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Case Report

Diagnostic imaging challenges of mammary Paget's disease presenting with subtle clinical and imaging features: A case report ☆,☆☆

Sawitri Darmiati, MD[a,1,*], *Andre Elton Heryanto, MD*[a], *Primariadewi Rustamadji, MD*[b]

[a] *Department of Radiology, Faculty of Medicine, Dr. Cipto Mangunkusumo National General Hospital, University of Indonesia, Jakarta, Indonesia*

[b] *Department of Anatomical Pathology, Faculty of Medicine, Dr. Cipto Mangunkusumo National General Hospital, University of Indonesia, Jakarta, Indonesia*

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ABSTRACT

Mamary Paget's disease presents with subtle and insidious symptoms leading to late diagnosis that poses medical challenges. This uncommon pathology often has underlying ductal breast cancer, including in situ or invasive breast cancer, which makes early recognition crucial for better prognoses. A 78-year-old postmenopausal woman presented with progressive and persistent eczematous skin lesions of the nipple without breast lumps. Additional imaging procedures revealed subtle findings, but the histopathology and immunohistopathology confirmed Paget's disease. This case highlights the importance of the correlation between clinical findings and the chosen diagnostic method for establishing a definitive diagnosis of mammary Paget's disease.

Introduction

Mammary Paget's disease (MPD) is a rare type of breast cancer presenting with diverse clinical signs, primarily on cutaneous alterations around the nipple or areolar area. The prevalence of MPD among all breast cancer cases is approximately 1 %-3 %, and MPD is mostly associated with underlying in situ or invasive breast cancer. In the United States, the incidence of MPD ranged from 0.44 to 1.31 cases per 100,000 woman-years between 1988 and 2011 [1,2]. (cari prevalensi di Indonesia atau di Asia).

Diagnosis of MPD continues to be a significant diagnostic challenge due to its inconspicuous early stage clinical manifestations, which can lead to misdiagnosis [3,4]. The eczema-like appearance on the skin of the nipple is often associated

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* Correspondence author.
E-mail address: pittyrad@gmail.com (S. Darmiati).

[1] Present address: Department of Radiology, Dr. Cipto Mangunkusumo National General Hospital, Faculty of Medicine, University of Indonesia, Jakarta, Indonesia, 10430.

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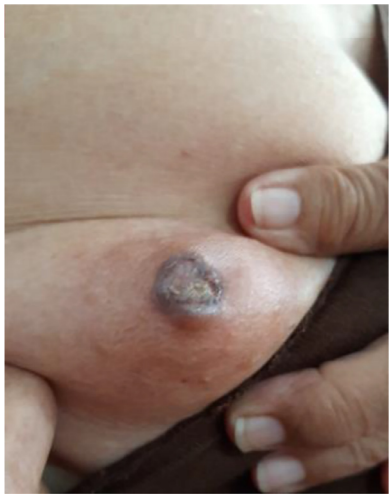

Fig. 1 – Initial presentation of the diseased right breast. Physical examination revealed nipple retraction and erosion, accompanied by slight hyperemia surrounding the lesion.

with itching and a burning sensation, which gradually progresses over a long time period. This often leads to other diagnoses, such as dermatitis or psoriasis, which are unresponsive to steroids and frequently delays the definitive diagnosis [5].

Despite the advancements in diagnostic knowledge, imaging procedures still have limited ability to detect MPD. Less than 10 % of MPD cases have been associated with a palpable mass, and mammography (MMG) only detects approximately 50 % of the cases without a palpable mass [5,6]. Under circumstances in which the MMG result is negative, breast ultrasound (US) might be warranted, even though false-negative results have been obtained in 13 % of cases [7]. Given the subtle and slowly progressive clinical manifestations and diagnostic imaging limitations, early detection and accurate management of MPD is challenging.

We present a case of a postmenopausal woman who presented with eczema-like skin changes on her nipple as the only symptom for almost 1 year on her right breast. After initially performing MMG and US, histopathological and immunohistochemistry (IHK) analyses revealed MPD as the underlying cause.

Case report

A 78-year-old woman visited our Surgical Oncology Clinic with a chief complaint of eczematous lesion on the skin around the nipple and areolar region of her right breast for almost 1 year without a palpable breast lump. The patient appeared fatigued without any issues, including decreased bodyweight. Physical examination revealed a reddening condition with nipple retraction and erosion on the right breast, slight hyperemia surrounding the lesion without any breast lump (Fig. 1), but the results of examinations of other body systems were unremarkable.

Mammography showed fatty tissue with multiple fine pleomorphic microcalcifications in a linear distribution within the superolateral quadrant of the right breast, indicating a probable malignant lesion. The inferomedial area of her left breast showed benign vascular calcification. There were no high-density lesions, stellate lesions, or architectural distortions (Fig. 2). Breast US only revealed skin thickening of the right-breast papilla area without intramammary abnormalities (Fig. 3). An upper abdominal US also did not reveal any significant findings.

For further investigation, a full-thickness biopsy from the right nipple-areolar complex (NAC) was performed, which revealed large pleomorphic central nuclei cells in the epidermis layer accompanied by prominent nucleoli and a pale cytoplasm in the intraepidermal layer (dermo-epidermal junction). Inflammatory cells covered the parenchymal part (Fig. 4). The tumor cells were positive for CK7, HER2 (2+), and CAM5.2 and negative for P63 in the IHK profile (Fig. 5). These findings were consistent with a diagnosis of MPD. However, no underlying cancer was identified in the other examinations. Noncontrast computed tomography scan of the thorax did not reveal signs of metastasis, hilar enlargement, effusion, or thoracic bone metastasis. The patient declined to undergo a microcalcification biopsy, so no further management was performed according to the patient's wish.

Two months later, the patient suffered an ischemic stroke accompanied by pneumonia due to COVID-19. After 1 month of intensive treatment, her condition gradually deteriorated until she died. Throughout her illness, no specific management for MPD was administered in accordance with the patient's request to forgo a biopsy.

Discussion

This case highlighted the importance of clinicians' awareness of the possibility of MPD with subtle clinical features and imaging findings when examining certain patients. Commonly observed in postmenopausal women, MPD primarily affects the nipple and areolar area. The majority of MPD cases (>93 %) are associated with underlying breast cancer. Both the epidermotropic and intraepidermal origin theory explain the involvement of carcinoma cells in MPD development, which are more prevalent in advanced age [6,8,9]. However, there have been some reports of MPD in adolescent patients [8].

The key diagnostic clue for identifying MPD is in its clinical presentation, which predominantly manifests on the skin. Signs of MPD are a long standing eczematous pruritic skin lesion on the nipple or areolar area, nipple scaling, and skin ulceration. Patients commonly present with associated symptoms, including bleeding, pain, and itching [1]. In a cohort study across 13 Swedish hospitals, Dalberg et al. [10] revealed that 98 % of 223 women who had histologically confirmed MPD experienced either eczema or nipple ulcerations as their primary signs and symptoms. Other signs and symptoms can be seen on suspicious mammograms indicating malignancy (32 %), palpable breast masses (15 %) and bloody nipple discharge (10 %). These findings suggest that clinical features

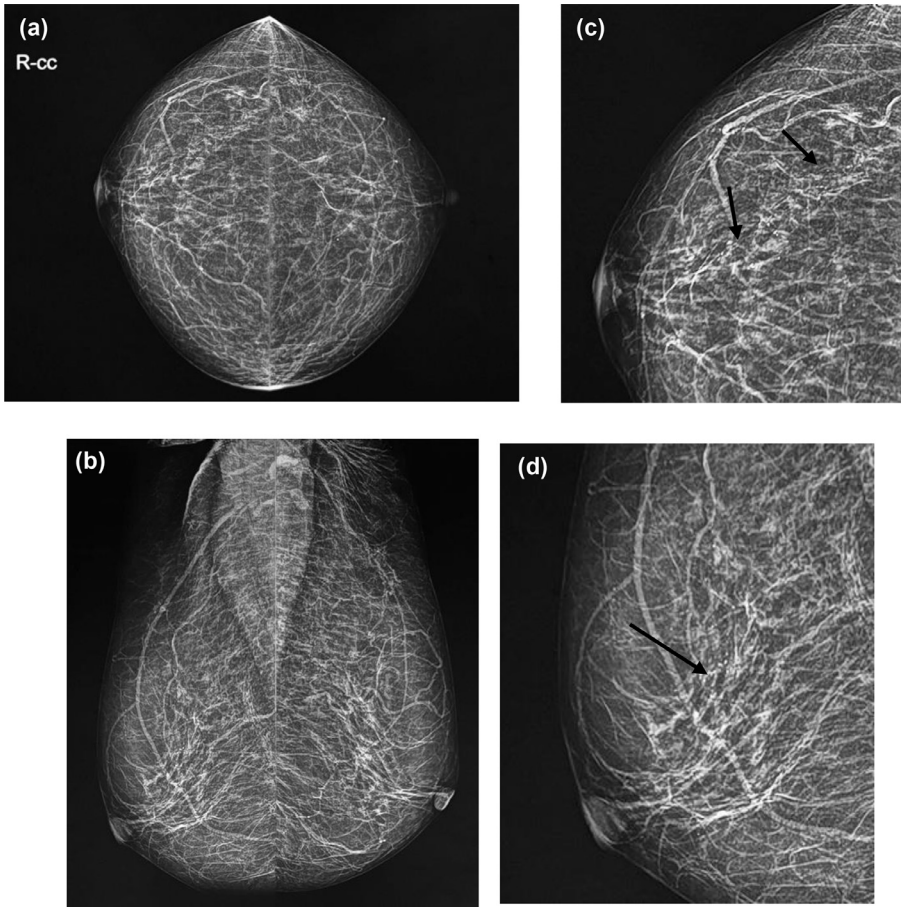

Fig. 2 – Bilateral mammogram in craniocaudal (a) and mediolateral oblique (b) views and the corresponding magnifications (c and d). There was slight thickening of the skin at the papilla area of the right breast. The fibroglandular composition was almost entirely fatty. Multiple fine pleomorphic microcalcifications were present in a linear distribution on the right superolateral quadrant. Magnified views (b and d) show the right-breast microcalcifications (black arrows). In the left breast, the inferomedial area shows benign vascular calcification. No high-density lesions, stellate lesions, or architectural distortions were identified.

other than eczema or nipple ulceration are rarely observed together, given their low-occurrence rates. Additionally, symptoms of MPD often develop gradually, and patients may initially complain of nipple itchiness without noticeable changes to their nipple, which can easily be mistaken for mild skin conditions [4,5]. A crucial distinguishing feature of MPD is that it specifically affects the NAC area, whereas any rash that spares the nipple is not suggestive of MPD [11]. Considering our patient's presentation with an eczematous skin lesion affecting the NAC, along with the absence of other symptoms and patient's age, further investigations were warranted to search for potential diagnoses of a malignancy.

Radiologic examinations have a crucial role in determining the appropriate management and treatment of MPD [12]. Although MMG is commonly used as the initial choice for radiological investigations, it has limited MPD detection ability. Mammography has high sensitivity for detecting underlying malignancies in MPD cases with palpable masses, but its effectiveness decreases to 50 % when there is no palpable mass [5]. Muttarak et al. [13] conducted a retrospective review of 16 patients with MPD who had undergone imaging studies from 2361 women diagnosed with breast carcinoma. They revealed that despite yielding 100 % positive results in patients with palpable breast masses and bloody nipple discharge, MMG only gave positive results in 50 % of the patients with clinically suggestive signs of MPD. The most common MMG findings were microcalcifications (62.5 %) and masses (56.25 %), whereas other notable findings included asymmetrical density (31.25 %), axillary nodes (25 %), nipple-areolar changes (18.75 %), and skin thickening (12.5 %) [13]. Another retrospective study by Günhan–Bilgen et al. [14] also reported that 33 % of the subjects exhibited nipple erythema, eczema, or ulceration. Among clinically evident MPD cases (17 patients), MMG revealed isolated microcalcifications in 18 %, mass associated with microcalcifications in 29 %, mass without microcalcifications in 12 %, and negative findings in 41 % of cases [14]. Breast lumps and microcalcifications were the most frequently observed findings, which were best seen through MMG [15]. From these studies, false-negative results obtained from MMG are still possible despite other clinically evident cases [16]. Although clinical features related to the NAC are commonly present in MPD, their translation into corresponding MMG

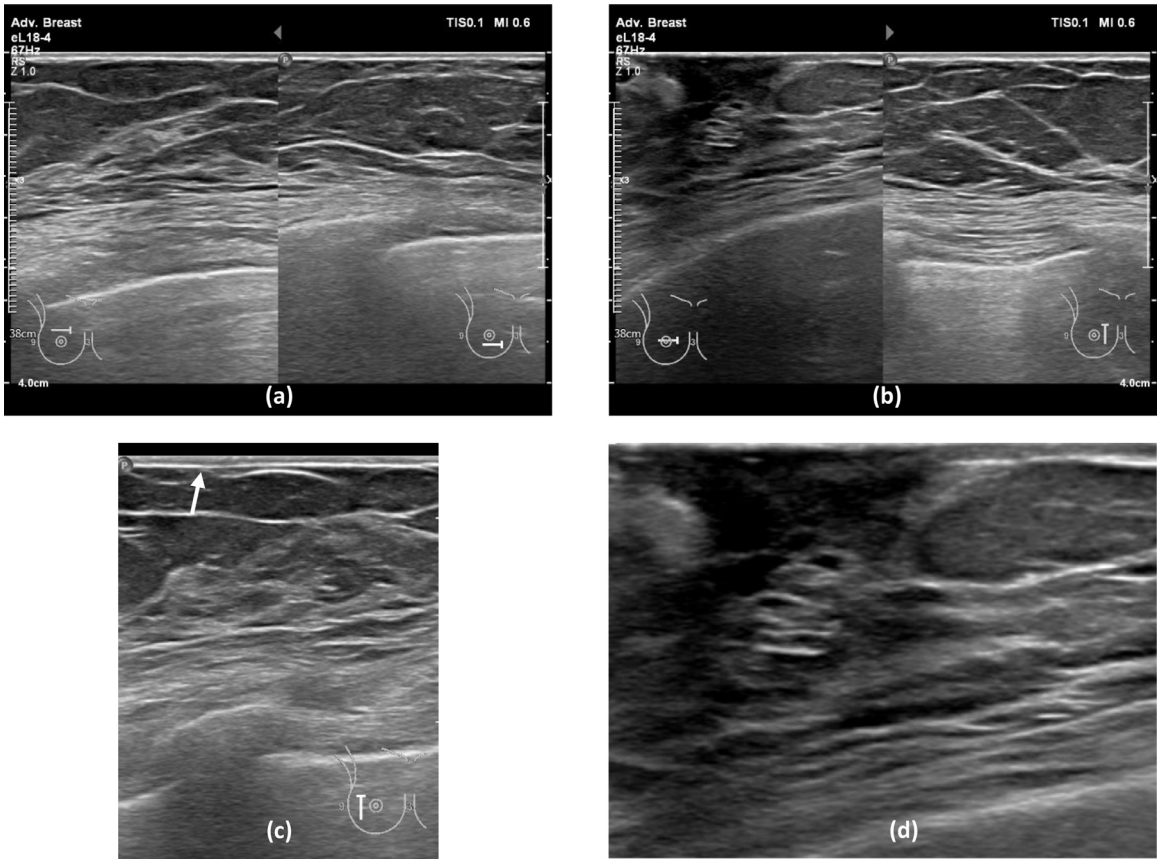

Fig. 3 – Breast ultrasound. (a,b) No significant abnormalities are detected in the fibroglandular tissue or the papilla area. (c) Ultrasound imaging showing skin thickening at the papilla area of the right breast (white arrow). (d) Magnified image clearly showing no lesions in the papilla and retro papilla region.

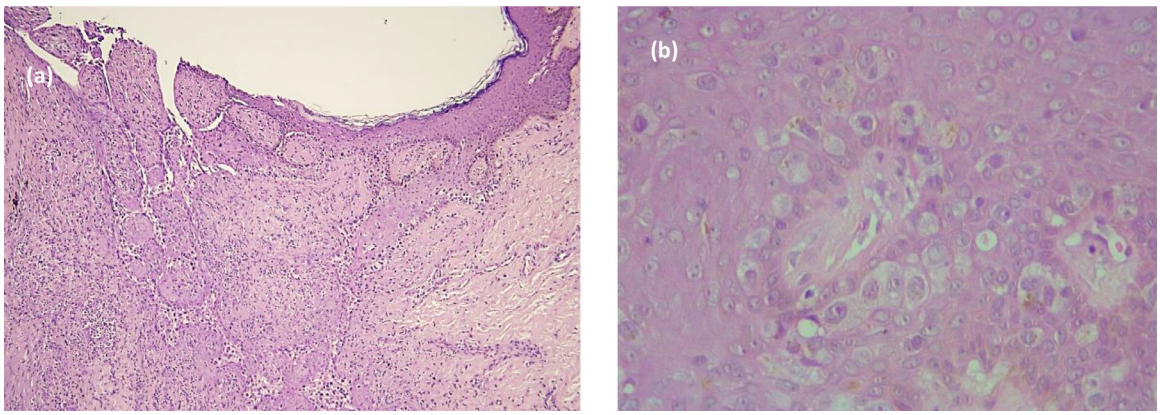

Fig. 4 – Histopathological images of MPD with hematoxylin and eosin staining at 100× (a) and 400× (b) magnification. Microscopic image showing large pleomorphic central nuclei cells accompanied by prominent nucleoli and pale cytoplasm, suggesting Paget cells.

findings is less frequent. Abnormal mammographic findings involving the NAC are not highly characteristic of MPD and do not definitively indicate the presence of the disease. Therefore, it is important to clinically correlate MMG findings concerning the NAC, and a negative mammogram does not definitively exclude the diagnosis [7,13]. When investigating this area, MMG evaluation should include magnified views of the NAC and the anterior third of the breast to increase the diagnostic rate [11]. The malignant pattern of microcalcifications observed in our case was easily detected by MMG, providing critical clues for a more serious diagnosis underlying the patient's clinical symptoms.

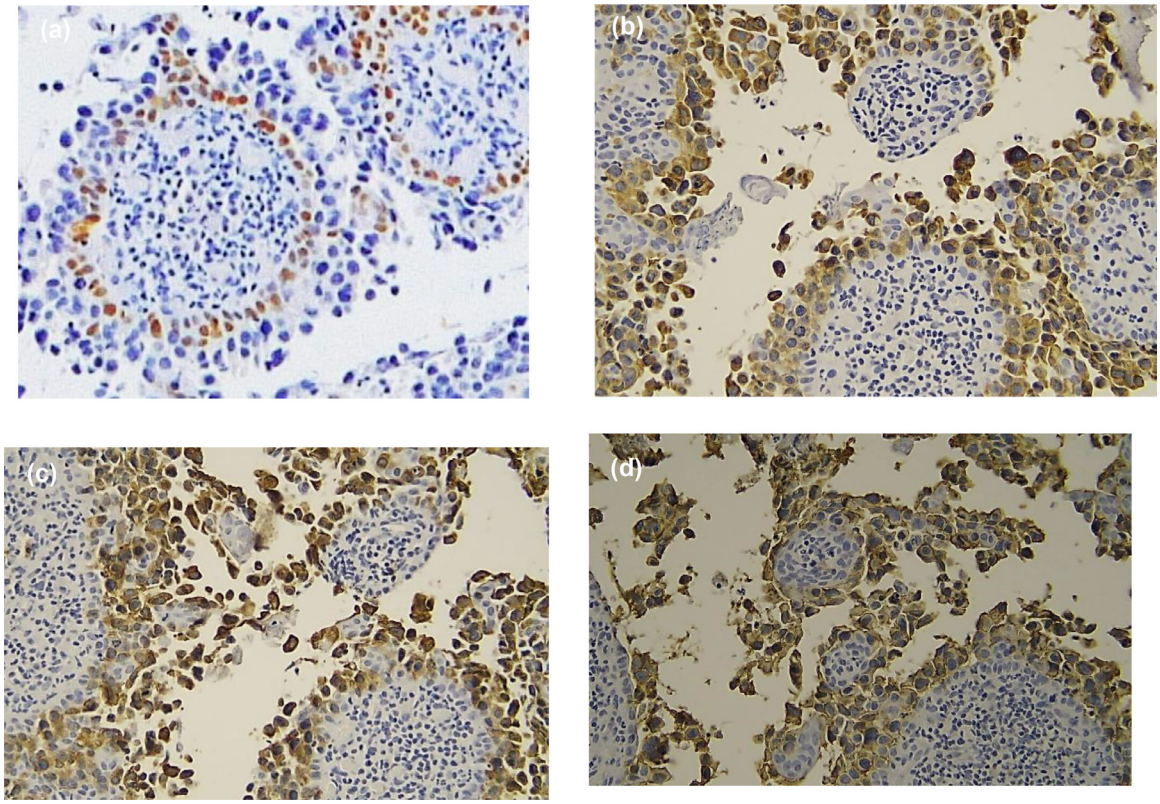

Fig. 5 – Immunohistochemistry profile at 400x magnification. The results were negative for P63 (a) and positive for CK7 (b), CAM5.2 (c), and HER2 (score of 2+) (d).

Although US is useful in patients with false-negative MMG results, it also has a crucial role in confirming MMG findings [12]. Further, US is highly effective for breast tumor assessment, including evaluating the size, location and distance of the tumor to the skin, detecting direct invasion of the skin, and identifying the thickness of the skin around the tumor [17]. A retrospective study by Liu et al. [18] demonstrated that the findings of abundant blood flow in the nipple (24.66 %) and malignant lesions in other parts of the breast (67.12 %) were significantly associated with MPD. Another retrospective study by Wei et al. [19] showed that in patients with either typical or atypical clinical findings, the main US findings are echoic abnormalities in the NAC and should be examined, particularly when a breast mass is detected. Additionally, echoic abnormalities in the NAC often exhibit rich blood flow in the nipple when assessed by color Doppler US [19], which might be a reliable diagnostic feature of MPD when the Doppler yields are more visible in the affected nipple than in the unaffected nipple. Conversely, no apparent effects were observed in the affected and unaffected nipples of simple dermatitis. The blood flow ratio and capillary density, as a quantitative pathological examination, were significantly higher in MPD than in non-Paget lesions [20]. Therefore, when conducting a US examination for MPD, it is crucial to perform Doppler sonography to visualize nipple blood flow, particularly in abnormal NAC. A protocol that integrates Doppler sonography in a breast examination, especially when a malignant etiology is suspected, may help increase the detection rate of abnormality to complement other clinical and radiological findings.

Following a full-thickness biopsy on the right NAC, we observed a substantial presence of large pleomorphic central nuclei cells with prominent nucleoli and pale cytoplasm within the intraepidermal layer, indicative of epidermal infiltration. These characteristics were consistent with Paget cells, which are the hallmark cells for diagnosing MPD [7]. Various options are available for conducting histopathological examinations, ranging from full-thickness biopsies to simple nipple scrapings (cytology), providing flexibility in diagnosis [7,21,22]. Immunohistochemical staining of carcinoembryonic antigen, mucin, and Her-2 oncoprotein can provide a comprehensive diagnostic value [21]. Furthermore, one study found that MPD also exhibited a negative P63 and positive CK7 and HER2 IHK profile. These findings, which were consistent with our case, further support the diagnosis [23]. In circumstances in which there is no corresponding mass detected on US, the use of stereotactic biopsy becomes essential for obtaining definitive diagnosis [24]. Unfortunately, further diagnosis was not pursued in this case, as the patient did not wish to undergo additional investigations.

MPD is commonly accompanied by an underlying breast carcinoma, which is typically of the ductal type, manifesting as either purely ductal carcinoma in situ (DCIS) or invasive ductal carcinoma (IDC) [6]. In a retrospective study by Liu et al. [18], only 1 of 16 confirmed patients with MPD was diagnosed without an underlying breast carcinoma. In these rare cases, the clinical presentation solely consisted of nipple changes suggestive of Paget's disease. However, when additional clinical features were present, all of them were associated with an

underlying breast carcinoma, primarily IDC (62.5 %) [18]. Another population-based retrospective study by Hu et al. involving 417 patients with MPD who were categorized according to the degree of malignancy, revealed that 95 % of the cases were associated with IDC, 3.4 % with DCIS, and only 1.7 % were without an underlying breast carcinoma [25]. These associations were found to be correlated with prognosis. A retrospective population-based study by Zhao Y et al. [26] using the Surveillance, Epidemiology, and End Results (SEER) database demonstrated that patients with MPD with IDC had the poorest prognosis, with a 5-year survival rate of 84.1 %. Therefore, it might be crucial to determine the presence of an underlying breast carcinoma in patients with MPD unless proven otherwise, as this not only confirmed the diagnosis but also helped predict the patient's prognosis.

In cases in which MMG or US results are inconclusive, magnetic resonance imaging (MRI) of the breast could have been performed. A retrospective study by Morrogh et al. [27] involving 34 patients with MPD revealed that after negative MMG results, MRI was able to detect occult disease in 50 % of the examined cases. Furthermore, MRI accurately demonstrated the extent of the disease and ruled out underlying cancer in all patients [27]. This examination technique potentially can provide results supporting a diagnosis even when clinical findings do not indicate a palpable mass or when MMG/US findings are inconclusive [28,29].

Conclusion

Diagnosing MPD can be challenging due to its subtle nature, and clinical findings may be the key foundation for diagnosing MPD. Radiological examinations are crucial for early detection of both MPD and its associated underlying cancer. Mammography is used for screening, but US is more sensitive for detecting pathological signs of the NAC associated with MPD. However, implementing a full-thickness biopsy is still recommended to define the diagnosis. Early diagnosis is crucial for determining the best management supportive of a good patient prognosis.

Patient consent

The authors declare that they have obtained written informed consent prior to writing the case report, including permission for publication of all photographs, images, and clinical data included herein.

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