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Paget's disease of the breast: diagnosis and management

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Abstract

Paget's disease of the breast typically affects postmenopausal women and is associated with an underlying malignancy. Skin changes are a common presenting symptom, as well as a lump, nipple discharge, pain and changes to the nipple shape. Imaging options include ultrasound for women under the age of 35 years or mammogram and ultrasound for women over the age of 40 years. The definitive diagnostic investigation is a tissue core biopsy. Cases are discussed by a multidisciplinary team to decide on the optimal management strategy. Management options are typically surgical and include breast-conserving surgery or mastectomy in addition to oncoplastic techniques. Sentinel lymph node biopsy is performed in all patients undergoing surgery. Adjuvant chemotherapy, radiotherapy or endocrine therapy can be used to treat concomitant invasive disease or ductal carcinoma in situ.

Key words: Breast cancer; Breast surgery; Paget's disease of the breast

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Epidemiology

Paget's disease of the breast typically affects postmenopausal women with a median age of onset of 64 years (Sisti et al, 2020), although cases have been reported in men (Akita et al, 2015; Yasir et al, 2022). It can be associated with an underlying malignancy, most commonly invasive breast cancer or ductal carcinoma in situ (Yasir et al, 2022). Between 1 and 4% of cases of breast cancer in the UK are associated with Paget's disease of the breast (Dubar et al, 2017).

Pathogenesis

Many theories have been suggested to explain the pathogenesis of Paget's disease. This article focuses on the two main theories suggested to explain the origin of the Paget cells that constitute the disease. The 'epidermotropic theory' suggests that Paget cells are in fact ductal cancer cells that have migrated from the basal membrane underlying the ducts to the epidermis of the nipple (Muir, 1935). This migration of Paget cells is thought to be mediated by the presence of human epidermal growth factor receptor 2 (HER2/neu) receptors on the Paget cells and a motility factor called heregulin-alpha, that is released from epidermal keratinocytes, promoting the ascension of Paget cells to the nipple epidermis via chemotaxis (Schelfhout et al, 2000). The second theory suggests that Paget's disease of the breast is an in-situ carcinoma comprised of malignant keratinocytes, which occurs independent to any underlying carcinoma of the breast (Lagios et al, 1984).

Clinical presentation of Paget's disease

The typical presenting feature of Paget's disease is an erythematous lesion of the nipple, which may involve the surrounding areola complex (Figure 1) (Kanitakis, 2007; Karakas, 2011). Complaints of pain, itching, burning and tingling are common and occur in 15–25% of cases (Kanitakis, 2007). As the disease advances, ulceration, bleeding from the nipple and serous discharge may occur; destruction of the wider nipple–areolar complex may also occur at advanced stages (Sakorafas et al, 2001). Nipple retraction or inversion is often quoted as a symptom of Paget's disease, but flattening of the nipple is more common, with retraction typically occurring because of an underlying tumour (Sakorafas et al,

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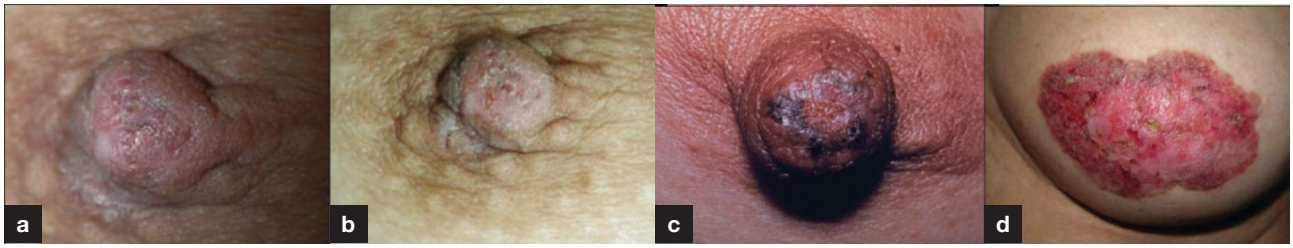

Figure 1. Clinical appearance of Paget's disease of the breast. a and b. Thickened crusted lesions of the nipple with irregular borders. c. Scaly and thickened plaque spreading to surrounding areola. d. Advanced lesion with destruction of the nipple–areolar complex with significant erythema, scaling and erosion. From Karakas (2011).

2001). Notably, the appearance of Paget's disease can be similar to that of inflammatory skin conditions such as eczema, which may result in patients being incorrectly treated with topical corticosteroids and thus a delayed diagnosis (Liu et al, 2015). Eczematous skin changes are usually bilateral and respond quickly to topical steroid therapy, although Paget's disease should still be suspected in someone presenting with bilateral eczematous nipple changes, especially if the changes persist for more than 3 weeks following steroid treatment (Yasir et al, 2022). Given that Paget's disease presents with skin changes, it may present differently on the skin of different ethnic groups, with erythema more likely to present as violaceous, rather than red, or being completely missed in patients with darker skin (Kaufman et al, 2018). While the authors were unable to identify any case reports that addressed how Paget's disease may present differently in ethnic minorities, the findings of wider dermatological studies could be extrapolated. For example, Ben-Gashir et al (2002) indicated that erythema was a misleading indicator of atopic dermatitis, which closely resembles the skin changes in Paget's disease, in a black population.

Referral for suspected breast cancer

In the UK, there is a 2-week wait referral pathway for patients with suspected cancers. For breast cancer, including Paget's disease of the breast, patients who are older than 30 years of age with an unexplained breast lump or older than 50 years of age with either nipple retraction, discharge or other concerning features, meet the criteria to be seen by a breast specialist within 2 weeks (National Institute for Health and Care Excellence, 2020).

Investigation

As with all cases of suspected breast malignancy, triple assessment is the standard sequence of investigation for Paget's disease of the breast, comprising clinical examination, imaging and tissue biopsy (Karim et al, 2020).

In addition to clinical features, a breast mass may be noted on clinical examination. Nance et al (1970) showed that an underlying breast mass was present in 61% of patients with mammary Paget's disease of the breast. Axillary lymphadenopathy may also be present on clinical examination, with axillary lymph node metastases being more common in patients with invasive ductal carcinoma with overlying Paget's disease than in those with invasive ductal carcinoma alone (Wong et al, 2015).

Imaging takes the form of either ultrasound or mammogram and is used to identify if suspected Paget's disease of the breast is associated with a mass in the breast tissue. Ultrasound is used to image the breasts of patients under 40 years of age and has a higher sensitivity and specificity for detecting breast cancer in younger women and those with denser breast tissue than mammography (Devolli-Disha et al, 2009).

A wedge biopsy (superficial scrape) or punch biopsy of the diseased skin is used for Paget's disease (Karakas, 2011). Biopsy of any concomitant underlying breast mass should also take place. The use of cytology has been postulated as an easy screening test for eczematous skin changes to the nipple, but core or surgical excision biopsy remains the gold standard (Gupta et al, 1996). Paget's disease is classified using the TNM staging system. In the absence of associated invasive breast cancer or ductal carcinoma in situ, mammary Paget's disease is classified as Tis (Paget) disease (Yasir et al, 2022). Typical

biopsy and cytology findings diagnostic of Paget's disease are malignant glandular cells with clear cytoplasm and eccentric, hyperchromatic nuclei (Hücümenoğlu et al, 2001).

Management

Treatment options for patients are discussed by a multidisciplinary team. The results from the triple assessment, as well as any genetic investigations that may predict how well any coexisting breast cancer may respond to different treatments, are considered when deciding the optimal treatment. Typical members of a breast cancer multidisciplinary team include breast and oncoplastic surgeons, a radiologist, a breast care nurse, oncologists, medical geneticists, a clinical psychologist and palliative care experts (Association of Breast Surgery at BASO, 2009). The treatment course for patients with Paget's disease is defined on a case-by-case basis by the multidisciplinary team members.

Surgical management

Surgical management of Paget's disease is typically either mastectomy or breast-conserving surgery. While historically, mastectomy has been the treatment option of choice, breast-conserving surgery with adjuvant therapies (wide local excision of the nipple–areolar complex with adjuvant radiotherapy) is an effective treatment with better outcomes in terms of patient satisfaction (Bijker et al, 2001). This is especially relevant for cases of Paget's disease with associated invasive ductal carcinoma or ductal carcinoma in situ, particularly where there is limited ductal carcinoma in situ (Bijker et al, 2001; Yao et al, 2019). The limitation of breast-conserving surgery is the risk of positive resection margins requiring a return to theatre for re-excision of margins or completion mastectomy.

One case series found that 29% of Paget's disease patients with no associated breast mass had a peripherally located tumour that was not amenable to wide local excision of the nipple–areolar complex (Kollmorgen et al, 1998). In cases of Paget's disease presenting without a palpable mass or mammographic density, the literature favours wire-guided wide local excision and definitive breast irradiation as an alternative to mastectomy (Marshall et al, 2003). There is evidence that breast-conserving treatments result in similar survival rates to mastectomy. One study found a 10-year disease-specific survival rate of 67% for patients treated with breast-conserving therapy and 79% for patients treated with mastectomy. A large disparity in the number of patients treated more conservatively (n=12) vs with mastectomy (n=92) prevented statistical comparison in this study (Kawase et al, 2005).

A systematic review by Helme et al (2015) sought to analyse the role of breast-conserving surgery in the treatment of Paget's disease. They concluded that breast-conserving surgery is a viable surgical treatment for Paget's disease where the underlying malignancy is excisable with clear margins and where adjuvant radiotherapy is used. Rather than directly comparing mastectomy and breast-conserving surgery for the treatment of Paget's disease, their emphasis was on the use of preoperative imaging to identify which patients are likely to be undertreated with breast-conserving surgery and therefore who may require mastectomy as the initial surgery.

A 2014 meta-analysis including 685 patients compared Paget's disease treated with mastectomy and breast-conserving surgery. They found a local recurrence rates of 5.6% and 13.2% respectively for mastectomy and breast-conserving surgery (an odds ratio of 0.38, 95% confidence interval 0.21–0.69; P=0.001). While this seems to suggest that mastectomy is superior to breast-conserving surgery, the authors emphasised that the variation in diagnostic (magnetic resonance imaging) and therapeutic (adjuvant radiotherapy, tamoxifen) options used and included in their analysis means that it would be presumptuous to suggest mastectomy is superior to breast-conserving surgery for every patient (Li et al, 2014).

The development of oncoplastic techniques has allowed for the establishment of oncologically and aesthetically satisfactory outcomes for centrally located breast cancers such as Paget's disease. The Grisotti flap and its modified versions are popular surgical options given appropriate patient selection. The Grisotti flap technique is a partial mastectomy with immediate volume replacement. It involves the use of a curvilinear flap from the inferior part of the breast which is then rotated superiorly to fill in the more central defect, immediately following the resection of a central breast lesion such as in Paget's disease (Grisotti, 1994).

This technique is versatile and has been further modified by the addition of pedicled skin flaps with skin islands for management of centrally located breast cancers and Paget's disease in women with breast dimensions that are less appropriate for the original flap (Chen et al, 2021).

Cone excision of the nipple alone is not recommended for the treatment of Paget's disease, with one case series concluding that cone excision of the nipple alone would have resulted in incomplete excision in 75% of study participants (Kothari et al, 2002). Another study found cone excision to be inferior to mastectomy with 40% of patients who underwent cone excision of the nipple for Paget's disease experiencing local recurrence at follow up (median time of follow up 56 months) vs only 5% of patients experiencing loco-regional recurrence at follow up when treated with mastectomy (Dixon et al, 2005).

The dense nature of the lymphovascular plexus deep to the nipple–areolar complex may explain the increased rate of axillary lymph node metastasis in patients with Paget's disease vs patients with invasive ductal carcinoma alone (Wong et al, 2015). Given the prevalence of axillary lymph node involvement, sentinel lymph node biopsy is recommended to investigate the axilla in all patients diagnosed with Paget's disease (Laronga et al, 2006). This also highlights the importance of thorough clinical examination of the axilla at first presentation of a patient with skin changes suggestive of mammary Paget's disease.

Adjuvant therapy

At present, no evidence supports the use of adjuvant systemic therapies such as endocrine therapy (eg tamoxifen or aromatase inhibitors), chemotherapy and trastuzumab (Herceptin) for Paget's disease itself. These therapies are only recommended for treatment of any coexisting invasive carcinoma or ductal carcinoma in situ (Yasir et al, 2022). In the complete absence of concomitant breast tumour, radiotherapy alone is an effective alternative to radical surgery (Fourquet et al, 1987). Despite this, most studies looking at the conservative management of Paget's disease advocate the use of adjuvant radiotherapy following breast-conserving surgery rather than solely as an alternative (Pierce et al, 1997; Marshall et al, 2003).

Psychological management

The psychological impact of total mastectomy vs breast-conserving surgery in the treatment of breast cancer is well documented, with breast-conserving surgery being associated with a significantly higher satisfaction rate of postoperative body image perception (Ng et al, 2019). Nipple-sparing mastectomy is associated with a higher rate of postoperative psychosocial and psychosexual wellbing in women with breast cancer (Wei et al, 2016). In patients with Paget's disease, nipple loss is mandatory in operative management so using a technique such as the Grisotti flap allows oncologically safe as well as aesthetically satisfactory outcomes. Successful oncological clearance and free tumour margins should not be compromised to achieve superior cosmetic results. In patients with Paget's disease, delayed-stage nipple reconstruction or three-dimensional nipple tattooing following surgery can allow satisfactory reconstruction of the nipple–areolar complex and improved psychosocial and sexual satisfaction (Goh et al, 2011; Bykowski et al, 2017).

Radiotherapy

Radiotherapy is associated with significantly poorer cosmetic outcomes (Rozen and Ashton, 2012). Irradiated breast tissue can become thickened and hyperpigmented, resulting in a smaller breast with or without distortion. The effects of radiotherapy to the breast must be discussed with women before initial surgery to ensure that they are well informed and that their expectations are managed. Techniques to improve the appearance of post-radiotherapy changes to the breast include the use of autologous flaps (local perforator or free flaps) as well as fat grafting or lipofilling. Alternatively, contralateral symmeterisation surgery can be considered once cancer treatment is complete.

Follow up

Once patients with Paget's disease have undergone treatment for breast cancer, including ductal carcinoma in situ, follow up includes annual mammography until the age of 40 years when they enter the NHS Breast Screening Programme in England or the Breast Test Wales

Screening Programme in Wales. Those with a diagnosis of breast cancer (including Paget's disease) who are already eligible for screening should have annual mammography for the next 5 years. This surveillance is done via an open access follow-up pathway, which is a nurse-led service designed to support and monitor patients during this surveillance period. In addition to mammography, patients should have clinical follow up under the supervision of a specialist as well as re-discussion in the breast multidisciplinary team if any concerns are raised from surveillance imaging (National Institute for Health and Care Excellence, 2018). The presence of Paget's disease may negatively impact breast cancer survival, which may be because tumours from patients with Paget's disease often express molecular markers typical of aggressive tumour behaviour (Fu et al, 2001; Ortiz-Pagan, 2011). Therefore, rigorous follow up is vital in patients with Paget's disease and clinicians must not overlook life after treatment as an important facet of management of patients with Paget's disease.

Conclusions

Paget's disease of the breast is often associated with underlying malignancy and typically affects postmenopausal women. Clinicians should have a high index of suspicion for Paget's disease in patients with unilateral erythematous nipple lesions as well as those who have failed to respond to topical steroid therapy. Urgent referral on the 2-week wait cancer referral pathway should be made to allow prompt triple assessment at a specialist breast unit. The breast cancer multidisciplinary team is crucial in guiding management, which is done on a case-by-case basis. Management is often surgical and can include wide local excision of the nipple–areolar complex or total mastectomy with sentinel lymph node biopsy with or without axillary node clearance. The development of oncoplastic techniques, specifically the Grisotti flap, allows more cosmetically satisfactory outcomes for patients with centrally located breast cancers. Patient selection is key and surgical options depend on the presence of an underlying malignancy, the location and extent of disease, breast size and associated comorbidities. Adjuvant therapies such as chemotherapy, radiotherapy and endocrine therapy are often used to treat co-existing invasive breast cancer and ductal carcinoma in situ.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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Key points

- Paget's disease of the breast accounts for 1–4% of all cases of breast cancer in the UK.
- Clinicians should have a high index of suspicion for patients presenting with unilateral erythematous nipple changes and those who have failed to respond to topical steroid therapy.
- Urgent referral via the 2-week wait cancer pathway is required for specialist review by a breast surgeon for triple assessment (clinical examination, imaging and tissue biopsy).
- A diagnosis of Paget's disease is confirmed by the presence of malignant glandular cells with eccentric, hyperchromatic nuclei on core biopsy.
- Discussion in the breast cancer multidisciplinary team guides management, typically with mastectomy or breast-conserving surgery, sentinel lymph node biopsy and adjuvant therapies.
- On completion of surgical and adjuvant treatment of Paget's disease, patients undergo surveillance via the nurse-led open access follow up pathway.
- Follow up includes annual mammography until the age of 40 years then surveillance every 3 years, or annual mammography for 5 years for women over 40 years of age.

Curriculum checklist

This article addresses the following requirements from the general internal medicine training curriculum.

- Managing patients in an outpatient clinic, ambulatory or community setting, including the management of long-term conditions
- Managing medical problems in patients in other specialties and special cases
- Managing a multidisciplinary team including effective discharge planning.

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