Cancer Association of South Africa (CANSA)

Fact Sheet on Paget’s Disease of the Scrotum

Introduction

The male genital system consists of both external and internal parts. The external male genitalia include the penis, urethra, and scrotum. The internal male genitalia include the seminal vesicle, testes, vas deferens, epididymis, prostate, bulbourethral gland, and ejaculatory duct.

The penis is the main part of external male genitalia, which has both sexual and bodily functions. It is able to ejaculate semen (containing sperm) during sexual intercourse and to relieve the body of urine. The urethra transports the urine from the bladder, out of the male body. Semen also travels through the urethra.

Each male has two scrotal pouches, which house certain parts of the internal male genitalia (epididymis, testes, and lower spermatic cords). The testes are the most important part of internal male genitalia because they make and store sperm, as well as supply the male body with hormones, which control the development of male characteristics and reproductive organs.

The epididymis stores, matures, and transports sperm between the testes and the vas deferens, which channels sperm toward the urethra. The seminal vesicles are adjacent to the urethra and secrete a milky fluid that is ultimately discharged through the ejaculatory duct. The bulbourethral glands also assist in the discharge of semen.

Paget’s Disease of the Scrotum

Paget’s disease of the scrotum is classified as extramammary Paget’s disease (EMPD). It is often confused with jock itch. Afrikaans men will refer to “jock itch” as onderbroekjeuk.
Paget’s Disease of the scrotum is an intraepidermal malignant neoplasm that arises in areas rich in apocrine glands. Common sites of occurrence include the vulva, perianal region, perineum, and scrotum. The lesion may be accompanied by an invasive adenocarcinoma or adenocarcinoma in situ of the apocrine glands. Generally, the prognosis is poor.

[Picture Credit: Paget’s Disease of Scrotum]


“Extramammary Paget’s disease (EMPD) is a rare cancer and is often mistaken for benign dermatologic disorders such as eczema or psoriasis. The cancer is mostly primary but can be secondary to another cancer. EMPD is treated by surgical excision but a prolonged diagnostic process can have consequences for the patient due to spread of the primary tumour or growth and spread of the associated cancer. EMPD should be considered as a differential diagnosis in patients, who do not respond to local treatment of skin lesions. Since the cancer can be secondary to other cancers, patients should be assessed with a PET-CT scan.”

**Lopes Eilho, L.L., Lopes, I.M., Lopes, L.R., Enokihara, M.M., Michalany, A.O. & Matsunaga, N.** 2015. “Paget’s disease, described by Sir James Paget in 1874, is classified as mammary and extramammary. The mammary type is rare and often associated with intraductal cancer (93–100% of cases). Extramammary Paget’s disease is considered an adenocarcinoma originating from the skin or skin appendages in areas with apocrine glands. The primary location is the vulvar area, followed by the perianal region, scrotum, penis and axillae. It starts as an ererythematous plaque of indolent growth, with well-defined edges, fine scaling, excoriations, exulcerations and lichenification. In most cases it is not associated with cancer, although there are publications linking it to tumors of the vulva, vagina, cervix and corpus uteri, bladder, ovary, gallbladder, liver, breast, colon and rectum. Differential diagnoses are candidiasis, psoriasis and chronic lichen simplex. Histopathology confirms the diagnosis. Before treatment begins, associated malignancies should be investigated. Surgical excision and micrographic surgery are the best treatment options, although recurrences are frequent.”


A patient with extramammary Paget’s disease (EMPD) had a plaque of the scrotum surgically removed. Histology and immunohistochemistry was consistent with primary EMPD. EMPD is a rare intraepidermal neoplasia mostly confined to regions of the skin with apocrine sweat glands. Clinical features include red plaques, which often will be mistakenly diagnosed as an infection or a rash. The treatment is surgical.

**Incidence of Paget’s Disease of the Scrotum in South Africa**

The outdated National Cancer Registry (2014) does not provide any information on the incidence of Paget’s Disease of the Scrotum in South Africa.
Risk Factors for Paget’s Disease of the Scrotum
Risk factors associated with Paget’s Disease of the Scrotum are:
• Advanced age
• Exposure to radiation
• Obesity
• Alcohol Consumption
• Smoking
• Race: being Caucasian

Having a risk factor does not mean that one will get the condition. A risk factor increases one's chances of getting a condition compared to an individual without the risk factors.

Also, not having a risk factor does not mean that an individual will not get the condition. It is always important to discuss the effect of risk factors with one’s healthcare provider.

Diagnosis of Paget’s Disease of the Scrotum
Symptoms are not specific - most patients report itching, burning, and soreness. A small subset of patients may be asymptomatic. Presence of pain, bleeding, and tumour formation are reported to be more common in patients affected by invasive disease. Signs and symptoms are skin lesions, often mistaken as eczema, that may be itchy or painful.

Extramammary Paget’s Disease (EMPD) typically presents in elderly white patients as a pruritic (itchy) white or red patch in the area of distribution of apocrine glands. Typically it affects a single site. However, Japanese investigators have documented triple lesions involving the anogenital regions and axilla simultaneously

Excision biopsy will confirm the diagnosis.

“Extramammary Paget’s disease (EMPD) is a rare cutaneous neoplasm. The aim of this study was to elaborate the clinical and pathological features of Chinese EMPD male patients. The study comprised 246 patients with EMPD at our institute from January 1993 to December 2012. Scrotum was the most common initial site. The average age of onset was 63.9 years but the mean delay in diagnosis was 3.6 years. EPMD spread exclusively to the inguinal lymph nodes and the right inguinal lymph nodes are more likely to suffered Paget cells infiltration. Accompanying malignancies were found in 20 patients. Pathological examination revealed 63 patients defined as invasive EMPD. Immunohistochemical detection showed various expression levels of EMA, CEA, CK7, HER2/neu, Ki67, P53, CK20 and S100 in tumor tissues, but negative expression of VIM, LCA and HMB45. HER2/neu protein exhibited a significant association with invasive EMPD. A novel histological type of EMPD with CK7-/S100+ was identified. Elevated serum PSA level was observed in only 16% patients. Invasive EMPD often had advanced age of onset. Metastatic EMPD showed significantly shorter in the delay in diagnosis and the greater length of skin lesion in contrast to others. This study demonstrates the clinical and pathological features of Chinese male EMPD patients, and may provide implications for the management of Chinese EMPD patients.”
INTRODUCTION: Extramammary Paget disease (EMPD) of the vulva has been shown to express p16 by immunohistochemistry (IHC), however, p16 expression in the vulva and scrotum has not been extensively studied in relation to human papillomavirus (HPV) within EMPD of both the vulva and scrotum.

DESIGN: Twenty-two cases of EMPD (vulva, 16; scrotum, 6) were found in our laboratory information system. P16 and HPV IHC were performed. Any p16 reactivity less than 10% was considered negative. HPV in situ hybridization for both low- and high-risk HPV was also performed on all cases.

RESULTS: Of the 6 scrotal EMPD, 3 (50%) showed weak to moderate positive reactivity for p16 by IHC. Of the 16 vulvar EMPD, 13 (81%) were positive for p16, with at least moderate (2+) intensity with a mean expression of 33.3% (range = 10% to 80%) and 62% (range = 20% to 95%) in scrotal and vulvar EMPD, respectively. None of the scrotal or vulvar cases showed positive reactivity for HPV either by IHC or in situ hybridization.

CONCLUSION: Both vulvar and scrotal EMPD can express p16 by IHC, more commonly vulvar than scrotal; however, no HPV was detected either by IHC or in situ hybridization. EMPD of vulva and scrotum does not appear to be related to HPV, and p16 expression may be regulated through a different mechanism.

Reducing the Risk for Paget’s Disease of the Scrotum
Since the exact cause of Paget’s Disease of the Scrotum is not known, no preventive methods have thus far been reported for this condition. Nevertheless, maintaining a healthy lifestyle could help one avoid/delay the onset of disease.

The following tips might be helpful:
- Maintaining healthy lifestyle habits
- Leading an active life
- Eating a healthy diet
- Limiting alcohol and smoking

Background: Extramammary Paget’s disease is an uncommon intraepidermal adenocarcinoma with poorly defined clinical implications.

Objective: The purpose of this research was to estimate the risk of second primary neoplasms in patients with extramammary Paget’s disease.

Design: This was a retrospective analysis of the Surveillance, Epidemiology, and End Results Registry (1973-2014).

Settings: The study included population-based cancer registries from the United States.

Patients: Patients who were diagnosed with anogenital Paget’s disease were included.

Main outcome measures: Risk of second primary development was measured.

Results: We identified 108 patients with anal Paget’s disease, 421 patients with male genital (scrotum or penis) Paget’s, and 1677 patients with female genital (vagina or vulva) Paget’s. Median follow-up time was 5.9 years. The risk of developing colorectal adenocarcinoma was 18.5% for patients with anal Paget’s disease. Eighty percent of colorectal adenocarcinoma diagnoses were synchronous (within 2 mo) to anal Paget’s diagnoses, whereas metachronous tumors occurred at a median time of 2.4 years. Of patients with anal Paget’s disease, 8.3% developed an anal
adenocarcinoma or non-small cell cancer. In male patients with genital Paget’s, the risk of proximal genitourinary malignancy was 9.7%, scrotal or testicular adenocarcinoma was 0.4%, and penile or scrotal squamous carcinoma was 1.7%. In female patients with genital Paget’s, the risk of proximal genitourinary malignancy was 3.0%, vaginal or vulvar adenocarcinoma was 1.4%, and vaginal or vulvar squamous neoplasm was 1.0%. Five-year overall survival was 59.7%, 73.5%, and 80.7% in patients with anal, male genital, and female genital Paget’s (p < 0.001).

Limitations: The registry did not record surveillance schedule, provider specialty, or nonprocedural therapies for extramammary Paget’s disease.

Conclusions: In the largest published cohort of patients with extramammary Paget’s disease, patients with anal Paget’s had a much higher risk of both proximal and local neoplasms as compared with patients with genital Paget’s. Patients with anal Paget’s also experienced worse survival as compared with those with purely genital Paget’s.

Management of Paget’s Disease of the Scrotum
Extramammary Paget’s Disease (EMPD) is associated with concurrent visceral malignancy in 12% to 50% of cases. The frequency and site of associated malignancies differ in various anatomic locations. The location of the EMPD predicts the underlying malignancy.

Vulvar and scrotal Paget’s disease are often associated with gastrointestinal malignancies, especially of the colon and rectum. This strong correlation between the presence of EMPD and underlying malignancy warrants lifelong endoscopic and radiographic evaluation to exclude this possibility.

EMPD that has well-defined margins with or without underlying adenocarcinoma is treated with wide local excision. Recurrence rates of 15% to 50% have been described, depending upon the site and type of resection.

Newer primary and adjuvant strategies for preventing recurrences are MMS, radiation, chemotherapy, CO₂ laser ablation and photodynamic therapy. Although local wide excision, MMS or chemoradiation are effective when used alone for the treatment of noninvasive, well-defined unicentric lesions, none of these used alone is well suited for invasive, poorly defined, multicentric EMPD.

Noninvasive EMPD usually responds well to primary and adjuvant radiation therapy, whereas the invasive type is poorly controlled with radiation therapy alone, with a 50% recurrence. As adjuvant therapy, radiation was effective in both types of lesions.

Chemotherapy remains controversial. Topical 5-FU application was effective for patients with scrotal and penile EMPD. Systemic chemotherapy using carboplatin, calcium folate and 5-FU has been found to be effective in patients with perineal EMPD. Besides adjuvant therapy, other methods of obtaining better control rates include perioperative tumour mapping. The method involves using photodynamic substances such as fluorescein, which is
taken up by EMPD cells preferentially to normal tissue. Besides ensuring completeness of excision, this method allows for conservation of uninvolved tissue leading to an optimal reconstructive result. (Chandawakar, et al., 2003).

Background: Penoscrotal extramammary Paget’s disease is a rare, slow-growing neoplasm with high frequency of local recurrence.
Aims: The aim of this study was to investigate the difference in clinicopathological characteristics between first-time and recurrent penoscrotal Paget’s disease, and to discover the potential risk factors of recurrence.
Methods: Between January 2007 and February 2014, a total of 164 Chinese patients with biopsy-proven extramammary Paget’s disease in penis and scrotum underwent wide local resection in our institution. Among them, 142 patients with first-time disease and other 22 patients with recurrent disease were enrolled in this retrospective analysis.
Results: The median duration of symptoms was much shorter in recurrent disease than in first-timers (3 vs. 24 months, P < 0.001). Patients with recurrent disease tended to have lower lesion exudation rates (27.3% vs. 51.8%, P= 0.032). In addition, patients with distant stage were more likely to obtain recurrent disease compared with first-time disease (P = 0.005). Through immunohistochemical detection of extramammary Paget’s specimen, we found that HER2/neu protein expression in the recurrent group was significantly higher than first-timers (P = 0.036).
Limitations: In this study, the information on familial history of most patients was insufficient. Moreover, due to the lack of follow-up data of our included cases, we were unable to evaluate the prognosis after diagnosis of extramammary Paget’s disease.
Conclusion: Patients with penoscrotal Paget’s disease, especially those with shorter duration of symptoms, exudation of lesions, distant-stage, Paget cells infiltrating into adnexa, and HER2/neu expression, should be followed up more carefully after surgery, as they were more likely to suffer recurrence.

Objective: To describe our surgical experience for the treatment and management of extramammary Paget’s disease (EMPD).
Methods: Our surgical approach involves excising a 2-cm margin of normal appearing skin around the EMPD-suspicious lesion. Prior to excision, the tissue is oriented and demarcated into predefined segments in coordination with a pathologist. Frozen sections are performed when necessary to guide additional excision. Xenograft or wet-to-dry dressings are applied depending on size and location of the wound while the specimen is expeditiously reviewed over the following 24-48 hours. If positive margins remain, further excision of the corresponding skin segment is performed. Delayed complex wound closure +/- split thickness skin grafting is performed once negative margins are confirmed.
Results: Ten EMPD patients were referred to two academic centers between 2014 and 2018. Two patients had positive lymph nodes at diagnosis and underwent palliative surgery and died within 12 and 29 months. The remaining 8 patients underwent a median of 1 surgery (range 0-3) with referring providers before undergoing a median of 3 surgeries (range 2-5) at our institutions to achieve negative surgical margins and wound reconstruction (7 split thickness skin grafts, 1 secondary closure). At mean follow-up of 15 months, 1 patient recurred, required further excision, and remains disease free.
Conclusion: EMPD is a rare malignancy with poorly described treatment methodologies. Due to its multifocal distribution and asymmetric spread, obtaining negative margins can be challenging. Our
systematic approach to obtaining wide margins and documenting excised skin has enabled us to achieve negative margins for this challenging malignancy.

**About Clinical Trials**
Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:
- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The *South African National Clinical Trials Register* provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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**International Support Group for Paget's Disease of the Scrotum**
An international support group can be contacted at the following URL:

https://www.myempd.com/contact/
Sources and References Consulted or Utilised


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Surgery for Scrotal Paget's Disease

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