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EXTRAMAMMARY PAGET'S DISEASE WITH METHOTREXATE THERAPY: A CASE REPORT

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ABSTRACT

Introduction: Extramammary Paget's Disease (EMPD) is an uncommon intraepidermal adenocarcinoma that develops in regions containing apocrine glands, including the scrotum, inguinal folds, and perineum. It is most frequently observed in older adults and is often initially mistaken for benign conditions such as dermatitis or fungal infections due to its vague clinical appearance.

Case Report: A 67-year-old man presented with a one-year history of erythematous, pruritic, and painful lesions located in the right groin and scrotal area. Physical examination revealed an erythematous patch with hyperpigmented macules, accompanied by erosion, scaling, and a plaque-like kissing lesion. Histopathological analysis confirmed the presence of characteristic Paget cells within the epidermis, leading to a definitive diagnosis of EMPD. The patient received therapy with topical methotrexate combined with topical gentamicin.

Discussion: Diagnosing EMPD is challenging because its clinical features mimic those of common inflammatory skin disorders. Histopathology remains the diagnostic gold standard. Although surgical excision is the conventional treatment, topical methotrexate represents a promising non-invasive alternative, especially for limited disease or when surgery is not feasible. In the present case, marked clinical improvement was noted after four weeks of treatment, including reduced erythema and erosion, along with complete resolution of pruritus and pain.

Conclusion: The combination of topical methotrexate and gentamicin produced favorable clinical results in this elderly patient with EMPD. This case supports the potential role of topical methotrexate as a safe, cost-effective, and well-tolerated therapeutic option for selected individuals with EMPD.

Keywords: Extramammary Paget's disease, methotrexate, topical therapy, case report, anogenital malignancy

INTRODUCTION

Paget's disease is a rare intraepithelial adenocarcinoma originating from apocrine glands, typically affecting individuals over 50 years of age. The most frequent sites include the unilateral nipple and milk ducts, referred to as Mammary Paget's Disease (MPD), as well as the vulva, perianal skin, scrotum, and penis, known as Extramammary Paget's Disease (EMPD). EMPD is a malignancy of the anogenital region, with an incidence ranging from 0.6 per 100,000 person-years to 0.11 per 100,000 person-years. The majority of cases occur in people between 60 and 80 years old.[1,2]

EMPD typically presents as erythematous, scaly patches accompanied by pruritus. Because these features resemble those of other dermatologic conditions, additional diagnostic procedures, including biopsy for histopathological evaluation, are necessary to confirm the diagnosis.[1–3]

This report describes a case of a 67-year-old man who presented with persistent redness in the groin over one year, which became increasingly bothersome due to lack of healing. This case is presented because of its rarity.

CASE REPORT

A 67-year-old man visited the hospital with complaints of redness in the groin area associated with itching and pain for the past year. He reported an erythematous sore in the groin that had been treated previously but never healed. The patient had no other significant medical history. Physical examination showed blood pressure 121/61 mmHg, temperature 36.7°C, pulse 88 beats/minute, respiration 18 breaths/minute, weight 44.75 kg, and height 160 cm. Local examination revealed an erythematous patch with hyperpigmented macules, accompanied by erosion and scaling, as well as a plaque-like kissing lesion in the right inguinal and scrotal regions. Laboratory findings were within normal limits.

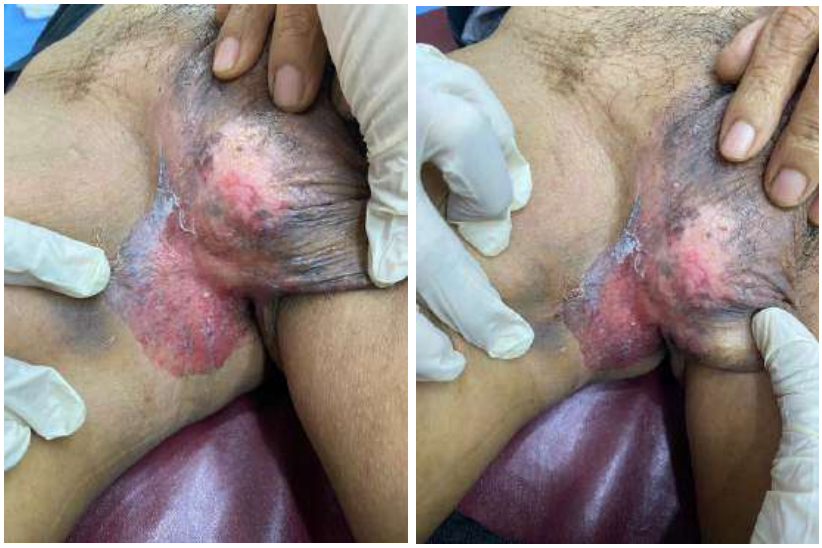

Figure 1. Local examination showing an erythematous patch with hyperpigmented macules, erosion, scaling, and a plaque-like kissing lesion in the right inguinal and scrotal regions.

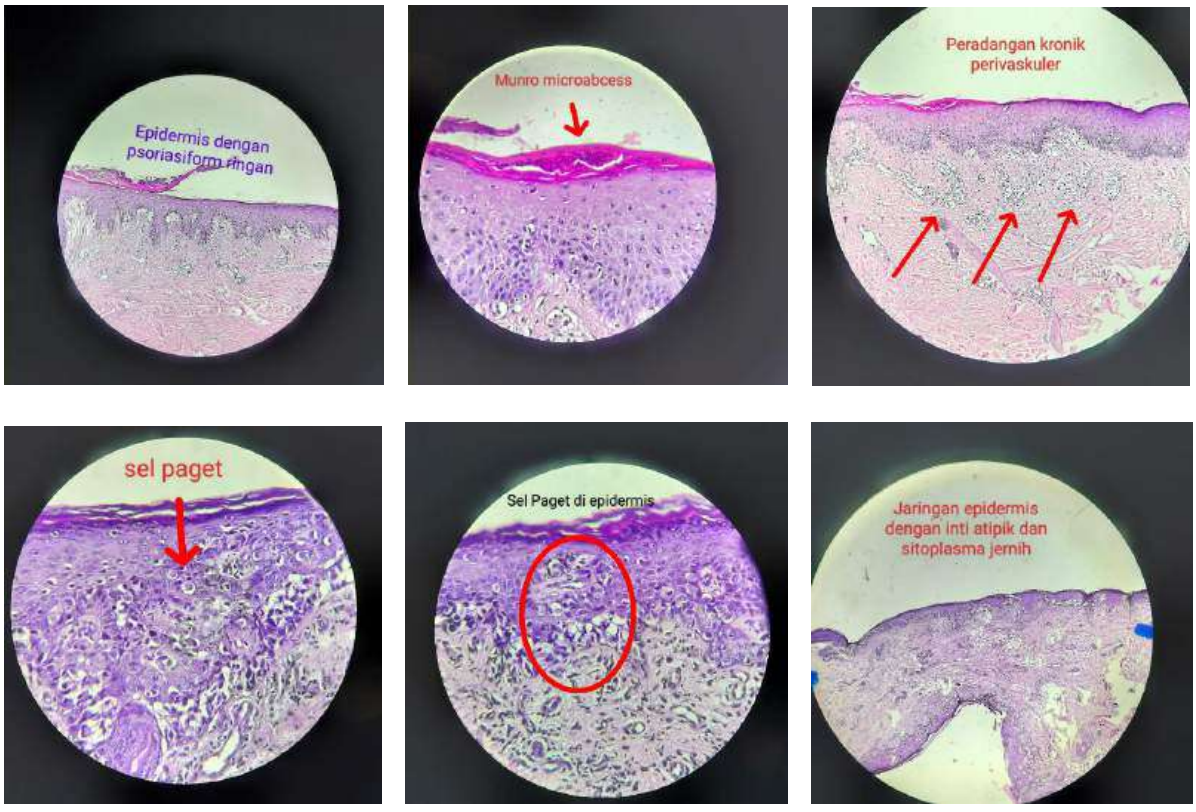

Figure 2. Histopathological examination revealed a specimen lined with focally hyperplastic squamous epithelial cells. Above the basal membrane, cells exhibited vacuolization and somewhat pleomorphic nuclei with focal prominent nucleoli. The subepithelial layer showed acute and chronic inflammatory cell infiltration. These findings are consistent with Paget's disease.

The patient was treated with methotrexate cream and gentamicin cream.

Eight weeks later, the patient returned for follow-up. He had no active complaints. The lesions were mostly dry, and redness had diminished. Physical examination showed blood pressure 129/74 mmHg, temperature 36°C, pulse 100 beats/minute, respiration 20 breaths/minute, weight 44 kg, and height 160 cm. Local status demonstrated reduced erythematous macules, persistent scaling (+), and a plaque-like lesion in the right inguinal and scrotal regions.

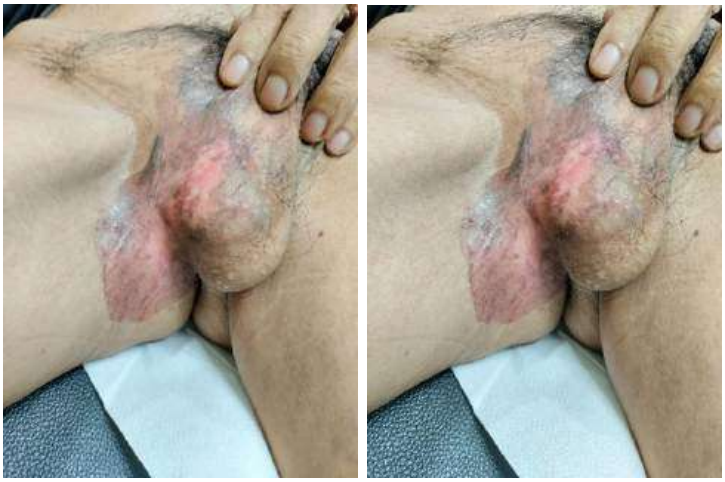

Figure 3. Local examination showing decreased erythematous macules and scaling (+) in the right inguinal and scrotal regions.

DISCUSSION

Extramammary Paget's Disease (EMPD) is an intraepidermal adenocarcinoma that arises in non-breast sites, including the vulva, penis, scrotum, perineum, and anus. EMPD was first described by Henry Radcliffe Crocker in 1889, who noted histopathological similarities to Mammary Paget's

Disease but localized to the scrotum and penis. EMPD is a rare anogenital malignancy, typically occurring between 60 and 80 years of age. Most cases are not linked to underlying adnexal or visceral carcinoma (which occurs in 20–30% of patients).[1–4]

Clinically, EMPD usually appears as erythematous, moist, unilateral, scaly plaques on apocrine gland-bearing skin (axillae and genitoperineal areas). Both hypopigmentation and hyperpigmentation may be observed. Pruritus can lead to excoriation and lichenification. Additional symptoms may include pain, bleeding, burning sensations, and serosanguineous discharge. These atypical features often delay accurate diagnosis.[1,3,5,6]

Unlike MPD, which is frequently associated with an underlying carcinoma, most EMPD cases occur without any associated malignancy—referred to as primary EMPD. In primary EMPD, malignant cells are thought to originate from the intraepidermal portion of apocrine glands or from pluripotent epidermal cells. Primary EMPD begins as in situ carcinoma and may progress by invading the dermis and spreading via lymphatic vessels. Secondary EMPD, accounting for approximately 20–30% of cases, arises from an underlying adnexal or internal malignancy due to epidermotropic spread of tumor cells. Common associated visceral malignancies include cancers of the colon, rectum, bladder, urethra, cervix, and prostate.[1,3,5,7]

A high index of suspicion is required for diagnosing EMPD. Punch, wedge, or full-thickness excisional skin biopsy is necessary for histopathological confirmation. A complete physical examination, including skin assessment and lymph node palpation, should be performed in all patients. A thorough evaluation for underlying malignancy is also essential. Histopathologically, Paget cells are dispersed among keratinocytes, often in clusters, and may extend into adnexal structures such as hair follicles and eccrine ducts. On hematoxylin and eosin staining, Paget cells are large and atypical, with clear, abundant, or occasionally eosinophilic cytoplasm. They may appear singly or in groups. The epidermis in EMPD frequently shows acanthosis with hyperkeratosis, parakeratosis, or ulceration. Immunohistochemistry plays a crucial role in accurate diagnosis, particularly in distinguishing primary from secondary EMPD.[1,3,5,7] In the present case, histopathological examination confirmed the presence of Paget cells within the epidermis.

The atypical presentation of EMPD as red plaques may mimic several conditions, including dermatitis, lichen simplex chronicus, lichen sclerosus et atrophicus, lichen planus, intertriginous psoriasis, Candida intertrigo, squamous cell carcinoma in situ (erythroplasia of Queyrat), human papillomavirus-induced squamous cell carcinoma in situ, and superficial spreading amelanotic melanoma. In this case, erythroplasia of Queyrat was considered in the differential diagnosis. After histopathological examination, the diagnosis of Paget's disease was confirmed.

Treatment options for EMPD are varied, but surgery remains the standard approach. Nevertheless, recurrence can occur even after surgical excision. When surgery is contraindicated or the disease is limited, alternative therapies such as 5% imiquimod cream, photodynamic therapy (PDT), and radiotherapy (RT) are available. Imiquimod 5% cream is an imidazoquinoline immunomodulator applied topically. Photodynamic therapy using topical photosensitizers like 5-aminolevulinic acid (5-ALA) or methyl-5-aminolevulinic acid (M-ALA), as well as the intravenous photosensitizer porfimer sodium, has also been used. Radiotherapy can be employed as monotherapy or as adjuvant/neoadjuvant treatment.[1,3,8]

Methotrexate (MTX) is a folate reductase antagonist with anti-inflammatory, antiproliferative, and immunosuppressive properties. MTX inhibits folinic acid activity by competitively blocking the enzyme dihydrofolate reductase, thereby suppressing deoxythymidylic acid synthesis, which is essential for DNA formation. In dermatology, methotrexate is effective for inflammatory skin disorders such as psoriasis, as well as atopic dermatitis, chronic urticaria, mycosis fungoides, pityriasis rubra pilaris, vesiculobullous diseases, skin carcinoma, lupus erythematosus, and scleroderma.[9,10]

The use of methotrexate in EMPD remains uncommon. A pilot study by Eve Lebas and colleagues investigated oxygen flow-assisted topical administration of methotrexate (OFAMTX) and found it to be effective and painless for EMPD. The results showed a 66.7% clinical improvement after one month of treatment. OFAMTX was well tolerated, with no reports of pain, neutropenia, or thrombocytopenia. Moreover, methotrexate is relatively inexpensive compared to biologic agents. The conventional treatment, Mohs surgery, removes affected skin layer by layer.[10] In the present case report, the patient was treated with topical methotrexate combined with topical

gentamicin. Within four weeks, significant clinical improvement was observed, including reduced erythema and erosion, and complete resolution of itching and pain.

CONCLUSION

Extramammary Paget's Disease (EMPD) is an intraepidermal adenocarcinoma occurring in non-breast regions such as the vulva, penis, scrotum, perineum, and anus. EMPD is generally rare. We report a 67-year-old man with complaints of redness in the groin area. Local examination revealed an erythematous patch with hyperpigmented macules, erosion, scaling, and a plaque-like kissing lesion in the right inguinal and scrotal regions. Due to its atypical presentation, additional diagnostic testing, including histopathological examination, demonstrated Paget cells in the epidermis, leading to a diagnosis of EMPD. The patient was treated with topical methotrexate combined with topical gentamicin. After four weeks, substantial clinical improvement was noted.

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