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Case Series

Navigating the Maze: Insights from a Case Series of Vulval Extramammary Paget's Disease

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Abstract

Extramammary Paget's remains a rare neoplastic condition, which although shares the name with Paget's disease of the breast, is a distinct entity. The condition predominantly affects the epidermis of the vulval skin of postmenopausal women. In this case series, we present the cases of two geriatric patients who were diagnosed with this rare condition and the different treatment options available in managing the disease. Despite its rarity, understanding of this neoplastic condition is vital due to its potential for misdiagnosis and its impact on patient quality of life.

Keywords: *Extramammary; Paget's; Vulva; Geriatric; Radical Vulvectomy*

Abbreviations

EMPD: Extramammary Paget's Disease; CT: Computed Topography; CEA: Carcinoembryonic Antigen; CA19.9: Cancer Antigen 19.9; CA125: Cancer Antigen 125; CK: Cytokeratin; HER: Human Epidermal Growth Factor Receptor; HPV: Human Papilloma Virus

Introduction and Case Reports

Clinical case 1

A 77 year old lady, known case of mild Alzheimer's dementia, ischaemic heart, hypertension, diabetes mellitus controlled on oral hypoglycaemic agents, recurrent falls, glaucoma and side-branch pancreatic intraductal papillary mucinous neoplasms was admitted to a long-term residential facility after having deconditioned following a Clostridium difficile infection requiring admission to an acute medical hospital. During her stay, was noted to have a haemoglobin drop from a baseline of 13 g/dL to 9 g/dL with iron saturations of 3.1 (normal range more than 5). Coeliac screen, immunoglobulin levels and serum protein electrophoresis were all normal. A CT of the thorax, abdomen and pelvis was performed while she was still in the acute hospital in order to exclude an underlying malignancy and this was reported as normal.

The patient was admitted to a closed dementia ward as she had a tendency to wander around. She was always in good spirits and was independent in mobility, transferring, toileting, feeding. She only required minimal assistance with help of one for bathing. Her regular medication included clopidogrel 75 mg daily, ferrous gluconate 300 mg twice daily, folic acid 5 mg daily, omeprazole 20 mg daily, perindopril 4 mg daily, vitamin A + D 1 tab Daily, risperidone 0.5 mg three times daily and simvastatin 40 mg at night.

On admission, the patient had already had an area of discolouration in her labia majora noted by nursing staff. Family were not aware of how long this had been there as the patient used to bathe unassisted when she was at her own home. Two months into the admission, it was noted that the leukoplakia was worsening and that there was a verrucous plaque with erosions, as shown in image 1. No masses were palpable in the groin area and dermatological examination was otherwise unremarkable.

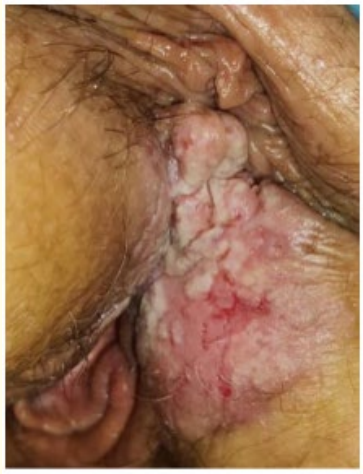

Image 1: *Lesion prior to biopsies were taken showing areas of thick leucoplakia, erosions and erythema.*

The case was discussed with a gynaecologist who reviewed the patient. Extensive thick leucoplakia with surrounding erythema and excoriations was noted predominantly in the left labia majora. Some areas of minor leukoplakia were also noted on the right labia majora. The gynaecologist proceeded with taking three biopsies of the lesion, using Keyne's punch 3 mm. Routine blood investigations during the meantime showed worsening of the hypochromic microcytic anaemia down to 7.6 g/dL (normal 12.5 - 15.5 g/dL).

Histology from the vulval lesion showed focally ulcerated, acanthotic epidermis with dense overlying hyperkeratosis and focal parakeratosis. Atypical vacuolated cells with prominent nuclei and pale cytoplasm were present within the basal layer of the epidermis, showing Pagetoid spread within the superficial layers of the epidermis as single cells or nests in keeping with extra-mammary Paget's disease. The cells were highlighted by CK7, CK200 and HER2.

Tumour markers were taken. Whereas CA19.9 and CA125 levels were within normal levels, levels of CEA were high at 91.8 (normal range less than 2.5). Mammography and ultrasound of the breasts were performed to exclude lesions within the breast and these investigations were normal. A magnetic resonance of the pelvis was also scheduled which confirmed the presence of lymph nodes in the inguinal region ipsilateral to the lesion. A repeat CT TAP was then performed in order to exclude metastatic lesions and to further investigate the elevated CEA. No metastatic lesions were evident in the lungs or liver however, note was made of a lesion in the hepatic flexure, suspicious for malignancy. The patient had an urgent colonoscopy, where two lesions were identified and biopsied. Biopsies showed two primary adenocarcinomas of the bowel.

The case was discussed at the gynaecology multidisciplinary team meeting. It was decided that because of the patient's frail baseline and the presence of colonic primary malignancies in addition to the vulval primary, the patient would not benefit from radical vulvectomy with inguinal lymph node clearance. Consensus favoured the use of Imiquimod cream to the area. Initially Imiquimod was applied twice a

week for sixteen weeks but this was increased thereafter to three times a week, as the lesion was responding to the treatment. The lesion improved drastically after 4 months, as shown in image 2.

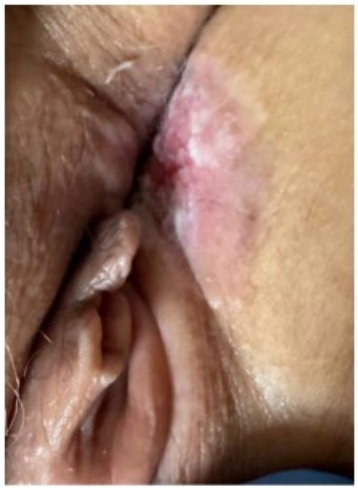

Image 2: *Lesion 16 weeks after treatment with Imiquimod twice a week.*

Case 2

A 73 year old lady, previously healthy, on no regular medication, known case of total abdominal hysterectomy and bilateral salpingo-oophorectomy at the age of 43 for heavy menstrual bleeding and a fibroid uterus presented to the outpatient clinic in view of a vulval lesion. The lesion had been slowly growing for over a year and was occasionally itchy. She had seen her general practitioner for this lesion who had prescribed topical corticosteroids, to no benefit.

On examination, the patient had a unilateral erythematous, well demarcated lesion of the right vulva as shown in image 3. A punch biopsy of the area was done and this was reported to show changes congruent with extramammary Paget's disease which was confined to the epidermis.

Image 3: *Lesion in the right labia majora which was congruent with extra-mammary Paget's disease on histology.*

Routine complete blood count, C-reactive protein, liver profile and electrolytes were all within normal limits. The patient had a CT of the thorax, abdomen and pelvis which was also reported as normal and any potential secondary tumours or metastatic deposits were absent.

The patient was discussed at the multidisciplinary meeting and she had a right sided vulvectomy with right superficial and deep inguinal lymphadenopathy as seen in image 4. Histological analysis of the tissue specimen confirmed that the extramammary Paget's disease was confined to the superficial dermal layer. There was no lymphovascular invasion or lymph node metastasis. The patient did not require any further interventions and remained well in subsequent follow-ups with no recurrence up to 3 years later.

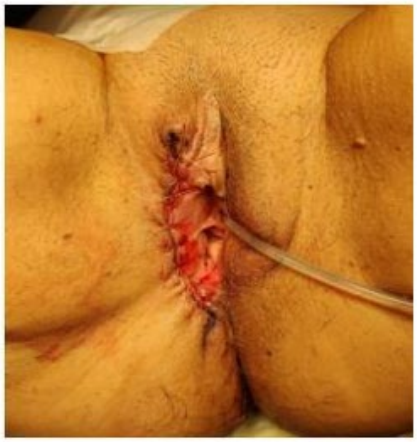

Image 4: *Appearance post vulvectomy on the right*

Discussion

Extramammary Paget's is a rare form of cutaneous intraepithelial adenocarcinoma that involves the epidermis and may extend into the dermis [1]. The aetiology of EPMD remains uncertain with some hypothesis claiming it arises from an underlying adnexal carcinoma, while others propose an intraepithelial neoplasia origin. It has a predilection for areas with a higher density of apocrine glands such as the perineum, vulva and the axilla [2]. Recent studies have implicated genetic mutations, chronic inflammation, and viral infections, such as HPV, in its pathogenesis [3]. EPMD of the vuvla and the perineum has also been linked to other malignancies; notably the urethra, bladder, prostate and colorectal neoplasia and thus patients should always be thoroughly investigated to exclude other malignancies [1] such as occurred in case 1. Vulval EPMD is the commonest of the EMPD and accounts for about 1 - 2% of all vulval neoplasia and effects post-menopausal women in their sixth to with decade [4].

Patients with EMPD often present with non-specific symptoms which might include pruritus, paraesthesia, pain, or they might present with an erythematous lesion on the vulva. Changes usually start at the labia majora and then spread to the labia minora, clitoris, inguinal fold and perineum. Patients are usually diagnosed at a locally advanced stage. These manifestations can mimic other benign or malignant conditions, leading to diagnostic challenges. The main diagnosis to exclude include eczema, psoriasis, fungal infections, lichen planus, lichen simplex, neurodermatitis or seborrheic dermatitis [5]. Moreover, due to its location in a sensitive area, patients may delay seeking medical attention, exacerbating the disease progression. The hallmark of EMPD is the relentless progression of the lesion and symptoms despite appropriate topical therapy [1].

EMPD has three variants; there is the In situ epithelial form without carcinoma, the epithelial form with carcinoma of the adnexa and the variant linked with visceral malignancy [5]. Histologically, Paget cells are seen as large clear cells with large atypical nuclei and abundant pale cytoplasm, confined within the epidermis. Immunohistochemistry staining for markers such as CK7 and CEA can help differentiate Paget cells from other epidermal cells [5]. Histopathologically, the lesions should be differentiated from pagetoid melanoma in situ and pagetoid Bowen's disease [6].

There is currently no global consensus on the optimal management of vulval EMPD. Although most patients are diagnosed when the lesion is in a locally advanced stage, and despite the high recurrence rate, the prognosis is overall good with a 90% survival rate over 5 years [4]. Management of EMPD depends on various factors, including disease extent, patient's age, comorbidities, and individual preferences [7].

Surgical excision remains the cornerstone of treatment both in the primary and tin the recurrent setting aiming for complete removal of the affected tissue with negative margins. The main surgical approach used in managing patients is wide local excision. Partial simple vulvectomy, radical vulvectomy, total simple vulvectomy, hemivulvectomy and skinning vulvectomy are other surgical modalities that might be employed depending on individual patient characteristics [4]. In patients who have positive resection margins or positive lymph nodes, external beam radiation (RT) might be employed. RT might also be given to patients who are not fit for surgery [4]. Chemotherapy using antineoplastic agents such as 5-fluorouracil, mitomycin, carboplatin, docetaxel and trastuzumab might be used in cases of distant progressive metastatic disease with palliative intent. They are very rarely used in the neoadjuvant or adjuvant settings [4].

In cases where surgery is not feasible or the patient is inoperable due to comorbidities, alternative treatment modalities such as topical therapies using imiquimod or topical 5-fluorouracil, photodynamic therapy, laser CO2 therapy or radiotherapy may be considered [4]. However, these options typically provide symptomatic relief rather than curative intent and may require long-term follow-up.

Imiquimod applied topically for localised lesions has shown promising results. Sendagorta., *et al*. report the complete clinical and histological remission of vulval EMPD in three patients who were treated with daily 5% topical Imiquimod for three weeks followed by daily application on alternate days for another three weeks (Sendagorta E, 2010). Other patients were reported to have remission when treated with topical agents for longer periods of time. Immunotherapy using checkpoint inhibitors has also been described in the setting of metastatic EMPD with favourable outcomes [8].

The prognosis of EMPD largely depends on the disease stage, depth of invasion, presence of associated malignancies, and adequacy of surgical margins. Local recurrence rates range from 10% to 61% [8] necessitating long-term surveillance with regular clinical examinations and imaging studies to monitor for disease recurrence or progression.

Conclusion

Extramammary Paget's disease poses diagnostic and therapeutic challenges due to its rarity and nonspecific presentation. No international consensus is available on the management of these patients as no one size fits all. This case series highlights the importance of a collaborative, multidisciplinary approach involving gynaecologists, oncologists, and pathologists in delivering optimal care to patients with EMPD.

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Conflict of Interest

The authors report no conflict of interest.

Bibliography

1. Sardesai VR AT. "Extra mammary Paget's disease: A rare case report". *Indian Journal of Dermatology* 60.1 (2015): 105.
2. Banarjee SCM. "Extramammary Paget' disease". *Indian Journal of Dermatology, Venereology and Leprology* 71.6 (2005): 417-420.
3. Honda YEK. "Extramammary Paget's disease not only mimicking but also accompanying condyloma acuminatum. A case report". *Dermatology* 210.4 (2005): 315-318.
4. Caruso GBA. "Vulvar paget's disease: A systematic review of the MITO rare cancer group". *Cancers (Basel)* 15.6 (2023): 1803.
5. Helwig EB GG. "Anogenital (extramammary) Paget's disease. A clinicopathologic study". *Cancer* 16 (1963): 387-403.
6. Chilukuri SPR. "Ectopic extramammary Paget's disease arising on the cheek". *Dermatologic Surgery* 28.5 (2002): 430-433.
7. Karam ADO. "Treatment outcomes in a large cohort of patients with invasive Extramammary Paget's disease". *Gynecologic Oncology* 125.2 (2012): 346-351.
8. Guercio BJ IG. "Treatment of metastatic extramammary Paget disease with combination ipilimumab and nivolumab: a case report". *Case Reports in Oncology* 14.1 (2021): 430-438.

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