Vulvar Paget's disease: review of the literature, considerations about histogenetic hypothesis and surgical approaches

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Summary

Paget's disease of the vulva is a rare neoplasm that occurs on the apocrine glands. It predominantly is an intraepithelial lesion, but has the potential for dermal invasion and on occasion has been associated with an underlying adenocarcinoma.

Key words: Paget's disease; Vulva; Pruritus; Histogenetic hypothesis.

The entity of Paget's disease bears the name of Sir James Paget, an English clinician-pathologist that in 1874 described a particular disease of the breast.

Paget's disease is subdivided according to the location: mammary Paget's disease (MPD) and extramammary Paget's disease (EMPD), as described in 1889 by Crocker.

Paget's disease is characterized by the presence of specific cells, called Paget cells, and occurs on the apocrine glands of the breast or genitalia, perineum and axillary regions, all of which contain apocrine glands. The most common location of EMPD is the vulva and perianal region.

EMPD of the vulva is a rare neoplasm accounting for 2.5% of all vulvar malignancies [1]. It is predominantly an intraepithelial lesion and on occasion has been associated with an underlying invasive adenocarcinoma. Generally lesions with purely intraepithelial involvement have good prognosis, but although most cases of Paget's disease of the vulva remain in situ for a long period of time, they have the potential for dermal invasion and thus, poor prognosis [2].

EMPD of the vulva is most commonly seen in postmenopausal Caucasian females and the mean age of diagnosis is about 65 years.

Clinically EMPD appears as red, eczematoid lesions.

Four histologic forms of vulvar Paget's disease have been recognized: 1) intra-epidermal, if the basement membrane is intact and the Paget cells are located and confined to the epidermis only; 2) minimally invasive, if the Paget cells break through the basement membrane and invade the underlying dermis < 1 mm.; 3) invasive, if the Paget cells break through the basement membrane and invade the underlying dermis > 1 mm.; 4) vulvar Paget disease with an underlying apocrine gland adenocarcinoma [1].

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In the past the origin of Paget's cells has been surrounded by controversy.

There were two prevailing theories. Some authors believed that Paget's cells had a multifocal origin and arose from the abnormal differentiation of the stratum germinativum, which was multipotential and gave rise to the basal layer of the squamous epithelium, pilary complex and apocrine eccrine glands. This theory was supported by the natural history of extramammary Paget's disease with its long in situ phase and apparently simultaneous and multifocal involvement of the epidermis, pilary complex, and sweat glands. Others believed that Paget's cells originated in an underlying adenocarcinoma with migration or metastasis of the cells into the epidermis. This theory is supported by Paget's disease of the breast, which is virtually always associated with an underlying adenocarcinoma [1, 2].

The current consensus is that > 90% of cases are primary epidermal neoplasms that arise from an epidermal stem cell or from cells of the porous portion of the sweat ducts. Only rare cases of vulvar Paget's disease represent intraepithelial spread or metastasis from an associated regional internal carcinoma [3]. The vulva originates from primitive endoderm and contains epidermal stem cells, reserve cells that are important to the mature cell cycle.

In our opinion, Paget's cells of EMPD arise from the totipotential epidermal stem cells which give rise to squamous and cylindric cells to create squamous epithelium, pilary complex and apocrine eccrine glands. Abnormal differentiation of stem cells, probably due to the stimulation of an unsettled oncogenic noxa, brings about a metaplastic condition and the beginning of Paget's cells.

Paget cells may migrate within the epidermis in a horizontal as well as a vertical fashion [1]. Prognosis and surgical treatment are different according to histological findings.

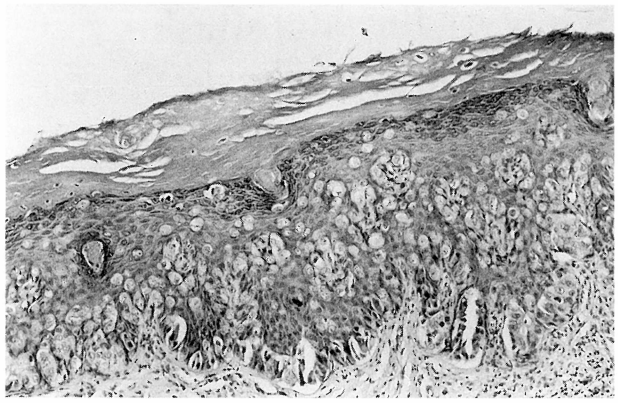

Figure 1. — Intraepidermal vulvar Paget's disease

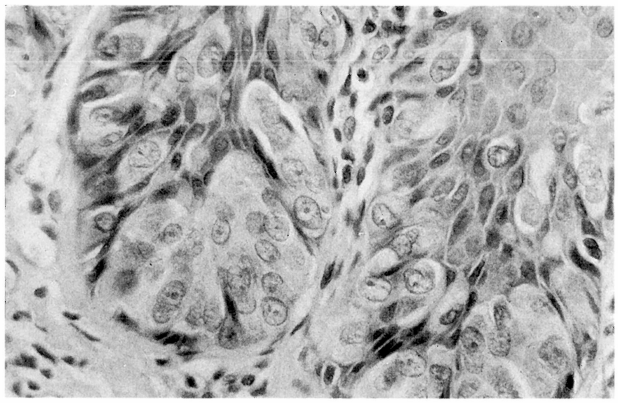

Figure 2. — The Paget's cells are visible as polygonal cells with abundant cytoplasm.

Intra-epidermal vulvar EMPD is generally managed by wide local excission, or at the most by simple vulvectomy. In May 2000, a 46-year-old gravida 2, para 2, with a past history of cystic mastopathy, was referred to the Department of Gynaecology of the University of Rome "La Sapienza" because of vulvar pruritus of two year's duration.

Physical examination of the external genitalia revealed a 6 x 5 cm erythematous lesion, with induration and leukoplakic areas, involving the right labium minor, near the clitoris. There was no inguinal lymphoadenopathy. Biopsy of the lesion demonstrated that the epidermis was infiltrated by typical large Paget cells while the basement membrane and the dermis were intact.

The patient underwent right partial vulvectomy with intraoperative evaluation of the surgical margins.

The histopathologic examination confirmed the diagnosis of intra-epidermal Paget's disease with lesion-free surgical margins (Figures 1 and 2). Currently, 23 months after the treatment, the patient is free of disease.

Minimally invasive vulvar EMPD is rare and its management is similar to that of intra-epidermal vulvar EMPD. Invasive vulvar EMPD is very rare and has generally been managed by radical vulvectomy and bilateral groin lymph node dissection. Vulvar EMPD with an underlying apocrine gland adenocarcinoma is treated by radical vulvectomy and bilateral groin lymph node dissection.

Recurrence is defined as surgically documented recurrent Paget's disease > 6 months after initial surgery. Since vulvar EMPD is a multifocal disease with a tendency for occult metastasis beyond the margin of the visible lesion and, hence, with a high rate (up to 40%) of local recurrence, it has been recommended that the width of excission should be at least 2.5 cm beyond the visible margin of surface changes [1-4].

Assessment of surgical resection margins is difficult in Paget's disease because the area of involvement is difficult to define on clinical examination and is often multifocal. In order to prevent recurrence, some authors have proposed surgical excission extending beyond the visible clinical lesions with intraoperative frozen sections. Fishman *et al.* described the implementation of a fast PAS staining technique which improves the capability of staining Paget's cells in frozen sections. This method was found to be useful in identifying Paget cells on the margins thought to be free of disease by conventional histological evaluation [5].

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