Cancer Association of South Africa (CANSA)

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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.

[Picture Credit: Genitalia]

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.

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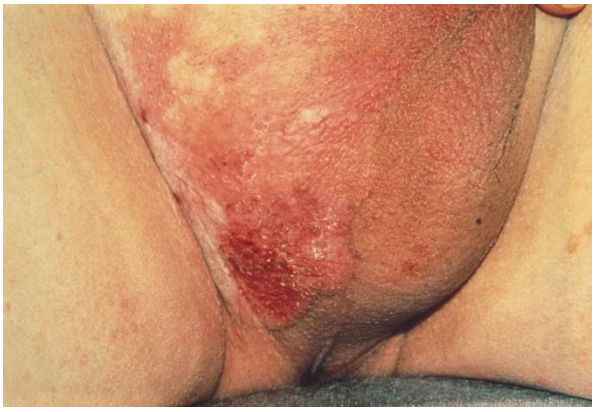
Paget's Disease of the scrotum is an intra-epidermal malignant neoplasm that arises in areas rich in apocrine glands. Common sites of occurrence include the vulva, perianal region, perineum, and scrotum. The lesion may be accompanied by an invasive adenocarcinoma or adenocarcinoma *in situ* of the apocrine glands. Generally, the prognosis is poor.

[Picture Credit: Paget's Disease of Scrotum]



Dauendorffer, J.N., Herms, F., Baroudjian, B., Basset-Seguin, N., Cavelier-Balloy, B., Fouéré, S., Bagot, M. & Lebbé, C. 2021.
"Paget's disease (PD) denotes an initially intra-epidermal adenocarcinoma that can later invade the dermis and metastasise. Among the extramammary forms of PD (EMPD), penoscrotal presentations are rarer than the vulvar and perianal forms. Once diagnosis has been confirmed by histopathological examination, a search for associated neoplasia must be conducted, although penoscrotal EMPD is less frequently associated with underlying neoplasia than mammary PD (MPD). The associated cancer most often involves a neighbouring organ, with prostate cancer being the most common, or in some cases consists of underlying cutaneous adnexal tumours. First-line therapy consists of surgical excision. Alternatives to surgery (imiquimod, CO_2 laser vaporisation, dynamic phototherapy) may be considered in certain cases."

Kruse, C., Day, D. & Lang, C. 2019. Extramammary Paget's disease can easily be overlooked. *Ugeskr Laeger*. 2019 May 27;181(22):V01190035.
"Extramammary Pagets 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."

Incidence of Paget's Disease of the Scrotum in South Africa
The outdated National Cancer Registry (2017) 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 ones 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.

Piras, A., Sanfratello, A., Boldrini, L., La Vecchia, M., Venuti, V., Amari, M.L., Orlando, M., Zichichi, L., Angileri, T. & Daidone, A. 2020.

"Extramammary Paget's disease (EMPD) is a rare cutaneous adenocarcinoma generally arising in the anogenital region. Surgery is still considered the treatment of choice for patients with EMPD, while Radiotherapy is a common alternative for inoperable cases and it's necessary in case of lack of surgical radicality. In this article, we described our experience and a review of the literature, with a particular focus on radiation-induced toxicity and on the feasibility of re-irradiation. A 70-year-old patient with EPMD underwent adjuvant radiotherapy in 2015. After 28 months for recurrence another radiant treatment was performed. No G3 (CTCAE v4) toxicity were recorded. In the last follow-up visit at 18 months, no signs of relapse were reported. A search strategy of the bibliographic database PubMed was performed. The inclusion criteria for the articles were case report, clinical prospective, or retrospective studies with histological confirmation of EMPD of scrotum and penis; studies with patients undergoing RT; studies in the past 30 years. In most of the 14 reported studies, RT was overall well tolerated. The major observed toxicity was G3 skin toxicity in one study. To our knowledge, there are no other cases of EPMD re-irradiation in literature. Our patient showed an excellent response and tolerated very well the high doses of both the radiation treatments. This suggests that the tolerance of skin to re-irradiation following a long period between the two treatments may be comparable to the normal constraints."

Al-Obaidy, K.I., Kao, C.S. & Idrees, M.T. 2018.

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

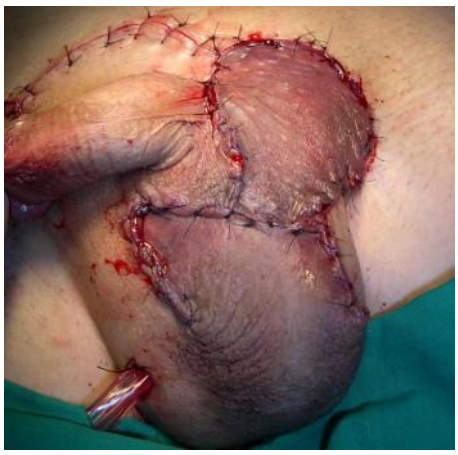
Lee, G.C., Kunitake, H., Stafford, C., Bordeianou, L.G. Francome, T.D. & Ricciardi, R. 2019.
Background: Extramammary Paget's disease is an uncommon intraepidermal adenocarcinoma with poorly defined clinical implications.
Objective: The purpose of this research was to estimate the risk of second primary 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 nonsmall 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.

[Picture Credit: Surgery for Scrotal Paget's Disease]

Newer primary and adjuvant strategies for preventing recurrences are MMS, radiation, chemotherapy, CO_2 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 fluorescin, 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).

Han, H., Niu, Y.N., Lei, H.E., Zhang, X.D., Zhou, X.G. & Tian L. 2020.

Objective: To evaluate the clinical efficacy and complications of skin graft and flap plastic technique covered the defect in perineal Paget's disease postoperatively.

Methods: The study comprised 6 patients diagnosed with perineal Paget's disease at Beijing Chao-Yang Hospital from June 2017 to July 2019, with all available clinical data reviewed. The defects after

resection of lesions were reconstructed with skin graft, advancement skin flap during the operation, respectively. The operation time, the skin graft or flap survival situation, intraoperative and postoperative complications were recorded.
Results: Of all 6 patients, Ray stage A1consisted of 1 case, A2 5 cases. The age was (68±9) years, the hospitalization time was (14.8±8.1) days, the BMI was (25.6±3.7) kg/m(2), the operation time was (132.0±80.7) min, and the average blood loss was (18.3±11.7) ml. Five cases was with Paget's disease, and 1 case with skin adenocarcinoma with Paget's disease were diagnosed by pathology. The defects of 4 cases and 2 cases after removal of the tumor were reconstructed with scrotal advancement skin flap and skin graft, respectively. The skin graft and flap survived well during afollow-up of (15.3±8.1) months.There has been no local recurrence. The foreskin edema and wound infection were noted in 4 cases and 1 case, respectively. There was no other related complications.
Conclusion: Perineal Paget's disease can be managed by resection and immediate reconstruction with skin graft or flap according to the size and location of the defect, and the clinical efficacy is distinct.

Zhang, J., Zhang, J., Zhang, J., Xiao, X., Su, Z., Liu, M. & Liang, W. 2020.
Background: Penoscrotal extramammary Paget's disease is a rarely found intraepithelial adenocarcinoma in older male patients. The challenge for surgeons to perform high-quality post-surgery reconstruction is mostly case-dependent. Here, we present a review of post-surgical reconstruction practice in 21 cases using various scrotal skin flaps.
Methods: During the 10-year study period (from 2008 to 2018), all 21 male patients diagnosed with penoscrotal extramammary Paget's diseases at Sun Yat-sen memorial hospital were enrolled in this study. All patients underwent expanding resections guided by frozen sections and penoscrotal reconstructions using various scrotal skin flaps alone or combined with pubic skin flaps and partial thickness skin graft depending on individual defects. The patient's clinical data, specifically the diagnosis, surgical outcome, and follow-up evaluation were retrospectively analyzed.
Results: The size of skin lesions ranged from 4 × 5 cm to 16 × 18 cm approximately. Out of 21 total cases, 13 patients received combined scrotal and pubic flaps, three patients received single scrotal flaps, and five patients received scrotal flaps and partial thickness skin grafts. Limited flap tip necrosis (two cases) and wound dehiscence (one case) were observed, and secondary resections were performed in four cases with positive post-operative pathological results. All patients experienced complete wound healing and had well-maintained penile morphology and function.
Conclusion: Various scrotal skin flaps alone or combined with pubic skin flaps designed for individual lesion conditions in patients with penoscrotal extramammary Paget's disease are efficient for scrotal reconstruction. A good match of the local skin texture helps to maintain the morphology and function of the penis and scrotum.

Phyo, A.K., Mun, K-S., Kwan, K.C., Ann, C.C. & Kuppusamy, S. 2020.
Background: Extramammary Paget's disease (EMPD) is a rare malignant disease originating from the apocrine glands involving the perineum, vulva, axilla, scrotum, and penis.
Objective: To study the clinical presentation, extent of disease, efficacy of treatment, and survival outcomes of the cases in a single institution.
Methods: Retrospective observation data analysis of 19 EMPD cases was performed. Demographic information, clinical management records, and histopathologic data of individual cases were obtained from the inpatient hospital data registry.
Results: The mean age (years) at time of diagnosis was 62.4 with equal gender distribution. Synchronous tumors were detected in 6 cases (31.5%). 18 out of 19 patients underwent definitive surgical management in the form of wide local excision (WLE) and reconstructive surgery. Positive margins were found in 11 (68.8%) cases and 7 out of these 11 cases underwent second look surgical

intervention to achieve oncological clearance or adjuvant oncology treatment. Follow-up period for living patients varied depending on time of diagnosis and definitive treatment. 10 out 19 cases (52.7%) were alive at the time of the study. Among the 7 cases of mortality from cancer, 5 cases died from progression of underlying associated malignancy and only 2 cases died with advanced stage of EMPD.
Conclusion: EMPD can be quite aggressive, especially in the secondary form, and surgical management is challenging with a high rate of residual tumor at the surgical margin. EMPD can easily mislead the clinician and patient, leading to unnecessary delay prior to definitive effective management.

Hu, J., Ge, W., Mao, S., Ding, Q., Hu, M. & Jiang, H. 2020.
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 tramammary Paget's diseaseex 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.

Chung, P.H., Leong, J.Y. & Voelzke, B.B. 2019.
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/

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Paget's Disease of the Scrotum
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