Case

A 67-year-old woman presented to the outpatient department with a genital lesion. One year back, the lesion was noticed, but the size increased over the last 5 months, and there was pruritus and burning pain. On examination, a well-demarcated polycyclic, 7 cm × 5 cm, erythematous plaque with a raised margin over the genital area was seen. In addition, there were erosions and whitish moist scales on the left side, while the right side had patchy hyperpigmentation. This plaque over the labia majora seemed to extend from the vaginal introitus [Figure 1].

Histopathological examination showed epidermis having large cells with pale cytoplasm and large nuclei with variations in size and shape and abnormal mitotic figures. These cells occupied most of the epidermis, sparing the basal layer. They were clustered predominantly in the lower epidermis at some places, with few cells reaching the mid and upper epidermis. In addition, the dermis shows a moderately dense superficial and perivascular and interstitial infiltrate of lymphocytes, plasma cells and neutrophils [Figure 2].

Question – What is the diagnosis?

Answer – Vulval Paget’s Disease.

Discussion

Extramammary Paget disease (EMPD) is a rare dermatologic neoplastic condition frequently present in apocrine areas, most commonly in the vulva (65%).[1] William Dubreuilh described vulval EMPD in 1901.[2] Precise incidence of EMPD is unknown. However, it has overall female predominance in their fifth to seventh decade, although one study showed male preponderance in the Asian population.[1]

The etiology of primary EMPD is unknown, although it seems to be of apocrine origin. Secondary EMPD can be due to the pagetoid spread of an underlying adnexal adenocarcinoma or an underlying visceral malignancy. Recently theories have postulated that the distribution along the milk line is associated with clear cells of Toker, which are present in both mammary and vulvar tissue.[3] C-erbB-2 oncoprotein is also implicated in some cases.[4]

Clinically, it presents well-demarcated, scaly plaques with crusts, weepy erosions, or even ulcerations that slowly expand with pruritus, burning sensation, tenderness,
and edema. Scattered white scaling and moist erosions can give rise to a “strawberries and cream” appearance. It can be focal or multifocal. Repeated trauma/excoriation or superimposed infection may alter long-standing lesions. Due to the presence of an underlying carcinoma, hard nodules and regional lymphadenopathy may develop. The term “underpants-pattern erythema” refers to erythema that spread peripherally to areas covered by underwear due to invasion of the lymphatic system by the tumour.

Histopathology shows proliferative neoplastic cells, the Paget cells (PCs). These are malignant glandular cells having ample, pale, often mucin containing cytoplasm and large pleomorphic hyperchromatic nuclei, with a prominent nucleolus and frequent mitoses. The cells are arranged singly or in small groups in the early stage and nested patterns or as glandular structures in the basal layer in later stages. It may rarely invade the dermis. Instead, dense mixed inflammatory infiltrates are commonly found in the upper dermis of EMPD.

Bowen’s disease should be considered as a close differential, especially for the genital lesions. The differences between Bowen’s disease and EMPD is briefed in Table 1. Immunohistochemistry plays a vital role in the differentiation of EMPD from other conditions. In immunohistochemistry, PC are typically stained for eccrine and apocrine derived markers like cytokeratin (CK), gross cystic disease fluid protein (GCDFP), carcinoembryonic antigen and periodic acid-Schiff. CK7 has 86-100% sensitivity, but CK20 has a higher specificity. 90% of primary EMPD tests positive for GCDFP-15.

Table 1: Differences between Bowen’s disease and Extramammary Paget’s Disease

| Characteristics                  | Bowen’s disease | Extramammary Paget’s disease |
|----------------------------------|-----------------|------------------------------|
| Age of presentation             | Sixth decade onwards | Fifth decade onwards         |
| Viral association                | HPV 16, 18      | Nil                          |
| Most common site                 | Lower legs      | Vulva in females, perianal in men |
| Lesion characteristics           | Precancerous    | Cancer.                      |
|                                 | Solitary plaque, white or yellowish scale, gets detached without much difficulty leaving a moist, reddened and granular surface without bleeding. | Slowly expanding erythematous plaque is typical, with a sharp demarcation between normal and involved skin. Scattered areas of white scale and erosion can give rise to a “strawberries and cream” appearance. There may be associated pruritus or burning or asymptomatic. Vaccumulated pagetoid cells in the epidermis are distinctive. However, but immunohistochemical staining is necessary to exclude pagetoid melanoma and intraepithelial neoplasia. There is frequently epidermal hyperplasia |
| Histopathology                   | Full-thickness epidermal dysplasia and disordered differentiation with loss of epithelial polarity- ‘windblown’ appearance | The intraepidermal portion of the cutaneous adnexa is usually affected. Parakeratosis and acanthosis are usually present; Keratinocytes show variable pleomorphism, nuclear hyperchromasia. Clear cell change may be observed. Giant forms and multinucleate cells may be seen, and mitotic figures can be frequent. The dermal-epidermal junction remains distinct. |
| Markers (PAS, CK7, CK20, CEA, CAM 5.2, GCDFP 15) | Negative | Positive (CK20 negative in primary extramammary Paget’s disease) |
| Treatment                        | Local excision  | Wide local excision or Mohs micrographic surgery |
| Prognosis                         | Chronic course with the development of single or multiple lesions over time with minimal complication and excellent prognosis with treatment | Recurrence is common The prognosis for the primary intraepithelial disease is excellent The invasive disease has a 5-year survival of 72% |

*Local excision or therapy using laser, cryotherapy or local use of cytotoxic drug-like 5-fluorouracil can be used in both diseases. (CK: Cytokeratin GCDFP: Gross cystic disease fluid protein, CEA: Carcinoembryonic antigen, PAS: Periodic acid-schiff)
while CK20 can be detected in up to 95% of secondary EMPD.[1]

If treated appropriately, the prognosis is optimistic. However, local recurrence is common, especially in cases with underlying visceral or adnexal carcinoma, metastases, where the mortality risk is high. The standard gold treatment for EMPD is surgery. While wide local excision has high morbidity; Mohs micrographic surgery lowers the recurrence rate with good results.[3] Adjuvant therapy with local application of bleomycin or 5-fluorouracil may reduce the margins before resection. Radiotherapy might be needed for inoperable lesions. Systemic chemotherapy can be used when neither surgery nor radiotherapy is feasible. Isolated reports of intralesional interferon, imiquimod, photodynamic therapy, and carbon dioxide laser showing some benefits are present.[2]

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms for publishing the case and the images without mentioning the names and initials.

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**Conflicts of interest**

There are no conflicts of interest.

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