full-thickness skin mapping biopsy specimens are presented; (**D**) Bilateral V-Y flaps have been isolated; (**E**) Bilateral V-Y flap reconstruction has been completed; (**F**) The resected specimen is displayed.

surgeons, dermatologists, pathologists, oncologists, and radiologists. Full-thickness skin mapping biopsies were recommended to delineate the resection margins of the cutaneous lesion prior to surgery. Mapping biopsies were conducted at a 1-cm margin around the lesion, with sampling performed at 1-cm intervals (Figure 1A). The resection margin was determined based on the distribution of negative biopsy sites. Where biopsy results were positive, additional biopsies were performed 1 cm beyond the positive sites until all biopsy sites were negative for tumor involvement. The preoperative full-thickness mapping biopsy results confirmed negativity across all sites. Fine-needle aspiration biopsy of the inguinal lymph nodes was also performed, with no evidence of carcinoma cells detected.

Ultimately, the patient underwent laparoscopic abdominoperineal resection combined with permanent colostomy and bilateral V-Y flap reconstruction. The proximal edge of the tumor was located approximately 4 cm from the anal verge. The tumor was situated at the anterior anorectal junction, occupying more than half of the luminal circumference. Continuity was observed between the primary lesion at the left quadrant and a secondary perianal lesion. In contrast, portions of apparently normal tissue were observed between the primary lesion and the secondary perianal lesion in the right quadrant. Preoperative and postoperative images of the patient are shown in Figure 1A–F and Supplementary Figure 1.

Histopathology revealed a moderately differentiated anorectal adenocarcinoma (pT2N0M0), involving the internal sphincter, with negative surgical margins and no lymph node metastasis (0/23). Hematoxylin-eosin staining revealed the presence of epidermal pagetoid cells, characterized by atypical large cells with abundant, pale cytoplasm, sometimes eosinophilic (Figure 2A and B). Immunohistochemical staining of the perianal skin lesion showed positivity for cytokeratin 7 (CK-7), cytokeratin 20 (CK-20) and caudal-related homeobox gene nuclear transcription factor 2 (CDX-2), but negativity for gross cystic disease fluid protein-15 (GCDFP-15) in the pagetoid cells (Figure 2C and F). The patient was ultimately diagnosed with adenocarcinoma of the anorectal junction combined with secondary PPD. For various reasons, the patient refused further radiotherapy and chemotherapy. During a 2-year follow-up, the patient survived without local recurrence or metastasis but was later lost to follow-up.

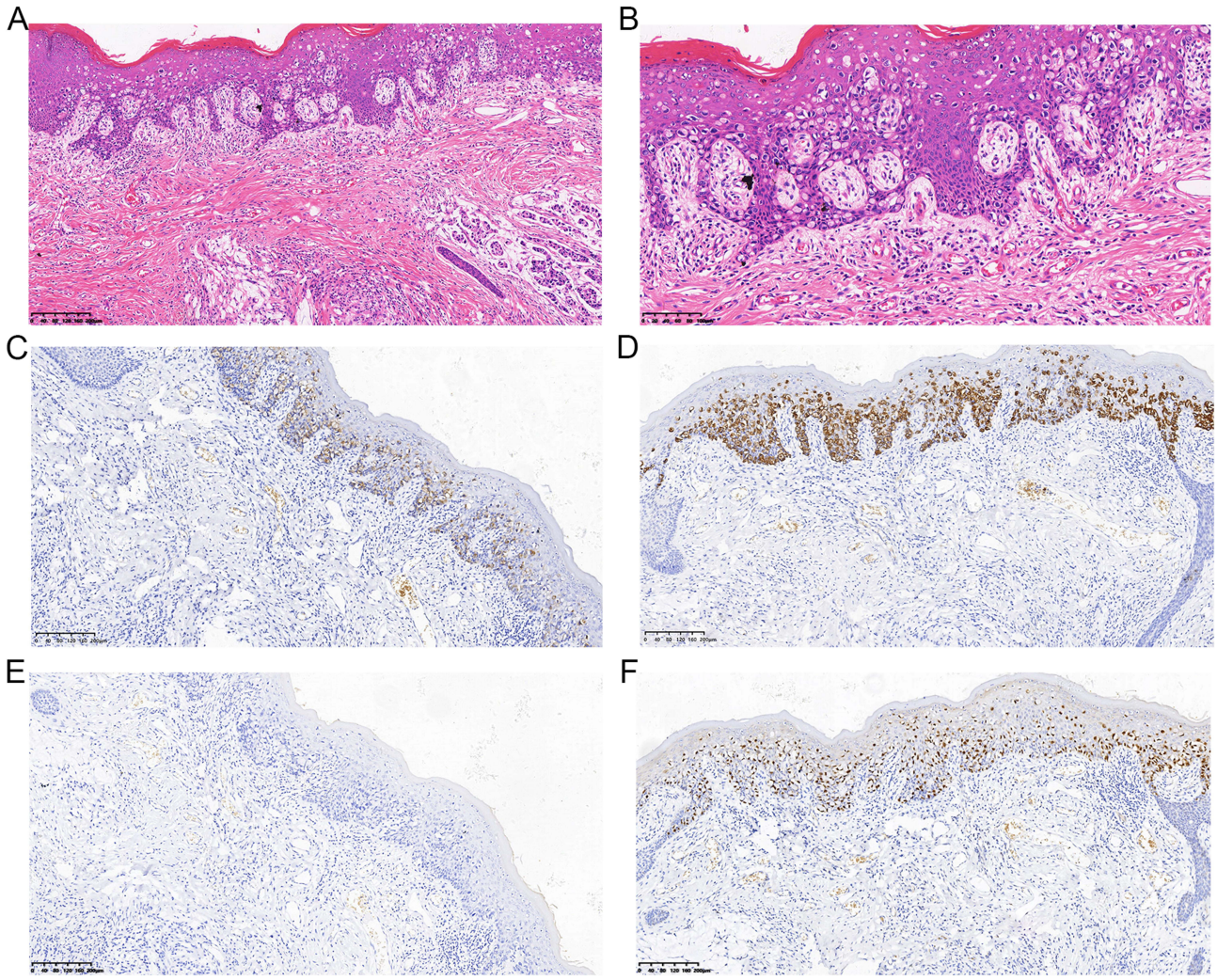

Figure 2 Histopathology and immunohistochemistry images. (**A**) Hematoxylin and eosin staining of the skin lesion reveals pagetoid spread of atypical cells forming solid clusters that infiltrate the dermis (×10); (**B**) Higher magnification highlights the details of Paget cells: large cells with abundant, pale cytoplasm, sometimes exhibiting eosinophilic features (×20); (**C**) Immunohistochemical staining demonstrates positive expression of CK-7 in Paget cells (×10); (**D**) Immunohistochemical staining confirms positive expression of CK-20 in Paget cells (×10); (**E**) Immunohistochemical staining indicates negative expression of GCDFP-15 in Paget cells (×10); (**F**) Immunohistochemical staining verifies positive expression of CDX-2 in Paget cells (×10).

Discussion

The etiology of EMPD remains incompletely understood. EMPD is prone to occur in areas where apocrine glands are distributed. It is most commonly found in the scrotum and penis in men and the external genitalia in women. It can also affect the perianal area, groin, axilla and other parts.[4,5] As a subtype of EMPD, PPD can be categorized into two distinct types: primary and secondary.[6,7] The former may be attributed to the abnormal proliferation of hair follicle stem cells that differentiate into sebaceous glands, while the latter represents a primary EMPD-like lesion resulting from the cutaneous invasion of malignant cells, such as those associated with colorectal carcinoma or urothelial carcinoma.[8–10] Tumor cells may spread and extend to the epidermis through blood vessels or lymphatic vessels.[10] Despite their distinct origins, the local manifestations are remarkably similar. A slowly progressive lesion in the perianal region, characterized by erythema, scaling, or hypopigmentation with well-demarcated borders, is commonly observed.[11] Patients with this disease often experience symptoms such as itching, exudation, bleeding, a burning sensation, or pain.[12,13] The clinical features of PPD may closely resemble those of inflammatory dermatological conditions, such as psoriasis, eczema, and fungal infections, which can be effectively managed with topical corticosteroids or other therapeutic interventions in the

short term.[14] Therefore, PPD should be considered in the differential diagnosis for patients exhibiting resistance to long-term topical corticosteroid or other drug therapy.[15]

In order to reduce diagnostic delay, examinations such as dermoscopy, reflectance confocal microscopy, and full-thickness skin biopsy are recommended for suspicious lesions.[16–18] Generally, an accurate diagnosis requires the combination of histopathology and immunohistochemistry. The histopathological hallmark of EMPD is the presence of Paget cells infiltrating the epidermis. These cells can be categorized into two main types: classic and signet ring. The classic type is distinguished by large, bubble-like nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm. In contrast, the signet ring type exhibits eccentric displacement of the nucleus and an increased amount of acidic mucin within the cytoplasm.[18] Immunohistochemistry plays a crucial role in the differential diagnosis of EMPD. CK7 is stably expressed in EMPD.[19] Trichorhinophalangeal syndrome type 1 (TRPS1) and CK20 serves as a reliable method to distinguish primary EMPD from secondary EMPD. Recent studies indicate that primary EMPD consistently exhibits diffuse and strong TRPS1 immunoreactivity, whereas the majority of secondary EMPD cases lack TRPS1 expression.[20] In addition, it should be noted that most primary PPD is also negative for TRPS1. Although CK20 can serve as an adjunct differential diagnostic marker, it should be noted that primary PPD cases may also express CK20.[21] Other pagetoid intraepithelial lesions, including melanoma in situ and pagetoid squamous cell carcinoma in situ, should be considered in the histopathologic differential diagnosis, as they typically show SOX10 (SRY-Box Transcription Factor 10) and tumor protein p63 expression, respectively.[22,23] In patients with PPD who are negative for GCDFP-15 staining, the possibility of an underlying visceral malignancy, such as rectal carcinoma, should be carefully considered.[20,21] Additionally, positivity for NKX3.1 (NK3 Homeobox 1), uroplakin, or CDX2 should raise suspicion for an underlying malignancy, such as prostate carcinoma, urothelial carcinoma, or colorectal carcinoma.[24–26] Based on the finding of cancer at the anorectal junction, this patient was diagnosed with PPD of anorectal origin. Based on the reported case, patient with PPD may present symptoms directly associated with the primary disease, including increased bowel frequency, rectal bleeding, and other alterations in bowel habits. Laboratory tests (eg, CEA), digital rectal examination, colonoscopy, cystoscopy, and imaging evaluations should also be included in the diagnostic process for PPD. In female patients, colposcopy may also be necessary to exclude gynecological causes.

Although there are various treatment options, surgery remains the primary treatment for EMPD. In light of the potential diffuse spread of EMPD, wide local excision (WLE) with a 2–5 cm margin of normal skin has been a popular surgical option for a long time.[13,27] However, in patients undergoing WLE, the resulting large skin defects can pose significant challenges for reconstruction. Studies have shown that when combined with mapping biopsy, resection margins of 1 cm around well-demarcated lesions are reliable.[28–30] In the present case, the lesion margins were relatively clear. Combined with the negative result of preoperative mapping biopsy, a 1 cm margin resection was finally performed. Since the patient presented with secondary PPD originating at the anorectal junction, the therapeutic principles for anorectal adenocarcinoma were followed. No signs of local recurrence were observed during the 2-year follow-up period. In recent years, Mohs micrographic surgery (MMS) has also been applied in the treatment of EMPD.[31–33] However, due to the high time and labor costs associated with MMS, its use in EMPD treatment has not yet become widespread. Compared with MMS, combining preoperative mapping biopsy significantly reduces the duration of surgery while maintaining an equivalent local recurrence rate.[30] Prolonged operative time has been shown to be positively associated with a variety of postoperative complications, including surgical site infection, intraoperative or postoperative bleeding, and deep venous thrombosis.[34] Therefore, compared to intraoperative frozen section biopsy, preoperative mapping biopsy allows for more efficient intraoperative management and significantly reduces the duration of definitive surgery, which may help enhance patient tolerance and minimize surgical risks. Additionally, alternative treatments such as topical imiquimod cream, photodynamic therapy, radiotherapy, chemotherapy and targeted therapy are available for EMPD.[35–39]

Although this report documents the patient's treatment process and short-term outcome in detail, long-term follow-up was interrupted two years after surgery. As a result, long-term prognosis could not be assessed. In the future, studies involving more patients and long-term follow-ups should be conducted.

Conclusions

In conclusion, PPD secondary to adenocarcinoma of the anorectal junction is relatively uncommon in clinical practice. Early diagnosis and treatment of secondary PPD are critical for prognosis. Biopsy of the perianal lesion and conducting

examinations, including digital rectal examination and colonoscopy, should be performed appropriately to avoid delaying diagnosis or misdiagnosis. Additionally, preoperative mapping biopsy may serve as an alternative technique for margin assessment.

Data Sharing Statement

The data involved in this study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

Written informed consent was obtained from the patient for the publication of this case report and the accompanying images. Institutional approval for the publication of anonymized case details was granted by the Ethics Committee of Hangzhou Third People's Hospital. This study was performed in accordance with the Declaration of Helsinki.

Consent Statement

The authors confirm that they have obtained all necessary patient consent forms. Additionally, the patient provided written consent for the publication of both the case details and associated images.

Acknowledgments

Jun He and Rong-Chao He are co-first authors for this study. The authors would like to thank all the people involved in this work.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was funded by the Zhejiang Medical Health Science and Technology Project (Grant No. 2023KY922), Zhejiang Basic Public Welfare Research Project (Grant No. LY24H03005), General Project of Zhejiang Administration of Traditional Chinese Medicine (Grant No. 2024ZL734), Hangzhou Sciensuppce and Technology Bureau General Project (Grant No. 20220919Y011).

Disclosure

The authors declare no conflicts of interest in this work.

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