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Research Paper

Diagnostic and therapeutic challenges in mammary and extra-mammary Paget disease: a retrospective case series

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ABSTRACT

Mammary and extramammary Paget disease (PD; MPD, EMPD) is a rare neoplastic disorder characterised by intraepithelial infiltration of malignant cells with glandular differentiation. Diagnosis of PD remains challenging, as its clinical presentation frequently mimics inflammatory diseases or other cutaneous neoplasms. It is estimated that approximately 10–15 % of EMPD cases and up to 50 % of MPD cases are invasive at the time of definitive diagnosis, largely due to diagnostic delays that may last several years.

In this retrospective case series, we analysed non-pigmented EMPD (n = 8) and MPD (n = 5) to evaluate the diagnostic performance of selected non-invasive imaging techniques, including dermoscopy, photodynamic diagnosis, and reflectance confocal microscopy, highlighting their limitations and advantages during the primary investigation and disease surveillance over several years.

Furthermore, we analysed diagnostic challenges in advanced, metastatic, and overlapping cases. The study also summarises the outcomes of multiple-line therapeutic approaches applied in high-risk EMPD patients and compares these results with data available in the current literature.

1. Introduction

Mammary Paget disease (MPD) and extramammary Paget disease (EMPD) are rare neoplastic disorders characterised by intraepithelial infiltration – predominantly of the epidermis –by malignant cells with glandular differentiation. These two entities differ significantly in their immunohistochemical profiles and hormonal receptor expression [1–6].

Approximately 25 % of EMPD cases represent a primary cutaneous adnexal carcinoma, most commonly of apocrine origin; however, tumours may also arise from periurethral, eccrine, perianal, or Bartholin glands [6–13]. In contrast, 7–40 % of EMPD cases are secondary and associated with an underlying internal malignancy, most frequently involving the bladder, rectum, cervix, prostate, or urethra [6–15]. EMPD occurs predominantly in Caucasian patients, with a higher incidence in women aged 50–80 years and a peak incidence around 65 years [6–12]. The most common anatomical sites include the vulva in women and the scrotum and penis in men, followed by the perianal region, axillae, buttocks, and external auditory canal in both sexes [6–15]. Regardless of the therapeutic approach, EMPD is associated with a high recurrence rate, reported in 30–60 % of cases [6–11].

MPD originates from either in situ or invasive ductal carcinoma of the underlying breast tissue [1,4,5] and accounts for approximately 1–5 % of all breast cancers. In 90–100 % of cases, MPD is associated with an underlying breast malignancy and typically presents as a central or multifocal tumour involving the nipple–areola complex (NAC) [1,4,5]. Nearly half of affected patients present with a palpable breast mass,

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indicating invasive disease [4,5,16,17]. MPD predominantly affects postmenopausal women over 60 years of age but has also been reported in adolescents and elderly patients [4,5]. Although rare, MPD in male patients exhibits clinical and pathological features similar to those observed in women [4,5].

Paget disease (PD), including both mammary and extramammary forms, poses a significant diagnostic challenge because its clinical presentation may resemble inflammatory dermatoses, melanoma, and non-melanoma skin cancers [4,12,13,18]. In its early, non-pigmented stages, PD typically presents as solitary or multifocal erythematous plaques with indolent growth and well-demarcated borders. Lesions often exhibit fine scaling, excoriations, ulcerations, and lichenification. These features closely mimic inflammatory skin conditions such as eczema, psoriasis, seborrhoeic dermatitis, or candidiasis, frequently leading to prolonged and ineffective treatment over several years [4,6,12,13,18].

Lesions may be multifocal within a single anatomical region or occur bilaterally in anatomically analogous areas, such as the axillary folds [4,12,13,18]. Paget disease rarely involves the auricles, where it may originate from sweat or sebaceous glands or hair follicles [1]. Due to its mild and slowly progressive course, an average diagnostic delay of approximately 3.8 years before referral to a dermatologist has been reported [4,7].

Although histopathological examination combined with immunohistochemistry remains the gold standard for PD diagnosis, increasing evidence supports the adjunctive role of non-invasive imaging techniques [4,7,14,15]. Recently, Bayan et al. reviewed the diagnostic utility of dermoscopy, photodynamic diagnosis, reflectance confocal microscopy (RCM), optical coherence tomography (OCT), magnetic resonance imaging (MRI), positron emission tomography–computed tomography (PET-CT), and ultrasonography (US) in the evaluation of EMPD [14]. Most available studies focus on a single diagnostic modality or on dermoscopy combined with complementary RCM [7,14,15], while others report the use of photodynamic diagnosis alone or in combination with RCM [15].

Therefore, this retrospective case series aimed to evaluate the non-invasive diagnostic methods available in our dermatological practice for addressing the most common clinical challenges associated with PD, including initial diagnosis, monitoring treatment response, and detection of disease recurrence. In addition, we analysed the outcomes of multi-stage therapeutic strategies applied in both early and advanced EMPD and compared our results with data reported in recent literature.

2. Methods

We conducted a retrospective analysis of medical records and clinical databases of patients referred to three dermatology departments between January 2018 and December 2025. Consecutive patients with clinical suspicion of PD and patients with EMPD undergoing follow-up were considered eligible for inclusion. Written informed consent for publication of this case series and accompanying clinical images was obtained from all patients.

Patients diagnosed with primary EMPD without an associated underlying malignancy were evaluated before and during treatment using a four-step diagnostic pathway designed to detect all potentially involved but clinically asymptomatic lesions. This pathway included dermoscopy/videodermoscopy (VD), photodynamic diagnosis (PDD), reflectance confocal microscopy (RCM), and mapping biopsies.

All patients underwent dermoscopic examination using polarised light with magnification ranging from 15 × to 70 × . Images were obtained using a videodermoscope (FotoFinder; TechScreen Software GmbH, Bad Birnbach, Germany; or Canfield D200 EVO; Canfield Scientific GmbH, Bielefeld, Germany) or a DZ-D100 dermoscope, as well as a 405-nm near-ultraviolet light-emitting diode (Casio Computer Co., Ltd., Tokyo, Japan). Dermoscopic features of PD and their morphological differentiation have been described in original publications [18–25].

Photodynamic diagnosis (PDD) was performed using freshly prepared 18 % aminolevulinic acid (ALA) ointment supplied by the hospital pharmacy. The ointment was applied with a 2-cm margin of clinically normal-appearing skin. After 4 h of occlusion, the treated area was examined using a Wood's lamp emitting ultraviolet light at 400-405 nm. The presence of characteristic bright brick-red fluorescence was considered a positive result. The application of PDD in PD diagnosis and assessment of treatment response in EMPD has been described previously [26–39].

RCM was performed using the VivaScope 1500 and 3000 system (MAVIG GmbH, Munich, Germany) within areas identified by dermoscopy or PDD. VivaBlock mosaics measuring 8 × 8 mm were acquired at the epidermis, dermoepidermal junction (DEJ), and superficial dermis, to a maximum depth of 200 μm. Characteristic RCM features of PD and those of conditions included in the differential diagnosis have been reported previously in original publications [40–54].

The diagnosis of PD was confirmed by histopathological (HP) examination combined with immunohistochemical (IHC) staining using a classical PD marker panel, adjusted individually according to the differential diagnosis [1–3,6,7,10,55]. Mapping biopsies were obtained from areas indicated by VD, PDD, or RCM in patients assessed using the four/three-step diagnostic approach.

Differentiation of PD from Bowen disease (BD) and superficial spreading melanoma was based on immunohistochemical staining for cytokeratin (CK) 7, CK20, p63, S-100, SOX-10, HMB-45 (Human Melanoma Black), and MART-1/MelanA (melanoma antigen recognised by T cells 1), as well as histochemical mucicarmine staining. A diagnosis of PD was supported by positive CK7 and mucicarmine staining in conjunction with negative CK20 and S-100 staining. Expression of CK7 in the absence of CK20, positive GCDFP-15 (Gross cystic disease fluid protein 15) were suggestive of primary EMPD [1–4,6]. Lack of expression of S-100, SOX-10, MART-1/MelanA, and HMB-45 excluded melanoma.

In all MPD cases and in one EMPD case requiring exclusion of prostate cancer metastasis, additional immunohistochemical markers were assessed as clinically indicated, including an expression of HER2 (human epidermal growth factor receptor 2), Ki67 (marker of proliferation), CEA (carcinoembryonic antigen), NKX-3 (marker of prostate differentiation), CD45-LCA (leukocyte common antigen), CK19, CK5/14, p53, p16, CD3, CD10, CD30, CD163, GATA3, EMA (epithelial membrane antigen), ECAD (e-cadherin), CAM 5.2 (anti-cytokeratin antibody) and the hormone receptors (estrogen – ER, progesterone – PR, androgen - AR)) ALK (anaplastic lymphoma kinase), TTF-1 (Thyroid Transcription Factor 1), PAX8 (Paired Box Gene 8), PAX2, napsin, calretinin, synaptophysin, and chromogranin.

Contrast-enhanced MRI was performed to assess disease extent and detect deep tissue invasion in patients with EMPD. All patients were screened and monitored for the presence of underlying malignancies using radiological examinations, including computed tomography (CT), MRI, PET-CT, as well as mammography (MMG), US, and endoscopic procedures (colonoscopy and cystoscopy), as clinically indicated [4,7,14]. Medical records of patients with EMPD were further analysed with respect to treatment modalities and clinical outcomes.

3. Results

The analysis included thirteen patients, comprising eight cases of extramammary Paget disease and five cases of mammary Paget disease. The median age of the study population was 65 years (range, 41–74 years), with a predominance of female patients. Clinical and anamnestic data, together with a description of the diagnostic challenges encountered, are summarised in Table 1.

Based on six representative patient cases, the variability in the clinical and dermoscopic morphology of non-pigmented PD was illustrated in Fig. 1. Two metastatic EMPD cases (cases 9 and 10) presented uncommon nodular, papular, and infiltrative lesions (Fig. 1j–l).

Table 1
Summary of clinical and demographic characteristics of patients diagnosed with mammary and extramammary Paget disease.

Case	Age/ Sex	Clinical presentation	Duration of disease	Diagnostic problem	Final diagnosis	Location
1	41/F	An erythematous plaque, partly ulcerative	3 years	Verification of the primary HP diagnosis (low-grade squamous cell dysplasia)	MPD	Right NAC
2	74/F	An eczematous lesion	6 months	Verification of the primary HP diagnosis (eczema)	MPD	Left NAC
3	48/F	An erythematous plaque, partially unevenly pigmented, with erosion	7 months	Primary differential diagnosis	MPD	Left NAC
4	71/F	An eczematous lesion of the nipple	5 months	Differential diagnosis between spongiotic eczema and MPD	Spongiotic eczema	Right NAC
5	65/F	An erythematous acanthotic lesion	8 years	Primary differential diagnosis	MPD	Left NAC
6	65/F	Ill-defined erythematous patches and postradiotherapy hypopigmented areas on the buttocks; An erythematous patch with erosions and small nodules in the perianal area	8 years	Verification of the primary HP diagnosis of the perianal area (BD) Monitoring of EMPD and assessment of the treatment response	Primary EMPD	Buttocks, perianal
7	56/M	Ill-defined erythematous and slightly pigmented patches	12 years	Monitoring of EMPD and assessment of the treatment response	Primary EMPD	Pubis, groins and scrotum
8	71/M	Ill-defined erythematous patches	3 years	Monitoring of EMPD and assessment of the treatment response	Primary EMPD	Groins and scrotum;
9	65/M	Primary ill-defined erythematous patch with desquamation, with recurrence of multiple papules and small nodules next to scars, erosions	6 years	Monitoring of EMPD and assessment of the treatment response	Primary EMPD	Left side of the scrotum and left groin Metastases to the bones, liver and adrenal gland
10	57/M	Hypochromic area with a yellow-pink nodule	3 years	Differentiation between cutaneous metastases of prostate cancer and primary or secondary PD due to lymphadenopathy of unknown primary	Primary EMPD (HER2 3+)	Right groin, pubis, lymph nodes in the pelvis and abdomen
11	43/F	Well-defined erythematous plaque with desquamation Well-defined red and brown macules	1 year 1 year	Differentiation between psoriasis and secondary MPD in the Li-Fraumeni syndrome case after bilateral breast cancer Differentiation between pigmented EMPD and pigmented lichen planus	Primary EMPD (HER2 3+) Pigmented lichen planus	Right axilla, periauricular area Left axilla, coccyx area
12	61/M	Ill-defined erythematous patches	6 years	Monitoring of EMPD and assessment of the treatment response	Primary EMPD	Pubis, groins and scrotum
13	74/F	Ill-defined erythematous patches	1 year	Primary differential diagnosis; Multiple myeloma, IgG kappa under ChT	Primary EMPD (HER 2+)	Vulva

Eight patients were evaluated using the four-step diagnostic approach to assess the diagnostic contribution of three non-invasive imaging methods in each PD case (Figs. 2 and 3), and two others with a three-step workflow (without PDD). The results, highlighting the advantages and limitations of each diagnostic modality in our cohort, are summarised in Table 2 and discussed in the context of previously published findings. The outcomes of individual diagnostic approaches, as well as discrepancies observed with photodynamic diagnosis in four cases, are presented in Figs. 4 and 5, further described in detail below.

3.1. Analysis of the diagnostic workflow in MPD

The duration of clinical symptoms in patients with mammary Paget disease ranged from 6 months to 8 years (median, 7 months), based on patient anamnesis. In three MPD patients, the primary diagnostic challenge involved verification of an initial clinical diagnosis of inflammatory disease of the nipple, which had been unsuccessfully treated with topical corticosteroids. In two additional patients, re-evaluation of previous histopathological diagnoses of low-grade squamous cell dysplasia (case 1) and eczema (case 2) was required.

Implementation of the four-step diagnostic pathway, with particular emphasis on RCM, enabled visualisation of Paget cells with good correlation to histopathological morphology and raised suspicion of MPD in cases 1–3. In case 4, both dermoscopy and RCM findings correlated with histopathological and immunohistochemical results supporting the exclusion of breast cancer, as discussed below. Ultimately, four patients were diagnosed with primary MPD, with positive HER2 expression observed in three cases. Underlying breast carcinoma was detected by magnetic resonance imaging and/or contrast-enhanced mammography in all patients.

Given the diagnostic complexity, two cases required a detailed presentation.

Case 4 involved a patient with a history of atopic dermatitis in childhood, without other atopic comorbidities and with long-term remission. Two years prior to referral, the patient developed severe pruritus and disseminated eczema and was referred for dermatological evaluation. A final diagnosis of disseminated spongiotic eczema was established based on inconclusive patch testing, low total IgE levels, and histopathological examination of two skin biopsies. Due to a lack of response to topical corticosteroids and systemic antipruritic therapy, a short course of systemic corticosteroids (prednisone up to 30 mg/day) was administered, followed by methotrexate therapy for six months (maximum dose 15 mg/week), resulting in partial improvement of skin lesions. During this period, routine mammography revealed a 10-mm lesion in the right breast. Partial mastectomy confirmed early-stage breast cancer (WHO 2019 classification: pT1b, pN0 (0/2)(sn), L0, V0, Pn0, R0) composed of three histological components: an 8-mm invasive tubular carcinoma, low-grade ductal carcinoma in situ, and columnar cell change/hyperplasia. Immunohistochemical analysis demonstrated ER (99 %) and PR (99 %) positivity, preserved E-cadherin expression, low proliferative activity (Ki-67 <5 %), and negative HER2 and p63 expression. Adjuvant radiotherapy and tamoxifen therapy were initiated. Following discontinuation of methotrexate, exacerbation of disseminated eczema and pruritus was observed. Treatment with potent topical corticosteroids and systemic antipruritic agents (pregabalin and antihistamines) resulted in clinical improvement. The patient remained under regular oncological follow-up, with no pathological findings on clinical examination, ultrasonography, or mammography three months prior to the final dermatological visit. Eleven months after completion of radiotherapy, the patient reported improvement of eczema on the trunk and extremities, with persistence of unilateral nipple involvement and serous discharge lasting one month. Despite misleading findings on photodynamic diagnosis (fluorescence within the nipple–areola complex and adjacent skin), dermoscopy, and RCM suggestive of spongiotic

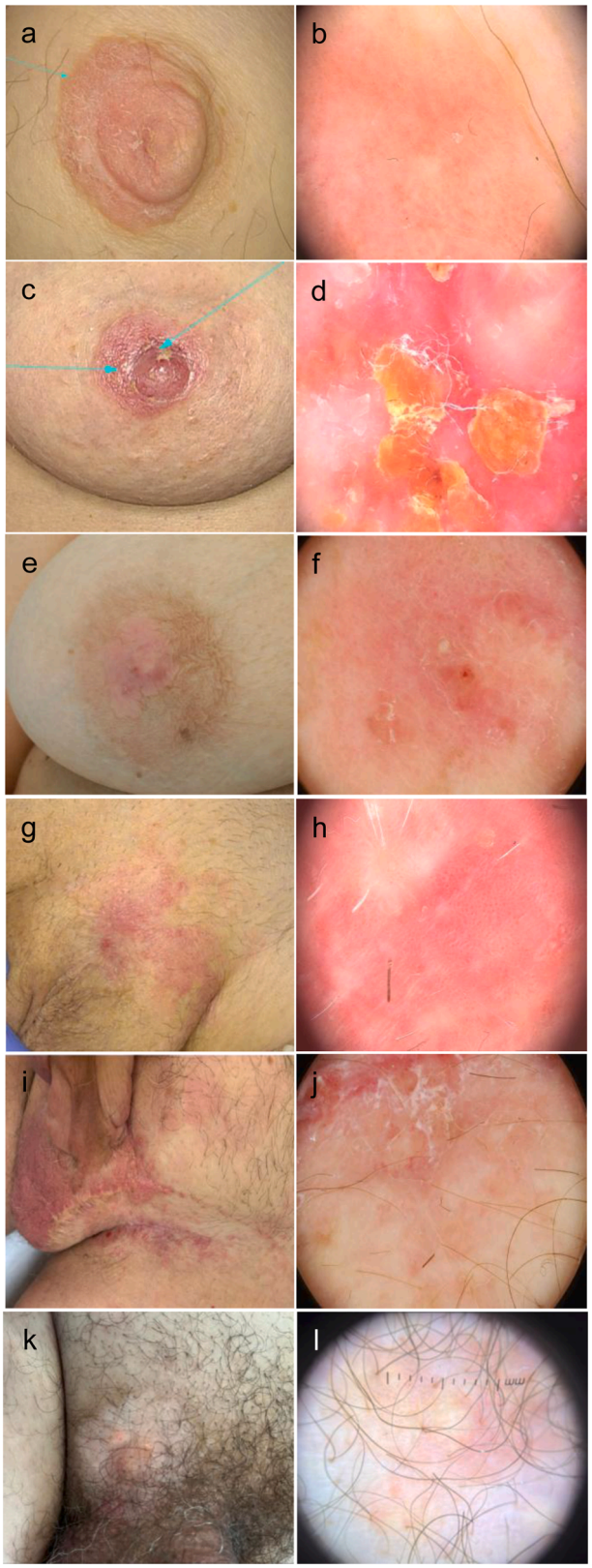

Fig. 1. Clinical presentation of the MPD (a, c, e) with the corresponding dermoscopic morphology (b, d, f); EMPD cases with clinical (g, i, k) and dermatologic structures (h, j, l). Case no. 1 (c, d), case no. 2 (a, b), case no. 5 (e, f), case no 8 (g, h), case no 9 (i, j), and case no. 10 (k, l) according to the detailed description in Tables 1 and 2.

eczema (Fig. 4a–c), the unilateral presentation raised suspicion of secondary MPD in the context of the patient's oncological history. The patient was referred to a Breast Cancer Unit, where mammography revealed dilatation of a lactiferous duct (4 mm over a length of 20 mm). However, histopathological examination confirmed spongiotic eczema, with negative CK7 and HER2 staining and absent melanocytic marker expression (MELAN-A ±).

The most distinctive feature of case 5 (Fig. 1e,f) was the 8-year persistence of a small, slightly erythematous lesion confined to the right nipple. The lesion was ultimately diagnosed as ductal carcinoma in situ of the breast associated with mammary Paget disease of the nipple (WHO 2019 classification of breast tumours: pTis). Despite its long-standing, clinically subtle appearance as a pinkish, acanthotic lesion, dermoscopic examination excluded Bowen disease and inflammatory dermatoses and raised suspicion of MPD. Immunohistochemical analysis demonstrated positive expression of CK7, CK19 (25 %), CAM5.2, E-cadherin, Ki-67 (25 %), GATA3, p16, and p53, with negative staining for HER2, estrogen receptor, progesterone receptor, CK20, and CK5/14.

3.2. *Analysis of the diagnostic and therapeutic process in EMPD*

The duration of clinical symptoms in patients with EMPD ranged from 1 to 12 years (median, 3 years) upon medical chart review. Difficulties in establishing the initial diagnosis were observed in two cases (cases 6 and 10). In four patients, response to different lines of treatment was assessed during follow-up using the four-step diagnostic approach (Figs. 2–5), and in three others, with VD-RCM guided biopsies. Surveillance for underlying malignancy revealed metastatic disease in case 9 despite multiple therapeutic interventions (Table 3). After nearly 12 years of follow-up, PET-CT demonstrated metastases involving the bones, liver, and adrenal glands. Clinically and dermoscopically, advanced EMPD in this patient was characterised by numerous nodules and infiltrated, elevated lesions located adjacent to scars following non-radical surgical excisions in the groin region (Figs. 1i,j and 2a,b). Three cases required a detailed presentation.

In case 6, four lines of treatment achieved partial disease control of EMPD primarily affecting both buttocks and the perianal region (Fig. 3e, f). During surveillance after three months of imiquimod therapy, photodynamic diagnosis revealed nodular lesions on the anal verge and a newly developed lesion on the labia majora. Reflectance confocal microscopy demonstrated skin infiltration to a depth of 6 mm and the presence of perilesional EMPD. Based on these findings, the patient was referred for inclusion in the AGENONMELA study, a phase II, open-label clinical trial evaluating the safety and clinical activity of balstilimab, an anti–PD-1 antibody, in non-melanoma skin cancers not amenable to curative local therapy (EudraCT No. 2020-004622-29; Protocol NIO-0001; ABM_01_00004_03). After 12 months of balstilimab therapy, complete clinical resolution of perianal erythema was observed. No measurable disease was detected on RCM or HP examination, although moderate fluorescence persisted on PDD (Fig. 4d,e). RCM could not be performed in the perianal region due to technical limitations related to probe attachment. Twelve months after treatment discontinuation, persistent fluorescence was still observed in this area (Fig. 4f), despite the absence of clinical or RCM features of EMPD. The patient reported a history of prolonged inflammation and impaired wound healing in the perianal region following radiotherapy administered four years earlier, which may explain the false-positive PDD findings.

In case 7, multiple surgical excisions and repeated sessions of skin-directed therapies (Table 3) involving the scrotum, pubic region, and both groins –predominantly adjacent to surgical scars –failed to reduce the extent of EMPD (Fig. 4g), although MRI excluded the presence of an underlying malignancy. Repeated application of the four-step diagnostic approach confirmed the lack of response to imiquimod and photodynamic therapy. As the patient was ineligible for participation in a clinical trial, brachytherapy was proposed. Fifteen months after radiotherapy, PDD revealed false-positive fluorescence (Fig. 4i)

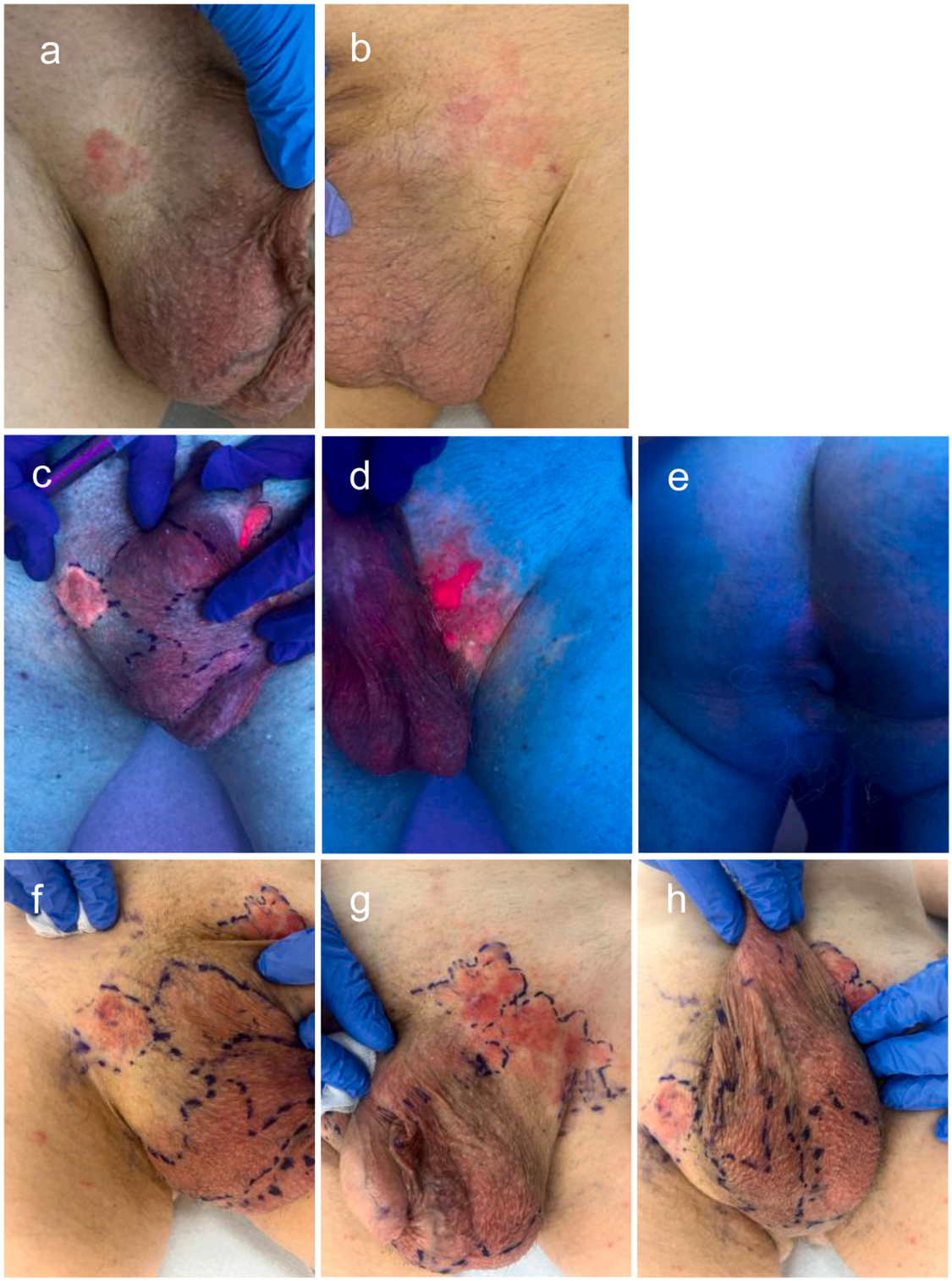

Fig. 2. Presentation of the implementation of the PDD in the 4-step diagnostic pathway of EMPD in case no.6. The clinical symptoms (a,b) seem to be limited to bilateral erythematous lesions on the pubis. The PDD visualised involvement of the scrotum and the lower surface of the penis (c,d). The perianal area showed weak fluorescence due to physiological microflora (e). Outlined EMPD extension based on PDD to be revised with RCM (f-h).

involving the penis, glans penis, and scrotum, confined to areas of severely damaged skin with prolonged healing. No Paget cells were identified on RCM, and dermoscopic findings were consistent with chronic radiodermatitis. Radiotherapy resulted in marked skin thickening and recurrent lymphoedema of the genital and pubic regions (Fig. 4h), ultimately precluding reliable MRI assessment of EMPD infiltration. Furthermore, radiodermatitis-associated increased metabolic activity limited the diagnostic utility of PET-CT. Consequently, dermoscopy and RCM currently remain the only reliable non-invasive diagnostic modalities for disease monitoring in this patient.

Case 10 was initially diagnosed with low-grade prostate cancer and underwent close oncological surveillance using CT and PET-CT. Two years prior to dermatological referral, bilateral lymphadenopathy involving the celiac, inguinal, and iliac regions was detected, initially

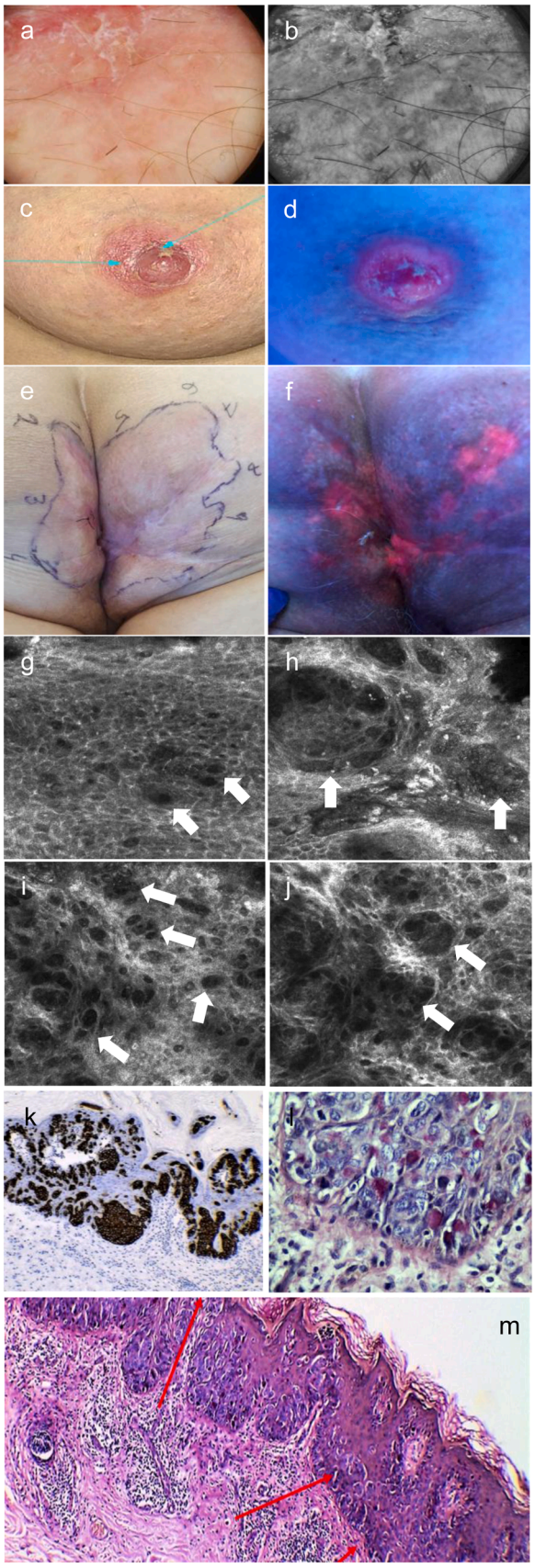

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Fig. 3. The RCM structures of Paget cells (white arrows) are found superficially in the epidermis as a single dark oval structure (g) or nests composed of dark cells (h) larger than keratinocytes. At the DEJ, the Paget cells' infiltration is enhanced and widespread (i); nests and glandular structures (j) are clearly visible in the deeper layer. The RCM features excellently correlate with HP and IHC (k,l,m). Numerous Paget cells (dark brown) are visible in the epithelium with CK7 IHC staining (k) 100X magnification; anoderm fragment with the presence of numerous Paget cells (red arrows) located along the entire thickness of the flat epithelium (H&E) 400X (l), 100x (m) magnification.

nonspecific in nature (SUVmax 4.2 on the right). After one year of follow-up, increased metabolic uptake was observed within the skin projecting to the mid- and paramedian right suprapubic region, while lymphadenopathy in the right iliac–obturator and inguinal regions became more prominent but with reduced metabolic activity (SUVmax 3.5). Clinically, multiple nodules were observed in the groin, raising suspicion of cutaneous metastases of the known primary malignancy. Histopathological examination of both skin and lymph node biopsies revealed findings consistent with primary EMPD. In the skin, Paget cells infiltrated the epidermis and adnexal structures in a pagetoid pattern (single cells and nests) as well as in an infiltrative pattern with cord-like extensions into the deep dermis (maximum thickness 1.6 mm, CAM5.2-positive). Notably, vascular neoplastic embolisation was also identified. IHC analysis of the skin biopsy demonstrated positive expression of CK7, EMA, CAM5.2, CEA, and AR, with absence of CK5/6, CK20, SOX10, CD45-LCA, and NKX3. Lymph node pathology confirmed metastatic involvement of unknown primary origin, with tumour cells positive for CD138, CK7, CK18, CK19, EMA (cytoplasmic), and Ki-67 (20–30 %), and negative for an extensive panel including vimentin, p63, TTF1, PAX8, PAX2, GATA3, SOX10, Napsin, CK20, CK5, NKX3, LCA, CD3, CD20, CD10, ALK, CD30, calretinin, synaptophysin, and chromogranin. The patient underwent surgical excision of cutaneous lesions followed by systemic chemotherapy combined with trastuzumab due to HER2 overexpression. As two treatment lines proved ineffective, further surgical excisions were performed, followed by chemotherapy with cisplatin and subsequently capecitabine. Despite these interventions, disease progression occurred with the development of bone metastases.

Case 11 involved a patient diagnosed with Li–Fraumeni syndrome associated with a germline TP53 mutation of autosomal dominant inheritance. The patient had a complex oncological history, including bilateral breast cancers treated with partial mastectomy and excision of the nipple–areola complex at 27 years (left breast) and 37 years (right breast), papillary thyroid carcinoma, and cancer of the hepatic ligament. Six years after treatment for right breast cancer, the patient was referred for evaluation of an erythematous plaque with superficial scaling located in the right axillary fossa and periauricular area (Fig. 5a,b). Based on clinical presentation and anatomical location, psoriasis was initially suspected, and topical corticosteroid therapy was initiated. Due to a lack of response in the axillary lesion, EMPD was suspected. PDD demonstrated characteristic brick-red fluorescence, and RCM revealed features consistent with Paget disease (Fig. 5c,d). HP and IHC examination confirmed the diagnosis, with positive staining for CK7, focal CEA, and HER2 (3+), and negative staining for CK5/6 and MelanA. The lesion was surgically excised, and no evidence of breast cancer recurrence was detected on imaging studies. Two years later, the patient represented with asymptomatic, well-demarcated red–brown macular lesions involving the left axilla, left groin, and coccygeal region (Fig. 5e,f). Dermoscopic examination raised suspicion of pigmented lichen planus or pigmented EMPD (Fig. 5g). RCM excluded EMPD, demonstrating a mixed inflammatory infiltrate at the DEJ and increased reflectance of the basal epidermal layer (Fig. 5h,i). Histopathological examination confirmed the diagnosis of pigmented lichen planus.

3.3. Treatment modalities implemented in EMPD patients with outcomes

Median number of treatment lines of eight EMPD was 4, with a range

Table 2
Analysis of the diagnostic utility of non-invasive imaging methods in Paget disease based on the present case series.

	Dermoscopy	PDD	RCM	Notes
Features	Non-pigmented PD White scales and pink structureless areas (as significant predictors), dotted vessels, erosion/ulceration and white shiny lines [19] Pigmented PD Pink structureless areas, white lines and grey granules and dots (positive predictors) [19], irregular brown to black pigmentation, irregular pigmented network (mainly at the areola) with open/closed polygonal rings and comedo-like structures [19,22,24]	The brick red fluorescence is indicative of PD lesions [26]	Paget cells are at least twice the size of keratinocytes, have a mildly bright nucleus, and dark cytoplasm. At the DEJ, tumour nests form dark glandular structures. Dilated vessels and inflammatory cells are common. A high density of dendritic cells is characteristic of pigmented PD [22,37–50]	Porcelain-white patches are the only key clinical feature distinguishing EMPD from mimicking diseases [25] RCM, more than dermoscopy, might be helpful in the differential diagnosis of inflammatory diseases (eczema, psoriasis) or NMSC [51–54]
Limitations	Non-pigmented superficial EMPD may resemble BD [20] Dermoscopic structures of pigmented PD may resemble melanoma (SSM or EFLM type) [22–24];	High costs and no refund of ALA/PDD Fungal or bacterial contamination causes autofluorescence, thus normal skin of intertriginous areas may produce some weak autofluorescence, but distinguishable from that of tumour tissue [27,31,32]. The fluorescence of eczema is unknown, but in some psoriasis lesions, the scale is punctate red [29,30]. Occlusion time (3-4h) The pigmented component of PD may show no/weak fluorescence (melanin absorbs light) [28]	Limited availability No cost refund Handheld probe required for examination of mucosal lesions or those located in narrow spaces, but prevents a precise description of the location. Crust, eroded surface or exudation limits the perception and interpretation of the structures Time-consuming with multiple lesions to outline	The most common HP and dermoscopic EMPD-mimicker is BD [21,55]. Truly pigmented PD may be dermoscopically, and to some extent, under RCM or HP, indistinguishable from melanoma and pigmented BD [22–24,50,51,55]. RCM may help differentiate MPD from eczema, inflammatory dermatoses or NMSC [52,53]
MPD Case 1-5	- milky-red structureless areas - scar-like areas - polymorphous vessels - dotted vessels (small clusters) - white shiny lines - scar-like areas with pigmented polygonal lines formed by blue-grey granules at the areola - erosions/ulcerations - scale	The brick red fluorescence corresponds to the clinical and dermoscopic lesion extension (fig. 3cd)	Typical for non-pigmented PD structures. Presence of glandular structures at the DEJ indicates the invasive PD	Dermoscopic structures of non-pigmented MPD may overlap with infiltrative NMSC; The fluorescence of eczema was positive (Fig. 4b).
Diagnostic impact	In correlation to the clinical manifestation of non-pigmented MPD, dermoscopy may help in differentiation from psoriasis or acute eczema	Assessment of the skin extension of MPD	Confirmation of the presence of Paget cells in symptomatic and asymptomatic areas Differential diagnosis with eczema (Fig. 4c).	
EMPD Case 6-13	- milky-red structureless areas - red background - polymorphous vessels - dotted/glomerular vessels. - light brown homogenous areas - shiny white short lines - yellow papules with thin linear vessels on their surface - yellow-pink nodule	The brick red fluorescence does not fully overlap with the clinical and/or dermoscopic extension (Fig. 3ef)	Typical for non-pigmented PD structures revealed within both indicative and non-indicative for EMPD-based prior VD and PDD (Fig. 3ghij)	1/ PDD - weak fluorescence of the anus sphincter area and partly on the scrotum is possible 2/ PDD may be falsely positive even a few years after RT conducted in NAC, anus sphincter and scrotum (Fig. 4 cefi). 3/ Prolonged inflammation caused by topical treatment may cause a false fluorescence in PDD, which interferes with the outcome evaluation
Diagnostic impact	Digital monitoring of disease morphology and skin extension under topical/skin-directed treatment Initial assessment of the EMPD extension before further diagnostic procedures Radiodermatitis, pigmented lichen planus, and PD may be distinguishable under dermoscopy	Extension of the clinically ill-defined and asymptomatic lesions Descriptions of PD margins for pretreatment planning;	Precise confirmation of PD margins in the presurgical approach. Assessment of topical/skin-directed treatment response. The perception of the recurrent/residual PD within severely damaged skin by RT skin is limited, but can be revised by RCM. Pigmented lichen planus and PD are distinguishable under RCM (Fig. 5)	In ill-defined non-pigmented EMPD, the dermoscopic vascular structures may be enhanced on UV images (DZ-D100 Casio) (Fig. 3ab). Differentiation between pigmented lichen planus and early-stage pigmented EMPD might be difficult based on dermoscopy

of 1-5 depending on the surveillance length (median 3.5 years, range 1.5–12 years). Analysis of the therapeutic course demonstrated slowly progressive invasiveness and cutaneous extension in six patients. In two cases (9 and 10), disease progression could not be effectively controlled with currently available treatment modalities (Table 3), and nodular or infiltrative lesions correlated with metastatic spread.

Surgical excisions were non-radical in most (7/8) patients, followed by adjuvant therapies, including topical treatments (imiquimod - IMQ or photodynamic therapy - PDT) or systemic chemotherapy (ChT). PDT was administered in four patients, and IMQ in six, but neither proved effective as monotherapy in any patient.

In case 7, the number of PDT sessions was limited by extensive

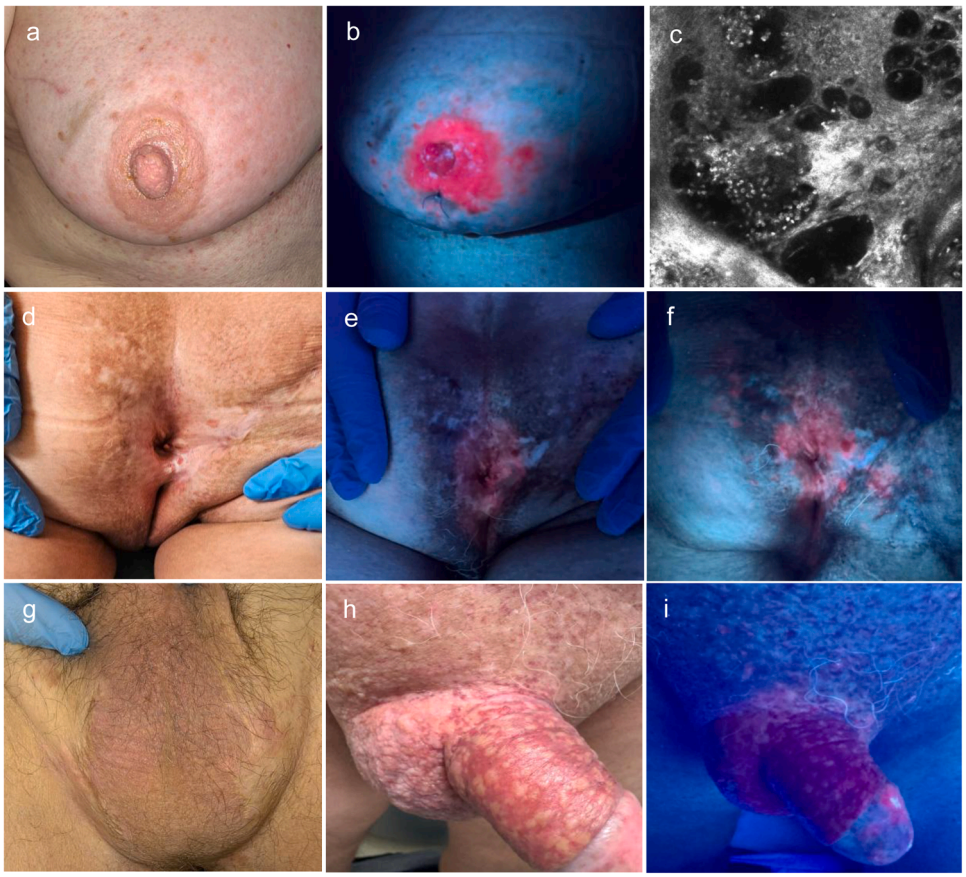

Fig. 4. Examples of diagnostic difficulties; Case 4 (a-c) eczematous lesions of NAC (a) requiring exclusion of the secondary MPD, with false positive fluorescence in PDD (b) revised by RCM (c) as spongiotic eczema; Case 6 (d-f) 12 months after immunotherapy clinically small papules and small erythematous areas are visible (d), the false positive fluorescence under PDD present in the perianal area at the end of immunotherapy (e) and after another year of follow-up (f) due to underwent RT 4 years ealier; Case 7 – clinical manifestation after many courses of surgical and topical treatment (g), enhanced radiodermitis with lymphoedema after 1.5 year of follow-up (h) with false positive fluorescence under PDD (i).

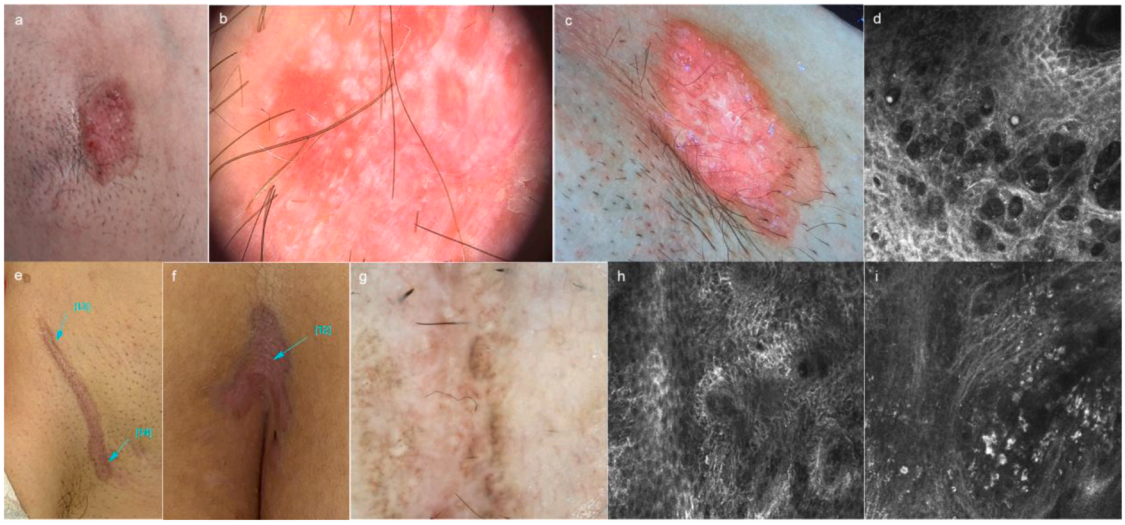

Fig. 5. Examples of diagnostic difficulties in Case 11 diagnosed with bilateral breast cancer, many years before, after bilateral mastectomy involving NAC; an erythemo-desquamative lesion of right axilla (a), under dermoscopy requiring exclusion of inflammatory dermatoses and the secondary EMPD (b), with positive fluorescence in PDD (c), was revised by RCM (d) as EMPD; After 3 years new lesions appeared in the left axilla (e) and intergluteal cleft (f), under dermoscopy resembling pigmented lichen planus or pigmented EMPD (g), was revised by RCM as lichenoid reaction (h, i). In the epidermis, an enhanced pigmentation of the basal layer was found at the lesions' outline (h), at the DEJ and in the superficial dermis, a dense mixed inflammatory infiltrate was revealed (i).

disease involvement of the genital and groin regions, painful and prolonged healing, and the development of oedema and ulcerations. Adverse effects persisting for approximately two weeks after monthly PDT sessions significantly impaired the patient's daily functioning and

Table 3
Treatment modalities implemented in patients with extramammary Paget disease and corresponding outcomes.

Case	Time of surveillance	1st line	2nd line	3rd line	4th line	5th line	Notes
6	7 years	ALA-PDT 3 sessions intolerance	Surgical excisions (R1) recurrence and extension	ChT-RT (levofolic, 5-fluorouracil) recurrence and extension	Imiquimod (IMQ) 5 % 12 weeks 1x/2days partial response	Clinical trial* (anti-PD1 – balstilimab)	Under MRI no measurable disease; False positive fluorescence in PDD (Fig. 3def) was not influenced by immunotherapy
7	4 years	Multiple surgical excisions (R0, R1) recurrence and extension	IMQ 5 % 12 weeks 1x/2days no response stable disease	ALA-PDT 5 sessions worsening	IMQ 5 % 16 weeks 1x/2 days stabile disease	Brachytherapy no recurrence after 15 months	Radiodermatitis caused thickening of the skin, false positive fluorescence in PDD (Fig. 4i) and lymphoedema in the genital and pubic area (Fig. 4h), which has an impact on the MRI evaluation
8	1.5 years	Clinical trial* (anti-PD1 – balstilimab) – early discontinuation due to AE	IMQ 5 % 12 weeks 1x/2days recurrence of a single lesion after 12 months	-	-	-	Under RCM and MRI no progression or measurable disease after 6 months of follow-up
9	12 years	Surgical excision (R1) + IMQ 5 % 13 weeks, 3x/ weekly (adjuvant) recurrence	Topical 5-FU 1x/day 2 weeks intolerance	Surgical excision (2x R1) progression	ChT (Docetaxel – 7 cycles) progression		Metastatic disease
10	3 years	Surgical excision + ChT (docetaxel + trastuzumab 7 cycles + trastuzumab maintenance) progression	Trastuzumab emtansine 8x/3 weeks new nodule (right groin) HER2 (-) progression	Surgical excisions recurrence	ChT (cisplatin) + Surgical excisions recurrence	Cht (capecitabine)	Disease progression
11	2 years	Surgical excision (radical)					No recurrence under RCM after 2 years
12	2 years	Surgical excision (nonradical)	ALA-PDT 16 sessions partial response confirmed by HP and RCM	IMQ 5 % 6 months 3x weekly			Under RCM and HP, EMPD was not detected one month after IMQ cessation
13	4 years	Surgical excisions (nonradical)	IMQ 5 % 4 months 3x weekly recurrence after 18 months	ALA-PDT 9 sessions			Under RCM and HP, EMPD was not detected one month after PDT cessation

*AGENONMELA study – the phase II, open-label trial evaluating the safety and clinical activity of balstilimab (anti–PD-1 antibody) in non-melanoma skin cancers (NMSCs) not amenable to curative local therapy (EUDRACT No. 2020-004622-29; Protocol NIO-0001; ABM_01_00004_03)

professional activity. Comparable limitations were observed during treatment with imiquimod. As skin-directed therapies proved ineffective, brachytherapy was ultimately selected for this patient. Approximately 15 months after brachytherapy, no clinical recurrence of EMPD was observed. However, three months following radiotherapy, the patient developed recurrent severe lymphoedema of the lower abdomen, groin, and genital region, necessitating urgent hospitalisation and urological consultation due to hydrocele formation. Long-term diuretic therapy was initiated to control lymphoedema, and the patient was advised to reduce business travel, which had exacerbated symptoms. In addition to clinical adverse effects, brachytherapy negatively affected the reliability of several diagnostic and monitoring modalities, including MRI, PET-CT, and PDD, thereby complicating long-term surveillance, as described above.

4. Discussion

Our study emphasises the clinical value of the four-step non-invasive diagnostic approach in the evaluation and long-term monitoring of PD. The combined use of VD, RCM, and PDD, supported by HP-IHC, provides complementary diagnostic information that improves accuracy compared with the use of individual techniques alone. Such an integrated strategy facilitates differentiation between PD and its clinical simulators, improves assessment of disease extent, and may reduce the need for repeated invasive biopsies during long-term surveillance.

Dermoscopy and RCM have demonstrated significant diagnostic value in MPD [19,37–39,41,49,50]. Cinotti et al. reported diagnostic accuracies of clinical, dermoscopic, and RCM imaging of the nipple-areola complex with sensitivities for malignancy of 83 %, 67 %, and 83 %, and specificities of 90 %, 97 %, and 94 %, respectively [39]. When distinguishing MPD from eczema, significant differences were found in the presence of spongiosis and dark Paget cells on RCM, whereas dermoscopic vascular structures did not differ significantly [39]. In our series, the four-step approach revealed a good correlation between VD, RCM, and HP-IHC in this differentiation, but also highlighted limitation of PDD, as MPD and eczema exhibited identical brick-red fluorescence. Finally in our MPD series, the initial clinical diagnosis was confirmed in three cases, while in a fourth patient, the diagnosis was established by excluding Bowen disease reported in HP.

According to the NAC–MPD classification, our patients were diagnosed as NAC–MPD without associated ductal carcinoma in situ (DCIS) (1/5), NAC–MPD with underlying lactiferous duct DCIS (2/5), and NAC–MPD with underlying lactiferous duct DCIS and DCIS or invasive breast cancer elsewhere at least 2 cm away (1/5). These findings are consistent with previous reports indicating the presence of underlying breast cancer in more than 90 % of MPD cases, with a reported range of 67–100 % [5]. It is worth noting that local recurrence of breast cancer in the form of MPD is uncommon - 5.6 % and 13.2 % for mastectomy and breast-conserving surgery, respectively [17]. However, it may occur at a very early age and after a long interval to recurrence, even up to 10 years following nipple-sparing mastectomy [16].

The utility of individual diagnostic methods was better visualised using the four-step approach in three high-risk EMPD patients during several years of surveillance. By implementing these methods into a multi-line treatment course, we critically assessed their limitations and real diagnostic impact in each case. We share the opinion of Bayan et al [14] and D'Oria et al [15] that both the initial presentation of EMPD and the evolving morphology of skin lesions during treatment make it impossible to accurately assess disease extent based solely on clinical examination or dermoscopy. Published data on dermoscopic diagnostics in EMPD remain scarce, limited to two larger studies. Mun et al. compared dermoscopic features of 35 EMPD cases with 46 simulator

lesions in the anogenital region [18], concluding that BD and PD exhibit overlapping vascular patterns, as both are primarily intraepidermal malignancies. Chen et al. analysed 49 EMPD cases and found that most were misdiagnosed when symptoms were present for less than 2.5 years [25]. Porcelain-white patches were identified as the only key clinical feature, whereas dermoscopic structures did not allow reliable differentiation from EMPD-mimicking conditions. Polymorphic vessels were more frequent in disease durations under 2.5 years, while glomerular vessels were observed in some longer-standing cases [25]. Based on dermoscopic findings in our EMPD cohort, we highlight nodular, infiltrative, or papular structures as indicators of invasive and potentially metastatic disease. Therapeutic interventions may induce vascular proliferation, erythema, or scar-like changes, limiting the reliability of dermoscopic assessment of treatment response. In cases with multiple, discontinuous EMPD lesions involving difficult-to-access anatomical sites (as in case 6), verification of equivocal dermoscopic findings by RCM may be challenging or only partially feasible.

RCM has established its place in the diagnostic and treatment process of EMPD. D'Oria et al [15] recently published a systematic review of non-invasive imaging in primary EMPD, including 16 studies. Seven of these evaluated RCM exclusively, either in the initial diagnosis of EMPD [40,41,44] or in assessment of treatment response following surgery alone [43,45,46] or combined treatment modalities [49]. Two studies demonstrated excellent correlation with histopathology, expressed by a kappa value of 0.93 ($p < 0.001$) in the studies by Navarrete-Dechent et al [46] and Kibbi et al [49]. Yélamos et al. suggested the use of handheld RCM as a highly specific diagnostic tool (sensitivity 75 %, specificity 100 %) for identifying recurrent or persistent EMPD and guiding scouting biopsies [45]. In their study of five patients with 22 clinically suspicious sites, 41 % (9/22) showed recurrent disease with perfect RCM–HP correlation, while 23 % (3/13) represented false-negative RCM results compared with histopathology. In our cohort, RCM proved helpful in distinguishing radiodermatitis from EMPD and in verifying false-positive fluorescence and dermoscopic findings. These observations have not been previously reported in this clinical context. It was also implemented in the treatment monitoring with a good HP correlation, which confirms previous reports [15].

Fluorescence diagnosis using 5-aminolevulinic acid (PDD) has been gradually introduced into dermato-oncology since the publication by Fritsch et al. in 1998 [26,27,32–39]. PDD alone or with RCM was used for margin delineation in EMPD, before/after surgical excision or before PDT in three studies [32–38]. These approaches enabled histological clearance of surgical margins by identifying tumour extension 0.5–2.0 cm beyond visible lesions [36] and reduced non-radical excision rates from 63.8 % (clinical assessment) and 35.4 % (PDD alone) to 20.8 % (PDD–RCM) [37]. In our EMPD cases, PDD supervised by RCM reduced the number of scouting biopsies required for clinically occult disease with skip areas and satellitosis, improving assessment of cutaneous disease extension during long-term therapy. However, we also observed false-positive fluorescence on PDD in patients treated with radiotherapy, even several years earlier (1–4 years in our study), in areas severely damaged by ionising radiation. This observation has not been previously reported and is relevant for PDD evaluation and qualification for PDT in actinic keratosis or non-melanoma skin cancers. In our cases, RCM remained the only reliable non-invasive method for assessing residual EMPD after brachytherapy. In the post-radiotherapy setting, Dilmé-Carreras et al. proposed periodic dermatological examination, topical 5-fluorouracil (5-FU) mapping, and screening for internal malignancies at 3, 6, 12, and 24 months following treatment of anogenital EMPD [56,57]. According to their protocol, 5-FU mapping involved application of 5 % 5-FU in an oil-in-water emulsion twice daily for seven days, aiming to induce an inflammatory response in premalignant and malignant epithelial lesions [56]. Considering the high cost of photosensitizers, which may limit widespread use of PDD in extensive EMPD, 5-FU mapping may represent a cost-effective alternative, although validation in larger cohorts is required.

The line-field confocal optical coherence tomography (LC-OCT) may represent a future alternative to RCM as a new emerging non-invasive technique. It enables visualisation of the deep dermis and subcutaneous tissue, potentially improving assessment of PD invasiveness and treatment response. In a preliminary study by Diet et al. involving six patients and 17 lesions, prospective analysis showed 64.7 % accuracy, 71.4 % sensitivity, and 33.3 % specificity, while retrospective analysis demonstrated 94.1 % accuracy, 100 % sensitivity, and 66.7 % specificity, with one false-positive case due to concomitant lichen sclerosus [58].

Histopathology supported by immunohistochemistry remains the gold standard for PD diagnosis, allowing differentiation between primary and secondary disease and their simulators [1–5,55]. Bowen disease is among the most common false clinical diagnoses; however, pagetoid BD and coexistence of EMPD and BD have been reported on histopathological and immunohistochemical examination [59–65]. Nonetheless, reliance on scouting biopsies alone remains insufficient for accurate margin delineation of multifocal disease, particularly before Mohs micrographic surgery. Implementation of non-invasive diagnostic techniques also aims to reduce the number of biopsies required in sensitive anogenital regions and to facilitate long-term monitoring of treatment efficacy.

The guidelines for screening EMPD patients for underlying malignancies recently published by Kibbi et al., emphasising the need for long-term follow-up due to recurrences reported more than 15 years after initial treatment [7,13]. For non-invasive EMPD, recommended follow-up intervals range from every 3–6 months for three years, then every 6–12 months up to five years, followed by annual visits for at least ten years. In invasive or secondary EMPD, follow-up is recommended every 3–4 months, with biopsy of any suspicious lesion. Screening for perianal EMPD includes periodic proctosigmoidoscopy and colonoscopy every 2–3 years, while vulvar EMPD follow-up requires regular gynaecological examination, punch biopsies of recurrent lesions, and hysteroscopy or pelvic ultrasound as indicated. Imaging for internal malignancies or metastatic disease may be considered in aggressive or invasive cases, although optimal imaging strategies remain undefined.

Overall prognosis in EMPD is favourable, except in cases associated with underlying visceral or adnexal carcinoma, where mortality exceeds 50 % [9]. In our study, EMPD patients exhibited high-risk features and, except for short follow-up cases, were largely unresponsive to multi-line topical and systemic therapies. In one case, brachytherapy was performed to prevent potential internal tumour invasion, achieving a complete response at 15 months, although complicated by recurrent lymphoedema and impaired imaging reliability. Another patient was referred for clinical trial enrolment, which currently appears to be a promising option for selected patients. After 12 months of balstilimab therapy and 12 months of treatment discontinuation, no measurable disease was detected on RCM, MRI or histopathology, representing the first report of this immunotherapy in this setting. Two additional patients developed metastatic disease despite multi-agent chemotherapy.

From a clinical perspective, precise assessment of primary EMPD manifestations and tailored selection of treatment modalities remain critical. Recent reviews by D'Oria et al [15] and Ren et al [26] reported complete response rates of 50 %–100 % for radiotherapy, 43 %–78 % for imiquimod, and up to 83 % for photodynamic therapy in monotherapy (overall response rates 66 %–78 %). Recurrence rates varied widely across modalities: Mohs micrographic surgery (8 %–26 %), conventional excision (33 %–60 %), radiotherapy (0 %–80 %), imiquimod (partial response 16 %–31 %), and photodynamic therapy (33.6 %) [15,26]. Stable disease was observed in 9.5 % of imiquimod-treated and 42.4 % of PDT-treated patients [15]. Interpretation of these outcomes is limited by small sample sizes, non-randomised designs, heterogeneous treatment protocols, variable outcome measures, and difficulty in evaluating combined or sequential therapies [15,26,66].

Outstanding results with wide surgical excision were reported by Hatta et al., who observed a recurrence rate of 4.4 % in stage 0–I disease

in a retrospective multicentre study of 643 patients [9]. Using the TNM staging system proposed by Ohara et al [67], five-year disease-specific survival rates were 98.7 % for stage 0, 94.5 % for stage I, 65.7 % for stage II, 68.4 % for stage IIIA, 49.5 % for stage IIIB, and 16.1 % for stage IV. Patients with stage 0–III disease were primarily treated with curative surgery (R0, 1–2 cm margins per Japanese guidelines), while chemotherapy, predominantly docetaxel-based, was used as first-line therapy in stage IIIB–IV disease. No prognostic differences by age, sex, or tumour location were identified in univariate analysis; however, female sex significantly predicted local recurrence in stage 0–I disease (HR 3.09; 95 % CI 1.13–8.43). Initial curative surgery was significantly protective for disease-specific survival in stage II–IIIA (HR 0.17; 95 % CI 0.04–0.71) and stage IIIB–IV disease (HR 0.16; 95 % CI 0.05–0.51).

Recently, novel therapeutic regimens for metastatic EMPD have been reported, including combined immunotherapy approaches such as ipilimumab with nivolumab, disitamab vedotin with serplulimab, tislelizumab combined with chemotherapy, and anlotinib with tislelizumab, all demonstrating favourable clinical outcomes and survival benefits [68–71].

5. Conclusions

The combined use of non-invasive diagnostic methods - dermoscopy, photodynamic diagnosis, and reflectance confocal microscopy - is highly effective in patients with skin lesions suspected of Paget disease, as these techniques guide scouting biopsies and accelerate both the diagnostic and therapeutic processes. Specialists involved in the long-term surveillance of Paget disease should be aware of the specific limitations and diagnostic impact of each method when applied to individual patients.

Further investigations aimed at introducing novel therapeutic options remain an unmet need for high-risk patients with extramammary Paget disease, as currently available treatment modalities are frequently ineffective.

Abbreviations

The following abbreviations are used in this manuscript:

ALA – aminolevulinic acid
ALK – anaplastic lymphoma kinase
AR – androgen receptor
BD – Bowen disease
CAM 5.2 – anti-cytokeratin antibody
CD – cluster of differentiation
CEA – carcinoembryonic antigen
CK – cytokeratin
CT – computed tomography
DEJ – dermo-epidermal junction
ECAD – E-cadherin
EFLM – extrafacial lentigo maligna
EMA – epithelial membrane antigen
EMPD – extramammary Paget's disease
ER – estrogen receptor
GATA3 – GATA-binding protein 3
GCDFP-15 – gross cystic disease fluid protein 15
HMB-45 – human melanoma black 45
HER2 – human epidermal growth factor receptor 2
HP – histopathology
IHC – immunohistochemistry
Ki-67 – proliferation marker Ki-67
LCA – leukocyte common antigen
LC-OCT – line-field confocal optical coherence tomography
MART-1/Melan-A – melanoma antigen recognized by T cells 1
MMS – Mohs micrographic surgery
MPD – mammary Paget's disease
MRI – magnetic resonance imaging
NKX3.1 – NK3 homeobox 1 (prostate differentiation marker)
PAX – paired box gene
PD – Paget's disease
PDD – photodynamic diagnosis
PET/CT – positron emission tomography/computed tomography
PDT – photodynamic therapy
PR – progesterone receptor
RCM – reflectance confocal microscopy
RT – radiotherapy
S-100 – S-100 protein
SOX10 – SRY-box transcription factor 10
SSM – superficial spreading melanoma
TTF-1 – thyroid transcription factor 1
US – ultrasonography
VD – dermoscopy/videodermoscopy

Approval of the ethics committee

Notification is not required for the retrospective analysis.

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the 1983 revised Helsinki Declaration.

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

The authors declare no conflict of interest.

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