

Primary Extra Mammary Paget's Disease of Vulva, With Apocrine Adenocarcinoma, Signet Ring Cell Differentiation and Distant Metastasis

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Abstract

Objective: Extramammary Paget's disease (EMPD) with invasive carcinoma and distant metastasis is extremely rare. In vulva EMPD associated apocrine carcinoma with signet ring cell differentiation has not been described in the literature so far. Its slow evolution, varied clinical presentation and histological appearances, lead to difficulty in diagnosis of this disease.

Case report: We hereby report a case of primary EMPD with invasive carcinoma and distant metastasis in a 59-year-old female who presented with erythematous indurated plaque over vulva. Histopathology revealed Paget cell infiltration throughout the epidermis with invasive carcinoma in dermis and liver metastasis on CECT. The immunohistochemical expressions of CK7, CK20, GCDFP-15, CEA, p40, CDX 2, Her-2/ neu, AR, ER, were examined to explicate the cellular differentiation of this carcinoma. According to the histological assessment, this case was diagnosed as primary EMPD with apocrine adenocarcinoma, signet ring cell differentiation, vulva.

Conclusion: Owing to poor prognosis, a high index of clinical suspicion along with histological and immunohistochemical assessment is of utmost importance in arriving at final diagnosis.

Keywords: Extramammary; Paget's Disease; Vulva; Apocrine Carcinoma; Signet Ring Cell

Introduction

Paget's disease is an uncommon intraepidermal malignant neoplasm, which can either be mammary or extramammary (1). While mammary Paget's disease (MPD) corresponds to 1-4.3% of all breast carcinomas, the exact incidence of extramammary Paget's disease is still unknown, owing to its rarity (2). It is seen however that a primary extramammary Paget's disease (EMPD)

is associated with invasive cancer in 4% and distant metastasis in merely 2.5% of all the cases reported so far (3). Moreover, a signet ring cell differentiation in an EMPD associated apocrine carcinoma of sites other than vulva has only been reported in 4 case reports earlier (4). During embryological development, the cells of the stratum germinativum give rise to the skin appendages including the apocrine glands and the overlying mature squamous epithelium (5). It is thought by some authors that like mammary gland is an apocrine differentiated skin appendage, Paget's cells as

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a neoplasm of the nipple or vulva can be considered to have an embryological kinship. Some authors also believe invasive EMPD to arise from the pluripotent stem cells. But unlike breast, Paget's disease in vulva is associated with an invasive carcinoma in only 4-20% of the cases (6). Based on these theories of origins Primary EMPD is further subdivided into three categories, namely intraepithelial Paget's disease (IEP), Invasive Paget's, and Paget's disease as a manifestation of an underlying adenocarcinoma of a cutaneous appendage or a vulvar gland. Currently there are no case reports describing the same in vulva (7).

Case report

A 59-year-old, otherwise healthy lady, presented with complaints of itching and redness in the vulva for the last 3 years and a diffuse vulvar swelling for the past 6 months. On examination there was an asymmetrical fairly well defined dull erythematous indurated plaque over the right labia majora extending onto the mons pubis 5 X 4 cm. Multiple papules and nodules along with a superficial ulcer measuring 1.5x 1cm was noted in the center of plaque extending onto the inner aspect of labia majora and labia minora (Figure 1).



Figure 1: Extra-mammary Paget's disease of vulva showing multiple papules and nodules in the plaque extending onto the inner aspect of labia majora and labia minora.

There was diffuse pitting edema of the entire vulvar region along with multiple firm non-tender inguinal lymph nodes bilaterally. A per speculum examination could not be done due to extreme discomfort and induration of the external genitalia. On the basis of clinical features, the diagnoses of cutaneous

tuberculosis, cutaneous Crohn's disease, invasive squamous cell carcinoma, amelanotic melanoma were considered. Biopsies from the plaque and nodule were taken. CT chest showed the presence of multiple metastatic nodules in the liver. No clinical or radiological evidence of a breast, lung, bladder or gastrointestinal neoplasm was found. PET-CT revealed uptake in liver along with bilateral inguinal lymph nodes and maximum uptake in the vagina was noted.

Biopsy from plaque revealed singly scattered tumor cells as well as nests in the epidermis. These cells had moderate to abundant amount of clear cytoplasm with round to oval nucleus and conspicuous nucleoli. Biopsy from nodule showed tumor in the form of nests and islands with foci of signet ring cell differentiation in the dermis. There was no glands formation or a cribriform pattern of involvement (Figure 2 A-D).

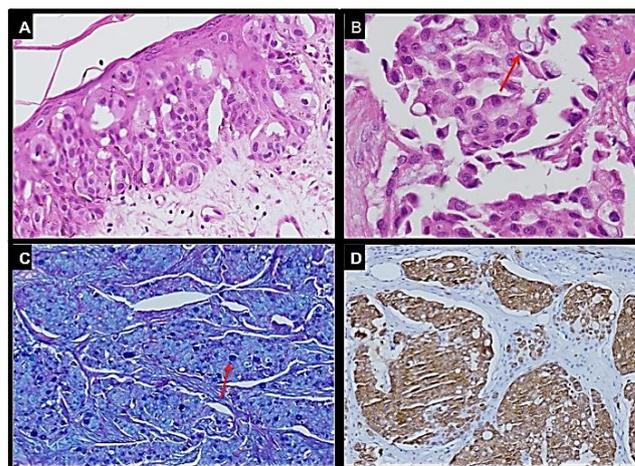


Figure 2: EMPD vulva; A. Shows intraepidermal Paget's cells in the vulva (200X; H&E). B. Shows associated invasive carcinoma with signet ring cell {red arrow} differentiation (400X; HE). C. Alcian blue Periodic Acid Schiff stained tumor highlighting the signet ring cell differentiation {red arrow} (100X; ABPAS). D. Tumor cells showing cyokeratin 7 cytoplasmic and membranous immunopositivity (100X; IHC)

Based on morphological findings we kept a differential diagnosis of primary or secondary EMPD vulva. On immunohistochemistry (IHC) study, tumor cells were positive for cyokeratin 7 (CK 7) carcinoma embryonic antigen (CEA), Her-2/ neu, gross cystic disease fluid protein (GCDFP) and androgen receptor (AR). They were negative for CK 20, p40, CDX 2, and Estrogen

receptor (ER). Periodic Acid Schiff with Alcian Blue demonstrated intracytoplasmic vacuoles of mucin within the signet-ring cells (Figure 3 A-D). Colonoscopy revealed no mass lesion except a single polyp, which was confirmed as hyperplastic polyp on microscopy. Taking all into consideration, a final diagnosis of primary invasive EMPD with apocrine adenocarcinoma and signet ring cell differentiation was rendered. The patient however refused further treatment and expired a month later.

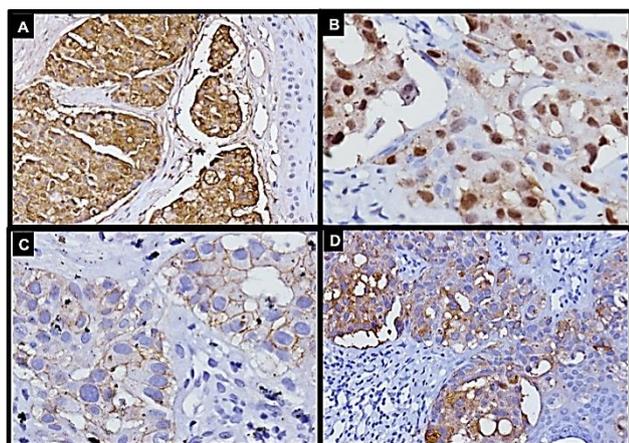


Figure 3: EMPD vulva; A. Tumor cells showing CEA immunopositivity (200X; IHC). B. Nuclear Immunopositivity for androgen receptor (400X; IHC). C. Membranous positivity for Her2/neu (400X; IHC). D. Diffuse cytoplasmic immunopositivity for GCDFP15 (200X; IHC).

Discussion

Mammary Paget's disease was first described by James Paget in 1874, it was later in 1889 that Radcliffe Crocker first described EMPD. EMPD is a disease of postmenopausal women ranging in age from 50-70 years. Although both MPD and EMPD have similar clinical features and identical histological morphology, owing to the rarity of invasive EMPD, it poses a potential diagnostic difficulty when encountered. In vulva, Paget's disease is extremely rare accounting for only 1% of vulval neoplasms. Though controversial in origin, a majority of these lesions are thought to have an apocrine origin involving skin and its appendages (8).

According to Parmley TH et al during embryological development, the cells of the stratum germinativum give rise to the skin appendages including the apocrine glands and the overlying mature squamous epithelium (9). It is thought by some authors that like mammary gland is an apocrine

differentiated skin appendage, Paget's cells as a neoplasm of the nipple or vulva can be considered to have an embryological kinship. Some authors also believe invasive EMPD to arise from the pluripotent stem cells. But unlike breast, Paget's disease in vulva is associated with an invasive carcinoma in only 4-20% of the cases (2). Based on these theories of origins Primary EMPD is further subdivided into three categories, namely intraepithelial Paget's disease (IEP), Invasive Paget's, and Paget's disease as a manifestation of an underlying adenocarcinoma of a cutaneous appendage or a vulvar gland (10, 12). Our case not only had a primary invasive EMPD with underlying adenocarcinoma, but she also developed distant metastasis to liver, bilateral inguinal lymph nodes and local spread to vagina which is only reported in 2.5% of the cases so far. In a series of 1,439 patients with invasive EMPD, 80.4% had localized disease, 17.1% had loco regional spread, and only 2.5% presented with distant disease (13).

On microscopy while the skin biopsy revealed the presence of Paget's cells in the epidermis, as seen in [Figure 2A], the biopsy from nodule showed the presence of an adenocarcinoma in nests along with some signet ring cell differentiation (Figure 2B). Histochemical reactions for acid mucin, was demonstrated using PAS Alcian Blue in these cells (Figure 2C). Based on these findings our list of differential diagnosis included secondary Paget's disease including metastasis from, gastrointestinal (GI) system mainly anorectal region and less likely metastasis from breast, bladder and lungs followed by primary Paget's disease including a pagetoid spread from bartholin duct adenocarcinoma. On IHC, it was noted that tumor cells were immunopositive for Carcinoembryonic antigen (CEA), cytokeratin 7, Her-2/neu, gross cystic disease fluid protein15 (GCDFP-15), Androgen Receptor (AR) and negative for Cytokeratin 20, CDX2 and P40 and Estrogen Receptor (ER). Following the detailed evaluation and in consensus with the IHC panel possibility of secondary Paget's disease from a GI primary was ruled out. Other less likely sites like bladder, breast or thyroid are also known to cause secondary Paget's of the vulva, were excluded based on immunonegativity for GATA3 and TTF 1.

Since the patient had maximum vaginal uptake on PET CT, the possibility of Bartholin duct adenocarcinoma was strongly considered. Bartholin duct carcinomas can also have a similar clinical presentation although majority of these tumors are

squamous cell carcinoma, and adenocarcinomas are less common. Tatsayu ohno et al. (14) reported a case of mucinous adenocarcinoma. But on microscopy unlike in our case, these tumors form glands and can have cribriform morphological patterns; they are negative for Estrogen receptor and can be negative for androgen receptor. Moreover, Her-2/ neu and GCDFP-15 expression that has been described in primary Paget's of vulva has not been described in Bartholin duct adenocarcinoma.

In cases of primary Paget's cells in vulva epidermis, intradermal migration of neoplastic cells from an underlying cutaneous appendage carcinoma is also a major possibility. Cutaneous apocrine carcinomas are commonly described as tumors with foci of glandular differentiation with apocrine snouts and secretions (15). They may have varied morphological patterns including tubular, papillary, solid, or mixed architecture. A pagetoid spread in the epidermis has also been reported in some of these cases (16). But a pure signet ring cell carcinoma of apocrine origin has only been reported in 3 cases in the axilla so far (17). Some cases of apocrine carcinoma with signet ring cell differentiation have been reported in eyelid (18) but occurrence of such a case in vulva is extremely rare. In a series by Piris et al. 14 of 14 cutaneous apocrine carcinomas of various sites expressed AR (19). In a study conducted by Songxia Zhou et al positive expression of AR was significantly higher in EMPD and ER negative and AR positive pattern was seen in almost 44% of cases (1). Since our case was positive for GCDFP15, AR and negative for ER we favored a diagnosis of apocrine carcinoma with signet ring cell differentiation.

The treatment of choice for primary EMPD is wide local excision with clear margins with or without regional lymph node dissection, however a high local recurrence rate has been reported in these cases (20). Postoperative chemotherapy or radiotherapy has been used as adjunctive treatments, but the prognosis still remains poor for advanced diseases. Recently due to Her-2/neu positivity of these tumors, a Her-2/neu antibody trastuzumab has been used successfully in cases of EMPD (1).

Conclusion

Primary EMPD of vulva has a slow evolution and varied clinical presentation with many mimickers leading to a delay in diagnosis. Since it has poor prognosis with local lymph node involvement and distant metastasis, a high index of clinical suspicion

along with histological and immunohistochemical assessment is of utmost importance in arriving at final diagnosis. Nevertheless, the role of ancillary investigations like CECT and PET-CT cannot be underestimated in identifying the primary source and to rule out distant metastasis. Moreover, the use of Her-2/neu inhibitors must be explored in future studies in the treatment of such cases.

Conflict of Interests

Authors have no conflict of interests.

Acknowledgments

There is no conflict of interest among the authors.

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