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REVIEW

Vulval extra-mammary Paget's disease: the master of disguise revealed

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Abstract

Extra-mammary Paget's disease is a rare cancer affecting the anogenital region and can present with a myriad of symptoms. In women, the diagnosis of Paget's disease can be challenging as it mimics several other vulval conditions. It is important to promptly recognise this disease because of its potential association with synchronous tumours, such as colorectal adenocarcinoma. The mainstay of treatment is with immunomodulating therapies or surgery, but unfortunately the risk of recurrence is high and appears to be independent of treatment choice and tissue margin status. There is growing evidence to move away from traditional surgical excision to using topical therapy, such as imiquimod, as surgery can often be extensive and disfiguring with a prolonged recovery time. There is considerable psychosexual and physical morbidity associated with Paget's disease, largely owing to multiple surgical recurrences. As recurrences can occur several years after the initial presentation, long-term follow up of patients is recommended.

Key words: Extra-mammary Paget's disease; Imiquimod; Surgical excision of Paget's disease; Vulval Paget's disease

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Introduction

Extra-mammary Paget's disease is a rare cutaneous neoplasm that presents with red eczematoid lesions which may cause itching, pain, burning or irritation. Owing to its rarity, there is limited research and evidence on the pathophysiology and management of extra-mammary Paget's disease. The hallmark diagnosis is the presence of 'Paget cells', which are histologically defined by their abundant pale cytoplasm.

Extra-mammary Paget's disease is a rare neoplasm and the precise incidence is unknown. It occurs more frequently in women than men, with a ratio of approximately 3:1 and a higher incidence among the Caucasian population (Chanda, 1985; Baehrendtz et al, 1994). The median age of presentation is between 50 and 80 years old. When confined to the epithelium Paget's disease can be described as 'intra-epithelial Paget's disease', but is described as 'Paget's disease' once the Paget cells penetrate through the basement membrane of the skin and invade the dermis. Vulval Paget's disease is an intra-epithelial carcinoma and delayed diagnosis can risk extensive disease with dermal invasion and metastasis via the lymphatic system (Delport, 2013). The frequency of invasive disease is approximately 5–25% (Awtrey et al, 2003; van der Linden et al, 2016), and it is thought to take around 11 years to progress from initial skin changes through to invasive disease (Hoffman and Cavanagh, 1997). Estimating the true incidence of vulval Paget's disease within the population is challenging owing to its rarity and a lack of differentiation within the literature between vulval Paget's disease with underlying malignancy, invasive vulval Paget's disease and non-invasive vulval Paget's disease.

Approximately 65% of extra-mammary Paget's disease cases occurs in the vulva (Delport, 2013), with vulval Paget's disease representing 1–2% of all vulval malignancies (Lloyd and Flanagan, 2000). A study by MacLean et al (2004) reported 8% of cases of vulval Paget's disease had an underlying vulval carcinoma and a further 20% of cases had an associated cancer, such as gastrointestinal (including cancer of the gallbladder, liver, colon and rectum), as well as breast, bladder, ovarian, uterus and cervical cancer. A standardised incidence ratio of 1.39 has been quoted for the association of vulval Paget's disease with an underlying malignancy (Van Der Zwan et al, 2012). Vulval Paget's disease

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mimics other vulval dermatoses which is the reason that diagnosis can be challenging and is often delayed. Table 1 summarises the differential diagnoses and how to differentiate these from Paget's disease.

Pathogenesis

This heterogenous condition is thought to be caused by two distinct pathways; those arising from primary lesions (75–96% of cases) (Love et al, 2011) and those arising from secondary lesions from epidermotropic spread of distant malignancies. There are two theories regarding the origin of primary lesions: pluripotential keratinocyte stem cells of the epidermis or adnexae (Teixeira et al, 1999), or from apocrine or eccrine glands within the epidermis (Sawada et al, 2010) because of the predilection for apocrine-bearing sites and positivity for apocrine differentiation markers within the epidermis.

An additional theory has been proposed whereby an oncogenic stimulus simultaneously induces an epidermal and visceral malignancy (Helwig and Graham, 1963), explaining multicentric tumours and tumours which appear concurrently at different sites of the body. The genomic profile of vulval Paget's disease has been studied, but no conclusive genomic aberrations have yet been identified (van der Linden et al, 2016).

Pathology

In vulval Paget's disease, the epidermis is infiltrated by Paget cells which can occur singly, in nests or as glandular structures at either the basal, supra-basal and/or at the granular layer of the epidermis (Figures 1 and 2). In order to gain a diagnosis and distinguish between primary and secondary vulval Paget's disease, immunohistochemistry staining of Paget cells following biopsy is required.

Table 1. Differential diagnoses of vulval Paget's disease and how to distinguish these from Paget's disease

Differential diagnoses			Differentiate from extra-mammary Paget's disease
Benign	Dermatological	Contact dermatitis	Patch test, avoid allergen
		Psoriasis	Trial of steroids +/- skin biopsy
		Fungal infection	Swab, antifungal treatment
		Seborrhoeic dermatitis	Wash with salicylic acid +/ topical antifungal +/- topical steroid
		Lichen sclerosis	Topical steroids
		Lichen planus	Biopsy, topical steroids, calcineurin inhibitors or retinoids
		Lichen simplex chronicus	Patch test or skin scrapings, avoid irritants, emollients
		Histiocytosis	Skin biopsy, chemotherapy or steroids
	Systemic	Crohn's disease	Biopsy of lesion
		Chronic vulval fixed drug eruption	Biopsy, oral challenge or patch test
Malignant	Pre-malignant	Bowen's disease	Biopsy
		Anogenital intraepithelial neoplasia	Biopsy
	Malignant	Melanoma	Biopsy
		Intertriginous basal cell carcinoma	Biopsy
		Vulval squamous cell carcinoma	Biopsy
		Mycosis fungoides	Biopsy

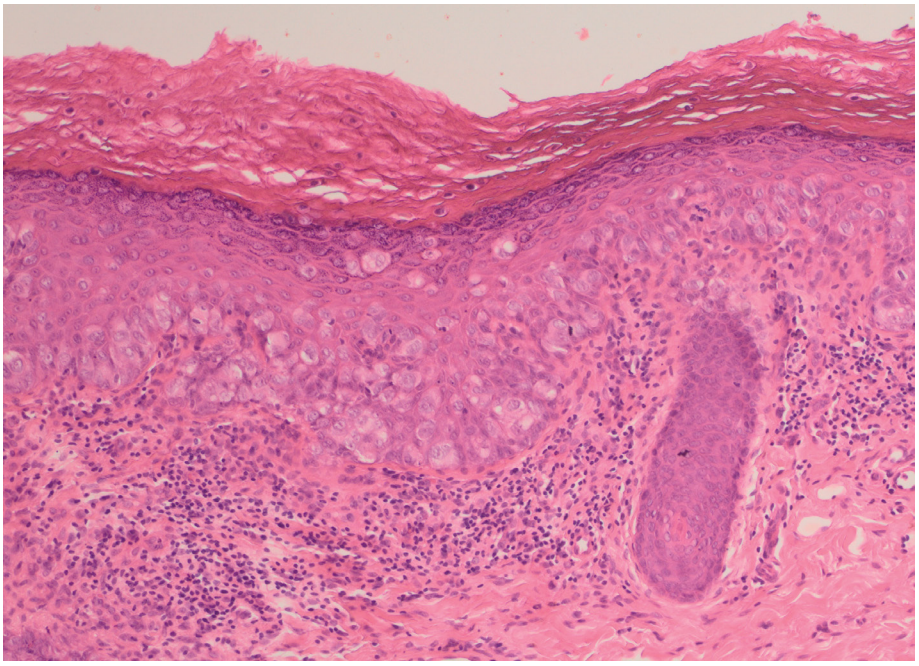

Figure 1. Low-power photomicrograph (10x magnification) using haematoxylin and eosin staining to show the histopathology of extra-mammary Paget's disease. The epidermis contains, scattered among the keratinocytes, larger cells with an abundance of pale cytoplasm (Paget cells). These form small clusters along the dermal-epidermal junction and ascend through the epidermis as single cells ('pagetoid ascent'). The epidermis also shows hypergranulosis and hyperkeratosis, and the superficial dermis contains chronic inflammation, all of which are also commonly seen in extra-mammary Paget's disease.

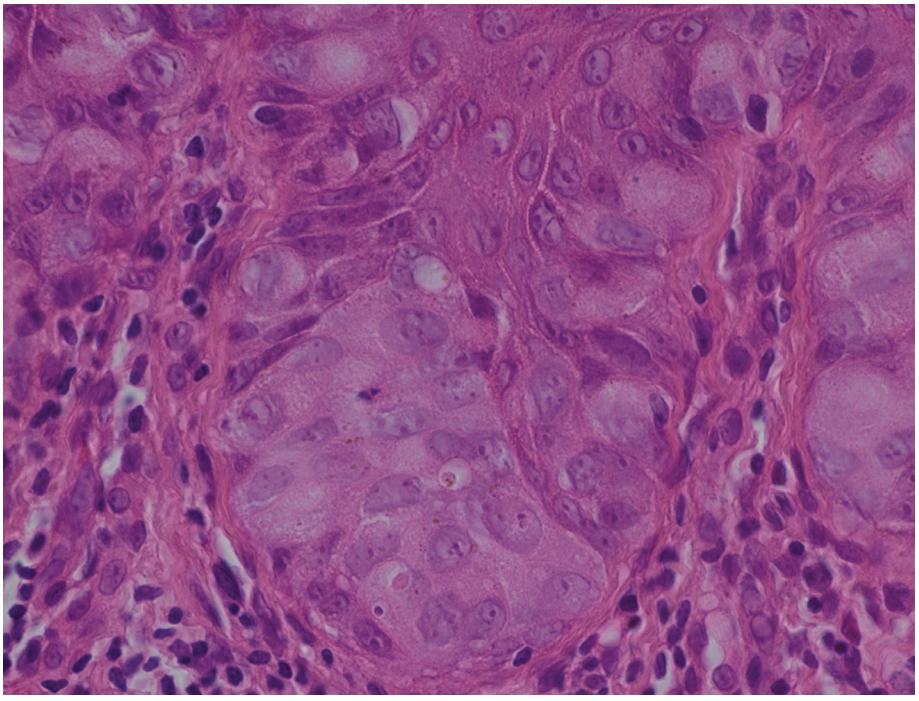

Figure 2. High-power photomicrography (40x magnification) using haematoxylin and eosin staining to show the histopathology of extra-mammary Paget's disease. The cytomorphology of the Paget cells is distinct from the surrounding keratinocytes. They have abundant, pale cytoplasm and enlarged, irregular nuclei. They typically contain multiple nucleoli and mitotic figures may be identified (not present here). The appearances are characteristic of extra-mammary Paget's disease, but immunohistochemistry is still required to exclude the differential diagnoses of melanoma and Bowen's disease.

Paget cells are of epithelial origin and are positive for pan cytokeratin antibodies, such as CAM5.2, and negative for melanocytic markers, such as S100 protein. Primary vulval Paget's disease is positive for benign breast epithelial markers, such as gross cystic disease fluid protein 15 (Figures 3 and 4), suggesting a similar histogenesis between mammary and extra-mammary Paget's disease. Paget cells can also be positive for other epithelial markers, such as epithelial membrane antigen and carcinoembryonic antigen.

The Paget cells show cytoplasmic staining for CAM5.2 (a low molecular weight cytokeratin), cytokeratin 7 and gross cystic disease fluid protein 15, all of which are negative in the surrounding keratinocytes. They are negative for cytokeratin 20 and S100 protein, which stains the normal melanocytes in the surround tissue.

The positivity of Paget cells for CAM5.2 and cytokeratin 7 allows for a differential diagnosis against Bowen's disease, and negativity for S100 protein militates against melanoma. The immunophenotype, cytokeratin 7 and gross cystic disease fluid protein 15 positivity and cytokeratin 20 negativity, is consistent with extra-mammary Paget's disease and favours a diagnosis of primary extra-mammary Paget's disease.

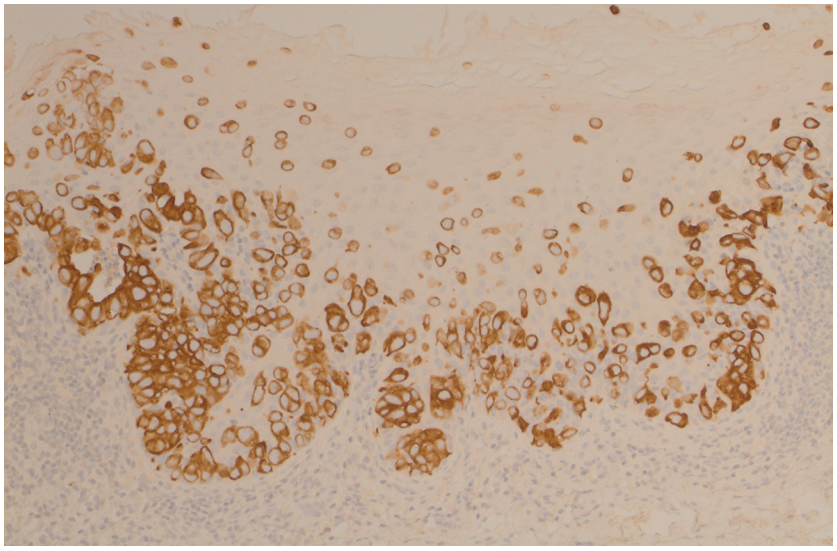

Figure 3. Immunohistochemistry staining for CAM5.2 using 10x magnification.

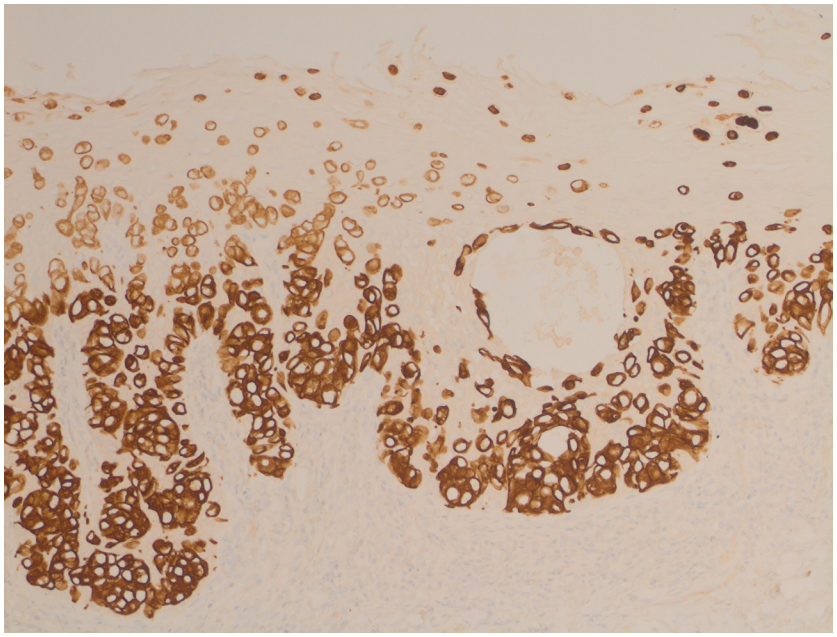

Figure 4. Immunohistochemistry staining for cytokeratin 7 using 10x magnification.

Clinical presentation and assessment

Vulval Paget's disease most commonly presents with persistent pruritus which is unresolved by simple measures, such as avoidance of irritants or topical steroids. It may present with a non-resolving eczematous lesion in the groin, genitalia or peri-anal region. Often, the patient experiences an associated burning sensation and soreness of the eczematous lesion with erythema, crusting and increased maceration. Pruritus may cause prominent excoriation leading to lichenification and eventually a unilateral or bilateral sharply marginated plaque with distinct erythema. There may be an overlying hyperkeratosis, known as a 'cake-icing effect', which is almost pathognomonic of vulval Paget's disease (Figure 5). Superficial erosion or scaling may develop in immature lesions, which may occur in isolation or be multi-focal. As the presentation of vulval Paget's disease mimics many other skin conditions, a high index of suspicion for diagnosis is required once a lesion has not responded to topical steroids and antifungal cream.

The clinical examination should include a full assessment of the anogenital region, the draining of the lymph nodes and an assessment of associated organs including the vagina, cervix and rectum to exclude local malignancy. Furthermore, clinical examination should include an assessment for further distant malignancies, including an examination of the breasts, and peripheral stigmata of underlying disease. Previously, invasive examinations, such as colonoscopy and cystoscopy, were advocated to identify any underlying malignancies. However, such procedures have been found to be unnecessary and can be safely omitted.

Either a punch biopsy or a wedge resection is required for histopathology analysis and immunohistochemistry staining, where the identification of Paget cells results in a diagnosis. It is good practice to photograph the lesions, with patient consent, and to clearly mark the sites of biopsy on the image or on a diagram in the clinical notes. Once a diagnosis of vulval Paget's disease is confirmed, or earlier if invasion is clinically suspected, a referral to a specialist vulval clinic with expertise in managing this condition is appropriate. For large and clinically difficult lesions, the specialist may consider conducting an examination under anaesthetic and the mapping of biopsies to make a diagnosis, exclude the possibility of occult invasion and decide upon the patient's treatment. The management of vulval Paget's disease is guided by the fitness of the patient, the disease burden and its proximity to vital structures, as well as any underlying malignancies and the degree of tumour invasion.

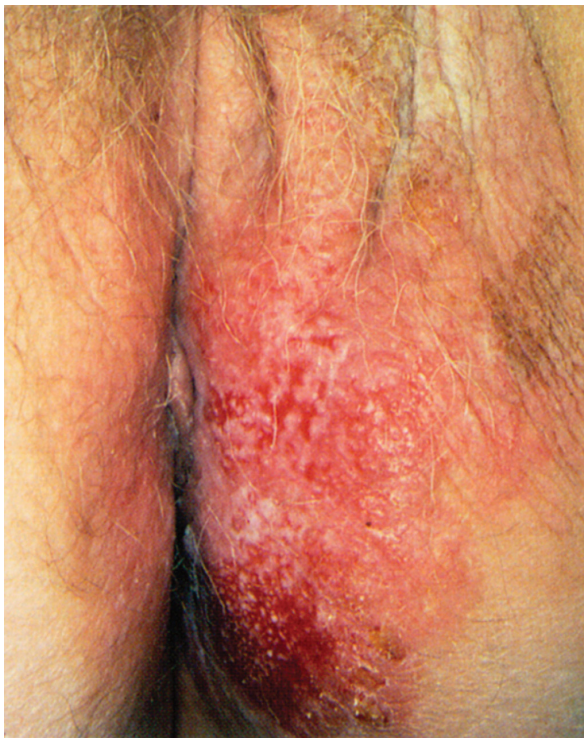

Figure 5. Sharply demarcated erythematous area with overlying 'cake icing' effect.

Management

Surgical treatment

Surgical excision is the standard choice of treatment and is tailored to the extent of the lesion. A complete excision of the lesion is complicated by high recurrence rates of vulval Paget's disease, likely secondary to patchy infiltration, multicentricity, finger-like projections emanating from the tumour which are only visible on immunostaining, and infiltration of cells under the dermis which all increase the propensity of the disease to be present in apparently normal-looking skin. The risk of recurrence has been cited to be as high as 70% (Parashurama et al, 2017).

Studies have demonstrated there is no correlation between surgical margin, tumour size and the rate of recurrence (Molinie et al, 1993; Tebes et al, 2002; Black et al, 2007; Shaco-Levy et al, 2010; Jones et al, 2011; Mendivil et al, 2012; Onaiwu et al, 2016). Parker et al (2000) demonstrated a recurrence rate of 31% in those with complete surgical resection compared to a 33% recurrence rate in those with inadequate margins. However, reducing the margin size could allow for less invasive surgery and therefore a reduction in the surgical time, anaesthetic risks and postoperative morbidity associated with radical surgery. This could be a better option for patients with a localised lesion. The recurrence rate of vulval Paget's disease following a radical vulvectomy, hemi-vulvectomy and wide local excision has been reported as 15, 20 and 43% respectively (Delport, 2013), demonstrating some evidence in support of an increased excision to reduce the recurrence of the disease. However, it should be noted that most women diagnosed with vulval Paget's disease will not be diagnosed with advanced, invasive stage vulval Paget's disease, and it is the depth of lesion invasion or metastasis which is associated with a poorer prognosis (Onaiwu et al, 2016). A review of a single-centre experience of vulval Paget's disease showed that, regardless of the original treatment choice, over half of the women treated had multiple recurrences, with one patient experiencing ten recurrences (Onaiwu et al, 2016).

Mapping biopsies has limited clinical value for preventing the recurrence of vulval Paget's disease, as the biopsies are not representative of the surrounding epithelium and may be subject to false negative results (Appert et al, 2005).

Intraoperatively freezing sections of a lesion has no clinical value since margin status is not predictive of disease recurrence.

Mohs micrographic surgery involves sampling seemingly uninvolved margins of the lesion to test for the presence of Paget's cells, with the aim of maximising the removal of cancerous cells. Mohs micrographic surgery is time-consuming, requires specialist staff, and is associated with a prolonged procedure and increased morbidity because of the extensive excision. In addition, it is associated with false negative results and, as margin status has no bearing on overall prognosis, is not routinely performed.

Topical application of 5-fluorouracil has been ascribed to aid delineation of the lesion during surgery. Misas et al (1991) described the use of fluorescein and ultraviolet light to visualise disease margins as an adjuvant to surgical management. Despite a positive predictive value of 97% and a negative predictive value of 99.9% this is not commonly used.

Sentinel lymph node biopsy has been suggested because of the high morbidity associated with lymph node dissection. However, there are currently no data to support the practice of sentinel lymph node biopsy. Inguinal lymph node dissection is recommended if there is evidence of invasive disease with depth of invasion >1 mm (Hatta et al, 2004; Morrison et al, 2020).

Topical treatment

Imiquimod is an immune modulating cream and promotes the action of the innate and adaptive immune system. It is currently licensed for the treatment of dermatological conditions such as actinic keratosis, warts and basal cell carcinomas. However, it has been used off-licence in patients with vulval Paget's disease and case reports, small scale case series and studies have shown promising results. Imiquimod is generally well-tolerated but does produce local side effects including erythema, oedema, pain, itching and erosion (Londero et al, 2013). A review of the literature in 2013 demonstrated a 50% clinical resolution of primary lesions and 73% of recurrent lesions (Sanderson et al, 2013). Despite these potentially promising results, its use should be evaluated on an individual basis, taking

into consideration the site of lesion, age of the patient, comorbidities for surgery and the risk to benefit ratio for surgery.

There are many studies describing the benefits of imiquimod (Table 2), but there is a lack of consensus on the treatment regimen. In the authors' practice, it is advised that imiquimod is thinly applied to the lesion at night, three times per week until the lesion disappears, which tends to take around 6–8 weeks but a maximum of 16 weeks can be given.

Other treatments trialed in the management of Paget's disease include: topical treatment with 5-flurouracil – a pyrimidine analogue which inhibits DNA synthesis (Del Castillo et al, 2000), systemic chemotherapy (Thirlby et al, 1990; Yamazaki, 1997), androgen-receptor antagonists because in 78% of extra-mammary Paget's disease cases, the Paget cells have been found to be androgen receptor positive (Londero et al, 2013; Kasashima et al, 2010), trastuzimab (Plaza et al, 2009), radiotherapy (Dilmé-Carreras et al, 2011; Yao et al, 2018) and photodynamic and laser therapy (Londero et al, 2013). Many of these treatments have been superseded by the use of imiquimod and, as no effective treatment regimens for have been developed, these treatments are not discussed in detail in this review. However, it has been described in the literature that in cases of extensive disease, where surgery or imiquimod therapy was not appropriate or possible, the use of these alternative treatments have been used to improve the outcome of the patient. A summary of the prescribed treatments for Paget's disease are described in Table 3, along with their quoted recurrence risk.

Table 2. Studies of the efficacy of imiquimod

Reference	Cases	Duration of treatment	Indication	Results	Recurrence and duration of follow up	Secondary treatment	Side effects and comments
Cowan et al (2016)	Eight women, median age 71.5 years	5% imiquimod 3 times per week (12 weeks)	Recurrent non-invasive Paget's disease	Six women (75%) clinical and histological remission	Recurrence was seen in four of these six women on a median follow up of 35 months	None opted for further surgery. Three of five surviving patients opted to continue on imiquimod	One patient withdrew because of an intolerance to the side effects. None progressed to invasive disease
Feldmeyer et al (2011)	One woman aged 59 years	5% imiquimod 3 times daily (18 weeks)	Primary lesion	Remission achieved	12 months	NA	NA
Herranz et al (2012)	Three women aged 58, 66 and 82 years	5% imiquimod once daily for 3 weeks then alternate days for 13 weeks	Primary lesion	Remission achieved	53 months	NA	NA
Hiraldo-Gamero et al (2011)	One woman aged 72 years	5% imiquimod nightly 6 nights per week for 16 weeks, reduced to three times weekly up to week 24 then weekly maintenance	Primary lesion	Remission achieved	14 months	NA	NA

General skincare

As with all vulval skin conditions, good skincare is important. Avoidance of irritants, such as panty-liners, soaps, talcum powder, wipes or deodorants, should be advised. Management of urinary incontinence should be optimised as the skin may become moist and macerated from the disease, and there is a risk of contact dermatitis if there is underlying urinary incontinence. Women should avoid washing the vulval skin more than once a day and are advised to wear cotton underwear and loose-fitting clothing. Non-perfumed, greasy emollients or ointments should be used as protective barrier creams. The high oil content of these products makes them preferrable to cream, lotion or gel preparations for use on the vulva as they are less likely to evaporate, which improves absorption and provides a more protective barrier. Barrier creams should be applied as regularly as possible throughout the day, but not used concomitantly with medicated topical preparations, such as steroid or antifungal creams; an interval of approximately 30 minutes should be advised between applying a barrier cream and application of a medicated treatment. Some patients may have a superimposed fungal or candida infection and therefore, a swab is recommended to exclude infection or allow the prescription of empirical treatment if an infection is suspected.

Prognosis

The diagnosis of vulval Paget's disease confined to the epidermis is associated with a good prognosis owing to the disease's slow progression and relatively low propensity to invade

Table 3. Potential treatments of vulval Paget's disease, with published recurrence data where possible

Treatment		Comments	Recurrence
Surgical	Wide local excision	Suitable for solitary small lesion, less invasive with reduced morbidity	43%
	Hemi-vulvectomy +/- pelvic lymph node dissection	Used for more extensive unilateral disease. Associated with surgical morbidity	20%
	Radical vulvectomy +/- pelvic lymph node dissection	Used in extensive disease and, because of radicality, is associated with greatest post-surgical morbidity	15%
	Mohs micrographic surgery	Allows for more accurate determination of margins for resection. Although is more accurate than wide local excision, it still has high false negatives and is associated with excision of large amounts of tissue	27%
	CO_2 laser	Is less cosmetically destructive, but use is limited because of minimal tissue penetration and associated pain	30—70% (Raspagliesi et al, 2006)
	Photodynamic therapy	Maintains good surrounding normal skin and is extremely well-tolerated. Case reports demonstrate good outcomes	Up to 50%
Medical	Systemic chemotherapy	Various regimens used with varying success. Used when surgery not appropriate or as an adjunct	Not stated
	Radiotherapy	Can be used as an adjunct to surgery or as primary therapy, especially in those with large disease or multiple comorbidities	Up to 60% (Hatta et al, 2008)
	Immunomodulating therapy	Imiquimod has shown promising results on primary and recurrent lesions and is generally well-tolerated. Off-licence use at present	See Table 2
	Hormone therapy	Androgen receptor antagonists have been used with disappointing results	Not stated
	Trastuzumab	Has been used in combination with paclitaxel to provide regression but limited to case report	Not stated

and metastasise. The 5-year survival of men and women with non-invasive vulval Paget's disease was 100%, dropping to 88% with the microinvasion of the papillary dermis and 15% once dermal invasion is >1 mm (Hatta et al, 2008; Ito et al, 2012). The prognosis for a diagnosis of advanced disease is very poor, with a 0% 5-year survival if inguinal lymph node metastasis is identified (DeVita et al, 1997).

The median overall survival for intraepithelial disease has been quoted to be 125 months, 71 months in those with invasive disease and 21 months in those with an associated carcinoma (Cai et al, 2013).The risk of progression from the non-invasive disease to invasive disease is 8% (van der Linden et al, 2019), and progression from non-invasive disease to invasive disease or metastasis following treatment is 2.8 and 1.9% respectively (van der Linden et al, 2016).

Follow up

There is a clear need for long-term follow up in a specialist vulva clinic because of the demonstrated progressive nature of the disease. For those who have had surgical treatment, postoperative re-examination is recommended every 3 months for 24 months to assess for recurrence, and annually thereafter.

Difficulties faced by patients or clinicians: to treat or not to treat?

Treatment of vulval Paget's disease can be challenging because of the rarity of the condition and the lack of evidence to guide clinical decisions and direction. Owing to its rarity, patients can struggle to access services which are available to people with more common conditions, such as specialist nurses, literature regarding the condition and support groups, making the diagnosis of vulval Paget's disease a somewhat isolating experience. Patients with vulval Paget's disease are often older, and may have multiple comorbidities, making frequent hospital appointments and many of the treatment options challenging. This emphasises the need to have the patient central to the decision-making process, with the support of the multidisciplinary team in order to provide a personalised management plan. Surgery, especially if extensive or involving lymphadenectomy, can be life-changing with issues of physical morbidity such as pain, irritation, dyspareunia, effect on urination and defaecation, prolonged recovery and lymphoedema and lymphocyst formation.

As mentioned earlier, invasive disease occurs in up to 25% of cases and takes just over a decade to occur. Therefore, the real question is whether the morbidity sustained by the treatment itself is worth the morbidity and potential mortality caused by the disease process. This is not something that can be advised upon on a population basis, it requires an in-depth individualised discussion with the patient, taking into account the extent of their disease and comorbidities, as well as exploring their ideas, concerns, expectations and current symptoms in order to devise a management plan that is appropriate for that particular patient. Once the disease has become invasive, the prognosis is significantly poorer, especially if metastasis has occurred and this needs to be understood by the patient, so close observation would be warranted to identify this early.

The psychosexual effects of surgery can be debilitating, causing the patient problems with their self-esteem, self-confidence, loss of femininity, change in cosmetic appearance and their sexual relationships, particularly the effect surgery may have on an existing relationship.

Many studies have shown a significant impairment to the quality of life and sexual function following vulval surgery (Likes et al, 2007; Aerts et al, 2012). Gunther et al (2014) demonstrated that 89% of patients suffered sexual complications following a radical vulvectomy and suffered worse quality of life with regard to global health status, emotional, physical and cognitive functioning, pain, sleep, appetite and fatigue, all of which impair the ability of that patient to fulfil activities of daily living and employment. This highlights the far-reaching effects vulval surgery may have on a patient's everyday life, which needs to be fully appreciated before committing a woman to disfiguring and life-changing surgery. The surgical approach and risk of recurrence should be discussed in depth with the patient, with support from clinical nurse specialists in order for her to provide informed consent.

Key points

- The diagnosis of Paget's disease can be challenging as it mimics several other vulval conditions.
- It is important to timely recognise this disease because of its potential association with synchronous neoplasms, such as colorectal adenocarcinoma.
- The management of vulval Paget's disease is difficult owing to the psychosexual and physical morbidity associated with multiple resections.
- The risk of recurrence is high and appears to be independent of modality of treatment and margin status. There is growing evidence to move away from traditional surgical excision to using topical therapy, such as imiquimod.
- Recurrences can occur several years following the initial presentation, therefore long-term follow up is recommended.

The potential use of alternative therapies, such as imiquimod, should be considered and discussed with the patient, including the lack of substantial evidence base for imiquimod and the other treatment options.

Conclusions

Vulval Paget's disease can become invasive and can be associated with an underlying carcinoma. Recommended treatment varies according to the stage of the disease, but invariably involves surgical excision. Topical chemotherapy with imiquimod appears to be an impressive emerging treatment for the management of primary vulval Paget's disease. Owing to its rarity, there are no randomised controlled trials to dictate optimal management. Results from self-selected case series are likely to be subject biased, so firm conclusions about the success rates of any one therapy cannot be made. The disease recurrence rate is very high and is difficult to predict with poor association to the size of the tumour and the excision margins. Metastasis can occur in advanced disease with very poor prognosis, necessitating prolonged follow-up care.

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Conflicts of interests

The authors declare that they have no conflicts of interest.

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Figure 5 is reproduced by kind permission of Mr David Nunns.

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