

Co-existence of extramammary Paget's disease and Bowen's disease of vulva

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ABSTRACT

Extramammary Paget's disease and Bowen's disease are histologically similar and immunohistochemistry is often required to make the diagnosis. We present a case of vulval Paget's disease with Bowen's disease in an elderly female. Strong positivity for cytokeratin 7, anti CAM 5.2, carcinoembryonic antigen (CEA) and periodic acid-Schiff (PAS) stain in clitoral, left labial and interface regions of the vulvectomy specimen confirmed the diagnosis of Paget's disease (PD) while positive staining for p63 in the right labial and interface regions helped in establishing the diagnosis of concurrent Bowen's disease (BD).

Key words: Bowen's disease, extramammary Paget's disease, Paget's disease, vulva

INTRODUCTION

Extramammary Paget's disease of the vulva is a rare neoplasm accounting for 2% of all vulval malignancies.^[1] Dubreuilh^[2] described the first case of vulval extramammary Paget's disease in 1901. Later, a report by Bowen^[3] highlighted the histological resemblance between extramammary Paget's disease and Bowen's disease. The term 'pagetoid Bowen's disease', was first used by Williamson *et al.*^[4] for a histologic variant of squamous cell carcinoma *in situ* showing nests of pale staining cytoplasmic cells with no immunohistochemical features of Paget's disease.

It is currently believed that most cases of vulval extramammary Paget's disease are primary, arising within the epidermis with a very small number associated with cutaneous sweat gland tumors.^[5,6] A new variant of "mammary like" cutaneous glands,

which combine morphological features of mammary, eccrine and apocrine glands, are found predominantly in the interlabial sulcus on the vulva. These glands have also been proposed as the site of origin of sweat gland-derived tumors from which extramammary Paget's disease arises.^[7] The most common symptoms are pruritus followed by pain and oozing.

The association of Bowen's disease of vulva with extramammary Paget's disease is rare with only a few previous reports of the association.

CASE REPORT

A 57-year-old woman presented with a itchy, eroded plaque over the vulva for two years with a history of rapid progression for 4 months. On examination, there was a single, well defined, hyperpigmented, erythematous, lacy reticular, verrucous plaque on the right labia majora and minora extending to the clitoris and the left labia minora, introitus and perianal regions. There were brightly erythematous moist areas in the clitoral and left labial region [Figure 1a]. On per speculum examination, the lesion was seen partially extending to the vaginal wall on the right side, but the cervix and left vaginal wall were uninvolved [Figure 1b]. There was no inguinal adenopathy. Ultrasound and CT imaging

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of abdomen and pelvis, barium enema, intravenous pyelogram, chest X-ray, mammography, cystoscopy and colonoscopy did not reveal any underlying mass or abnormality. All routine blood investigations were within normal limits. ELISA (enzyme-linked immunosorbent assay) for human immunodeficiency virus (HIV) was non-reactive. A punch biopsy was performed from two sites, the hyperpigmented area and the erythematous area. Features of Bowen's disease were noted in the hyperpigmented lesion while Pagetoid cells were noted in the erythematous moist area.

Subsequently, the patient was planned for surgical excision and vulvectomy was done under general anesthesia.

Histopathological examination of the entire vulvectomy specimen was undertaken. It showed acanthosis, full thickness cellular atypia, focal hyperkeratosis and parakeratosis with no Paget cells from the right-sided region comprising of labia majora, minora and adjacent areas [Figure 2a]. On higher power, pleomorphic hyperchromatic keratinocytes typical of Bowen's disease were noted. The interface between the two clinically different lesions showed basal Pagetoid cells with upper areas showing Bowen's disease [Figure 2b]. The left side of the lesion showed Paget's cells [Figure 2c] with abundant clear cytoplasm, atypia and nucleolar prominence.

The results of immunohistochemical staining are shown in Figures 3 and 4. In the right labial regions, p63 and CK 7 were strongly positive in the neoplastic cells in a nuclear and membranous pattern respectively while CK5/6 was weakly positive in a membranous staining pattern. Overall this suggested Bowen's

disease. [Figures 3 and 4]. The immunohistochemistry on the clitoral and left labial regions showed positivity of cytokeratin 7 in a membranous pattern, anti CAM 5.2 and PAS positivity indicating presence of mucin. In addition, CEA was positive indicating that the cells were not Merkel or Toker cells. Thus a diagnosis of Bowen's disease of vulva with extramammary Paget's disease in the same lesion, from right to left, with a sharp demarcation was confirmed.

As there was no lymphadenopathy and imaging studies were normal, lymph nodes were not excised. She is currently under follow-up with no complications or recurrence 6 months after surgery.

DISCUSSION

Our case showed clinical features of Bowen's disease but the biopsy revealed features of both Paget's disease and Bowen's disease. Subsequently, the vulvectomy specimen revealed changes of both these diseases in sharply demarcated areas.

We were able to find only a few previous reports of simultaneous occurrence of vulval extramammary Paget's disease with Bowen's disease.^[8-11] The histological findings in these diseases can be overlapping and in such cases, immunohistochemical markers are helpful in differentiating the disorders.

The clinical differential diagnoses of such lesions are tinea cruris, candidiasis, psoriasis, lichen planus, dermatitis, and melanoma. The histopathological differentials for the distinctive pattern of 'pagetoid spread' throughout the epithelial layer include pagetoid Bowen's disease, mycosis fungoides, Langerhans cell histiocytosis and Spitz nevus.



Figure 1: (a) A well defined, lacy reticular, hyperpigmented, verrucous looking plaque involving vulval and perianal regions. (b) Per-speculum examination showing involvement of lateral vaginal wall

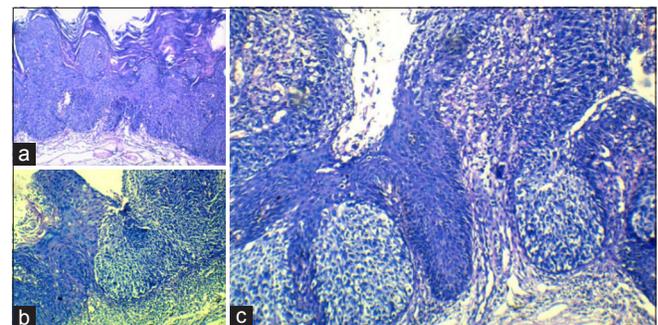


Figure 2: (a) Bowen's disease with acanthosis, full thickness cellular atypia, focal hyperkeratosis and parakeratosis. (H and E, $\times 10$) (b) Interface of Bowen's and Paget's disease (H and E, $\times 100$). (c) Nests of Paget's cells in basal locations in erythematous clitoral and peri-clitoral areas (H and E, $\times 100$)

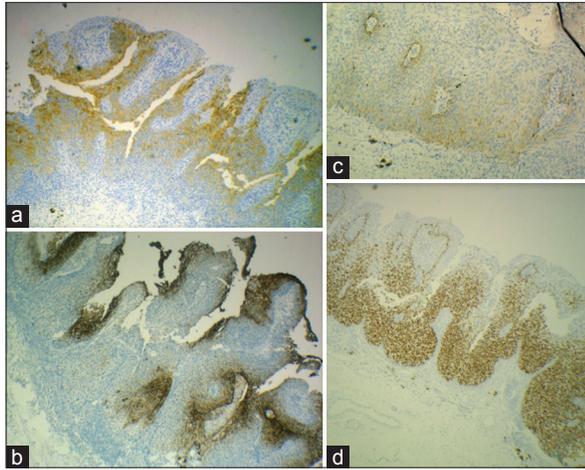


Figure 3: (a) Strong positivity of CK 7 in cells of Bowen's and Paget's disease ($\times 100$). (b) Positive carcinoembryonic antigen staining in Paget cells ($\times 100$). (c) Weakly positive CK-5/6 in Bowen's disease ($\times 100$). (d) Strongly positive p 63 in Bowen's disease ($\times 100$)

In general, Paget cells stain with PAS stain (and are diastase resistant), mucicarmine, Alcian blue at pH 2.5 and colloidal iron. The cells also stain strongly with the immunohistochemical stains, cytokeratin-7 and anticytokeratin CAM 5.2. However, Merkel cells and Toker cells may also show similar staining properties. The CEA, epithelial membrane antigen (EMA), Ber-EP4, BRST-2 and HER-2 neu which are positive for Paget cells but not for Merkel and Toker cells are helpful in differentiation. p63 marker is strongly positive in pagetoid Bowen's disease but not in Paget's disease.^[12] Further, co-existent Paget's and Bowen's disease has to be differentiated also from Bowen's disease showing the Borst-Jadassohn phenomenon. Lora *et al.*^[13] found that the cells of Bowen's disease which show clonality and the Borst Jadassohn phenomenon are positive for epidermal growth factor receptors (EGF-R), Ki-67, p53 and p63 and negative for cytokeratin 5/6 and cytokeratin 7. In our case, CK 7 was strongly positive ruling out the Borst Jadassohn phenomenon as the explanation for our findings.

Raju *et al.*^[14] described 2 cases of pagetoid squamous cell carcinoma *in situ* and showed that CK 7 can be positive in such cases, but added that these would then be non-reactive for GCDFP-15, CEA, CAM-5.2 and c-erbB2. In our case, both CEA and anti CAM-5.2 were positive in the areas showing changes of Paget's disease indicating the coexistence of these two entities. The proposed origin of Pagets cells in extramammary Paget's disease from intraepidermal portions of eccrine/

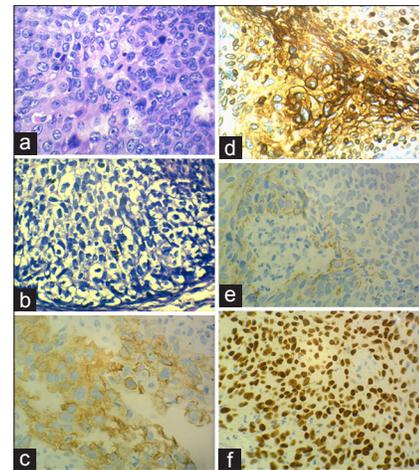


Figure 4: (a) Typical pleomorphic hyperchromatic keratinocytes of Bowen's disease. (H and E, $\times 400$) (b) Paget's cells showing abundant clear cytoplasm, atypia and nucleolar prominence (H and E, $\times 400$). (c) Cytokeratin 7 positivity in a membranous pattern in cells of both Bowen's disease and Paget's disease ($\times 400$). (d) Carcinoembryonic positive Paget's cells ($\times 400$). (e) CK 5/6 weakly positive cells of Bowen's disease ($\times 400$). (f) p63 positive cells of Bowen's disease ($\times 400$)

apocrine glands or from primitive basal cells within the epidermis is supported by Matsumoto *et al.*^[11] who found that the cells showed CK8 and CK7 positivity.

The treatment of choice remains surgical excision. Radical vulvectomy, radical hemivulvectomy (if localized to one side), wide local excision and Moh's micrographic surgical excision have all been tried with variable recurrence rates.

For those patients who decline or are unfit for surgery, alternative treatment options include topical chemotherapy and immunomodulators such as 5-fluorouracil (5-FU), bleomycin and imiquimod as adjunctive or primary modalities of treatment. There are some reports of the use of combinations of these topical chemotherapeutic agents with systemic chemotherapy agents including cisplatin, mitomycin C, epirubicin, vincristine and docetaxel. In general, a diagnosis of intraepidermal Paget's disease with underlying adenocarcinoma, invasive Paget's disease clitoral location or Paget's disease with coexisting cancer predicted a poor survival rate.^[15] The survival rate was higher with excision with a wide local margin.

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