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REVIEW

Extramammary Paget's disease

Introduction

Extramammary Paget's disease (EMPD) is a rare neoplastic condition of apocrine gland-bearing skin. The most common site of involvement is the vulva, although perineal, perianal, scrotal and penile skin may also be affected. It is important because diagnosis is frequently delayed and there is a high incidence of associated invasive disease. This article reviews the clinical and histopathological features and the various treatment strategies that have been used.

Methodology

Medline was searched using the following terms: 'Vulval Paget's', 'Extramammary Paget's', 'EMPD', 'vulva AND Paget's' and 'vulva AND EMPD'. All published studies and trials on EMPD were evaluated for appropriateness for inclusion in the review.

History

Sir James Paget reported malignant change of the areola skin in association with underlying breast carcinoma in 1874.[1] He believed the neoplastic cells derived from large lactiferous ducts and that changes in the skin both preceded and induced malignant change in the underlying breast tissue. He suggested that similar changes might be seen at other epithelial sites and some years later, EMPD of the scrotum and penis were described.[2] Perianal EMPD was first described in 1893[3] and the first case of vulval EMPD in 1901.[4]

Incidence

EMPD is rare but the precise incidence is unknown. It affects individuals between the ages of 50 and 80 years and is more common in women and white-skinned races.[5] Familial occurrence is rare, with six reports in the Japanese and one in the British literature.[6] Vulval EMPD represents 1% to 5% of all vulval malignancies, with a peak age incidence of 65 years.[7,8]

Clinical features

The most frequently affected site is the vulva, followed by perineal, perianal, scrotal and penile skin. Less commonly, the axilla, buttocks, thighs, eyelids and external auditory canal may be affected.[9] If EMPD arises at sites relatively free of apocrine glands, it is referred to as 'ectopic EMPD'. Multifocal Paget's disease has been reported, usually comprising coincident anogenital and axillary disease, or less frequently concurrent mammary and extramammary disease.[10]

Patients present with well-demarcated, erythematous or leucoplakic plaques. Most cases appear eczematous but others are crusting, scaling, papillomatous, lichenified, leucokeratotic, ulcerated or bleeding.[11] Dubreuilh[4] was the first to describe the characteristic 'cake-icing' appearance of vulval EMPD, consisting of erythematous changes associated with white islands and bridges of hyperkeratotic epithelium. A palpable mass with or without lymphadenopathy raises suspicion of invasive disease.

Pruritus is the most common symptom, occurring in around 70% of patients. Other complaints include burning, irritation, pain, tenderness, bleeding and swelling. The disease is asymptomatic in 10% of patients. The average time interval from the onset of symptoms to diagnosis is two years.[5,12,13]

Differential diagnosis

Diagnosis and definitive treatment are often delayed as the non-specific clinical findings result in misdiagnosis, and elderly patients frequently present late.[14] EMPD is commonly mistaken for: contact dermatitis, psoriasis, fungal infection, seborrhoeic dermatitis, lichen sclerosis, anogenital intraepithelial neoplasia, melanoma, histiocytosis and mycosis fungoides.[15] Vulval or perianal EMPD may also be misdiagnosed as: leucoplakia, basal cell carcinoma, squamous cell carcinoma, condylomata accuminata, Crohn's disease or hidradenitis suppurativa.[8] Skin biopsies should be performed in all patients with pruritic eczematous lesions of apocrine gland-bearing areas that have failed to respond to four to six weeks of standard topical treatment.[5,8,12]

Histopathology

The diagnosis of both mammary and extramammary disease rests on the histological identification of unique

infiltrating intraepithelial neoplastic cells showing glandular differentiation.[16,17] Paget's cells are large round cells with abundant pale cytoplasm and large vesicular nuclei, which may be central or laterally compressed. Mitotic figures are unusual. They may be distributed singly or in groups (as strands, nests or glandular patterns) within the epidermis and epithelium of adnexal structures. Hyperkeratosis, acanthosis and parakeratosis can occur in other areas. In the upper dermis, there may be a dense inflammatory infiltrate of small round cells and plasma cells.

Immunohistochemistry has been used both to diagnose Paget's disease and to identify the likely cell of origin.[18,19] Paget's cells typically stain for markers of apocrine and eccrine derivation including low molecular weight cytokeratins (CK), gross cystic disease fluid protein (GCDFP-15), periodic acid-Schiff (PAS) and carcinoembryonic antigen (CEA). Staining for S100, an acidic calcium binding protein, is negative.[20–22] Mammary and extramammary Paget's disease show characteristic, although slightly different immunophenotypes and it is now becoming apparent that there are antigenic differences between primary intraepidermal Paget's disease (CK7 positive, CK20 negative, GCDFP-15 positive) and Paget's disease that has spread from an associated internal carcinoma (CK7 negative, CK20 positive, GCDFP-15 negative).[8] The main histological diagnoses to exclude in the vulva are anogenital intraepithelial neoplasia (S100 negative, PAS negative) and superficial spreading malignant melanoma (S100 positive, PAS negative, CEA negative, cytokeratin negative).

Pathogenesis

Mammary Paget's disease almost always arises as a result of epidermotropic metastasis.[23] Malignant cells extend into the epidermis from an underlying breast carcinoma via the lactiferous ducts. By contrast, the histogenesis of EMPD remains controversial. An apocrine origin is suggested by its predilection for apocrine gland-bearing sites and its staining with markers of apocrine differentiation such as CEA and GCDFP.[20] However, it can occur in apocrine poor (ectopic) sites and the abovementioned markers are not specific for apocrine glands (e.g. GCDFP has been found in eccrine glands). Other suggested origins include eccrine glands, 'mammary-like' glands, pluripotent keratinocyte stem cells or direct spread from an underlying adenocarcinoma.[8]

At present, the most popular theory is that EMPD may arise either as a primary intraepidermal neoplasm of the epidermis (primary EMPD) or less commonly as a result of spread from an underlying internal malignancy (secondary EMPD).[24] In primary EMPD, Paget's cells probably originate from intraepidermal portions of sweat/apocrine glands or from primitive basal cells within the epidermis. Primary Paget's disease may progress from *in situ* intraepidermal neoplasia to dermally invasive adenocarcinoma, which may in turn metastasise to local lymph nodes and distant sites.[8] Paget's disease may also arise following epidermotropic spread of malignant cells from an underlying neoplasm in a dermal adnexal gland or a local internal organ with contiguous epithelium (secondary EMPD).[25]

Some investigators believe that EMPD may be associated with a generalised tendency to neoplasia, especially adenocarcinoma, as there is a high rate of synchronous and metachronous cancers in these patients.[8] A spatial and temporal association of EMPD of the vulva and high grade vulval intraepithelial neoplasia (VIN) has been reported by some authors, although this is extremely rare.[26]

Associated malignancy

There appear to be important regional differences in risk of underlying adnexal or visceral malignancy, with perianal EMPD having a higher frequency of associated cancer than vulval EMPD (Table 1). Diagnosis of EMPD should be accompanied by a thorough investigation for an underlying carcinoma. Suitable investigations may include: pelvic ultrasound scan, hysteroscopy, laparoscopy and/or an MRI scan of the pelvis; colonoscopy, sigmoidoscopy and/or barium enema; cystoscopy and IVP; mammogram and chest X-ray.

Table 1. The frequency of associated adnexal carcinoma and underlying internal visceral malignancy in case series of patients with EMPD.

Study	Total no. of cases of EMPD reviewed	% patients with an associated adnexal carcinoma	% patients with an underlying visceral malignancy
Chanda[27]	197	24	12
Besa *et al.*[28]	65	0	26
Fanning *et al.*[29]	100 (vulval)	4	20
Parker *et al.*[12]	76 (vulval)	17	11
Goldblum and Hart (1998)[30]	11 (perianal)	10	45
Marchesa *et al.*[31]	14 (perianal)	7	14

Treatment

Surgery

Although generally accepted to be the standard modality of treatment, all surgical procedures, even extensive resections, are complicated by high local recurrence rates. This is due to several troublesome features displayed by EMPD, namely, irregular margins, multicentricity and the propensity of the disease to involve apparently normal skin.[32,33] Zollo and Zeitouni[5] reviewed the surgical results of 30 cases of vulval or perianal EMPD and found a recurrence rate of 44% overall. Perhaps not surprisingly, patients with invasive disease had higher rates of local recurrence than those with *in situ* disease (67% compared with 35%). In a similar review by Fanning *et al.*,[29] 100 patients treated surgically for vulval EMPD had a composite recurrence rate of 34% at a median of three years. More radical procedures were associated with lower rates of recurrence with radical vulvectomy, radical hemivulvectomy and wide local excision being associated with recurrence rates of 15%, 20% and 43%, respectively.

Frozen section analysis of surgical margins can be misleading in EMPD, appearing negative intra-operatively but proving to be positive on later permanent histological analysis.[34] This is partly because of the multicentric nature of EMPD and partly because time constraints preclude the totality of margin status from being assessed intra-operatively.[35] Fishman *et al.*[34] found that the ability to differentiate surgical margins by frozen section analysis on the one hand, and visual judgement on the other, was not statistically different, with false negative rates of 38% and 35%, respectively. Furthermore, in that study, permanent margin status was not predictive of local recurrence, as 33% with negative margins and 40% with positive margins showed disease recurrence.

By contrast, others have reported a reduction in local disease recurrence by up to 50% following surgical excision of vulval EMPD where intra-operative frozen section analysis was used.[36] Positive margins were shown to be associated with a shorter time interval to recurrence with a mean time of 1.4 years in those with positive margins compared with 4.4 years with negative margins. The disadvantage of intra-operative margin status analysis was that patients often ended up with a complete vulvectomy because of clinically unapparent extensions of disease.[37]

Mohs' micrographic surgery (MMS) has shown promise as a method for reducing local recurrence rates in EMPD. The key to MMS is the excision and control of complete peripheral and deep resection margins in one plane, allowing orientation, mapping and re-excision of microscopic tumour extension. This procedure allows maximal tissue sparing of critical anatomic structures and is performed under local anaesthesia in the outpatient department.[38] Coldiron *et al.*[32] described six cases of EMPD treated with MMS, two of which recurred. They combined their data with 42 cases obtained from a written survey of members of the American College of Mohs' Micrographic Surgery and reported a composite recurrence rate of 23% *versus* 33% for standard surgery. Zollo and Zeitouni[5] also reported higher recurrence rates in patients with vulval or perianal EMPD treated by wide local excision (43% of patients with vulval and 50% of patients with perianal EMPD) compared with those treated by MMS (27% and 28% recurrence rates, respectively). Some Mohs' surgeons believe that EMPD is poorly suited to MMS because it is a multifocal non-contiguous neoplasm, thus explaining treatment failures. Attempts have been made to enhance lesion demarcation with the pre-operative use of topical 5-fluorouracil and this has shown some benefit.

Radiotherapy

Surgery for EMPD can be extensive and mutilating and may not be suitable for some frail patients. Initial reports dismissed the use of radiotherapy in the management of this condition as it was thought that the recurrence rate was too high. However, several more recent reports in the literature suggest otherwise. Brierley and Stockdale[39] treated six cases of EMPD with local radical radiotherapy. None of the patients had an underlying adnexal carcinoma. Four patients were controlled by radiotherapy. One patient had a central relapse, which was controlled with simple excision. Another had a marginal recurrence and was retreated with radiotherapy, but died three months later from colorectal carcinoma. Besa *et al.*[28] treated nine patients with radiotherapy. The seven patients with non-invasive disease responded completely with no local recurrences. By contrast, one of the two patients with invasive EMPD experienced recurrent disease. Burrows *et al.*[40] treated five patients over a three-week period. None of the patients had an underlying adnexal carcinoma but one had carcinoma of the colon and another of the breast. They were treated with fractionated radiotherapy to an area that included a 2-cm margin clear of visible disease. All of these patients showed disease clearance extending over a mean follow up period of four years. Finally, Moreno-Arias *et al.*[41] treated two men with anogenital EMPD. Both patients received radiotherapy to a field three cm clear of the visible disease for three days a week over three weeks. No local recurrences or internal malignancies were detected at two or three years of follow up.

There are no data from randomised controlled trials directly comparing surgical excision with primary radiotherapy for EMPD. Results from self-selected case series are likely to be subject biased, so firm conclusions about the success rate of one therapy over another cannot be made. However, radiotherapy for EMPD may be indicated in patients medically unfit for surgery; for recurrence following surgery; in any patient who wishes to preserve the functional and structural integrity of the vulva by

avoiding mutilating surgery; or as an adjuvant to surgery in patients with an underlying adenocarcinoma, where there is a high risk of local recurrence with surgery alone.[42]

Chemotherapy

Topical chemotherapy

Topical chemotherapeutic agents including 5-fluorouracil, bleomycin and imiquimod have been used to treat EMPD.

5-Fluorouracil (5-FU) may be useful for symptomatic relief, pre-operative delineation of disease extent, cytoreduction prior to surgery and post-operative detection of early disease recurrence.[43,44] It is unlikely to be a curative agent in EMPD for several reasons. 5-FU reliably penetrates the skin to a depth of only 1 to 2 mm, representing the superficial layers of the epidermis. By contrast, EMPD often involves deeper epidermal layers and adnexal structures which extend into the dermis. 5-FU cannot adequately treat EMPD which extends beyond its depth of penetration and certainly cannot reliably treat underlying adenocarcinoma. Moreover, hyperkeratosis is common in EMPD and this will further impair the ability of 5-FU to penetrate effectively to the full depth of the lesion. In addition, the severe discomfort associated with chemoinflammation reduces the likelihood of patients using 5-FU frequently enough to achieve an adequate therapeutic effect.

Bleomycin was used to treat seven patients with recurrent vulval EMPD and no associated invasive carcinoma by Watring *et al.*[45] Patients received topical applications of 3.5% bleomycin ointment twice daily for two weeks, followed by a four- to six-week rest period to allow healing and to assess the response. No more than four cycles were given to any individual patient. Four patients (57%) underwent complete remission but one relapsed at 30 months and required a further treatment with bleomycin to achieve prolonged disease remission. One patient died of intercurrent illness, another developed systemic toxicity to bleomycin and one refused further treatment after achieving a partial response. Side effects included moderate to severe local pain, moist desquamation and allergic reactions.

Imiquimod was used to treat two cases of EMPD over a period of 7.5 to 12 weeks. Both patients demonstrated clinical and histological cure at the end of treatment.[46] Self-application is possible with imiquimod but severe local reactions and a subsequent lack of compliance have been described by some authors.[47]

Systemic chemotherapy

Systemic chemotherapy has also been used to treat EMPD, although the most appropriate and effective treatment regimen(s) has not yet been formulated. There have been case reports of complete responses to mitomycin C and 5-FU,[48] and carboplatin and 5-FU,[49] and partial responses have occurred with other combinations. Watanabe *et al.*[50] gave low dose combination chemotherapy consisting of mitomycin C, etoposide and cisplatin to three patients with dermally invasive vulval EMPD. Patients were treated monthly for a period of six months, and there was one complete response and two partial responses after this time. At present, the available clinical evidence supports the use of systemic chemotherapy when surgery and radiotherapy are contraindicated.[5] It may also be used to reduce disease bulk prior to surgery, allowing extensive vulval resection and skin grafting to be avoided.[50]

Photodynamic therapy

The literature contains a couple of promising reports of photodynamic therapy (PDT) being used to treat EMPD. This technique uses a tumour-localising photoreactive drug (e.g. 5-aminolevulinic acid) in combination with light of an appropriate wavelength to kill tumour cells.[51] The advantage of this approach is that it produces minimal scarring; it preserves the structural and functional integrity of the vulva and is extremely well tolerated. Furthermore, it is tumour-specific and avoids the difficulty of margins. Henta *et al.*[52] reported a case of a 74 year old woman with extensive inoperable vulval EMPD with lymph node and pulmonary metastases. Initial treatment with chemoradiotherapy achieved a 60% reduction in tumour size. The residual lesion was then treated with PDT. Topical 20% 5-aminolevulinic acid (ALA) was used to treat the superficial lesion, followed by serial intralesional instillations of 10% ALA to treat the deeper components. The patient received a total of 10 treatments, at the end of which she had near complete remission clinically and biopsy specimens confirmed the lack of tumour cells to a depth of 7 mm.

Zollo and Zeitouni[5] reported a case of penile EMPD which was treated initially with PDT to reduce the tumour size. Residual disease was then removed by MMS. Repeated lesion reduction PDT and tissue-sparing MMS continued over 42 months, resulting in minimal tissue excision and preservation of sexual function. Shieh *et al.*[53] treated a total of 16 EMPD lesions on five patients using PDT. Using topical and/or systemic PDT, three of five patients achieved complete responses.

Laser therapy

It was hoped that laser therapy would afford the successful treatment of EMPD while allowing the preservation of vulval anatomy. Unfortunately, laser therapy for

EMPD appears to be complicated by a very high recurrence rate. Louis-Sylvestre *et al.*[54] compared 52 patients who were treated either by wide local excision, laser alone or a combination of limited surgery and laser. At one year, recurrence rates were as follows: wide local excision, 23%; laser and surgery, 33%; and laser alone, 67%. The high recurrence rate following laser therapy may be due to remnant tumour or inadequate depth of treatment. It has been argued that aesthetically pleasing results are only achieved with laser if the deeper portions of hair follicles and apocrine glands are left intact, therefore leaving a possible source of residual EMPD. Another problem with laser is that it is extremely painful in the postprocedure period and many patients refuse subsequent treatment with it.[55]

Becker-Wegerich *et al.*[56] theorised that the high recurrence rate with laser is due to the multicentric nature of EMPD. In order to overcome this problem, the authors performed CO_2 laser ablation guided by photodynamic diagnosis, which allows the delineation of tumour cells using ALA-induced fluorescence. Their one patient was clear of disease at 14 months' follow up.

Peri-operative tumour mapping techniques

These techniques are of great theoretical value as EMPD is inherently a multicentric, ill-defined neoplasm. They may help to reduce recurrence rates by delineating disease extent prior to definitive treatment. Possible techniques include: photodynamic diagnosis[56]; fluorescein visualisation[57]; staged, square excisions as for lentigo maligna[58]; and the use of tumour markers, such as anti-cytokeratin 7 antibodies.[59]

Prognostic factors

The prognosis for primary EMPD confined to the epidermis is excellent. The challenge for these patients is symptom control and the early detection of local recurrence. By contrast, invasive primary EMPD carries a poor prognosis, particularly if lymphovascular invasion is present. While the number of cases available for long term study is small, it seems likely that the depth of invasion is important, with microscopic invasive disease (less than 1 mm dermal invasion) having a more favourable prognosis than lesions showing deeper invasion.[22,30] The prognosis decreases substantially with lymphovascular involvement, with a five-year survival rate of 0% in the presence of inguinal lymph node metastases.[60] Lengthy follow up is advocated in all cases of primary EMPD and each patient should be thoroughly investigated to rule out an underlying malignancy, particularly in cases of perianal or male genital disease. The prognosis of secondary EMPD depends on the prognosis of the underlying carcinoma but is generally worse than that for primary EMPD.[8]

Follow up

Follow up needs to be long term as some patients develop recurrences more than 15 years after initial treatment. Follow up is necessary to exclude both local recurrence and the development of associated internal malignancies. It is suggested that follow up for perianal EMPD should involve an annual complete examination, proctosigmoidoscopy and punch biopsy of any new lesion. Colonoscopy should be carried out every two to three years. Vulval EMPD may be similarly followed up with regular inspection of the vulva, the liberal use of punch biopsies to exclude invasive disease in any recurrent lesion and regular pelvic ultrasound scans and hysteroscopy.

Summary

EMPD is a rare condition that poses difficulties of diagnosis and management. Suspicious skin lesions not responding to topical therapy after four to six weeks should be biopsied to exclude EMPD. There is an associated malignancy in 20% to 30% of cases and a detailed investigation of the patient should be carried out at presentation to exclude invasive disease. Surgery remains the mainstay of treatment for EMPD but carries a 40% local recurrence rate. As a result of this, other treatment modalities have been used mostly on an experimental basis to treat EMPD, including radiotherapy, topical and systemic chemotherapy, Mohs' micrographic surgery (MMS), laser therapy and PDT. The British Society for the Study of Vulval Disease (http://www.bssvd.fsnet.co.uk) has established a national register of cases and patients may benefit from referral to centres of expertise in treating vulval conditions. Because EMPD is so rare, there is currently a lack of appropriately controlled clinical trials comparing the various methods of treatment and the precise role of each modality of treatment in the management of this condition has yet to be elucidated. Nevertheless, it is clear that follow up of treated EMPD must be long term whatever the primary mode of treatment, because of the propensity of this condition to recur. Multicentre randomised controlled trials are required to compare different treatments.

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