

Histopathological changes in primary extramammary Paget disease with emphasis on syringomatous structures and syringocystadenocarcinoma papilliferum *in situ*-like changes

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Abstract. Primary extramammary Paget disease (PEMPD) is a rare adenocarcinoma, and is histopathologically characterised by intraepithelial proliferation of carcinoma cells with abundant amphophilic cytoplasm. Minor histopathological findings in PEMPD, including syringomatous structures and syringocystadenocarcinoma papilliferum (SCACP) *in situ*-like changes, have rarely been reported. The present study aimed to analyse histopathological changes in PEMPD. Consecutive patients with PEMPD who underwent surgical resection were included. Melanin within carcinoma cell cytoplasm, syringomatous structures and SCACP *in situ*-like changes were assessed on haematoxylin and eosin-stained slides. Overall, 55 patients (16 female and 39 male patients) were included; 23 patients (41.8%) had an invasive carcinoma component and the remainder had only *in situ* lesions. Melanin pigment within carcinoma cell cytoplasm was observed in 85.5% of patients, while 17.4% of patients with invasive PEMPD exhibited melanin pigment in invasive carcinoma cells. Syringomatous structures, characterised by ductal, tadpole-like or small cystic structures composed of bland epithelial cells, were observed in 9.1% of patients (31.3% of all female patients), including in areas outside the PEMPD lesions. SCACP *in situ*-like changes, characterised by papillary epidermal hyperplasia with replacement of carcinoma cells, were also observed in 9.1% of PEMPD cases. These findings demonstrated that a high frequency of the presence of melanin pigment within carcinoma cell cytoplasm, including in invasive carcinoma

cells, could lead to misdiagnosis as malignant melanoma. Additionally, syringomatous structures (especially in female patients) and SCACP *in situ*-like changes may lead to the misdiagnosis of syringoma and SCACP *in situ*, respectively. Therefore, recognition of these histopathological changes in PEMPD is required for accurate diagnosis.

Introduction

Extramammary Paget disease is a rare adenocarcinoma that most often involves the vulva, perianal region, scrotum, and penis (1). Primary extramammary Paget disease (PEMPD) may arise from cutaneous adnexal structures or multipotent epidermal cells, whereas the secondary form reflects intraepithelial involvement by adenocarcinoma from an underlying primary site, most commonly the lower gastrointestinal or urinary tract (1). The histopathological hallmark of PEMPD is intraepithelial proliferation of carcinoma cells with abundant amphophilic cytoplasm and vesicular nuclei with prominent nucleoli, also known as Paget cells. These cells are seen as solitary cells or solid nests and may occasionally form glandular structures. Hair follicle and eccrine duct involvement is commonly observed (1).

Several minor histopathological changes have been reported in PEMPD, including pigmentation, syringomatous structures, and syringocystadenocarcinoma papilliferum (SCACP) *in situ*-like changes (2-9). Hyperpigmented PEMPD is a rare variant that is clinically black or brown in colour, reflecting intracytoplasmic melanin pigment within carcinoma cells and/or an increased number of melanocytes within the lesion; therefore, it can be clinically misdiagnosed as malignant melanoma (2-4). A study employing Masson-Fontana staining reported that 60% of PEMPD had melanin pigment within the cytoplasm of carcinoma cells (5). However, a dedicated histopathological validation study of intracytoplasmic melanin pigment in PEMPD has not yet been reported.

Syringoma is a benign skin appendage tumour arising from the eccrine ducts (10). The most common sites are the lower eyelids and periorbital area, although it may also occur in the genital region (10). Histopathologically, syringoma is characterised by epithelial cells forming ducts, cords, or small cysts, comprising a double-layer of cuboidal cells within

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Abbreviations: SCACP, syringocystadenocarcinoma papilliferum; PEMPD, primary extramammary Paget disease

Key words: extramammary Paget disease, pigmentation, syringoma, SCACP

sclerotic upper dermal stroma (10). Konstantinova *et al* (6) reported syringomatous structures in 10 of 98 (10.2%) patients with PEMPDP. Although most of this component was present beneath the PEMPDP lesion, some structures were also present outside the lesion (6). SCACP is an extremely rare malignant skin appendage tumour characterised by papillary proliferation of adenocarcinoma cells, usually arising in a pre-existing syringocystadenoma papilliferum (11). Additionally, Konstantinova *et al* (8) reported SCACP *in situ*-like changes in 11 of 174 (6.3%) patients with PEMPDP. Therefore, PEMPDP may be accompanied by these histopathological changes, potentially leading to misdiagnosis as other entities. Nonetheless, few studies have examined these histopathological changes in PEMPDP (7,9). This study aimed to analyse minor histopathological changes in consecutive surgical cases of PEMPDP.

Materials and methods

Patient selection. We selected consecutive patients with PEMPDP who underwent surgical resection at Osaka Medical and Pharmaceutical University Hospital between January 2016 and December 2024. Secondary forms were excluded.

This retrospective, single-institution study was conducted per 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 #2025-030 and #2020-124). All data were anonymised. Informed consent was obtained from the patients using the opt-out method because of the retrospective study design, as medical records and archived samples were used with no risk to the participants. Moreover, the present study did not include minors. Information regarding this 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. Histopathological features were independently assessed on all slides by two researchers (YF and MI).

Melanin pigment in the cytoplasm of carcinoma cells was assessed on haematoxylin and eosin-stained sections. Tumours with dark brown melanin pigment in the cytoplasm of carcinoma cells were classified as pigmented PEMPDP. Neither immunohistochemical staining nor Fontana-Masson staining was performed to detect melanocytes or melanin pigments. Additionally, melanin-laden dermal macrophages were not considered pigmented PEMPDP in this study.

A syringomatous structure was defined as ductal, cord-like, tadpole-like, or small cystic formation by bilayered, attenuated epithelial cells without atypia, surrounded by sclerotic stroma in the upper dermis (6,10). Syringomatous foci were evaluated in areas affected by and/or outside PEMPDP lesions.

SCACP *in situ*-like changes were defined as epidermal hyperplasia with replacement of PEMPDP carcinoma cells, preservation of pre-existing basal cells, occasional glandular structures and/or apocrine secretion, and dense plasma cell-rich infiltrate in the papillary dermis (8,11).

Table I. Clinicopathological features of the present cohort (n=55).

Variable	No. (%)
Sex	
Male	16 (29.1)
Female	39 (70.9)
Location	
Scrotum	31 (56.4)
Vulva	16 (29.1)
Anus	4 (7.3)
Penis	3 (5.5)
Axilla	1 (1.8)
Invasiveness	
<i>In situ</i>	32 (58.2)
Invasive	23 (41.8)

Results

Patient characteristics. Table I summarises the clinicopathological features of the study cohort. This study included 55 Japanese patients [16 females (29.1%) and 39 males (70.9%)]. The median age at the time of surgery was 77 years (range, 45-89 years). The primary tumour sites were the scrotum, vulva, anus, penis, and axilla in 31 (56.4%), 16 (29.1%), 4 (7.3%), 3 (5.5%), and 1 (1.8%) patients, respectively. Lymph node dissection was performed in eight patients.

Histopathological characteristics. Overall, 23 tumours (41.8%) comprised both invasive carcinoma components (regardless of invasion depth) and *in situ* lesions (Fig. 1A), whereas the remaining 32 tumours (58.2%) had only *in situ* lesions. Among the eight patients who underwent lymph node dissection, metastatic carcinoma was identified in the lymph nodes of two patients, and both had an invasive carcinoma component.

Hair follicle involvement, with or without sebaceous units (Fig. 1B), and eccrine duct involvement (Fig. 1C) were observed in 53 (96.4%) and 54 (98.2%) patients, respectively (hair follicles: except for one *in situ* and one invasive PEMPDP; eccrine ducts: except for one *in situ* PEMPDP).

Melanin pigment. Cytoplasmic melanin pigment in carcinoma cells was observed in 47 patients (85.5%) in this series (Fig. 1D). Among them, melanin pigmentation was observed in 27 of 32 (84.4%) and 20 of 23 (87.0%) cases of *in situ* and invasive PEMPDP, respectively. In invasive PEMPDP, 4 tumours (17.4%) exhibited melanin pigment in both *in situ* and invasive lesions (Fig. 1E), whereas the remaining 16 tumours had melanin pigment only in *in situ* lesions.

Syringomatous structures. Five of 55 PEMPDP (9.1%) had syringomatous structures (Fig. 1F). Table II summarises the clinicopathological features of these five patients. All were female, and female patients accounted for 31.3% (5 of 16 patients). The locations of PEMPDP with syringomatous

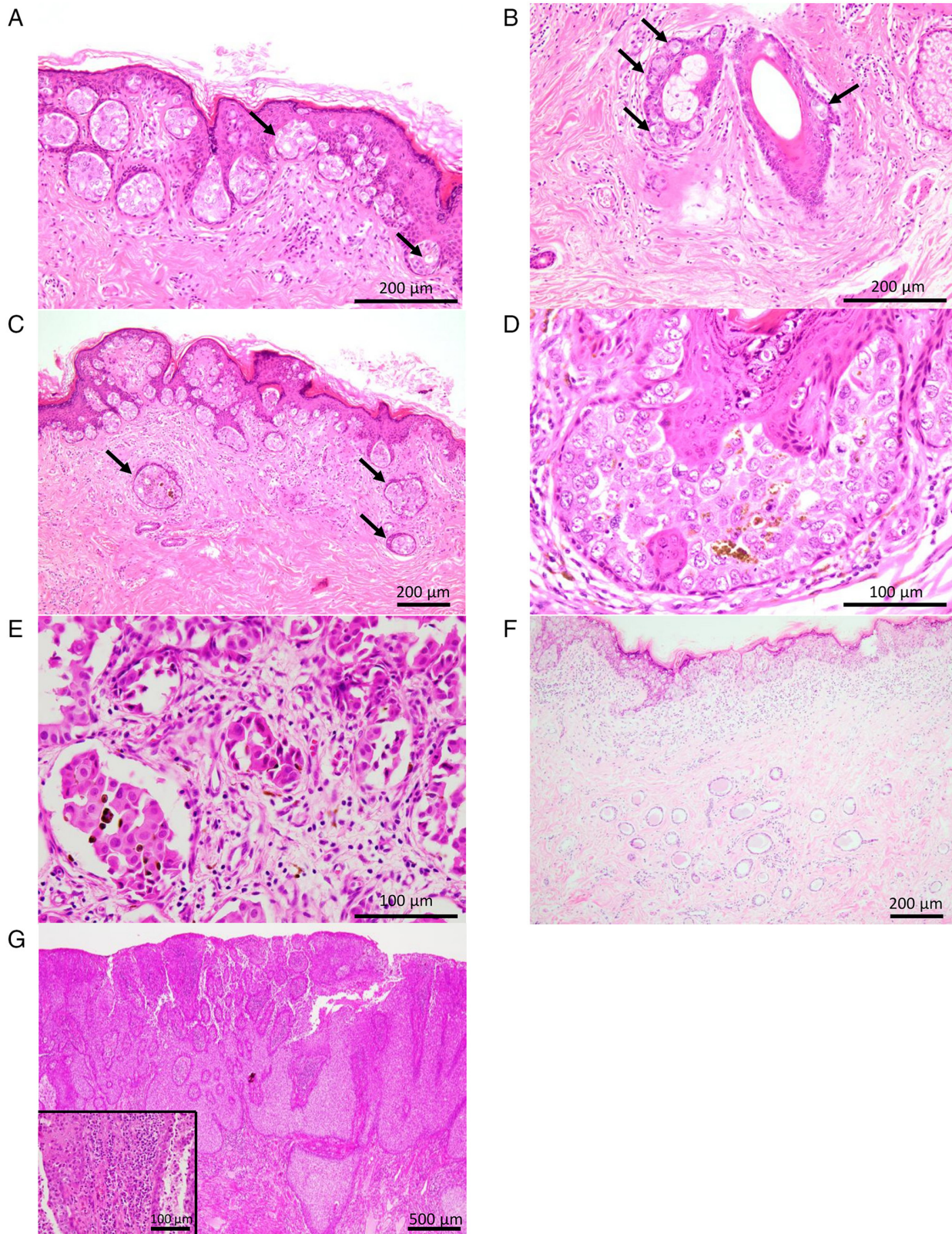


Figure 1. Histopathological features of PEMP. (A) Proliferation of carcinoma cells containing rich cytoplasm and large, round to oval nuclei showing nest formation within the epidermis. Within the nests of carcinoma cells, focal glandular formation was observed (arrows; haematoxylin and eosin staining; magnification, x200). (B) Involvement of carcinoma cells into the hair follicles and sebaceous ducts (arrows; haematoxylin and eosin staining; magnification, x200). (C) Involvement of carcinoma cells into the eccrine ducts (arrows; haematoxylin and eosin staining; magnification, x100). (D) Presence of melanin pigment within the cytoplasm of carcinoma cells in the *in situ* lesion (haematoxylin and eosin staining; magnification, x400). (E) Invasive carcinoma cells also contained melanin pigment in their cytoplasm (haematoxylin and eosin staining; magnification, x400). (F) Syringomatous structures in PEMP. Small ductal or tadpole-like structures comprised of attenuated bland epithelial cells within the sclerotic stroma were observed in the upper dermis. A syringomatous structure was present under the *in situ* lesion of extramammary Paget disease. (haematoxylin and eosin staining; magnification, x100). (G) Syringocystadenocarcinoma papilliferum *in situ*-like change in PEMP. Epidermal hyperplasia with papillary proliferation containing carcinoma cells was noted. Dense plasma cell infiltration in the papillary dermis was observed (inset) [haematoxylin and eosin staining; magnification, x100 or x400 (inset)]. PEMP, primary extramammary Paget disease.

Table II. Clinicopathological features of PEMPDP with syringomatous structures.

Patient no.	Age, years	Sex	Location	Invasiveness	Distribution of syringomatous structures
1	62	Female	Vulva	<i>In situ</i>	Both inside and outside of PEMPDP
2	76	Female	Vulva	<i>In situ</i>	Both inside and outside of PEMPDP
3	68	Female	Vulva	<i>In situ</i>	Both inside and outside of PEMPDP
4	73	Female	Vulva	Invasive	Both inside and outside of PEMPDP
5	68	Female	Vulva	Invasive	Only inside of PEMPDP

PEMPDP, primary extramammary Paget disease.

Table III. Clinicopathological features of primary extramammary Paget disease with syringocystadenocarcinoma papilliferum *in situ*-like changes.

Patient no.	Age, years	Sex	Location	Invasiveness
1	71	Male	Scrotum	Invasive
2	78	Male	Scrotum	<i>In situ</i>
3	79	Female	Vulva	Invasive
4	70	Female	Anus	<i>In situ</i>
5	62	Male	Scrotum	Invasive

structures were the vulva in all patients. No carcinoma cell involvement was observed in these structures. These structures were present beneath the PEMPDP lesions in all five patients and were also observed around the PEMPDP lesions in four patients.

SCACP in situ-like changes. *SCACP in situ*-like changes were observed in 5 of 55 PEMPDP cases (9.1%; Fig. 1G). Table III summarises the clinicopathological features of these five patients (three males and two females). This feature was observed in two *in situ* and three invasive PEMPDP cases. Typical PEMPDP lesions were observed in all five patients. Additionally, none of the patients had syringomatous structures, and *SCACP in situ*-like changes were not observed elsewhere.

Discussion

This study demonstrated that melanin pigment was present in 85.5% of PEMPDP, including in invasive carcinoma cells in four tumours. Syringomatous structures and *SCACP in situ*-like changes were observed in 9.1% of cases each in this cohort. These results highlight a spectrum of minor histopathological findings in PEMPDP that may pose a diagnostic pitfall in this rare skin adenocarcinoma.

The characteristic histopathological feature of PEMPDP is intraepithelial proliferation of carcinoma cells (1). Involvement of carcinoma cells in the pre-existing pilosebaceous apparatus and eccrine ducts is a common finding (1), as also observed in this study. Nonetheless, minor histopathological features of this rare skin adenocarcinoma, such as pigmentation, syringomatous structures, and *SCACP in situ*-like changes, have been reported (5-9). Most patients with PEMPDP present with erythematous lesions, whereas a few patients show clinically

brown-to-black lesions, termed hyperpigmented PEMPDP (2-4). Differentiation from malignant melanoma is critical in patients with hyperpigmented PEMPDP (2-4). Moreover, 60% of anogenital Paget disease showed varying amounts of melanin pigment within the cytoplasm of carcinoma cells on Fontana-Masson staining, although clinical information regarding the colour of the lesion was not available in these cases (5). Here, melanin pigment was observed in 85.5% of patients. The reason for the difference in melanin pigment frequency remains uncertain. However, it may depend on the ethnic background, i.e., the present cohort consisted solely of Japanese individuals, whereas this information was not available in the previous report (5). Although Fontana-Masson staining allows for easier identification of melanin pigment than haematoxylin and eosin staining (5), the difference in melanin pigment frequency might be related to staining methodology. The current study is also the first to report melanin pigment in 17.4% of invasive carcinoma cells in PEMPDP, although clinical information on the lesion colour was not available. The relatively high melanin pigment content in PEMPDP, even in invasive carcinoma cells, may lead to misdiagnosis as malignant melanoma. Therefore, careful evaluation of histopathological features and immunohistochemical stain panels may be useful for correct diagnosis (3). Although the detailed mechanism underlying melanin pigment within carcinoma cells of PEMPDP remains unresolved, it has been speculated that some chemotactic factors stimulate melanocytic proliferative activity and mediate transfer of melanin pigment from melanocytes to carcinoma cells (3). Additional molecular studies are required to clarify the underlying mechanisms.

Only two previous reports [one case series (6) and one case report (7)] have described syringomatous structures in PEMPDP. In the case series of PEMPDP with syringomatous structures,

10 of 98 patients (10.2%) with PEMPDP (including institutional and consultation files) demonstrated this change both beneath and outside the lesions (6). The results of the present study were in line with those of that report (6), as syringomatous changes were observed in 9.1% of PEMPDP cases, and 80% were also present outside the lesions. Moreover, syringomatous structures were observed only in female patients in the current and previous cohorts (6), as well as in the single case report (7). The incidence of this feature among female patients in the current cohort was 31.3%, whereas this information is not available in the previous report (6). Although syringomas most commonly occur on the lower eyelid and in the periorbital area, this benign tumour can occur in the genital area, particularly in females (10). Therefore, the presence of syringomatous structures in PEMPDP, especially when located outside the lesion, may be misdiagnosed as a syringoma, representing an important diagnostic pitfall of PEMPDP. Careful observation and consideration of the clinical diagnosis are needed to avoid overlooking PEMPDP lesions, particularly in female patients. The pathogenesis of syringomatous changes in PEMPDP has been hypothesised to reflect secondary hyperplasia or dilatation of dermal eccrine ducts caused by obstruction of flow in the intraepidermal acrosyringia by carcinoma cells (6). Nonetheless, these changes can occur outside carcinoma lesions, for which obstruction theory cannot account for; nor can it explain their exclusive occurrence in females. Although the reason for this sex predilection remains uncertain, syringoma preferentially occurs in the female genital area (10). Anatomical differences between the sexes may be responsible for this female predilection. Moreover, we could not completely rule out the coexistence of syringomas.

The occurrence of SCACP *in situ*-like changes in PEMPDP has only been reported in one case series (8). Although a slight female predilection was observed [nine of 16 patients across the present cohort and a previous report (8)], SCACP *in situ*-like changes can occur in male patients. Sheldon *et al* (9) reported a case of PEMPDP showing marked epidermal hyperplasia, intraepidermal glandular formation, and plasma cell infiltration in the papillary dermis of the entire lesion, resembling SCACP *in situ*-like changes. In previous reports, these lesions were diagnosed as acantholytic anaplastic EMPD or PEMPDP mimicking acantholytic squamous cell carcinoma *in situ* (12-15), and SCACP *in situ*, particularly when associated with pagetoid spread in the anogenital region, may represent PEMPDP with SCACP *in situ*-like changes (16-19). Whereas the case series by Konstantinova *et al* (8) and ours included typical PEMPDP lesions with SCACP *in situ*-like changes (11 and 5 patients, respectively), lesions entirely showing this feature might have been previously diagnosed as SCACP (9). PEMPDP with SCACP *in situ*-like changes can be misdiagnosed as squamous cell carcinoma *in situ* or SCACP, particularly when tumours entirely show this change, because of underrecognition of SCACP *in situ*-like changes in PEMPDP (9). Therefore, recognising SCACP *in situ*-like changes in PEMPDP is essential for correct diagnosis. Although the detailed pathogenesis of this change in PEMPDP remains unresolved, Konstantinova *et al* (8) speculated that SCACP *in situ*-like changes may result from a combined response to chronic rubbing and direct epidermal destruction (or cytokine production) by carcinoma cells. Dense plasmacytic infiltration

of the papillary dermis is a characteristic, albeit not specific, feature of SCACP *in situ*-like changes. This infiltration may be related to epidermal changes by carcinoma cells, as dense plasmacytic infiltration are not characteristic for all PEMPDP, even among lesions occurring in the same anatomical location. Dense plasmacytic infiltration may be related to epidermal change and/or remodelling by carcinoma cells via immune crosstalk (20).

This study had some limitations. First, it was conducted on a single institute cohort; thus, a selection bias cannot be ruled out. Second, melanin pigment within the cytoplasm of carcinoma cells was assessed only via haematoxylin and eosin staining, and neither Fontana-Masson staining nor immunohistochemical staining was performed. This may limit the strength of our assertion regarding the presence of melanin pigment. Moreover, lipofuscin deposition cannot be completely ruled out because it has reported in apocrine hidrocystoma (21).

In conclusion, this study demonstrated a high frequency of cytoplasmic melanin pigment in PEMPDP carcinoma cells, including invasive carcinoma cells. Syringomatous structures and SCACP *in situ*-like changes were observed in approximately 9.1% of PEMPDP. Recognition of these histopathological features in PEMPDP is important because they may lead to misdiagnosis.

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Availability of data and materials

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

Authors' contributions

MI conceived and designed the study. YF and MI analysed the histological features. YF and MI confirmed the authenticity of all raw data. YF, MI and YH analysed the data. YF and MI wrote the manuscript, and prepared figures and tables. All the authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

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 nos. 2025-030 and 2020-124; Takatsuki, Japan). All data were anonymised. Informed consent was obtained from the patients using the opt-out methodology because of the retrospective study design, as medical records and archived samples were used with no risk to the participants. Furthermore, the present study did not include minors.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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