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Anal canal adenocarcinoma with pagetoid spread and inguinal lymph node metastasis treated with preoperative chemoradiotherapy: A case report

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Abstract. Perianal Paget's disease is a rare condition, which is not usually accompanied by cancer. Here, a case of anal canal carcinoma with pagetoid spread and inguinal lymph node metastasis, which exhibited a significant response to preoperative chemoradiotherapy (CRT), is presented. A 58-year-old woman was admitted to The University of Tokyo Hospital with a complaint of discomfort around the anus. Physical examination revealed an erythematous inflamed skin lesion in the perianal region and a tumor of 15 mm in diameter detected on palpation in the left inguinal region, which was diagnosed as metastatic adenocarcinoma by excisional biopsy. Colonoscopy revealed moderately differentiated adenocarcinoma of 15 mm in diameter in the anal canal. Skin biopsy of the perianal region revealed an infiltration of pagetoid cells, which were positive for cytokeratin 7, and negative for cytokeratin 20 and gross cystic disease fluid protein 15. Based on these results, the patient was diagnosed as having anal canal adenocarcinoma with pagetoid spread. The patient received preoperative CRT including the bilateral inguinal region. After CRT, robotic-assisted laparoscopic abdominoperineal resection was performed. The macroscopic findings of the surgical specimen confirmed the formation of a scar as a result of the preoperative CRT. Microscopic examination of the anal tumor revealed no residual carcinoma or lymph node metastasis. In conclusion, this case may suggest the potential applicability of preoperative CRT for the local control of anal canal carcinoma with pagetoid spread.

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Abbreviations: CRT, chemoradiotherapy; PET, positron emission tomography; CK7, cytokeratin 7; CK20, cytokeratin 20; GCDFP15, gross cystic disease fluid protein 15; CDX2, caudal-type homebox transcription factor 2

Key words: anal canal adenocarcinoma, pagetoid spread, preoperative chemoradiotherapy, inguinal metastasis, robotic surgery

Introduction

Paget's disease has been classified as mammary and extramammary. Mammary Paget's disease is an adenocarcinoma originating mainly in the mammary duct and characterized by eczematous erosion. Extramammary Paget's disease is a rare condition typically presenting as a reddish patch and/or nodule and is commonly found in the vulvar area, followed by the perianal area, scrotum, penis and axillae. Perianal Paget's disease, defined as intraepithelial adenocarcinoma of the perianal skin (1,2) is a rare condition. There are two types of perianal Paget's disease: Primary and secondary. When an underlying adenocarcinoma is present, perianal Paget's disease usually represents intraepidermal extension of an invasive carcinoma from an adjacent internal organ and generally regarded as secondary.

During the early years of this century, preoperative chemoradiotherapy (CRT) and total mesorectal excision were reported to remarkably reduce rates of local recurrence and this approach facilitates tumor downstaging, increases sphincter preservation and CRT plus total mesorectal excision has gained acceptance as the gold standard for surgical treatment of rectal cancer. In our department, we performed preoperative CRT in patients with advanced carcinoma of the lower rectum. But in perianal Paget's disease the role of preoperative CRT is presently unclear because of the rarity of the disease.

Here, we report a case of anal canal cancer with pagetoid spread and inguinal lymph node metastasis, which showed a significant response to preoperative CRT and discuss on the clinical and pathological findings.

Case report

A 58-year-old woman was admitted to University of Tokyo Hospital (Tokyo, Japan) complaining of discomfort around her anus. She had no history of abdominal or anal surgery, no

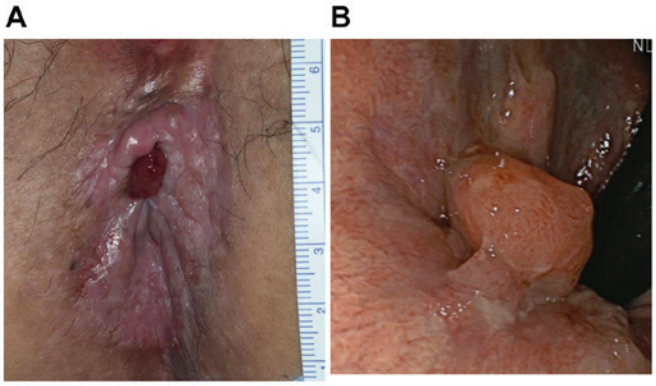

Figure 1. Images of the perianal region and colonoscopy prior to chemoradiotherapy. (A) Erythematous inflamed skin lesion in the perianal region. (B) Tumor of 15 mm in diameter in the left posterior wall of the anal canal located just on the dentate line observed by colonoscopy.

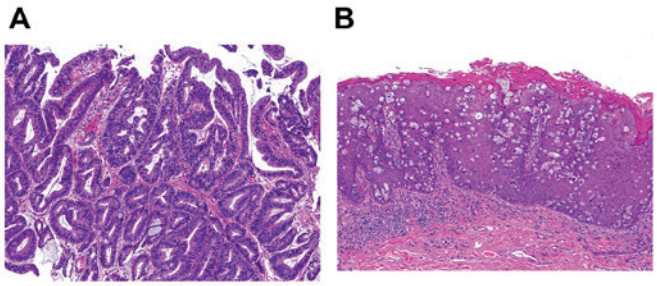

Figure 2. Pathological findings. (A) Moderately differentiated adenocarcinoma cells in the tumor biopsy of the anal canal tumor. HE staining. Magnification, x200. (B) Epidermal infiltration of pagetoid cells, characterized by mucin-filled cytoplasm demonstrating signet ring morphology, in the skin biopsy. A moderately differentiated glandular structure, similar to the original anal canal carcinoma, was observed. HE staining. Magnification, x200. HE, hematoxylin and eosin.

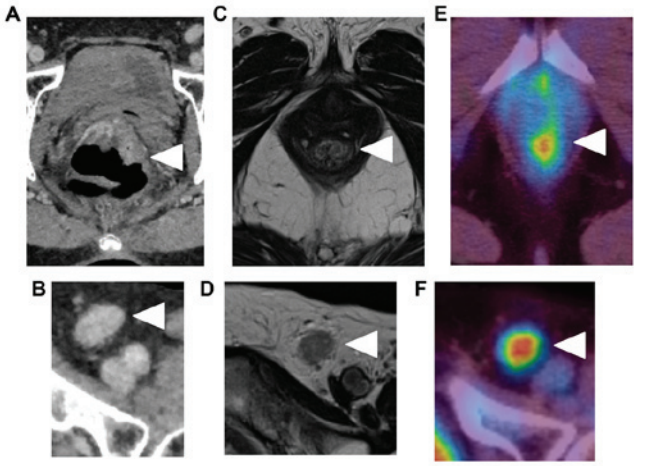

Figure 3. Main tumor and left inguinal lymph node. (A) Thickness of the lower rectum wall (arrowhead) in the abdominal CT. (B) Left inguinal lymph node of 15 mm in diameter (arrowhead) detected by the abdominal CT. (C) Thickness of the lower rectum without evident invasion into muscular propria (depth, T1; arrowhead), identified by MRI. (D) Left inguinal lymph node of 15-mm in diameter (arrowhead) revealed by MRI. (E) Lower rectum tumor (arrowhead) confirmed by PET. (F) Left inguinal lymph node (arrowhead) confirmed by PET. CRT, chemoradiotherapy; PET, positron emission tomography.

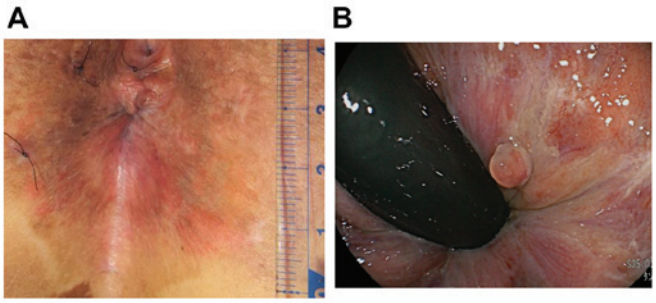

Figure 4. Images of the perianal region and colonoscopy after CRT. (A) Following CRT, the erythematous inflamed skin lesion in the perianal region was reduced in the physical examination. (B) Tumor regression was confirmed by the post-CRT colonoscopy. CRT, chemoradiotherapy.

family history of malignancy, no change in bowel habits, and no gastrointestinal symptoms. Laboratory data revealed elevation of carcinoembryonic antigen (CEA) (13.2 ng/ml), and anti-P53 antibody (105 U/ml), but not carbohydrate antigen 19-9 (CA19-9) (1 U/ml) nor SCC (3.0 ng/ml). The patient had normal renal and liver functions and a normal hemoglobin level.

Physical examination of the patient revealed an erythematous inflamed skin lesion in the perianal region (Fig. 1A) and a tumor of 15 mm in diameter detected on palpation in the left inguinal region. Digital examination and colonoscopy revealed a tumor of 15 mm in diameter in the left posterior wall of the anal canal located just on the dentate line (Fig. 1B). Tumor biopsy of anal canal revealed moderately differentiated adenocarcinoma cells (Fig. 2A). Skin biopsy revealed an epidermal infiltration of pagetoid cells, characterized by abundant cytoplasmic mucin showing signet ring cell morphology (Fig. 2B), which were positive for cytokeratin 7 (CK7) and Caudal-type homebox transcription factor 2 (CDX2), and negative for cytokeratin 20 (CK20) and Gross cystic disease fluid protein 15 (GCDFP15).

Abdominal computed tomography (CT) showed thickness of the wall of the lower rectum (Fig. 3A) and a left inguinal lymph node of 15 mm diameter (Fig. 3B). Magnetic resonance imaging (MRI) confirmed thickness of the lower rectum without evident invasion into the muscular propria (depth: T1) (Fig. 3C), and a left inguinal lymph node of 15 mm diameter (Fig. 3D). Positron emission tomography (PET) revealed lower rectum tumor (Fig. 3E) and a left inguinal lymph node (Fig. 3F).

Excisional biopsy of the left inguinal lymph node, performed for the staging of the tumor, revealed metastatic involvement of the left inguinal lymph node (adenocarcinoma). Taking the results of resection of left inguinal lymph node, the patient was diagnosed as anal canal cancer with lymph node metastasis. So preoperative CRT (oral tegafur-uracil 300 mg/day and leucovorin 75 mg/day, 1.8 Gy x28 fr, a total dose of 50.4 Gy) including bilateral inguinal region to improve local control was indicated.

After the CRT, physical examination of the patient revealed a reduced erythematous inflamed skin lesion in the perianal region (Fig. 4A) and the colonoscopy revealed regression of the tumor (Fig. 4B). It could not be detected in either the CT or the MRI.

Figure 5. Surgical specimen. Scar formation, as a result of preoperative chemoradiotherapy, was observed in the macroscopic examination of the surgical specimen (arrowhead).

Robotic-assisted laparoscopic abdominoperineal resection was performed. Antibiotics were administered for the control of surgical site infection from post-operative day 7. No post-operative urinary dysfunctions were observed, and the patient was discharged on post-operative day 25. The macroscopic findings of the surgical specimen confirmed the formation of a scar due to the preoperative CRT (Fig. 5). Microscopic examination of the anal tumor revealed no residual carcinoma including the perianal pagetoid lesion nor lymph node metastasis.

Discussion

Anal cancer accounts for 2-3% of all GI malignancies, and among them, 95% are squamous cell carcinomas and the remainder, primarily adenocarcinomas (3). Anal canal adenocarcinomas are rare. According to the World Health Organization classification, anal canal adenocarcinomas are subclassified into adenocarcinoma arising from the anal mucosa and extramucosa, adenocarcinoma arising from anorectal fistula or adenocarcinoma of anal glands (4). In the present case, the subclassification of the anal tumor was adenocarcinoma of anal gland according to the findings of colonoscopy and the tumor biopsy.

Paget's disease was first described by Sir James Paget in 1874 (4) and it is classified into mammary and extramammary. About one-third of patients affected by Paget's disease have an underlying malignancy, often represented by an anorectal carcinoma (5,6). Extramammary Paget's disease is a rare condition typically presenting as a reddish patch and/or nodule (7) and is commonly found in the vulvar area, followed by the perianal area, scrotum, penis and axillae (8). Perianal Paget's disease is classified as an extramammary Paget's disease. The true incidence of the disease is difficult to estimate due to its rarity, but it is known to represent <1% of all anal diseases and about 6.5% of all cases of Paget's disease (9). There are two types of perianal Paget's disease, the primary disease, which consists of intra-epithelial neoplasm from an apocrine source, and the secondary disease, which consists of a 'pagetoid' spread from an anorectal malignancy (9). Immunostaining for GCDFP15, CDX2, CK7, CK20 is useful in enhancing the accuracy of diagnosis, such as the type and the origin of Paget's disease. GCDFP15 is considered as apocrine epithelium-specific tissue marker and is usually not expressed in secondary perianal Paget's disease (1). The expression of CDX2 is a sensitive and specific marker for the secondary type, arising from anorectal or colonic adenocarcinoma, but CDX2 fails to distinguish between the primary disease and the secondary type to urothelial or prostatic malignancy (1). Although most anal gland adenocarcinomas, similar to the normal anal gland, are CK7 positive, but CK20 negative, several cases of secondary type arising from anal gland carcinoma were reported to be positive for both CK7 and CK20 (1). In our case, the skin biopsy revealed an infiltration of pagetoid cells, which were positive for CK7 and CDX2, and negative for CK20 and GCDFP15. From these findings, we diagnosed as perianal Paget's disease secondary to the anal canal carcinoma.

There are no reports of clinically T1 anal gland adenocarcinoma with pagetoid spread that caused inguinal lymph node metastasis in English literature. Only one report of total pelvic exenteration with lateral and inguinal lymph node dissection followed by skin reconstruction in a case of T1 anal canal cancer with pagetoid spread was found in the Japanese literature (10). It is suggestive that anal canal adenocarcinoma with pagetoid spread may cause inguinal lymph node metastasis in an early stage.

Lateral lymph node metastasis occurs in 15-20% of lower rectal cancers, and treating such metastases is critical for reducing local failure rates after surgical treatment of rectal cancer (11). In Japan, mesorectal excision with lateral lymph node dissection is the standard treatment, suggestive that lateral lymph node dissection significantly reduces local recurrence (12). However, lateral lymph node dissection is also associated with postoperative urinary and sexual dysfunctions, which can significantly deteriorate the patients' quality of life. Furthermore, in Western countries, lateral lymph node metastasis is treated with preoperative CRT (11). Previously, we demonstrated that lateral lymph node dissection is not required in terms of curability for patients with advanced carcinoma of the lower rectum without apparent lateral pelvic lymph node metastasis treated with preoperative radiotherapy (13). Therefore, in our department, lateral lymph node dissection was only indicated to patients with lateral lymph node metastasis and it was avoided in those without, treated with preoperative CRT (a total dose of 50.4 Gy in 28 fractions with concomitant fluorouracil-based chemotherapy) (11,14-17). Consensus has not yet been achieved concerning preoperative CRT against anal canal cancer with pagetoid spread, but our present report is supportive of its effectiveness for the safe resection of this condition.

In conclusion, we experienced a rare case of early anal canal adenocarcinoma with pagetoid spread and inguinal lymph node metastasis, which could be effectively managed by preoperative CRT followed by surgical resection. This case supports the potential effectiveness of preoperative CRT for the safe resection of pagetoid spread associated with anal canal adenocarcinoma, and it should be carefully considered as a therapeutic modality.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

TN decided the treatment strategy and drafted the article. TU diagnosed the anal canal adenocarcinoma with pagetoid spread and inguinal lymph node metastasis and designed the pathological comments and drafted the pathological pictures. SE, KM, MK, HS, KS, YS, TT, KH, KK and HN decided the treatment strategy of this case and revised the article critically for important intellectual content. SI contributed to the conception of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was conducted in accordance with the Ethical guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of the University of Tokyo (approval no. 3252-9; Tokyo, Japan). The opportunity to opt out is always available to the patients on our website.

Patient consent for publication

Written informed consent for the publication of data and associated images was obtained from the patient.

Competing interests

The authors declares that they have no competing interests.

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