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Clinical and Pathological Analysis of Perianal Paget's Disease: A Case Report and Review of 89 Cases

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Abstract. *Background/Aim: Perianal Paget's disease (PPD) is an intraepithelial invasion of the perianal skin that is frequently associated with anorectal carcinoma. Rectal canal carcinoma with Pagetoid spread (PS) is a relatively rare disease, and few reports on its outcomes are available. The relatively rare nature of this disease makes the development of treatment recommendations difficult. This study aimed to clarify the characteristics of the disease and factors related to prognosis. We present a case report and review of 89 cases, including those from the existing literature and our own experience. Case Report: The patient was an 81-year-old man who was referred to our hospital for surgery after endoscopic examination of the lower gastrointestinal tract revealed cancer of the anal canal with PS. Physical examination revealed erythema and erosions around the anus. Lower gastrointestinal endoscopy revealed an erythematous area and a continuous raised lesion in the anal canal. We diagnosed the patient with anal canal carcinoma with PS, and robot-assisted abdominoperineal resection was performed. Conclusion: Our findings indicate that the five-year survival rate for PPD patients was 63%, comparable to that of anal canal cancer without PS. The histological type and presence of lymph node metastasis may be related to the prognosis. The study suggests that early-stage patients with favorable histological types and no lymph node involvement may benefit from less invasive treatment options, such as endoscopic submucosal dissection.*

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Perianal Paget's disease (PPD) is an intraepithelial invasion of the perianal skin and is classified into two types: primary and secondary. PPD is an uncommon form of neoplasm arising from the apocrine glands of the perianal skin (1). In secondary Paget's disease, a carcinoma of the mucosa, such as anal cancer, spreads into the epithelium and extends to the skin at the orifice, where skin lesions are observed clinically. Extension to the skin is known as Pagetoid spread (PS) (2, 3). Primary and secondary PPD require different treatment strategies (4, 5). However, distinguishing between primary and secondary tumors using hematoxylin and eosin (H&E) staining is often difficult, and immunostaining is considered useful for this purpose. In such cases, the determination is made using immunostaining with a combination of gross cystic disease fluid protein-15 (GCDFP15), which is present in apocrine and eccrine sweat glands, cytokeratin 20 (CK20), which is a marker for the epithelium of the digestive tract and bladder, and cytokeratin 7 (CK7), which is a marker for glandular epithelium (such as anal glands) and endothelial cells other than the digestive tract. This study aimed to analyze the clinical and pathological features of PPD and to explore treatment options and follow-up for this disease. Anorectal carcinoma with PS is relatively rare and only a

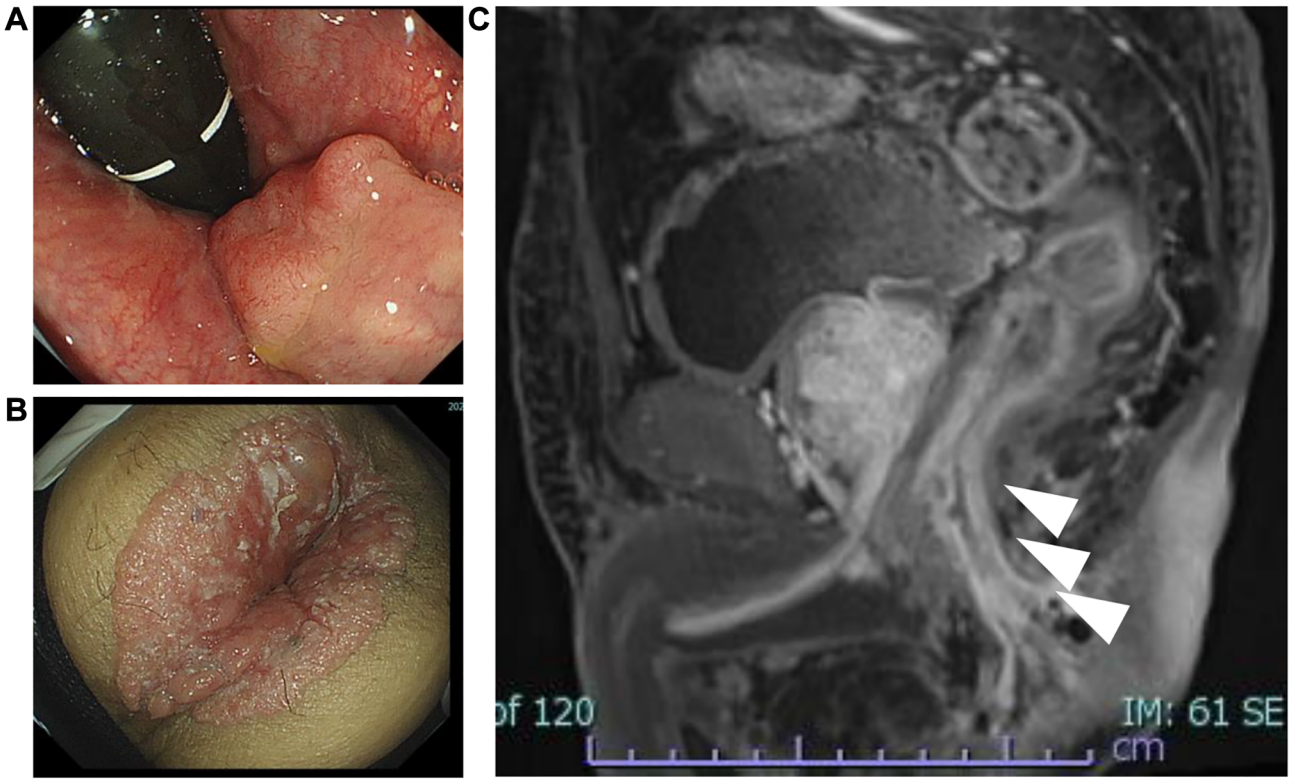

Figure 1. *Examination findings of the lesion A) Colonoscopy image showing a flattened, elevated lesion measuring 15 mm in size in the anal canal. B) Colonoscopy image showing full circumferential anal lesions extending to the anal canal. C) Magnetic resonance imaging T1-weighted sequence 1 revealing mild wall thickening measuring 55 mm in the lower rectum (arrowhead), with no significant lymphadenopathy.*

small number of cases have been reported, with no comprehensive reports available in the literature. To clarify the clinicopathological features and treatment results, we reviewed 89 cases, including those reported to date and our own experience.

Patients and Methods

We searched for case reports in the PubMed database using "rectal", "anorectal", "anal", and "Pagetoid spread" as keywords, and 88 cases of rectal or anal canal carcinoma with PS excluding primary PPD were identified (3-40). In total, the study included 89 patients, including one patient with anorectal cancer with PS treated at our hospital. The clinicopathological characteristics, treatment methods, and outcomes were reviewed.

The characteristics of the 89 patients were investigated with respect to age, sex, primary site, depth, presence or absence of lymph node metastases, presence or absence of distant metastases, recurrence site, and treatment. The immunohistochemical characteristics of CK20, CK7, and GCDFP15 in PS and the histological classification were also examined.

Case report. Our patient was an 81-year-old male who presented to his local physician with difficulty defecating. Lower endoscopy was performed and revealed a circumscribed lesion in the anus and a flattened, elevated lesion measuring 15 mm in size in the anal canal (Figure 1A).

The patient was diagnosed with PS as he had a contiguous lesion extending from the rectum to the perianal skin (Figure 1B). Magnetic resonance imaging (MRI) and computed tomography (CT) showed no lymph node or distant metastases (Figure 1C).

A biopsy showed that the lesion in the anal canal was an adenocarcinoma classified as tub1>tub2 and group 5. The anal skin was positive for caudal-type homeobox transcription factor 2 (CDX2) and CK7, and diffusely positive for CK20. These results were consistent with a diagnosis of secondary PPD originating from rectal canal carcinoma.

Two months later, the patient was referred to a higher medical institution where the same diagnosis was made. The patient was subsequently referred to our department for surgery.

In such cases, robot-assisted abdominoperineal resection (APR) and plastic surgery reconstruction are typically performed. The patient underwent these surgical procedures at our institution. The specimen showed a grossly elevated lesion in the anal canal, with white epithelium extending on the anal side (Figure 2A).

The pathological results were as follows: adenocarcinoma, P, tub1>tub2>por2, no metastatic carcinoma in the lymph nodes, and a maximal tumor diameter of 62 mm. These results showed that the raised lesion in the anal canal was an adenocarcinoma (tub1>tub2>por2) and that the tumor had invaded the submucosal layer. The distance of the invasion from the surface was 2,200 μm,

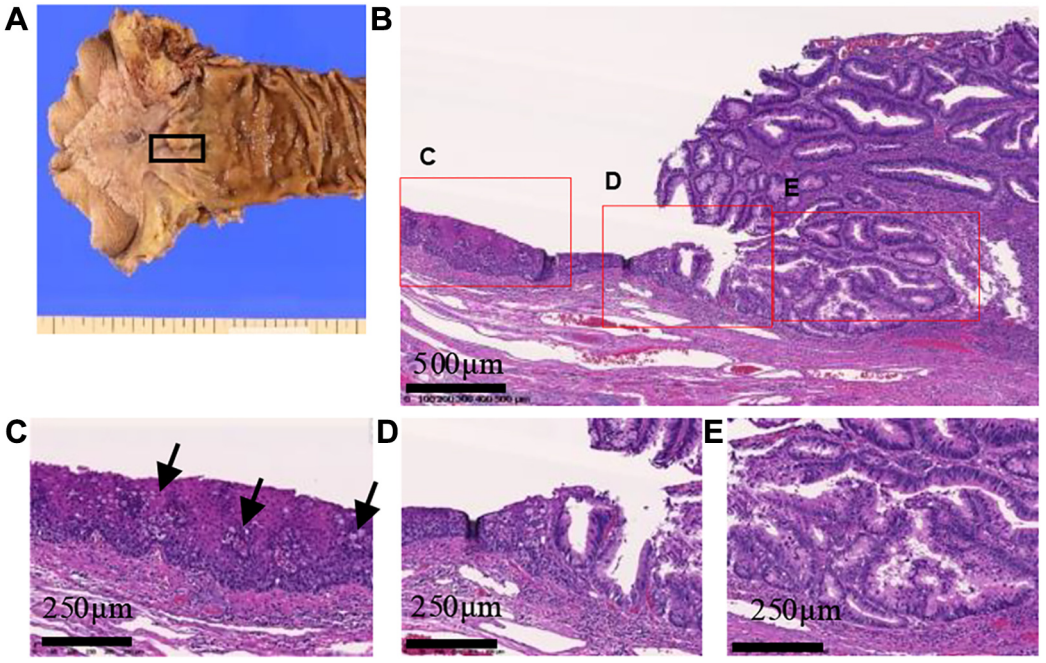

Figure 2. *Macroscopic and pathological findings of the lesion A) Macroscopic image of the resected specimen; the square represents the excised specimen shown in Figure 2B. B) Hematoxylin and eosin staining. C) Microscopic image of the distal side in B, showing Pagetoid spread within the stratified squamous epithelium. The arrows indicate Pagetoid spread. D) Border between Pagetoid spread and glandular epithelium. E) Proximal side showing nodular lesions with adenocarcinoma. The tumor invades the submucosa. No obvious image of vascular invasion.*

and no obvious vascular invasion was noted. Normal mismatch repair functions were observed and the malignancy was characterized as having proficient mismatch repair (pMMR). *KRAS* was a mutant type (G12V), and *BRAF* was wild-type. In addition, PS was seen within the stratified squamous epithelium on the anorectal side (Figure 2B-D). No recurrence was observed as of 12 months after surgery.

Results

Patient characteristics. The age of the 89 included patients ranged from 46 to 91 years, and 35 patients were female (Table I). The primary lesions were located in the anal canal in 41 patients and in the rectum in six patients. The depth of the primary lesion was Tis in 12 patients and T1 in 15 patients, and lymph node metastasis was observed in 29 patients. Distant metastasis was observed in nine patients. Recurrence was observed in 15 of 89 patients, excluding unknown cases; this included eight cases of systemic recurrence and six cases of local recurrence. Surgery was performed in 59 patients, with APR in 37, local excision (LE) in 10, total pelvic exenteration (TPE) in three, and chemotherapy alone in 17, most frequently as adjuvant or non-surgical therapy.

Immunohistochemical characteristics of Pagetoid spread. Upon pathological examination, immunostaining was positive for CK20 in 71 of 75 patients (94.7%) and CK7 in 43 of 64

Table I. *Characteristics of 89 patients*.

Factor	No .
Age (years)	46-91
Sex	
Male/female/unknown	45/35/9
Primary origin	
Rectum/anal gland/unknown	6/41/42
Depth	
Tis/T1/T2/T3/T4/unknown	12/15/11/9/2/40
LN metastasis	
Yes/no/unknown	29/29/31
Distant metastasis	
Yes/no/unknown	9/29/51
Recurrence site*	
Systemic/local/inguinal lymph node/ other lymph node/unknown	8/6/5/1/57
Therapy*	
Surgery	
APR/LE/TPE/ISR/ASR/no/unknown	37/10/3/1/1/2/28
Adjuvant therapy or non-surgical therapy	
ESD/post chemotherapy/chemotherapy/ sigmoid colostomy/radical resection EB/RT/CRT/preoperative radiotherapy/	1/10/7/1/1/1/1/1/2

APR: Abdominoperineal resection; LE: local excision; TPE: total pelvic exenteration; ISR: intersphincteric resection; ASR: abdominosacral resection; ESD: endoscopic submucosal dissection; EB: electro beam therapy; RT: radiation therapy; CRT: chemoradiotherapy. *There are duplicates.

Table II. *Immunohistochemical characteristics of Pagetoid Spread.*

	(+)	(–)	Unknown
CK20	71	3	15
CK7	43	21	25
GCDFP15	0	59	30

CK20: Cytokeratin 20; CK7: cytokeratin 7; GCDFP15: gross cystic disease fluid protein 15.

Table III. *Histology of 89 patients.*

Histology	n=89
Well/mod	23
Adenocarcinoma (unspecified)	10
Sig	9
Por	5
Muc	5
NEC	2
Pap	1
Goblet cell carcinoid	1
Unknown	33

Well/mod: Well and moderately differentiated adenocarcinoma; sig: signet-ring cell-like adenocarcinoma (SRCC); por: poorly differentiated adenocarcinoma; muc: mucinous adenocarcinoma; NEC: neuroendocrine carcinoma; pap: papillary adenocarcinoma.

patients (67.2%). In contrast, immunostaining was negative for GCDFP15 in 59 of 59 patients (100%) (Table II).

Histological types. Twenty-three cases of well-differentiated and moderately differentiated adenocarcinomas were observed, representing the most frequent types. Additional findings included 10 cases of adenocarcinoma (unspecified), nine cases of signet-ring cell-like adenocarcinoma (SRCC), five cases of poorly differentiated adenocarcinoma (por), five cases of mucinous adenocarcinoma (muc), and two cases of neuroendocrine carcinoma (NEC) (Table III).

Prognosis and survival. Of the 89 patients, the survival curves for the 50 patients with known prognoses are shown in Figure 3A, demonstrating an estimated five-year survival rate of 63%.

The survival curves for patients with and without lymph node metastasis are shown in Figure 3B. The five-year survival rate was 74% for patients without metastases and 35% for those with metastases.

The survival rate for patients without lymph node metastasis was significantly higher than that for patients with metastasis, with a *p*-value of 0.0218 using the Wilcoxon signed-rank test. Figure 3C shows the survival curves for well-differentiated and moderately differentiated adenocarcinomas

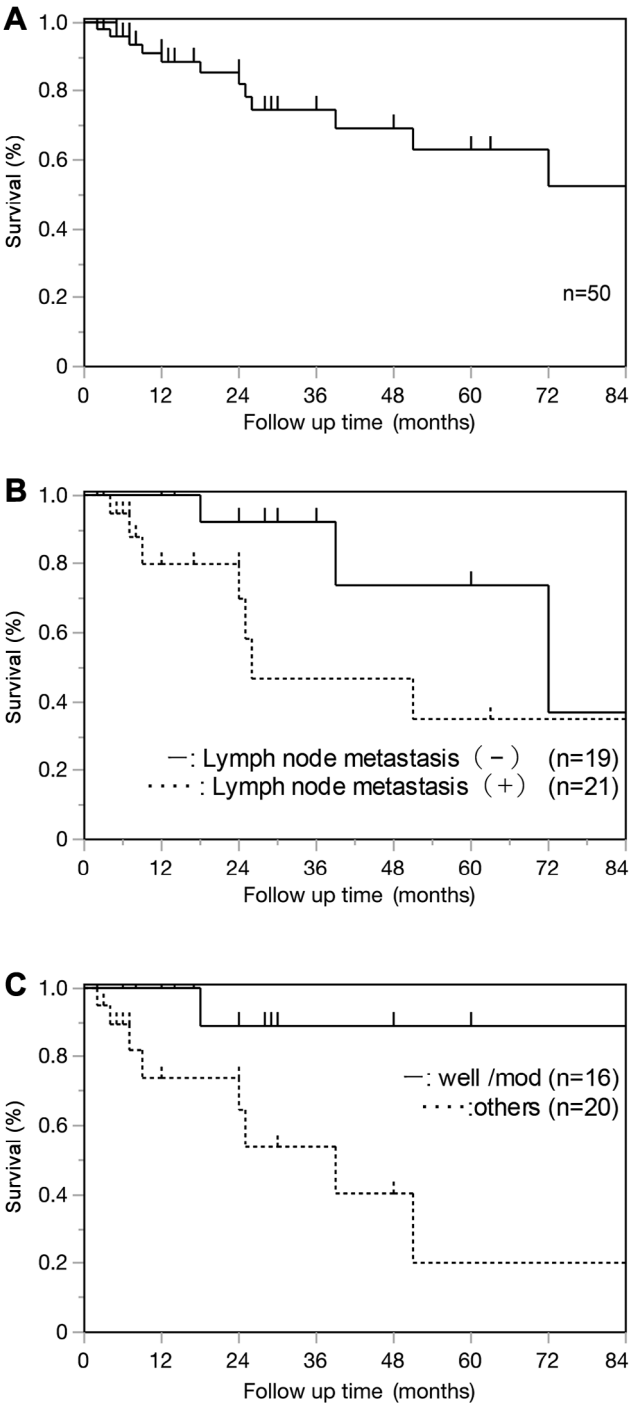

Figure 3. *Overall survival rates for patients. A) Survival curves for the 50 cases with known prognoses, showing an estimated five-year survival rate of 63%. B) Survival curves stratified by the presence or absence of lymph node metastasis. The five-year survival rate was 74% for those without metastases and 35% for those with metastases. C) Survival curves for well-differentiated and moderately differentiated adenocarcinomas as well as other histological types. The five-year survival rate for the well-differentiated and moderately differentiated adenocarcinoma group was 88%, compared with 20% for the other histological groups. well/mod: Well-differentiated and moderately differentiated adenocarcinoma.*

and other types according to histological classification. The five-year survival rate for the well-differentiated and moderately differentiated adenocarcinoma group was 88%, compared with 20% for the other histological groups. A significant difference was observed between these groups, with a *p*-value of 0.0245 using the Wilcoxon test.

Discussion

Rectal and anal canal carcinoma is frequently observed in PPD (33-80%) (41-43), and secondary PPD is more common than primary PPD. Therefore, close examination of the gastrointestinal tract is important. The frequency of PS associated with anal canal cancer is reported to be 6.1%, making it a relatively rare condition (44).

The five-year survival rate of adenocarcinoma of the anal canal is reported to be 52-60% (45, 46). Previous reports have shown that the five-year survival rate of rectal canal carcinoma with PS is 45.4%, which is comparable to or slightly worse than that of normal canal carcinoma without PS (2). In this study of 89 cases, the five-year survival rate was 63%, which may be comparable to that of normal anal canal cancer. PS of anal canal cancer is a rare disease, rendering prospective studies to investigate this condition infeasible; therefore, the characteristics of the disease were examined through a review of previous literature.

In this study, we focused on PS of rectal canal cancer. The five-year survival rate was 63%, which may be equivalent to the five-year survival rate of rectal cancer as a whole, indicating that this condition may be treated similarly to normal rectal cancer. The results also showed that the presence or absence of lymph node metastasis and the histological type were associated with prognosis. In particular, the five-year survival rates of other histological types were significantly worse than those of well-differentiated and moderately differentiated adenocarcinomas; therefore, we considered histological type an important prognostic factor for PS. Consequently, diagnosing the histological type by biopsy before surgery is important.

Currently, the standard treatment for rectal canal cancer is surgical resection of the entire tumor. Our study suggests that in the early stages, patients with well-differentiated and moderately differentiated adenocarcinomas and no lymph node metastasis have a good prognosis, and that minimally invasive treatments such as endoscopic submucosal dissection (ESD) and LE may be feasible without necessarily requiring standard APR. However, depending on the histological type, patients with advanced cancer have a low survival rate even if surgery is performed, and further multidisciplinary treatment is necessary. In recent years, radiotherapy for the treatment of anorectal cancer has also progressed (47). In the present case, our patient underwent curative surgery, which is consistent with previous reports.

Study limitations. This study had a strong bias owing to its retrospective design, which involved retrieving previous reports. Another limitation is that data were not available for all cases, and the number of cases was small. In addition, the usefulness of inguinal lymph node dissection was not discussed, leaving room for further investigation.

Conclusion

We reviewed previous reports on rectal canal carcinomas with PS. The histological type and presence of lymph node metastasis may be related to the prognosis. Further prospective studies are needed to determine appropriate treatment strategies.

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Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

K.I. collected the clinical data of the patients, analyzed the data, designed the report, and wrote the manuscript. K.I. and H.T. coordinated and drafted the manuscript. All the Authors have read and approved the final version of the manuscript.

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