

CASE REPORT

Extramammary Paget's disease: a report of 2 cases and a review of the literature

Joon Joon KHOO, *MBBS, MPath*, and Siew Eng CHOON*, *MBBS, MRCP*.

*Departments of Pathology and *Dermatology, Sultanah Aminah Hospital, Johor Bahru, Malaysia.*

Abstract

Extramammary Paget's disease (EMPD) is a rare disorder and may be found in the vulva, scrotum, penile area, perianal region and the groin. Frequently, it is associated with an underlying regional neoplasm or internal malignancy. We report 2 cases of EMPD; one involving the scrotal area and the other the vulva. Both were elderly patients who presented to the dermatologists with chronic eczematous lesions in the perineum that did not respond to topical treatment. Skin biopsies confirmed extramammary Paget's disease. Investigations for internal malignancies were negative. However, one of the patients defaulted treatment before surgery. The other patient had two excision surgeries with skin grafting to try to achieve tumour free margins. A long term follow-up was planned for him to look for recurrences.

These cases emphasise that EMPD can mimic exudative dermatitis and present as a chronic non-healing lesion in the perineum for many years. Clinicians should have a high index of suspicion to pick up the disease early by biopsy. Various immunohistochemical markers not only can help differentiate other histological diagnoses but also help predict the presence of underlying malignancies. Management of EMPD included thorough search for occult or underlying malignancy followed by complete excision surgery with intraoperative frozen sections. Even then, recurrences are high for this disease and long term follow-up is advocated.

Key words: extramammary, Paget's disease, intraepithelial, perineum.

INTRODUCTION

Sir James Paget first described Paget's disease of the nipple in 1874 in 15 patients with underlying ductal breast carcinoma.¹ In his original description, Paget himself suggested an extramammary location of the disease. However this was based on clinical impression and it was only in 1889 when Crocker² reported lesions affecting the scrotum and penis with histological features similar to that described by Paget. This was the first case of extramammary Paget's disease proven histologically. In 1901, Dubreuilh proceeded to describe Paget's disease of the vulva.³

Extramammary Paget's disease (EMPD) is an uncommon intraepithelial adenocarcinoma. It has been observed in areas with numerous apocrine glands in the anogenital region, groin, axilla, external ear canal^{4,5} and eyelid⁶.

We reviewed the literature and report 2 cases of this disease in the perineum to demonstrate

the clinical presentation, pathology and management of these patients. It is also to remind us of this entity in the differential diagnosis of a long-standing 'inflamed' skin lesion in the perineum that does not respond to medical treatment. Clinicians should have a high index of suspicion to proceed with a biopsy to confirm the diagnosis. Delayed diagnosis would lead to a poorer prognosis if invasion had occurred.

CASE REPORTS

Case 1

A 68-year-old Chinese man presented with a 17-year history of recurrent itchy lesions affecting the groin and scrotal skin. He had allergic rhinitis for more than 40 years and bronchial asthma for the past 10 years. He was currently on Betamethasone valerate and terbutaline inhalers for bronchial asthma and perindopril for hypertension. His general health was otherwise good.



FIG. 1: Extramammary Paget's disease presenting as an ill-defined erythematous scaly plaque affecting left scrotal skin.

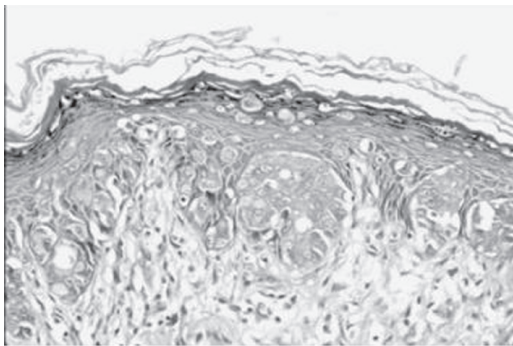


FIG. 2: Photomicrograph of the skin with Paget's disease. Groups and single lying large pale tumour cells are seen within the epidermis. (Haematoxylin and eosin stain, original magnification X 200).

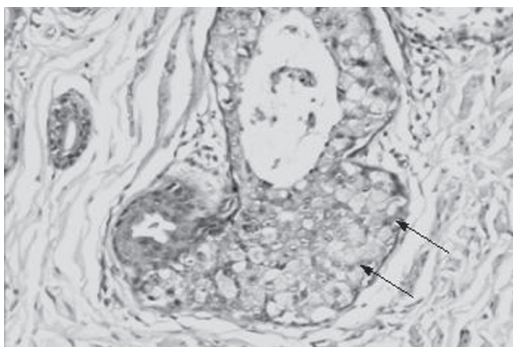


FIG. 3: Photomicrograph showing groups of Paget's cells (arrows) extending into the eccrine sweat ducts. (Haematoxylin and eosin stain, original magnification X 400).

Physical examination revealed an erythematous plaque with central scaling over the left scrotal skin and proximal penile skin dorsally. He also had an erythematous plaque with minimal scaling and central maceration on

his left groin. A provisional diagnosis of scrotal eczema and taenia cruris was made. The taenia cruris settled with a course of oral Itraconazole, but the scrotal plaque (Fig. 1) persisted. A biopsy was performed which revealed Paget's disease (Fig. 2).

A proctosigmoidoscopy, cystoscopy, and chest X-ray showed no abnormality. The patient subsequently underwent a wide local skin excision of the left scrotum and the base of the penis. No frozen section was done. Histopathology of the specimen revealed extramammary Paget's disease. There were groups of large round tumour cells with atypical nuclei extending throughout the epithelial layer in a pagetoid fashion. Small groups of tumour cells also extended into contiguous epithelium of hair follicles and eccrine sweat ducts (Fig. 3). The cytoplasm of the tumour cells was abundant, lightly eosinophilic and contained intracytoplasmic mucin. The underlying dermis showed chronic inflammatory infiltrates with a few small foci of tumour cells in the superficial dermis. The depth of invasion was less than 1mm from the basement membrane. The tumour cells were reactive to epithelial membrane antigen and carcinoembryonic antigen but not to S100 or HMB 45. The margins of the excision showed tumour involvement.

Six weeks later a re-excision was performed with skin grafting but unfortunately the inferior margin was still not clear of tumour cells. The patient declined further excision and he was closely followed-up. There was no evidence of a clinical relapse 12 months after surgery.

Case 2

An 85-year-old Chinese female presented with a non-healing pruritic lesion on the right labium majora for a duration of 8 months. Physical examination showed a flaky and inflamed-looking lesion. She had no significant medical history. She was diagnosed to have eczema and was treated with topical steroids. The lesion did not improve and appeared the same after 3 months. A biopsy of the lesion showed groups and nests of large, pale and vacuolated tumour cells within the epidermis. The epidermal basement membrane was not breached. There was no invasive carcinoma in the biopsy. The tumour cells contained intracytoplasmic mucin, staining positively with mucicarmine stain. They were reactive to epithelial membrane antigen and carcinoembryonic antigen but not to S100 or HMB 45. The diagnosis was histologically confirmed as extramammary Paget's disease.

Complete physical examination including abdominal and breast examination did not show any tumour masses. Chest X-ray, per-rectal examination and Papanicolaou cervical smear showed no abnormality. She was advised to undergo a simple vulvectomy with more investigations planned before surgery viz. colonoscopy and cystoscopy. However, the patient refused treatment and defaulted follow-up.

DISCUSSION

Extramammary Paget's disease is an uncommon entity. It arises in areas rich in apocrine glands. The common sites include the vulva, scrotum, penile area, perianal region and the groin. Other possible sites are the axilla, external ear canal and the eyelid.

Although the histogenesis is uncertain, it is generally believed to be of apocrine origin. The lesion follows the pattern of skin with a high density of apocrine glands. Moreover, some of these lesions show sialomucin production and glandular formation. However, other authors suggested that Paget's disease might arise from keratinocytes, melanocytes, pluripotential germinative epidermal cells or eccrine gland sweat cells⁷. Some cases have been supposed to have an eccrine origin, suggesting a common primitive origin that allows differentiation into apocrine or eccrine glands.

Most cases of extramammary Paget's disease are intraepithelial neoplasms and remain in-situ for a long period of time with a potential for dermal invasion. Lesions with purely intraepithelial involvement have a good prognosis while those with deep dermal invasion have a poorer prognosis. The concept of minimally invasive Paget's disease was introduced by Feuer et al.⁸, who defined it as invasion of Paget's cells to a depth of no more than 1mm below the basement membrane. After the first surgical excision of the tumour, the first patient was found to have a minimally invasive tumour but it has been noted that minimally invasive Paget's disease has no adverse effect on the prognosis compared to the pure intraepithelial form.⁹

Primary EMPD are intraepithelial tumours with no underlying malignancy while secondary EMPD are those with associated malignancy. It is said EMPD has the potential to develop from or be the cause of an underlying adenocarcinoma. There is an overall increased rate of associated malignancy that ranges from 12%¹⁰ to 33%.¹¹

Most cases of vulvar Paget's disease, almost 95% of the Goldblum et al. series,⁹ began as primary cutaneous intraepithelial neoplasm with no associated malignancy. However, a great number of perianal EMPD are associated with regional or internal malignancy. The rate of associated malignancy in perianal Paget's disease ranged from 33 to 86 % according to available literature. In common with perianal EMPD, Paget's disease of male genitalia is thought to have a more frequent association with internal malignancy than vulvar Paget's disease. This may be internal malignancy or underlying associated regional malignancy from the sweat glands or anal glands.

Extramammary Paget's disease of external male and female genitalia may be associated with neoplasms arising in the bladder and urethra or, in men, the prostate while vulvar Paget's disease had also been described in association with breast carcinoma.^{12,13} On the other hand, EMPD of the perianal skin is strongly associated with adenocarcinoma of the anus and colorectum. Thus, a thorough work-up is required for these patients to find any occult or associated internal malignancies before proceeding with surgery. A full physical examination with per-rectal examination and palpation of the breasts for female patients are essential preliminary examinations. Cystoscopy, proctosigmoidoscopy, colonoscopy, CT scan of abdomen and in addition for the female patients: mammography and Papanicolaou smears are advocated. There was no occult malignancy found in the first patient before surgery was planned. He would be grouped as primary extramammary Paget's disease. This has a better prognosis than one associated with an underlying malignancy. The prognosis for EMPD with an underlying malignancy depends on the prognosis of the underlying carcinoma. The second patient also did not show any underlying malignancy in the preliminary investigations but she defaulted treatment before further investigations could be completed.

Extramammary Paget's disease is more common in elderly patients. The mean age of patients with penoscrotal extramammary Paget's disease was 76 years in one series of 6 patients¹⁴ while that for vulvar Paget's disease in a study of 100 cases¹⁵ was 70 years. Both our patients were in this age range. Clinically, extramammary Paget's disease of the perineum is manifested as a non-healing eczematous lesion. The patients commonly complain of pruritus and rash. Most patients had the symptoms for a long period of

time. Our first patient had complained of intermittent skin irritation for more than 17 years. In both patients, an incorrect diagnosis was made at the first few visits and various topical creams were given over a period of time before biopsy. Both the cases highlighted the important point that extramammary Paget's disease could easily be mistaken for some benign eczematous lesions or skin infections. There is no characteristic clinical presentation of extramammary Paget's disease. It could be missed if no biopsy was done. Therefore, any eczematoid lesion in the perineal region that has not improved with medical treatment should have a biopsy to rule out Paget's disease histologically.

The diagnosis of Paget's disease can only be confirmed by histology. On haematoxylin and eosin staining, there are intraepithelial tumour cells that are large with faintly eosinophilic cytoplasm that stands out in contrast to the surrounding epithelial cells. The cells may occur singly or in clusters. They are found in the epithelial layer in a pagetoid spread. In more than 90% of cases, the tumour cells contain intracytoplasmic mucin. These were demonstrated in both our cases. Paget's cells are reactive to epithelial membrane antigen and carcinoembryonic antigen but not to S100 or HMB45. This helps to exclude other differential diagnoses. Possible differential diagnoses are superficial spreading malignant melanoma, pagetoid Bowen's disease, mycosis fungoides, and Langerhans cell histiocytosis. These stains were done for both our cases to help conclude the histological diagnosis of EMPD and exclude the other differential diagnoses mentioned.

More recent studies^{9,16,17} suggested that the pattern of immunohistochemistry staining in particular cytokeratin (CK) and gross cystic disease fluid protein (GCDFP15) expressions could help predict the presence or absence of associated internal malignancy. Tumour cells in EMPD with an underlying carcinoma frequently show reactivity to both cytokeratin 7 and 20 while pure intraepithelial EMPD are cytokeratin 7 positive but cytokeratin 20 negative. GCDFP15 is strongly expressed in cases of vulvar and perianal EMPD without an underlying malignancy. In their analysis of 11 perianal Paget's disease, Goldblum et al.¹⁶ found 5 with rectal adenocarcinoma. The immunophenotype in four cases with rectal carcinoma studied was CK7+/CK20+/GCDFP15-. The 6 remaining patients had no documented rectal carcinoma. Four such cases studied with no rectal carcinoma

showed CK7+/CK20-/GCDFP15+. In another study, Goldman et al.⁹ also found that eleven of the 13 pure intraepithelial vulvar Paget's disease (85%) had Paget's cells that were CK7+ and GCDFP15+ but not for CK20. Only 2 of these 13 cases with no associated malignancy had Paget's cells that were CK7+/CK20+/GCDFP15+. Unfortunately, our laboratory does not have these immunohistochemical markers and thus the expressions of these markers for both our cases were not known. However, where these tests could be performed if the results showed CK7+/CK20+/GCDFP15-, we could suspect a higher possibility of an underlying or associated malignancy and perform a more thorough search. We could also be more vigilant in these cases in the follow-up and perhaps repeat investigations periodically.

The treatment of choice for extramammary Paget's disease is wide local excision with microscopically clear margins. Ideally, there should be a 1cm margin of normal skin. In some cases surgical excision may require split-thickness skin graft, as in our first case. However, as the lesion is usually ill defined, complete excision with tumour-free surgical margins may be difficult. This was seen in the first patient who required multiple excisions when the margins of both excision surgeries were not clear. No frozen section was done in both surgeries for him and visual 'eyeballing' of the lesion by the surgeon appeared inadequate. This case highlighted the difficulty in achieving tumour-free surgical margins in EMPD. The possible reason for not getting clearance was the tumour might have extended beyond the clinically apparent borders. Whenever possible, the edges of the resection should be checked intra-operatively by frozen section¹⁸ as this can help reduce the need for subsequent surgeries.¹⁹ Some workers even suggested fluorescein-aided visualisation of margins to predict the extent of the lesion.²⁰ On the other hand, recurrences after resection with Mohs micrographic surgery occurred in some cases and diagnostic accuracy of intraoperative frozen section could be poor.^{21,22} This was because extramammary Paget's disease not only extended beyond the visible lesion but was often multifocal. In many cases, skip lesions had been demonstrated histologically away from the main lesion viz. the urethra, upper vagina and the cervical epithelia.^{23,24} Thus, inadequate histological sampling by the surgeon for frozen section might result in missed positive lesions. Perhaps, preoperative multiple punch biopsies to map out the lesion in the first sitting and then

followed by definitive excision surgery at the second sitting, with adequate sampling intraoperatively for frozen section could help achieve tumour-free surgical margins.

The rate of local recurrences is high for extramammary Paget's disease. In one study²⁵ of 30 patients with Paget's disease of the vulva, perianal region, perineum and scrotum, Zollo et al. found 44% of their patients developed recurrence following conventional surgical treatment. Local recurrences occurred even in patients with tumour-free margins. The multifocal nature of the condition might account for this. In their study²¹, Fishman et al. found nine of the 11 (82%) recurrences of Paget's disease had permanent surgical margins that were negative for Paget's disease at the preceding operation. In our first patient the tumour had micro-invasive components with one surgical margin involved after the second surgery. The patient had further refused resection and his prognosis is guarded. Close monitoring and follow-up for recurrences would be the best plan for him. Any new skin lesions would be biopsied. It is generally agreed that local recurrences are treated the same way with multiple resections and wide surgical excision with tumour-free margins. This may require simultaneous reconstructive procedure. However, alternative treatment such as laser surgery, topical chemotherapy and radiotherapy can be given for local control when wide local excision is not possible. Distant metastasis rarely occurs although it can be fatal.

The management of extramammary Paget's disease associated with an underlying neoplasm is directed towards the appropriate treatment for the associated neoplasm.

Close long-term follow-up is essential in all cases of extramammary Paget's disease. This is because of the increased risk of developing invasive cancer and association with other internal malignancies and also to look for local recurrences. In cases of perianal Paget's disease, Bech et al.²⁶ and Jensen et al.²⁷ suggested a follow-up programme which included complete physical examination and a random biopsy of the perianal region once a year with a colonoscopy at 2 to 3-year intervals. Others advocated punch biopsy of any new lesion and even random biopsy at the edges of split-thickness skin graft at timely intervals.

ACKNOWLEDGEMENTS

We would like to thank the Director General, Ministry of Health, Malaysia, for his permission to publish this paper and Dr. K.E. Tey and Mr. K.C. Saw who helped manage the first patient and Ms CW Chin for helping in preparation of the manuscript.

REFERENCES

1. Paget J. On disease of mammary areola preceding cancer of the mammary gland. *St Bartholomews Hosp Rep* 1874; 10:87-9.
2. Crocker HR. Paget's disease, affecting the scrotum and penis. *Trans Pathol Soc* 1889; 40:187-91.
3. Dubreuilh W. Paget's disease of the vulva. *Br J Dermatol* 1901; 13:407-13.
4. Fligel Z, Kaneko M. Extramammary Paget's disease of the external ear canal in association with ceruminous gland carcinoma. *Cancer* 1975; 36:1072-6.
5. Gonzalez-Castro J, Iranzo P, Palou J, Mascaro JM. Extramammary Paget's disease involving the external ear. *Br J Dermatol* 1998;138(5):914-5.
6. Whorton CM, Patterson JB. Carcinoma of Moll's glands with extramammary Paget's disease of the eyelid. *Cancer* 1955; 8:1009-15.
7. Nagle RB, Lucas DO, McDaniel KM, Clark VA, Schmalzel GM. Paget's cells: New evidence linking mammary and extramammary Paget's cells to a common cell phenotype. *Am J Clin Pathol* 1985; 83(4):431-8.
8. Feuer GA, Shevchuk M, Calanog A. Vulvar Paget's disease: the need to exclude an invasive lesion. *Gynecol Oncol* 1990; 38:81-9.
9. Goldblum JR, Hart WR. Vulvar Paget's disease: A clinicopathologic and Immunohistochemical Study of 19 cases. *Am J Surg Pathol* 1997; 21(10):1178-87.
10. Jones RE, Austin C, Ackerman AB. Extramammary Paget's disease: A critical re-examination. *Am J Dermatopathol* 1979; 1(2):101-32.
11. Nadji M, Morales AR, Girtanner RE, Ziegels-Weissman J, Penneys NS. Paget's disease of the skin: A unifying concept of histogenesis. *Cancer* 1982; 50(10):2203-6.
12. Popiolek DA, Hajdu SI, Gal D. Synchronous Paget's disease of the vulva and breast. *Gynecol Oncol* 1998;71(1):137-40.
13. Tsukada Y, Lopez RG, Pickren JW, Piver MS, J Barlow JJ. Paget's disease of the vulva: A clinicopathologic study of eight cases. *Obstet Gynecol* 1975;45(1):73-8.
14. Park S, Grossfeld GD, McAninch JW, Santucci R. Extramammary Paget's disease of the Penis and Scrotum: excision, reconstruction and evaluation of occult malignancy. *J Urol* 2001; 166(6): 2112-7.
15. Fanning J, Lambert HCL, Hale TM, Morris PC, Schuerch C. Paget's disease of the vulva: Prevalence of associated vulvar adenocarcinoma, invasive Paget's disease, and recurrence after surgical excision. *Am J Obstet Gynecol* 1999;180(1):24-7.

16. Goldblum JR, Hart WR. Perianal Paget's disease: a histologic and immunohistochemical study of 11 cases with and without associated rectal adenocarcinoma. *Am J Surg Pathol* 1998; 22(2):170-9.
17. Nowak MA, Guerriere-Kovach P, Pathan A, Campbell TE, Deppisch LM. Perianal Paget's disease: distinguishing primary and secondary lesions using immunohistochemical studies including gross cystic disease fluid protein-15 and cytokeratin 20 expression. *Arch Pathol Lab Med* 1998; 122(12):1077-81.
18. Mohs FE, Blanchard L. Microscopically controlled surgery for extramammary Paget's disease. *Arch Dermatol* 1979;115(6):706-8.
19. Stacy D, Burrell MO, Franklin EW, 3rd. Extramammary Paget's disease of the vulva and anus: use of intra-operative frozen section margins. *Am J Obstet Gynecol* 1986;155(3):519-23.
20. Misas JE, Cold CJ, Hall FW. Vulvar Paget disease: Fluorescein-aided visualisation of margins. *Obstet Gynecol* 1991;77:156-9.
21. Fishman DA, Chambers SK, Schwartz PE, Kohorn EI, Chambers JT. Extramammary Paget's disease of the vulva. *Gynecol Oncol* 1995; 56(2):266-70.
22. Coldiron BM, Goldsmith BA, Robinson JK. Surgical treatment of extramammary Paget's disease. A report of six cases and a re-examination of Mohs micrographic surgery compared with conventional surgical excision. *Cancer* 1991;67(4):933-8.
23. Costello TJ, Wang HH, Schnitt SJ, Ritter R, Antonioli DA. Paget's disease with extensive involvement of the female genital tract initially detected by cervical cytospin. *Arch Pathol Lab Med* 1988;112(9):941-4.
24. Lloyd J, Evans DJ, Flanagan AM. Extension of extramammary Paget disease of the vulva to the cervix. *J Clin Pathol* 1999;52(7):538-40.
25. Zollo JD, Zeitouni NC. The Roswell Park Cancer Institute experience with extramammary Paget's disease. *Br J Dermatol* 2000; 142(1): 59-65.
26. Beck DE, Fazio VW. Perianal Paget's disease. *Dis Colon Rectum* 1987; 30:263-6.
27. Jensen SL, Sjolín KE, Shokouh-Amiri MH, Hagen K, Harling H. Paget's disease of anal margin. *Br J Surg* 1988; 75:1089-92.