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Rectal Phenotype of Perianal Paget Disease: Rare Concomitant Phenomena

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Abstract. *Aim: Classically, 'Paget disease' refers to a distinct histological pattern in breast carcinoma. Here, we review the clinicopathological features of anorectal adenocarcinoma with 'pagetoid' spread. Materials and Methods: Histological and immunohistochemical records for 11 cases of anorectal adenocarcinoma with pagetoid spread among 958 Japanese patients with primary rectal/anal carcinoma were reviewed. Results: Grossly, nine of 11 cases had areas of invasive carcinoma: Tubular adenocarcinoma in eight and neuroendocrine carcinoma in one. Pagetoid components were positive for cytokeratin 7 in eight cases, cytokeratin 20 and caudal type homeobox 2 in all 11 cases, and p63 in one case, but were negative for estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2 (HER2), gross cystic disease fluid protein-15, and GATA binding protein 3. Conclusion: The prevalence of perianal Paget disease in this series was 1.1%, with two cases of genuine perianal Paget disease with a rectal phenotype without invasive carcinoma. The rectal phenotype of perianal Paget disease may not be associated with HER2 overexpression.*

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Classically, 'Paget disease' refers to a distinct histological pattern in breast carcinoma (1). Intraepidermal single-cell extension of carcinoma is called pagetoid spread or extension. The World Health Organization (WHO) classification defines mammary Paget disease as mammary ductal carcinoma with intraepidermal extension of carcinoma cells (1). Conversely, extramammary Paget disease is a distinct, site-specific category skin tumor characterized by the predominant intraepithelial growth of neoplastic cells (2). Extramammary Paget disease occurs exclusively in the skin of the vulva, axillary, navel, vulvar, and perianal region (2).

'Pagetoid spread' is also a histological term for growth patterns in other carcinoma types, such as rectal adenocarcinoma and urothelial carcinoma (3). The histological distinction between the pagetoid spread of these carcinomas and that of extramammary Paget disease may be an important diagnostic point because of differences in their biological behavior and therapeutic choices. Only few studies have systematically reviewed pagetoid spread in these carcinomas (3, 4).

In this study, we reviewed cases of anorectal adenocarcinoma cases with pagetoid spread to reveal their clinical and immunohistochemical features.

Materials and Methods

This study was conducted according to the principles of the Declaration of Helsinki, and was approved by the Ethics Committee of Kyushu University (no. 2020-476).

The records of 958 cases of primary carcinoma of rectal and anal origin (924 cases of rectal adenocarcinoma, 24 cases of anal canal adenocarcinoma, 10 cases of perianal extramammary Paget disease) in the files of the Department of Anatomic Pathology, Graduate School of Medical Sciences, Kyushu University (Fukuoka, Japan) were reviewed, and 11 cases (1.1%) of perianal Paget disease with a rectal phonotype were identified. The rectal phenotype of all 11 cases was confirmed by positive immunohistochemical staining for caudal type homeobox 2 (CDX2).

Table I. *Immunohistochemical antibodies used in this study.*

Antibody	Source	Clone	Species	Dilution
Cytokeratin 7		OV-TL 12/30	Mouse	1:50
Cytokeratin 20		Ks 20.8	Mouse	1:500
Estrogen receptor		EP1	Rabbit	1:1
Progesterone receptor	DAKO, Santa Clara, CA, USA	PgR 636	Mouse	1:1
Human epidermal growth factor receptor 2		Polyclonal	Rabbit	1:250
p63		DAK-p63	Mouse	1:1
Caudal type homeobox 2	BioGenex, Fremont, CA, USA	CDX2-88	Mouse	1:100
GATA-binding protein 3	CELL MARQUE, Rocklin, CA, USA	L50-823	Mouse	1:100
Gross cystic disease fluid protein-15	Leica, Wetzlar, Germany	23A3	Mouse	1:20

Table II. *The summary of clinical information for study patients.*

Case no.	Age, years	Gender	Classification*			Clinical course
			T	N	M	
1	64	F	T1	Nx	M0	SWD 136 months
2	67	M	T3	N0	M0	DOD 46 months
3	75	M	T1	N0	M0	NED 21 months
4	81	F	T3	N1a	M0	SWD 6 months
5	74	F	T3	N1a	M0	DOD 11 months
6	61	F	T3	N0	M0	DOD 37 months
7	80	M	T3	N1a	M0	DOD 34 months
8	85	F	T3	Nx	M0	NED 15 months
9	68	F	T3	N1a	M0	SWD 14 months
10	83	M	Tis	N0	M0	NED 20 months
11	48	M	Tis	N0	M0	NED 7 months

DOD: Dead from disease; F: female; M: male; NED: no evidence of disease; SWD: survival with disease. *According to the Union for International Cancer Control (18).

Clinicopathological and histopathological findings. Age, sex, and tumor size were evaluated. Clinical outcomes were evaluated based on the history of local recurrence, distant metastasis, and death as a result of the tumor. Histopathological progression of each carcinoma was also evaluated using TNM classification.

Immunohistochemistry. Immunohistochemical staining was performed for all 11 cases. Formalin-fixed, paraffin-embedded tissue was sectioned (3 μm). The primary antibodies used, their dilutions, and antigen retrieval are summarized in Table I. The immune complexes were detected using the DAKO EnVision Detection System (Santa Clara, CA, USA). Immunohistochemical staining of >10% of carcinoma cells was considered a positive result.

Results

Clinicopathological and histopathological findings. Survival data were available for all 11 patients (100%), with follow-up ranging from 6 to 136 months (mean=31.6 months, median=20 months). Clinicopathological findings are summarized in Table II. The age of the patients ranged from 48 to 85 years (mean=71.5 years, median=74 years) and the male:female ratio was 5:6. The area of the invasive carcinoma ranged in size from 0.2 to 8.5 cm in diameter (mean=3.9 cm, median=4.0 cm) and the size of the pagetoid spread ranged from 0.2 to 17.5 cm in diameter (mean=6.5 cm, median=8.0 cm). Local recurrence occurred in one (9.1%) case, distant metastasis occurred in five (45%) cases, and four (36%) patients died from their disease.

Grossly, areas of invasive carcinoma were evident in nine cases but were lacking in the remaining two. Representative histological findings are shown in Figure 1. Histopathologically, all tumors contained areas of pagetoid spread, and nine tumors had invasive carcinomatous components. The TMN classification for each tumor is summarized in Table II. Of the nine tumors with invasive carcinomatous components, tubular adenocarcinoma was present in eight and neuroendocrine carcinoma (NEC) without tubular adenocarcinoma was present

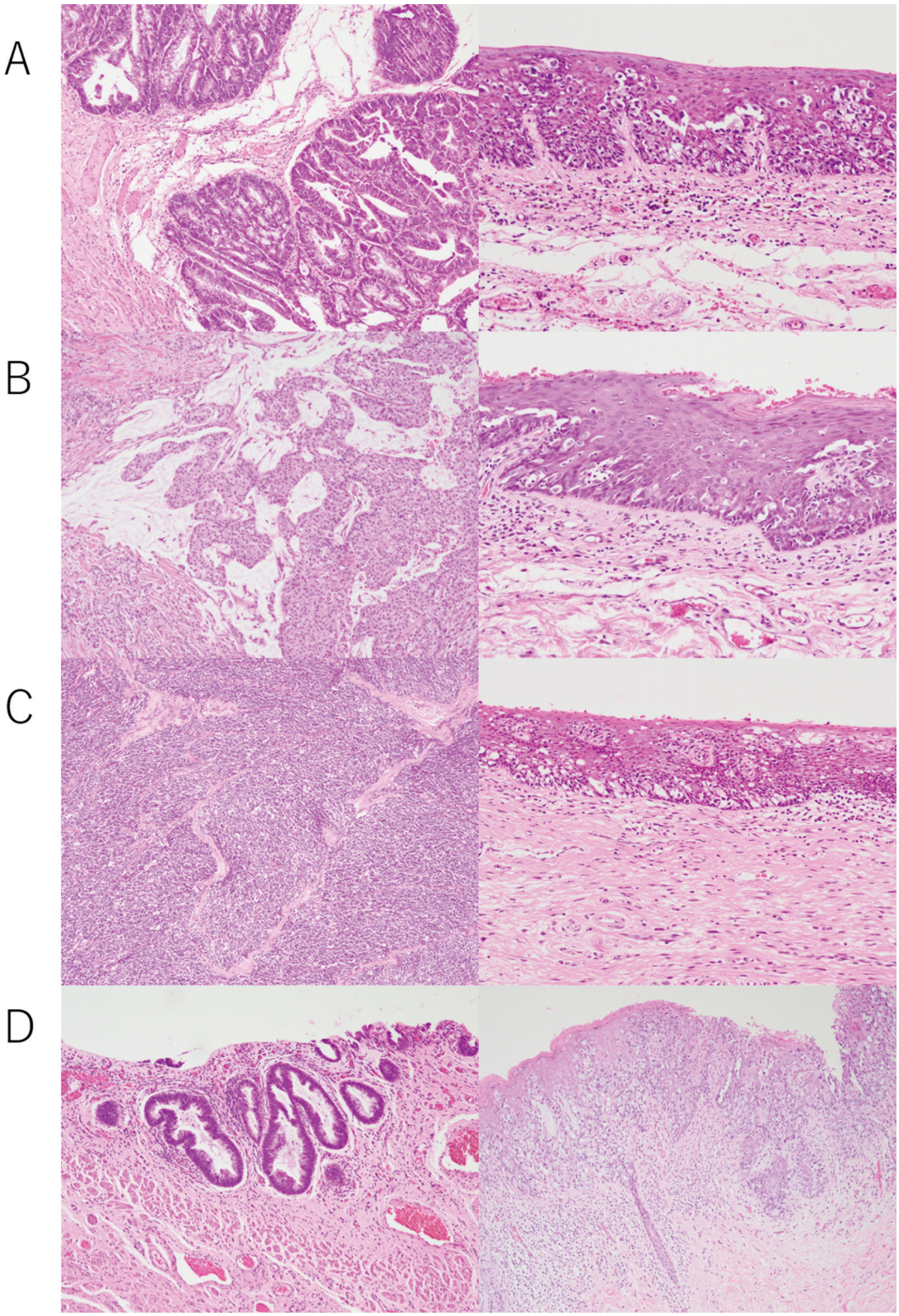

Figure 1. *Representative images of histological staining of (left) invasive adenocarcinoma and (right) pagetoid components. A: Case 3: Tubular adenocarcinoma and pagetoid components. B: Case 7: Mucinous carcinoma and pagetoid components. C: Case 6: Neuroendocrine carcinoma and pagetoid components. D: Case 11: small adenomatous lesion and pagetoid component; note that there was no continuity between the small adenomatous lesion and the pagetoid component in this case. Original magnification ×200.*

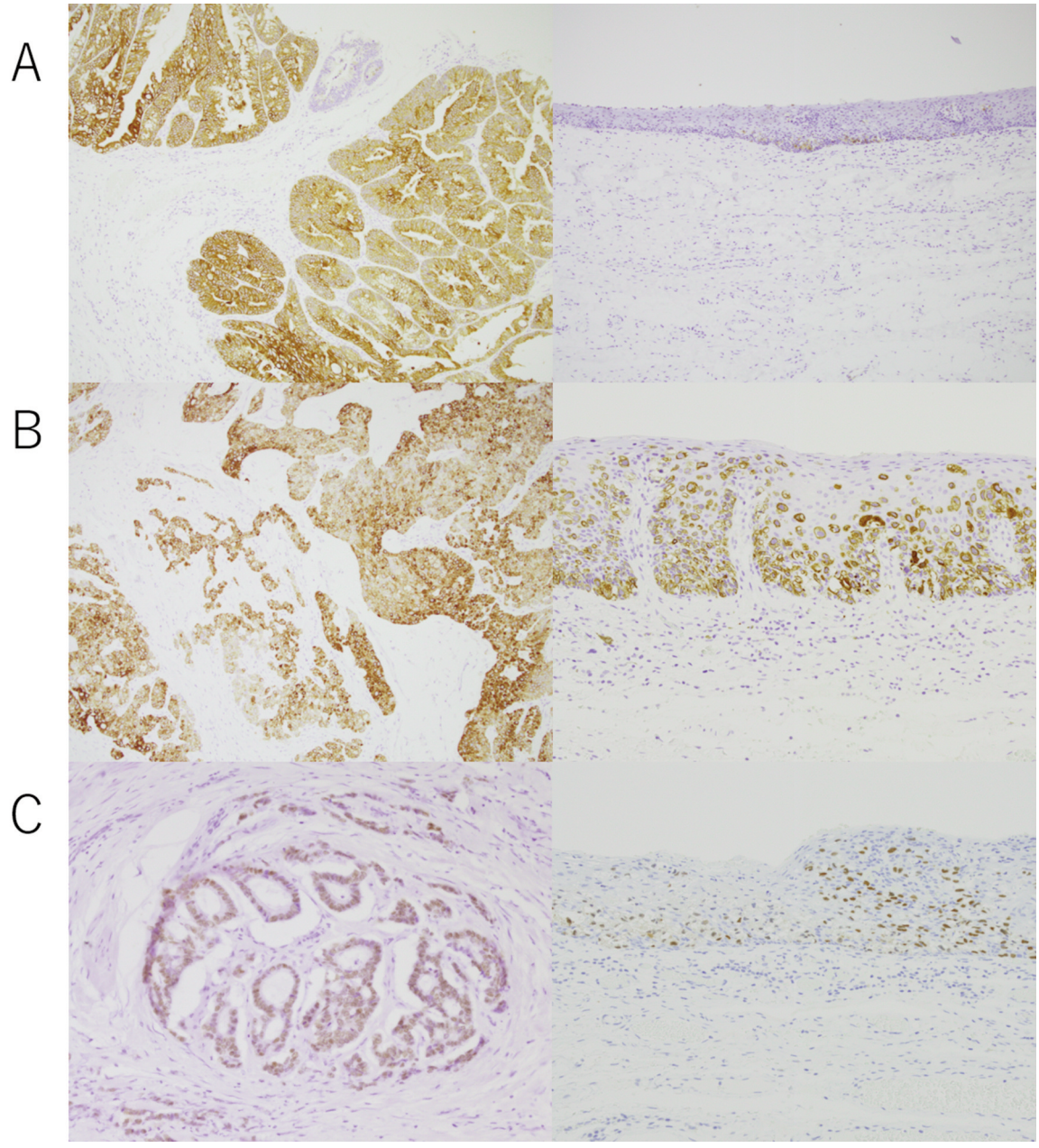

Figure 2. *Representative images of positive immunohistochemical staining for (A) cytokeratin 7, (B) cytokeratin 20 and (C) caudal type homeobox 2 in invasive tubular adenocarcinoma (left) and pagetoid components (right). Original magnification ×200.*

in one. There was no evidence of venous invasion, lymphatic vessel permeation, or neural invasion in any of the 11 cases.

Immunohistochemistry. Representative images of immunohistochemical staining are shown in Figure 2. Among the 11 cases of anorectal adenocarcinoma with pagetoid spread, the components of the pagetoid spread stained positively for cytokeratin 7 (CK7) in eight (73%) cases, for CK20 and CDX2 in all 11 (100%) cases, and for p63 in one (9%) case but all samples were negative for estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2 (HER2), gross cystic disease fluid protein-15 (GCDFP15), and GATA-binding protein 3 (GATA3). Of the nine tumors with invasive carcinomatous components, six (67%) were positive for CK7,

seven (78%) were positive for CK20, eight (89%) were positive for CDX2, and one (11%) was positive for p63; none was positive for estrogen receptor, progesterone receptor, HER2, GCDFP15, or GATA3.

Discussion

As far as we are aware, this is the first report to reveal genuine pagetoid tumors arising in the anorectal region with the immunohistochemical features of rectal-type adenocarcinoma. This study also identified two cases of anorectal adenocarcinoma without apparent intramucosal or invasive tubular adenocarcinoma of the anorectal mucosa. All 11 cases had a pagetoid growth pattern of round-shaped tumor cells, like signet-ring cells, spreading within the squamous epithelium of the anal canal that were not continuous with the rectal mucosa. Immunohistochemical staining confirmed the molecular features of rectal-type adenocarcinoma, including CK20 and CDX2 expression, in nine tumors. Conversely, the 11 pagetoid tumors showed no apparent features of extramammary Paget disease. We consider that these anorectal pagetoid tumors may possess similar biological features to rectal adenocarcinoma.

Pagetoid spread of rectal adenocarcinoma is usually accompanied by an invasive lesion attached to the area of pagetoid spread (5-11). Rectal intramucosal adenocarcinoma with pagetoid spread has never been reported to our knowledge. The two pagetoid tumors in this study lacked apparent intramucosal and invasive rectal carcinoma. In one case, the adenomatous lesion was present near, but apparently separated from, the pagetoid area. We consider there are two possible mechanisms for the formation of these pagetoid tumors: (i) Anorectal pagetoid tumors may arise from rectal intramucosal adenoma or adenocarcinoma and directly break into the anal squamous epithelium; or (ii) they may be the result of the spontaneous regression of the tubular adenocarcinomatous component, although spontaneous regression of rectal cancer is an extremely rare phenomenon (12, 13). In any case, the immunohistochemical features of rectal adenocarcinoma need to be confirmed to determine the best therapeutic option for pagetoid neoplasm of the anorectal region.

Pagetoid spread has a histologically distinct growth pattern for each carcinoma but the underlying mechanism remains unknown. It is known that in almost all cases of mammary Paget disease there is membranous overexpression of HER2 protein and *HER2* gene amplification (14, 15). It was also reported that HER2 protein is overexpressed in patients with extramammary Paget disease (16). Together, these observations suggest that pagetoid spread may be associated with HER2 overexpression. However, in the present study, none of the carcinomas with pagetoid spread overexpressed HER2. Thus, the pagetoid spread of anorectal adenocarcinoma may not be associated with HER2 overexpression and gene amplification.

The histological features of the pagetoid area of anorectal adenocarcinoma are similar to those of extramammary Paget disease. Both tumor types contain round-shaped tumor cells and intracytoplasmic mucin. The two tumor types cannot be distinguished based on histological results only, and immunohistochemical staining, such as for cytokeratins, CDX2, and GCDFP15, is needed. The present systematic review confirmed that it is possible to differentiate between the two types of tumors based on their immunohistochemical profiles.

In the present series, there was one case in which NEC was the invasive carcinomatous component; anorectal NEC with pagetoid spread has only been reported in one previous case (17). In that report, NEC with neuroendocrine differentiation was also a component of the pagetoid spread. In the present study, in the case in which NEC was the invasive carcinomatous component, the pagetoid component had the immunophenotype of rectal mucosal epithelium. Our case is the first of rectal NEC with a pagetoid component that had a rectal mucosal phenotype. We consider that the pagetoid component in this case may have been derived from an invasive tubular adenocarcinoma that collapsed as a result of the proliferation of the NEC.

In conclusion, we reported on 11 cases (1.1%) of perianal Paget disease among 958 Japanese patients with primary rectal and anal carcinomas, with two cases of genuine perianal Paget disease with a rectal phenotype without invasive carcinoma. Perianal Paget disease with a rectal phenotype may not be associated with HER2 overexpression.

Conflicts of Interest

The Authors declare that there are no potential conflicts of interest.

Authors' Contributions

Yuki Tateishi and Yuichi Yamada performed the research and wrote the article. Takeo Yamamoto, Taisuke Sasaki, Shinichiro Kawatoko, Jun Kawata, Yutaka Yamada contributed to the research design and slide review. Masafumi Nakamura and Masaki Mori contributed to the sample collection and research design. Yoshinao Oda designed the research and gave final approval of the article. All Authors critically reviewed and approved the article.

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