

Anal canal carcinoma with pagetoid spread: Two case reports

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ABSTRACT

Pagetoid spread of anal canal carcinoma is a rare phenomenon, mimicking perianal primary extra-mammary Paget's disease. We report two cases with perianal pagetoid spread associated with submucosally invasive adenocarcinoma in the anal canal. Both cases presented at our hospital with perianal skin lesions. In each case, histological examination of the biopsied specimens from the lesions revealed that Paget cells had infiltrated all levels of the epidermis. The tumor cells were positive for CK7 and CK20, but negative for GCDFFP-15. According to a diagnosis in both cases of anal canal carcinoma by endoscopic examination, one patient underwent laparoscopic abdominoperineal resection and extensive lymph node dissection, and the other patient received preoperative radiotherapy, rectal amputation and lymphadenectomy. In both cases, a diagnosis of primary anal canal carcinoma was made by skin biopsy of the lesions as pagetoid spread. Immunohistochemical analysis was helpful in the differential diagnosis between primary Paget's disease and pagetoid spread with anorectal carcinoma. Furthermore, we found that management of perianal Paget's disease is necessary for estimating prognosis and selecting appropriate treatment according to the patient's condition.

Keywords: Pagetoid spread, Perianal Paget's disease, Cytokeratin 20

INTRODUCTION

Pagetoid spread of anal canal carcinoma is a rare phenomenon, mimicking perianal primary extra-mammary Paget's disease (EMPD). EMPD is thought to be an epidermotropic neoplasm arising from the apocrine glands of extra-mammary organs such as the valve, penis scrotum, perineum, axilla, and perianal region [1-3]. On the other hand, pagetoid spread occurs in cases of anal canal, rectal, cervical, and bladder carcinomas [4-7]. Specifically, perianal pagetoid spread is suggested to be skin infiltration of anal canal carcinoma or rectal carcinoma [4-5]. We report two cases with perianal pagetoid spread associated with submucosally invasive adenocarcinoma in the anal canal.

REPORT OF CASES

Case 1: A 64-year-old woman was referred to our hospital with a one-year history of a well-marginated, erosive, erythematous plaque with pain and itchiness on the perianal skin (Figure 1). Histological examination of the biopsied specimens from the lesion revealed large atypical cells with ample pale-staining cytoplasm, pleomorphic nuclei, and occasional prominent nucleoli, indicative of Paget cells. Tumor cells infiltrated throughout all levels of the epidermis (Figure 2a). Immunohistochemical staining of the cells was positive for CK7 and CK20, but negative for

GCDFFP-15 (Figure 2b-d). Endoscopic examination showed a large sessile polyp in the anal canal, and normal findings above the dentate line (Figure 3). The patient underwent laparoscopic abdominoperineal resection and extensive lymph node dissection, and was diagnosed as having anal canal carcinoma.

Case 2: A 76-year-old woman who was followed up for proctoptosis for one year presented with a burning pain in the anus that she had developed one month previously. Physical examination revealed a well-marginated, erosive, erythematous, circular plaque around the anus (Figure 4).

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Figure 1. Clinical appearance of the perianal lesion. A well-margined, erosive, erythematous plaque around the anus.

Skin biopsy showed the invasion of Paget cells, which formed nests in the epidermis and dermis. The tumor cells were strongly positive for CK7 and CK20, but negative for GCDFP-15 (Figure 5). Proctoscopic examination showed a large polypoid lesion on the anal canal, but no abnormal findings in the anterior wall from the dentate line. A CT scan revealed swollen inguinal lymph nodes (Figure 6). The patient was treated with preoperative radiotherapy for both Paget's disease and anal canal carcinoma, as well as rectal amputation and lymphadenectomy of the swollen lymph nodes.

DISCUSSION

Perianal Paget's disease is rare and often associated with anorectal malignancy. The cases of anorectal carcinoma with

Pagetoid spread have been reported as extra-mammary secondary perianal Paget's disease. Helwig EB et al reported that seven of 40 patients with perianal Paget's disease had primary internal or extracutaneous malignancy and four of those seven patients had concomitant rectal adenocarcinoma [8]. In another report, 33% of the perianal Paget's disease cases coexisted with anorectal carcinoma [4].

Previous publications regarding immunohistochemistry of EMPD lesions have confirmed that primary EMPD is usually CK7, GCDFP-15 positive and CK20 negative. In contrast, secondary EMPD with colorectal carcinoma is positive for CK7, CK20 and negative for GCDFP-15 [9-11]. CK20 strongly marks Paget cells associated with large bowel carcinoma but it is not specific [11].

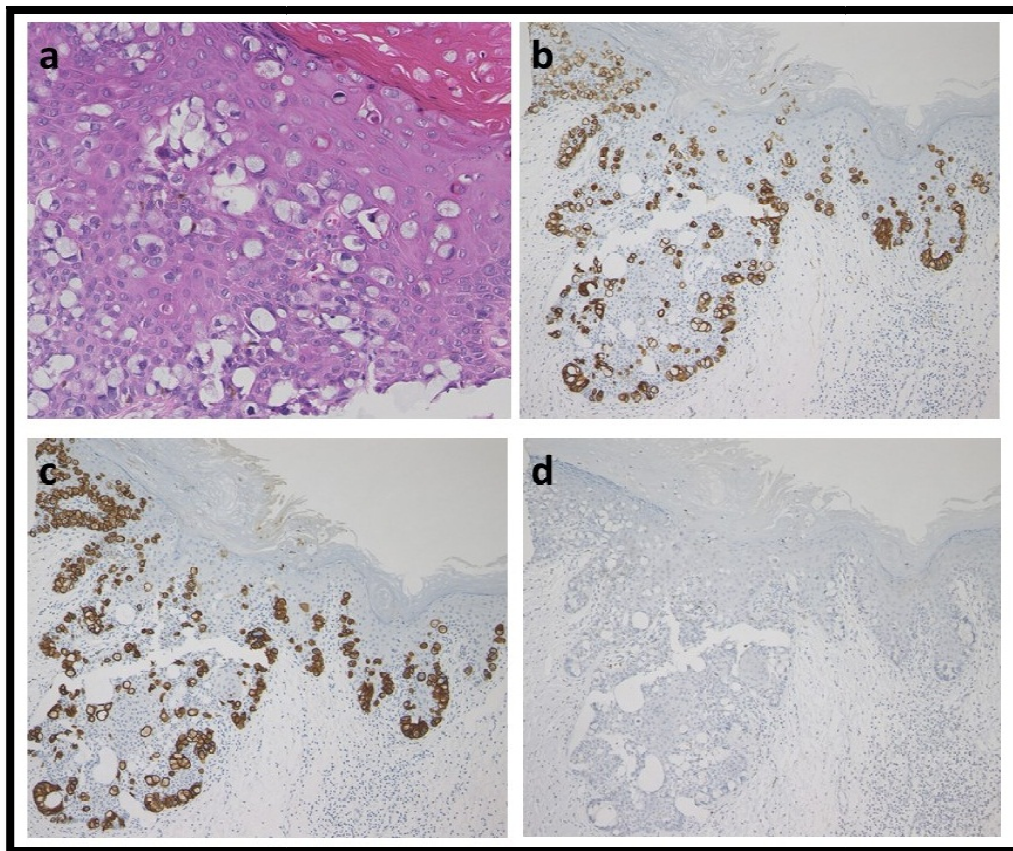


Figure 2. (a) Histological features of the perianal lesion showing numerous intraepidermal Paget cells(hematoxylin-eosin, original magnification $\times 400$). Immunohistochemical stained with (b) CK7, (c) CK20, (d) GCDFP-15. Paget cells were stained positive for CK7 and CK20 but negative for GCDFP-15 (original magnification $\times 200$).

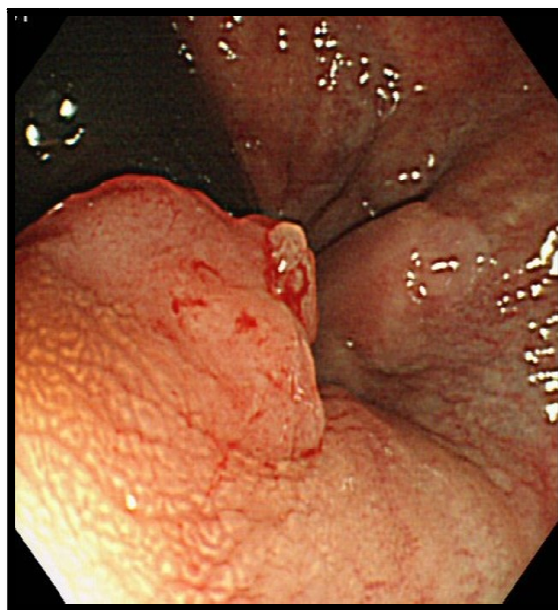


Figure 3. Endoscopic examination finding was a large sessile polyp in the anal canal.



Figure 4. The perianal skin revealed an erosive, erythematous, eczematous and circinate lesion resembling Paget's disease

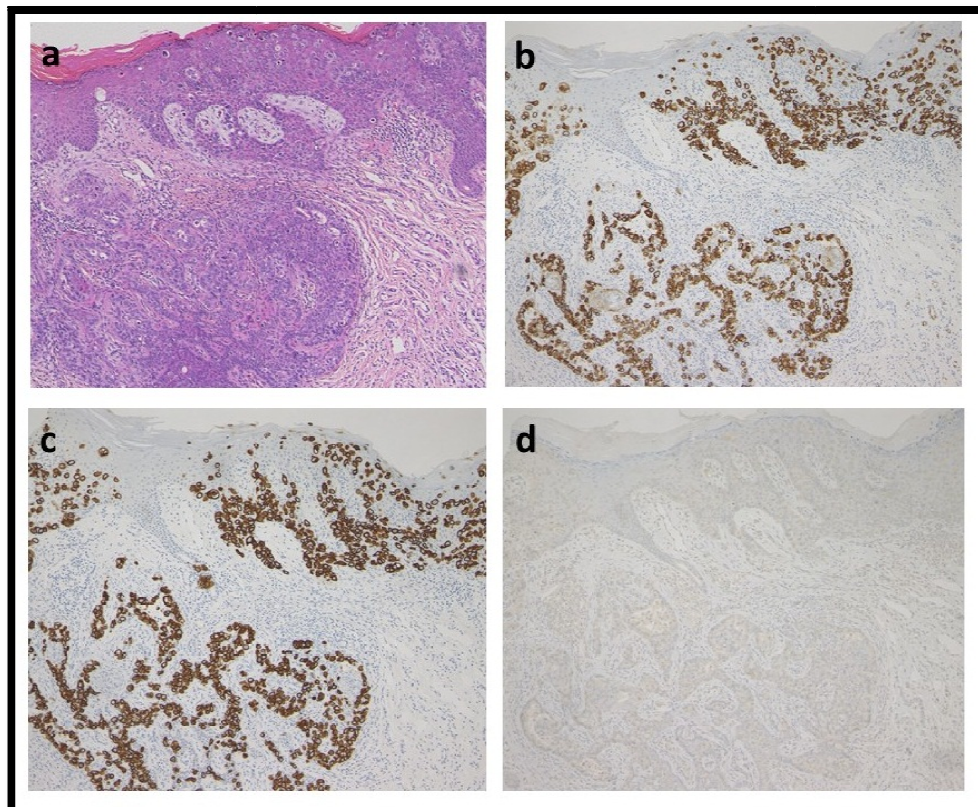


Figure 5. (a) Histological examination showing massive invasion of Paget cells into the epidermis and dermis (hematoxylin-eosin, original magnification $\times 200$). Paget cells were stained positive for (b) CK7 and (c) CK20 but negative for (d) GCDFP-15 (original magnification $\times 200$).

The treatment of perianal Paget's disease is recommended by many oncologists to be selected in accordance to each stage (Table 1) [2]. According to this staging system, our Case 1 was grouped as stage IIB and abdominoperineal resection should be recommended. This patient was additionally treated with regional lymph node dissection. Case 2 was grouped as stage III and inguinal lymph node dissection with wide local excision or abdominoperineal resection. The treatment which with preoperative radiotherapy, rectal amputation and lymphadenectomy of swollen lymph nodes as a palliative treatment was selected with consideration for the patient's quality of life. Recently, some reports revealed that molecular targeted drugs, such as bevacizumab (VEGF inhibitor) and ceuximab (EGFR inhibitor), were effective against advanced rectal carcinoma [13-14] and may also improve the prognosis of the patients with Pagetoid spread lesion.

Survival of primary Paget's disease is generally favorable, however, that of perianal Paget's disease is poor. Lian Pet al reported that eight cases of perianal Paget's disease with anorectal adenocarcinoma, including seven synchronous lesions and one with metastatic lesions [15]. The median follow-up time for all patients was 61.5 months (range 10-204 months). One patient died from lung metastases 10 months after the abdominoperineal resection. The other seven patients were free of disease during the study. Marchesa P et al reviewed that ten patients of perianal Paget's disease with a mean follow-up of longer than five years were studied to determine the outcome after surgical treatment [16]. Eight-year survival was 0% in the local excision group and 40% in wide local excision. These reports suggested that it is important that the treatment should be selected depending on stage of perianal Paget's disease and anorectal cancer.



Figure 6. A CT scan showed swollen inguinal lymph nodes

In conclusion, in both of our cases, a diagnosis of primary anal canal carcinoma was made by skin biopsy of perianal lesions as a pagetoid spread. Immunohistochemical analysis of CK7, CK20 and GCDFP15 was helpful in the differential diagnosis between primary Paget's disease and pagetoid

spread with anorectal carcinoma. Furthermore, we found that the management of perianal Paget's disease is necessary for estimating prognosis and selecting appropriate treatment according to the patient's condition.

Table 1. Stage and management of perianal Paget's disease

Stage	Description	Management
I	Paget cells found perianal epidermis and adnexa without primary carcinoma	WLE
IIA	Cutaneous Paget's disease with associated adnexal carcinoma	WLE
IIB	Cutaneous Paget's disease with associated anorectal carcinoma	APR
III	Paget's disease in which associated carcinoma has spread to regional nodes	ILND + WLE/APR
IV	Paget's disease with distant metastases of associated carcinoma	CT + RT + LPM

WLE: Wide local excision, ILND: Inguinal lymph node dissection,
CT: Chemotherapy, RT: Radiotherapy, LPM: Local palliative management

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