SHORT COMMUNICATION

Paget's Disease of the Male Breast: A Diagnostic Challenge

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Paget's disease (PD) of the breast, mammary Paget's disease, or PD of the nipple is a rare condition that typically affects the nipple–areolar complex and is often associated with underlying breast malignancies; PD is observed in 1–3% of all breast cancers (BCs) (1). Histologically, it is characterized by Paget cells, which are large, malignant cells with a clear cytoplasm and hyperchromatic nuclei, infiltrating the epidermis. Clinically, it typically includes erythema, scaling, and itching of the nipple–areola complex, which can be mistaken for benign inflammatory dermatological conditions, delaying diagnosis. This delay is concerning given the high likelihood of underlying invasive ductal carcinoma (IDC) or ductal carcinoma in situ (DCIS), which are observed in 93–100% of cases (2). Male breast Paget's disease (MBPD) poses significant diagnostic and therapeutic challenges owing to its rarity, the general lack of awareness, and the limited data on optimal management strategies, which are often extrapolated from data on female patients and case reports. The mainstay of treatment involves surgical excision, from local excision of the nipple–areola complex to more extensive procedures such as mastectomy, depending on the extent of the underlying disease (3). Adjuvant therapies, including radiation, chemotherapy, and hormonal therapy (HT), are considered on the basis of the presence and nature of invasive cancer. This case series aims to consolidate current knowledge on the epidemiology, clinical presentation, pathophysiology, immunohistochemical profile, treatment and outcomes of MBPD, highlighting the need for heightened awareness and early intervention to improve outcomes for men.

MATERIALS AND METHODS

This was a multicentre retrospective cohort study involving 5 patients diagnosed with MBPD who were recruited from hospitals and private dermatology practices in Normandy, France, with no time limit in the past, until June 2024. The inclusion criteria were a diagnosis of MBPD and the existence of pictures. The exclusion criterion was the absence of histological information. The main outcomes and measures focused on the clinical presentation of MBPD, immunohistochemical profiles, treatments, and outcomes. Informed consent was obtained.

RESULTS

We report 5 cases of MBPD (**Figs 1 and 2**). In 2002, a 47-year-old man with no medical history of interest presented with depigmentation of the right nipple. Cutaneous nipple biopsy histological analysis revealed PD. Histological analysis after right mastectomy revealed intermediate-grade DCIS, TisN0M0. No complementary treatment was initiated; active surveillance only was performed, and no relapse occurred.

In 2014, a 57-year-old man with no medical history of interest presented with wide (6x4 cm) polychrome hyperpigmentation of the right nipple with total nipple retraction. Cutaneous nipple biopsy histological analysis revealed PD. Histological analysis after right mastectomy revealed grade II IDC that was HER-2 positive. The sentinel lymph node (SLN) biopsy was free of micrometastases, and the tumour stage was T1bN0M0. The patient received the following adjuvant chemotherapy: 3 cycles of epirubicin, cyclophosphamide, and docetaxel and 1 year of trastuzumab. No relapse occurred.

In 2014, a 77-year-old man with no medical history of interest presented with a polycyclic erythematosquamous lesion of the left nipple. Cutaneous nipple biopsy histological analysis revealed PD. Histological analysis after left mastectomy revealed intermediate-grade DCIS that was hormone receptor (HR)-positive and HER-2-negative. The SLN biopsy was free of micrometastases, and the tumour stage was TisN0M0. No complementary treatment was initiated; active surveillance only was performed, and no relapse occurred.

In an 86-year-old man with a medical history of primary cutaneous diffuse large B-cell lymphoma (leg type) treated with rituximab and prostate adenocarcinoma under active surveillance, grade II IDC of the right breast (T2N0M0, HR-positive, and HER-2-negative) was discovered in 2017 and treated with an aromatase inhibitor (AI) HT. In 2023, half-yearly surveillance PET-CT revealed an asymptomatic hypermetabolic right axillary node (6 mm). Axillary node biopsy histological analysis revealed IDC progression to tumour stage T2N1aM0. Clinically, we observed partial right nipple retraction with an eczematiform plaque, which is indicative of PD. As the patient refused surgery, a therapeutic switch to tamoxifen was chosen.

Recently, in 2024, a 62-year-old man with a medical history of resected cavernoma presented with itchy keratinized hypertrophy of the left nipple that had lasted for 1 year. Cutaneous nipple biopsy histological analysis revealed grade I IDC that was HR-positive and HER-2-negative. Left mastectomy followed by SLN biopsy histological analysis revealed 2 metastatic nodes, with a tumour stage of pT1cN1a(sn)M0, leading to the initiation

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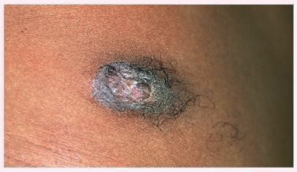
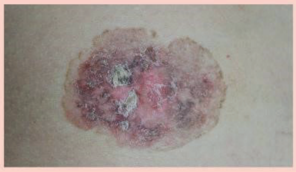
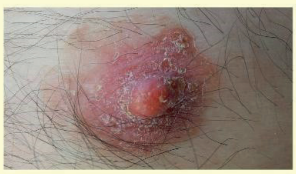
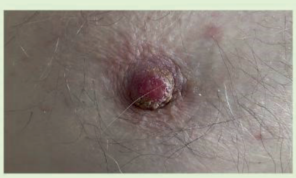
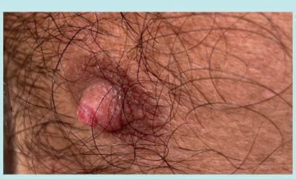
PATIENTS	PICTURES	FEATURES
1		• Right • Intermediate grade DCIS • TisN0M0
2		• Right • Grade II IDC • T1bN0M0 • HER-2 +
3		• Left • Intermediate grade DCIS • TisN0M0 • HR + HER-2 -
4		• Right • Grade II IDC • T2N1aM0 • HR + HER-2 -
5		• Left • Grade I IDC • pT1cN1a(sn)M0 • HR + HER-2 -

Fig. 1. Pictures and features of 5 cases of male Paget's disease of the breast. DCIS: ductal carcinoma in situ; IDC: invasive ductal carcinoma; HR: hormone receptor.

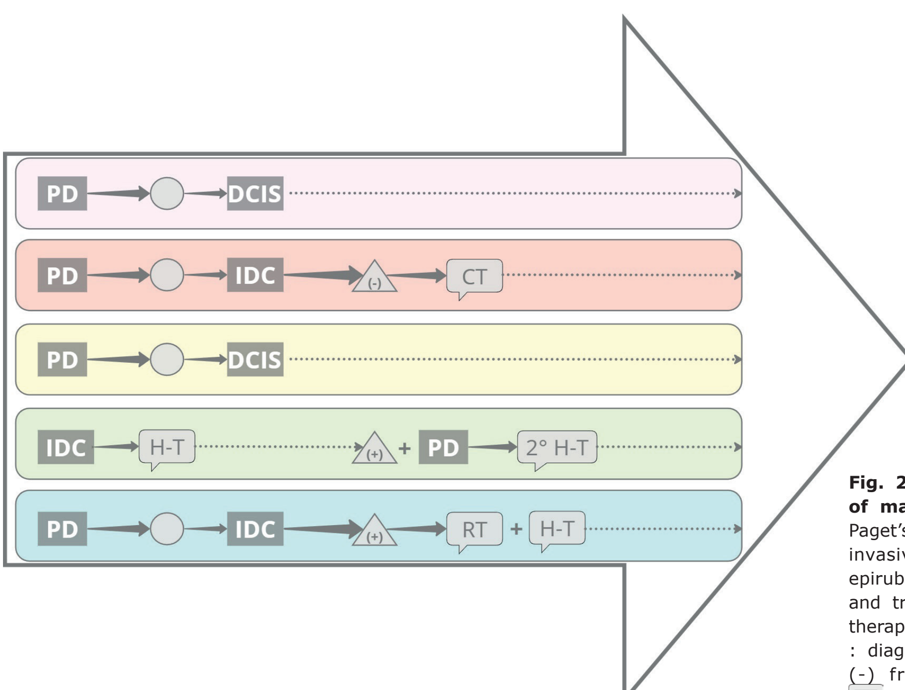


Fig. 2. Diagnosis and management of 5 cases of male breast Paget's disease: Timeline. PD: Paget's disease; DCIS: ductal carcinoma in situ; IDC: invasive ductal carcinoma; CT: chemotherapy (3 epirubicin-cyclophosphamide 100, 3 docetaxel 100 and trastuzumab); RT: radiotherapy; H-T: hormone therapy; 2°H-T: second-line hormone therapy; XX : diagnosis; ◯: mastectomy; (+): node surgery, (-) free of metastasis, (+) node metastasis; TTT: systemic treatment; ⋯: surveillance.

of tumour bed and lymph node adjuvant radiotherapy followed by 5 years of treatment with an AI.

DISCUSSION

This case series highlights the diagnostic and therapeutic complexities associated with MBPD, a rare and under-recognized condition. Male BC (MBC) accounts for 1% of BC cases, whereas MBPD accounts for only 1.45% of MBC cases (4). Due to the fact that it affects males and to the characteristics of the disease itself, MBPD is usually diagnosed late. It can be difficult to distinguish from other diseases, such as eczema, psoriasis, or Bowen's disease. Topical glucocorticoid treatment can lead to cutaneous changes, which greatly increases the chance of misdiagnosis. Thus, delayed diagnosis and misdiagnosis are among the reasons for the poorer prognosis in male patients. Some studies have suggested that MBC is more clinically aggressive than BC is in females, mainly because of anatomical factors such as a lack of breast tissue in males and the proximity of the tumours to the skin and nipple (5). Another reason for the worse prognosis of MBPD may be related to ineffective treatment because of the lack of case studies involving male patients.

Moreover, the pathogenesis of PD remains incompletely understood. Emerging research highlights the role of the PI3K–mTOR pathway in PD, potentially opening new avenues for targeted therapy (6). One study recently reported MSI1 ectopic overexpression in the basal epithelial cells of human PD (7). MSI1, an oncoprotein frequently overexpressed in extramammary PD and MPD tissues, can activate the PI3K–mTOR pathway by promoting HER-2 activity. Mechanistically, the Msi1-mTOR pathway drives keratinocyte-Paget-like cell conversion, and the suppression of mTOR signalling with rapamycin was found to significantly rescue the Paget-like phenotype (7). Temsirolimus and everolimus, two mTOR inhibitors derived from rapamycin, have been approved by the FDA for the treatment of different cancer types, suggesting new treatment options for PD and MBPD that need to be explored.

Furthermore, the majority of our cases were HER-2-negative and HR-positive (Luminal A subtype), unlike those reported in the literature, in which only 2–13% of cases had those characteristics (8, 9); however, those cases were in women. This case series provides important examples of this rare disease and suggests that the IHC profile differs between female and male breast PD, which needs to be explored to better identify MBPD-specific features.

In conclusion, MBPD is an exceedingly rare condition that presents significant diagnostic and therapeutic challenges because of its rarity and the general lack of awareness among both the public and healthcare professionals. While MBPD treatment strategies are extrapolated from cases involving female patients, there may be distinct differences in the IHC profile between the sexes, suggesting a need for tailored therapeutic approaches. Clinicians should remain suspicious and alert to the possibility of MBPD in male patients presenting with nipple–areolar complex changes, and they should advocate for prompt histological evaluations. Additional reports and research on MBPD are essential for deepening our understanding and improving the quality of care.

The authors have no conflicts of interest to declare.

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