Immunohistochemical evaluation of gastric-type markers in primary extramammary Paget disease: Differential MUC5AC expression between *in situ* and invasive lesions

NAOTO KOHNO[1], MITSUAKI ISHIDA[1,2], SHIZUKA ONO[1] and YOSHINOBU HIROSE[1,2]

[1]Department of Pathology, Osaka Medical and Pharmaceutical University, Takatsuki, Osaka 569-8686, Japan;
[2]Division of Pathology, Osaka Medical and Pharmaceutical University Hospital, Takatsuki, Osaka 569-8686, Japan

Received December 25, 2025; Accepted February 23, 2026

DOI: 10.3892/etm.2026.13133

Abstract. Primary extramammary Paget disease (EMPD) is a rare cutaneous adenocarcinoma characterised by intraepithelial proliferation of mucin-containing carcinoma cells, with invasive carcinoma occasionally present. A characteristic immunohistochemical feature of primary EMPD is expression of MUC5AC, a gastric-type mucin core protein; however, the expression of MUC5AC in invasive EMPD remains controversial. Furthermore, the expression of other gastric-type markers, including hepatocyte nuclear factor 4α (HNF4α) and claudin 18, has not been fully investigated in primary EMPD. The present study aimed to clarify the expression profiles of MUC5AC in both *in situ* and invasive EMPD lesions, as well as to evaluate HNF4α and claudin 18 expression in primary EMPD. Consecutive patients with primary EMPD who underwent surgical resection were included. Immunohistochemical staining for MUC5AC, HNF4α and claudin 18 was performed, and the results were semi-quantitatively assessed using a four-tier scoring system (0, <5%; 1, 5-25%; 2, 26-50%; 3, >50% positive neoplastic cells) in *in situ* and invasive components, when present. A total of 40 patients (9 female patients and 31 male patients) were included, comprising 25 cases *in situ* and 15 invasive cases. MUC5AC expression was observed in 24 *in situ* and 14 invasive EMPD cases. No significant difference in MUC5AC expression scores in *in situ* lesions was observed between *in situ*-only and invasive EMPD cases (P=0.35). By contrast, MUC5AC expression scores in invasive components were significantly lower than those in the corresponding *in situ* lesions of invasive EMPD (P=0.0015). Neither *in situ* nor invasive EMPD lesions showed immunoreactivity for HNF4α or claudin 18. These findings obtained from the second-largest cohort study to date suggested that MUC5AC expression was reduced in invasive lesions. Furthermore, MUC5AC expression in EMPD was not associated with the expression of HNF4α, despite its role in inducing MUC5AC expression in normal gastric tissues.

Correspondence to: Dr Mitsuaki Ishida, Department of Pathology, Osaka Medical and Pharmaceutical University, 2-7 Daigaku-machi, Takatsuki, Osaka 569-8686, Japan
E-mail: mitsuaki.ishida@ompu.ac.jp

Abbreviations: EMPD, extramammary Paget disease; HER2, human epidermal growth factor receptor 2; HNF4α, hepatocyte nuclear factor 4α

Key words: EMPD, gastric-type marker, claudin 18.2, HNF4α, MUC5AC

Introduction

Extramammary Paget disease (EMPD) is a rare cutaneous adenocarcinoma characterised by predominant intraepithelial growth of carcinoma cells (1). Primary EMPD originates from skin appendages, whereas secondary EMPD represents intraepithelial involvement by an underlying adenocarcinoma, most commonly originating from the lower gastrointestinal or urinary tract (1). The most common sites of primary EMPD include the vulva, perianal region, scrotum, and penis (1,2). The characteristic histopathological features of this rare carcinoma include intraepithelial proliferation of neoplastic cells with abundant amphophilic cytoplasm, mucin, and vesicular nuclei with prominent nucleoli, known as Paget cells. These cells appear as solitary cells, solid nests, or occasionally glandular structures, and may involve hair follicles and eccrine ducts (1). The origin of primary EMPD remains controversial, as this adenocarcinoma is hypothesised to arise from pluripotent germinative cells within the epidermis or skin adnexa. Alternatively, Toker cells, mammary gland-related intraepithelial cells present in the epithelium of the normal external genital region, have been proposed as a potential cell of origin (3-5).

The hallmark immunohistochemical characteristic of primary EMPD is positive immunoreactivity for MUC5AC (6-10), a gastric-type mucin core protein (10,11). MUC5AC is expressed in normal mucous cells of the surface foveolar epithelium of the stomach but not in the pyloric and fundic glands (11,12). MUC5AC expression has been reported in several types of carcinomas, including gastric, lung, and pancreatobiliary carcinomas (11). Its expression has also been described in non-digestive system carcinomas, such as primary EMPD and endocervical adenocarcinoma (6-10,13). However, whether MUC5AC expression

correlates with the invasiveness of EMPD remains controversial. Two studies reported higher MUC5AC expression in *in situ* lesions than in invasive lesions (6,9), whereas another study demonstrated higher MUC5AC expression in invasive lesions compared with *in situ* lesions (7).

Recently, several gastric-type markers have been utilised in pathological diagnosis through immunohistochemical analysis and explored for targeted therapeutic applications. Claudin 18 is a member of the claudin family and a major component of tight junction complexes (14). Its expression is restricted to non-neoplastic gastric mucosa and alveolar epithelial cells (14) and is frequently observed in gastric carcinoma, oesophageal and pancreatobiliary tract adenocarcinomas, as well as mucinous carcinomas of the female genital tract (15-18). Accordingly, analysis of this tight junction protein may aid in identifying the primary origin of metastatic carcinoma (17). Moreover, claudin 18 has recently attracted attention as a promising therapeutic target in claudin 18-expressing malignant tumours (15,16). Zolbetuximab, a monoclonal antibody targeting claudin 18.2, a gastric mucosa-specific isoform, has been shown to improve survival in patients with claudin 18.2-positive advanced gastric cancer (15). In addition, hepatocyte nuclear factor 4α (HNF4α) is a nuclear transcription factor involved in liver and kidney development and intestinal functions; accordingly, its expression is observed in normal liver, kidney, stomach, and intestinal tissues (19,20). Although HNF4α is not a specific gastric-type marker, it has been shown to induce MUC5AC expression in the normal stomach (21), and most gastric adenocarcinomas demonstrate positive immunoreactivity for this marker (22). To date, the expression profiles of claudin 18 and HNF4α in primary EMPD have not been fully investigated. Therefore, the present study aimed to examine the expression profiles of MUC5AC, claudin 18, and HNF4α in EMPD, as well as the differences in MUC5AC expression between *in situ* and invasive lesions.

Materials and methods

Patient selection. Consecutive patients with primary EMPD who underwent surgical resection at Osaka Medical and Pharmaceutical University Hospital between January 2016 and December 2024 were included. Patients who underwent biopsy without subsequent surgical resection were excluded.

This retrospective, single-institution study was conducted in accordance with the tenets of the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board of Osaka Medical and Pharmaceutical University Hospital (Approval No.: #2025-030). All data were anonymised. Informed consent was obtained using the opt-out method because of the retrospective study design, in which medical records and archived samples were used and posed no risk to participants. In addition, the present study did not include minors. Information regarding the study, including the inclusion criteria and the opportunity to opt out, was provided on the institutional website (https://www.ompu.ac.jp/u-deps/path/img/file36.pdf).

Histopathological analysis. Surgically resected specimens were fixed in 10% neutral buffered formalin, sectioned, and stained with haematoxylin and eosin. Two researchers (NK and MI) independently evaluated the histopathological features of the slides. When invasive neoplastic growth was identified (defined as the growth of carcinoma cells over the basement membrane of the epidermis or skin appendages into the dermis), the tumours were classified as invasive EMPD, regardless of the depth of tumour invasion.

Immunohistochemical analysis. Immunohistochemical analysis was performed using an automated immunostainer (Discovery Ultra System; Roche Diagnostics), according to the manufacturer's instructions. The OptiView DAB Universal Kit (cat. no. 518-111427; Roche Diagnostics) was used for immunostaining. The primary antibodies used in the present study were mouse monoclonal antibody against claudin 18 (43-14A; Abcam, Cambridge, UK, diluted 1:8,000), rabbit monoclonal antibody against HNF4α (C11F12; Cell Signaling Technology, Danvers, MA, USA, diluted 1:200), and mouse monoclonal antibody against MUC5AC (45M1; Thermo Fisher Scientific Inc., MA, USA, diluted 1:4,000). Non-neoplastic gastric and colon mucosae and skin tissues were concurrently stained as the positive and negative controls, respectively, for these three markers.

Expression of these markers was assessed semi-quantitatively as follows: 0, <5%; 1, 5-25%; 2, 26-50%; 3, >50% of positive neoplastic cells, using the same method as in a previous study (7). Immunohistochemical expression in *in situ* and invasive lesions (when present) was evaluated separately.

Two researchers (NK and MI) independently evaluated the immunohistochemical findings. In cases of discrepancy, a final consensus was reached through reassessment using a multi-headed microscope.

Statistical analysis. Differences between the two groups were analysed using the Mann-Whitney *U* test or the Wilcoxon signed-rank test. Statistical significance was set at $P<0.05$.

Results

Patient characteristics. This study included 40 patients with EMPD, comprising nine women (22.5%) and 31 men (77.5%). The median age at the time of surgery was 74 (range: 45-89) years. Tumour locations were as follows: scrotum (26 patients), external genitalia (10 patients), penis (2 patients), and anus and vulva (1 patient each). Lymph node dissection was performed in seven patients. No follow-up analysis including recurrence was performed in the present study.

Histopathological characteristics. This cohort included 25 *in situ* and 15 invasive EMPD cases. In all invasive EMPD cases, *in situ* lesions were present overlying and/or surrounding the invasive components. Typical histopathological features of *in situ* and invasive EMPD are shown in Fig. 1A and B. Lymph node metastasis was identified in two patients with invasive EMPD; among the seven patients who underwent lymph node dissection, five had only *in situ* lesions, and no metastasis was observed in these cases.

Immunohistochemical characteristics. Table I summarises the expression scores of MUC5AC in both *in situ* and invasive EMPD. MUC5AC expression was observed in 23 *in situ*

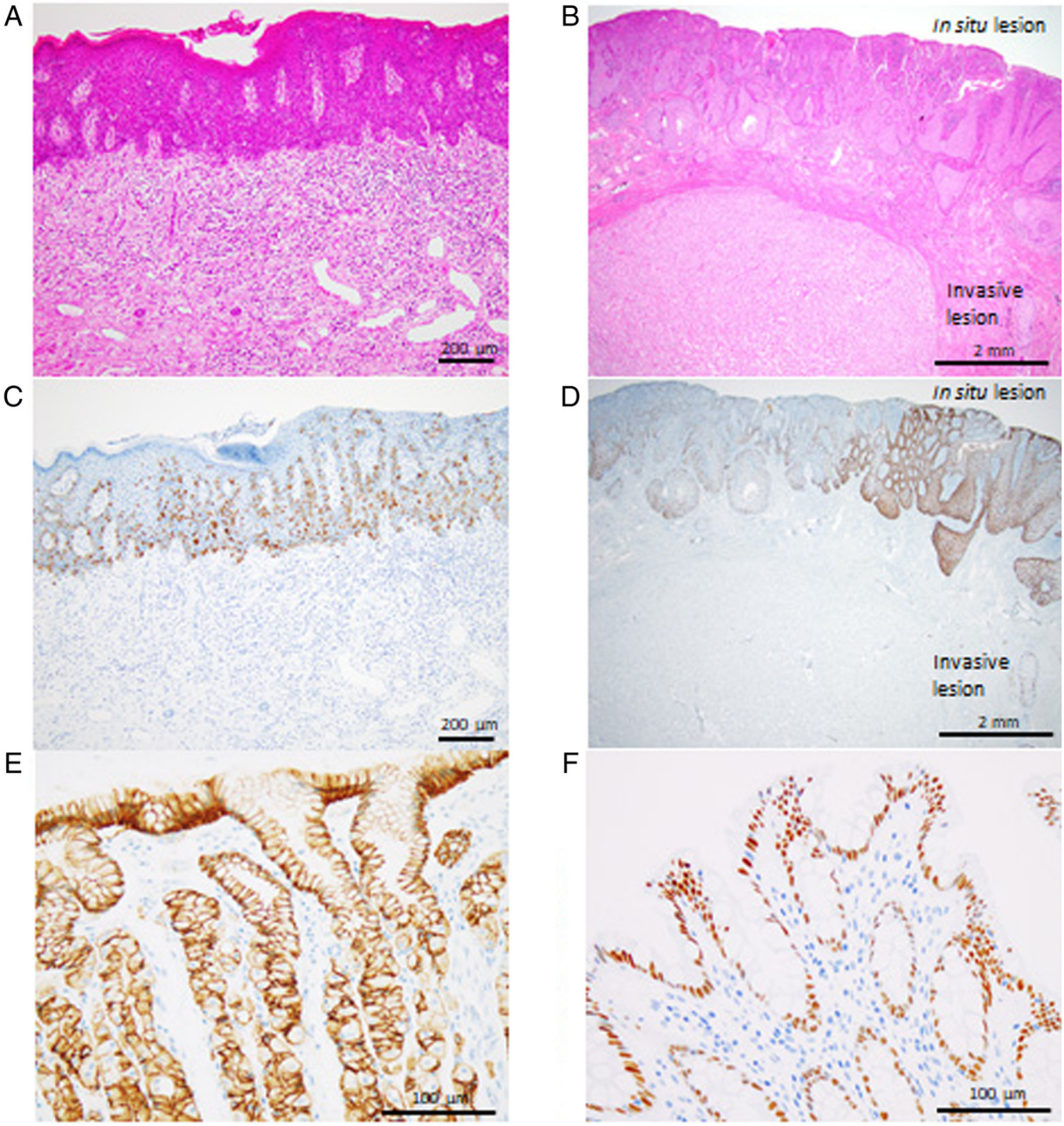

Figure 1. Histopathological and immunohistochemical features of primary EMPD. (A) Typical histopathological features of *in situ* EMPD, showing intraepidermal proliferation of the neoplastic cells with slightly eosinophilic cytoplasm, predominantly in a single-cell pattern (haematoxylin and eosin staining; original magnification, x200). (B) Typical histopathological features of invasive EMPD. Intraepidermal proliferation (*in situ* lesion) and invasive neoplastic growth into the dermis (invasive lesion) are present (haematoxylin and eosin staining; original magnification, x20). (C) Immunohistochemical staining for MUC5AC showing cytoplasmic positive immunoreactivity in the neoplastic cells of the *in situ* lesion (original magnification, x200). (D) Immunohistochemical staining for MUC5AC showing positive immunoreactivity in the *in situ* lesion, but not in the invasive lesion (original magnification, x20). (E) Immunohistochemical staining for claudin 18 as a positive control. Membranous positivity is noted in the non-neoplastic gastric epithelial cells (original magnification, x400). (F) Immunostaining for hepatocyte nuclear factor 4α as a positive control. Nuclear positivity is noted in the non-neoplastic colon epithelial cells (original magnification, x400). EMPD, extramammary Paget disease.

and 15 invasive EMPD cases, whereas no MUC5AC expression was observed in one *in situ* case and one invasive case. Representative immunohistochemical features of *in situ* and invasive EMPD are shown in Fig. 1C and D.

There was no significant difference between the MUC5AC expression scores of *in situ* lesions in patients with *in situ*-only and invasive EMPD, as the mean expression score was 2.36 (range, 0-3) in patients with *in situ* EMPD and 2.07 (range, 0-3) in those with invasive EMPD (P=0.35) (Fig. 2A).

In patients with invasive EMPD, MUC5AC expression scores in the invasive EMPD lesions were significantly lower than those in the corresponding *in situ* lesions, with mean expression scores of 2.07 (range, 0-3) for *in situ* lesions and 0.33 (range, 0-2) for invasive lesions (P=0.0015) (Fig. 2B).

Moreover, MUC5AC expression scores in lymph node metastasis were 0 in both patients. Neither HNF4α nor claudin 18 expression was observed in any *in situ* or invasive EMPD lesions. Notably, claudin 18 and HNF4α positivity were

Table I. Immunohistochemical staining results of patients with primary EMPD.

A, EMPD				
	MUC5AC expression score			
Group	0, n	1, n	2, n	3, n
In situ EMPD	1	4	5	15
Invasive EMPD	1	4	3	7
B, Invasive EMPD				
In situ lesions	1	4	3	7
Invasive lesions	11	3	1	0

EMPD, extramammary Paget disease.

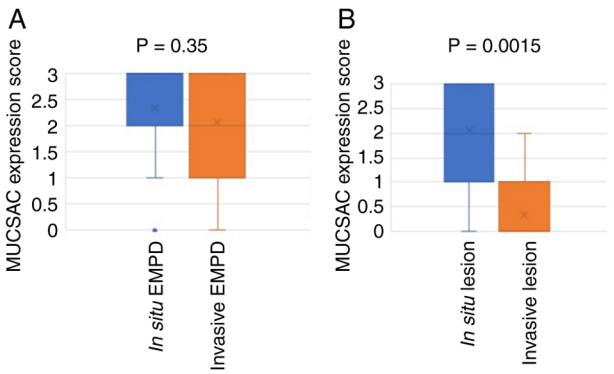

Figure 2. MUC5AC expression scores in primary EMPD. (A) Comparison of MUC5AC expression scores in *in situ* lesions between patients with *in situ*-only EMPD (n=25) and those with invasive EMPD (n=15). (B) Comparison of MUC5AC expression scores between *in situ* and invasive lesions in patients with invasive EMPD (n=15). EMPD, extramammary Paget disease.

observed in the non-neoplastic gastric and colon mucosae used as positive control (Fig. 1E and F).

Discussion

This study clearly demonstrated that MUC5AC expression scores were significantly lower in invasive lesions than in the corresponding *in situ* lesions of invasive EMPD, and that MUC5AC expression in *in situ* lesions did not differ significantly between *in situ*-only and invasive EMPD. Moreover, the present study is the first to demonstrate the absence of immunohistochemical expression of HNF4α and claudin 18 in primary EMPD.

It is well recognised that MUC5AC expression is present in primary EMPD, with reported positive expression rates ranging from 42.1 to 89% (6-10). The findings of the present study are consistent with previous reports (6-10), as 95% (38 of 40) of primary EMPD cases showed positive immunoreactivity for MUC5AC. In normal gastric mucosa, MUC5AC expression is induced by HNF4α (21), and most gastric adenocarcinomas also demonstrate positive immunoreactivity for this transcription factor (22). Although MUC5AC expression is observed in normal endocervical glandular cells and respiratory epithelium (13,23), HNF4α expression is not detected in these normal epithelial tissues (24). These findings suggest that the mechanisms regulating MUC5AC expression may differ among organs. In the present study, no immunohistochemical expression of HNF4α was detected in primary EMPD, including both *in situ* and invasive tumours. Further studies are required to elucidate the hitherto unknown molecular mechanisms underlying MUC5AC expression in patients with primary EMPD.

The expression profiles of MUC5AC in *in situ* and invasive lesions of primary EMPD remain controversial. Table II summarises the expression profiles of MUC5AC in invasive EMPD reported in previous studies, as well as in the present study (6,7,9). Three of four studies, including the present one, demonstrated that MUC5AC expression was significantly lower in invasive lesions than *in situ* lesions, although the methods used to evaluate MUC5AC expression differed among these studies. Specifically, the cut-off value for positivity was set at 5% of carcinoma cells in three studies including the present one (6,7), whereas the tumour was considered to be positive for MUC5AC expression when more than one MUC5AC-positive cell was present in one study (9). Moreover, expression scores were evaluated separately for *in situ* and invasive lesions in two studies, including the present study (9); however, the methods for evaluating MUC5AC expression scores in invasive EMPD were not fully described (whether only invasive lesions or both *in situ* and invasive lesions were evaluated) in the remaining two studies (6,7). The present study represents the second-largest cohort of both total and invasive EMPD cases (Table II) (6,7,9) and included a statistical comparison of MUC5AC expression scores between *in situ* and invasive lesions. Accordingly, MUC5AC expression may be decreased in invasive EMPD lesions, although further analyses in larger cohorts are required to clarify the expression profiles of MUC5AC in EMPD. In the present cohort, both lymph node metastases showed loss of MUC5AC expression implying that metastatic EMPD cells might lack MUC5AC expression; however, this preliminary

Table II. Expression profiles of MUC5AC in invasive EMPD.

First author/s, year	MUC5AC-positive, n (%)		(Refs.)
	In situ EMPD	Invasive EMPD	
Rao *et al*, 2022	64/72 (88.9)	23/46 (50.0)	(6)
Hata *et al*, 2014	12/28 (42.9)	9/11 (81.8)	(7)
Yoshii *et al*, 2002	23/23 (100.0)	11/13 (84.6)	(9)
Present study	24/25 (96.0)	4/15 (26.7)	-

EMPD, extramammary Paget disease.

observation was seen in only two patients. Finally, the molecular mechanisms underlying these changes remain unresolved, and it is still unclear whether these changes are the cause or the effects of invasion. Therefore, further studies are required to elucidate the mechanisms responsible for altered MUC5AC expression in invasive EMPD.

Claudin 18 is a major component of tight junction proteins and plays an important role in epithelial barrier function and cellular polarity (14). Its expression is restricted to non-neoplastic gastric mucosa and alveolar epithelial cells of the lung (14). Claudin 18 has two splice variants, among which claudin 18.2 is a gastric mucosa-specific isoform (14). Recent advances in molecular-targeted therapy have demonstrated that zolbetuximab, a monoclonal antibody against claudin 18.2, significantly improves survival in patients with claudin 18.2-positive advanced gastric cancer (15). In addition, positive immunoreactivity for claudin 18 has been reported in pancreatobiliary tract adenocarcinomas and mucinous carcinomas of the female genital tract (15-18), suggesting that patients with these malignancies may be candidates for molecular-targeted therapy. However, the present study demonstrated a lack of claudin 18 expression in all primary EMPD cases examined. Accordingly, patients with primary EMPD are unlikely to benefit from anti-claudin 18-targeted therapy. Moreover, a monoclonal antibody against claudin 18 (clone 43-14A) was used for immunohistochemical detection in the present study. This antibody reacts with both claudin 18.1 and 18.2. Although the specific antibody against claudin 18.2 might have helped retrieve more information regarding expression of gastric-type marker in EMPD, we used this claudin 18 antibody clone because it was used for detecting claudin 18 expression in cancer tissues in a clinical trial that demonstrated the significant survival benefits of zolbetuximab in patients with claudin 18-positive gastric cancer (25) and is used as a companion diagnostics tool.

The present study had a few limitations. First, although this is the second-largest cohort of EMPD to be studied so far, it included a relatively small number of patients with EMPD (25 *in situ* and 15 invasive EMPD). As this study was a pilot study, further study with a larger cohort is required to overcome statistical bias. Moreover, the relationship between MUC5AC expression status and survival was not analysed, because this cohort included only two patients with metastatic EMPD. Second, the methods used to evaluate MUC5AC expression profiles differed among studies, as mentioned earlier, resulting in bias. Further analysis using standardized methods for evaluation of MUC5AC expression in a larger cohort is required. Third, the present study demonstrated that MUC5AC expression in EMPD was not correlated with HNF4α expression. Although different mechanisms of MUC5AC expression may be present, molecular analysis was not performed in the present study. Thus, further molecular study is needed to clarify the mechanism underlying MUC5AC expression in EMPD.

In conclusion, the present study demonstrated that MUC5AC expression was significantly lower in invasive lesions than in *in situ* lesions of invasive EMPD; however, MUC5AC expression in *in situ* lesions did not differ significantly between *in situ*-only and invasive EMPD. Although HNF4α induces MUC5AC expression in normal gastric mucosa, HNF4α expression was not detected in primary EMPD. Therefore, the molecular mechanisms underlying MUC5AC expression in primary EMPD warrant further investigation.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

NK and MI conceived and designed the present study. NK and MI analysed histological and immunohistochemical staining. NK and MI confirm the authenticity of all the raw data. NK, MI, SO and YH analysed the data. NK and MI performed the statistical analyses. NK and MI wrote the manuscript and prepared figures and tables. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present retrospective, single-institution study was conducted in accordance with the tenets of The Declaration

of Helsinki, and the study protocol was approved by the Institutional Review Board of Osaka Medical and Pharmaceutical University Hospital (approval no. 2025-030; Takatsuki, Japan). All data were anonymised. Informed consent was obtained from the patients using the opt-out methodology because of the retrospective study design, in which medical records and archived samples were used. The present study did not include minors.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Prieto VG, Kazakov DV, Konstantinova AM, McCluggage WG and Michal M: Extramammary Paget disease. In: WHO classification of tumours, Skin Tumours. 5th edition. IARC, Lyon, pp313-314, 2025.
2. Ishizuki S and Nakamura Y: Extramammary Paget's disease: Diagnosis, pathogenesis, and treatment with focus on recent developments. Curr Oncol 28: 2969-2986, 2021.
3. Shah RR, Shah K, Wilson BN, Tchack M, Busam KJ, Moy A, Leitao MM, Cordova M, Neumann NM, Smogorzewski J, *et al*: Extramammary Paget disease. Part I. Epidemiology, pathogenesis, clinical features, and diagnosis. J Am Acad Dermatol 91: 409-418, 2024.
4. Simonds RM, Segal RJ and Sharma A: Extramammary Paget's disease: A review of the literature. Int J Dermatol 58: 871-879, 2019.
5. Belousova IE, Kazakov DV, Michal M and Suster S: Vulvar toker cells: the long-awaited missing link: A proposal for an origin-based histogenetic classification of extramammary Paget disease. Am J Dermpathol 28: 84-86, 2006.
6. Rao Y, Zhu J, Zheng H, Ren Y and Ji T: Cell origin and genome profile difference of penoscrotum invasive extramammary Paget disease compared with its in situ counterpart. Front Oncol 12: 972047, 2022.
7. Hata H, Abe R, Hoshina D, Saito N, Homma E, Aoyagi S and Shimizu H: MUC5AC expression correlates with invasiveness and progression of extramammary Paget's disease. J Eur Acad Dermatol Venereol 28: 727-732, 2014.
8. Liegl B, Leibl S, Gogg-Kamerer M, Tessaro B, Horn LC and Moinfar F: Mammary and extramammary Paget's disease: An immunohistochemical study of 83 cases. Histopathology 50: 439-447, 2007.
9. Yoshii N, Kitajima S, Yonezawa S, Matsukita S, Setoyama M and Kanzaki T: Expression of mucin core proteins in extramammary Paget's disease. Pathol Int 52: 390-399, 2002.
10. Kuan SF, Montag AG, Hart J, Krausz T and Recant W: Differential expression of mucin genes in mammary and extramammary Paget's disease. Am J Surg Pathol 25: 1469-1477, 2001.
11. Krishn SR, Ganguly K, Kaur S and Batra SK: Ramifications of secreted mucin MUC5AC in malignant journey: a holistic view. Carcinogenesis 39: 633-651, 2018.
12. Johansson MEV, Sjövall H and Hansson GC: The gastrointestinal mucus system in health and disease. Nat Rev Gastroenterol Hepatol 10: 352-361, 2013.
13. Riethdorf L, O'Connell JT, Riethdorf S, Cviko A and Crum CP: Differential expression of MUC2 and MUC5AC in benign and malignant glandular lesions of the cervix uteri. Virchows Arch 437: 365-371, 2000.
14. Niimi T, Nagashima K, Ward JM, Minoo P, Zimonjic DB, Popescu NC and Kimura S: Claudin-18, a novel downstream target gene for the T/EBP/NKX2.1 homeodomain transcription factor, encodes lung- and stomach-specific isoforms through alternative splicing. Mol Cell Biol 21: 7380-7390, 2001.
15. Nakayama I, Qi C, Chen Y, Nakamura Y, Shen L and Shitara K: Claudin 18.2 as a novel therapeutic target. Nat Rev Clin Oncol 21: 354-369, 2024.
16. Hashimoto T, Iida N, Nakamura Y, Nonomura N, Morizane C, Iwata H, Okano S, Yamagami W, Yamazaki N, Kadowaki S, *et al*: Landscape analysis of CLDN18 expression and isoform distribution in solid tumors: Insights from MONSTAR-SCREEN-2 study. Cancer Sci 116: 2218-2231, 2025.
17. Li WT, Jeng YM and Yang CY: Claudin-18 as a marker for identifying the stomach and pancreatobiliary tract as the primary sites of metastatic adenocarcinoma. Am J Surg Pathol 44: 1643-1648, 2020.
18. Kiyokawa T, Hoang L, Pesci A, Alvarado-Cabrero I, Oliva E, Park KJ, Soslow RA and Stolnicu S: Claudin-18 as a promising surrogate marker for endocervical gastric-type carcinoma. Am J Surg Pathol 46: 628-636, 2022.
19. Sladek FM, Zhong WM, Lai E and Darnell JE Jr: Liver-enriched transcription factor HNF-4 is a novel member of the steroid hormone receptor superfamily. Genes Dev 4: 2353-2365, 1990.
20. Qu N, Luan T, Liu N, Kong C, Xu L, Yu H, Kang Y and Han Y: Hepatocyte nuclear factor 4 a (HNF4α): A perspective in cancer. Biomed Pharmacother 169: 115923, 2023.
21. Jonckheere N, Vincent A, Franquet-Ansart H, Witte-Bouma J, Korteland-van Male A, Leteurtre E, Renes IB and van Seuningen I: GATA-4/-6 and HNF-1/-4 families of transcription factors control the transcriptional regulation of the murine Muc5ac mucin during stomach development and in epithelial cancer cells. Biochim Biophys Acta 1819: 869-876, 2012.
22. van der Post RS, Bult P, Vogelaar IP, Ligtenberg MJL, Hoogerbrugge N and van Krieken JH: HNF4A immunohistochemistry facilitates distinction between primary and metastatic breast and gastric carcinoma. Virchows Arch 464: 673-679, 2014.
23. Okuda K, Chen G, Subramani DB, Wolf M, Gilmore RC, Kato T, Radicioni G, Kesimer M, Chua M, Dang H, *et al*: Localization of secretory mucins MUC5AC and MUC5B in normal/healthy human airways. Am J Respir Crit Care Med 199: 715-727, 2019.
24. Tanaka T, Jiang S, Hotta H, Takano K, Iwanari H, Sumi K, Daigo K, Ohashi R, Sugai M, Ikegame C, *et al*: Dysregulated expression of P1 and P2 promoter-driven hepatocyte nuclear factor-4alpha in the pathogenesis of human cancer. J Pathol 208: 662-672, 2006.
25. Shitara K, Lordick F, Bang YJ, Enzinger P, Ilson D, Shah MA, Van Cutsem E, Xu RH, Aprile G, Xu J, *et al*: Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): A multicentre, randomised, double-blind, phase 3 trial. Lancet 401:1655-1668, 2023.