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Case report

# Vulvar Paget's Disease – A Case Report

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## ABSTRACT

*Vulvar Morbus Paget (MP) represents a rare intraepithelial adenocarcinoma. It accounts for less than 1% of all vulvar neoplasia and usually appears in postmenopausal women. Histologically it is analogous to Paget's disease of the breast. The most common clinical symptom is pruritus. The lesion appears as an erythematous or as an eczematous lesion with islands of hyperkeratosis. Occasionally, single anaplastic Paget's cells can be found on the vulvar smears which make cytological diagnosis of the disease possible. However, the disease can be diagnosed only by biopsy. We present a case of 49-year old woman with vulvar symptoms of pruritus, who had liver and kidney transplantation two years ago. During the standard gynecological examination the vulvar smear was taken for cytological evaluation. The smear was scanty, with inflammatory background, overloaded with squamae. There were two types of cells: dysplastic squamous cells from lower layer of the epithelium and the single, anaplastic cells with a high nuclear:cytoplasmic ratio who possessed eccentric, large nucleus. Nucleoli were rare. Cytoplasm varied from pale and delicate to densely basophilic. Accordingly, cytological diagnosis vulvar intraepithelial neoplasia (VIN III) with differential diagnosis of vulvar Paget's disease was made. The pathological verification supported the diagnosis of MP and an immunohistochemistry panel confirmed type III of Paget's disease and an evaluation of bladder was suggested.*

***Key words***: *vulvar Paget's disease, Paget's cells, vulvar cytology and immunostaining*

## Introduction

The most common neoplasia of the vulvar skin is squamous vulvar intraepithelial neoplasia (VIN) and in the most cases it is associated with atypical keratinocytes of human papillomavirus (HPV) positive cells. It is considered as a precursor of vulvar squamous cell carcinoma. Vulvar Morbus Paget (MP) represents a rare adenocarcinoma[1], first described in 1901 by Dubreuilh and it is accounts for less than 1% of all vulvar neoplasia[2]. Histologically it is similar to Paget's disease of the breast and vulva is the most common extramammarial localization[3]. The histogenesis is not completely understood but it is known that MP occurs most frequently in areas rich with apocrine glands and it seems that the disease is not connected with human papillomavirus (HPV) infection[4,5]. A high incidence of other malignancies (breast, colon, cervix, ovary and bladder) warrants careful examination of these patients[6]. In cases of Paget's disease of the vulva, primary cytological diagnosis is possible[7]. The cytologic differential diagnosis must include squamous intraepithelial lesion, nonkeratinizing squamous cell carcinoma, adenocarcinoma of other sources[8], lichen sclerosis and malignant melanoma[9]. But definitive diagnosis can be made only by histology.

## Case Report

We present a case of 49-year old woman, menopausal for six years with history of the vulvar skin irritation, itching and diffuse painfull erythematous lesions of the labia major and the perineum. The main symptoms appeared two years after kidney and liver transplantation. During the standard gynecological examination, cervical and vulvar smears were taken. Low-grade squamous intraepithelial lesion was found on routinely taken cervical smear. The vulvar smear was very scanty. On the in-

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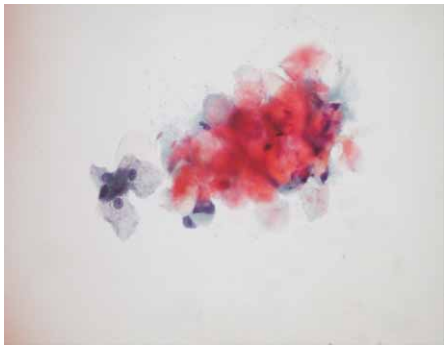


*Fig. 1. Squamae, dyskaryotic squamous cells from inner layer of epithelium and anaplastic cell (Papanicolaou x400).*

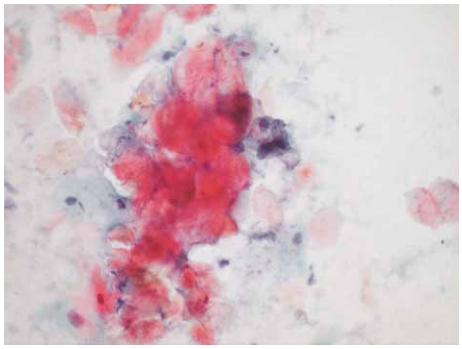
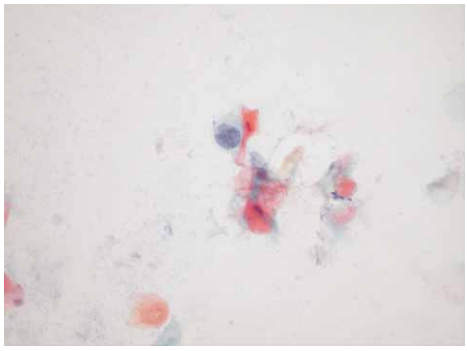


*Fig. 2. Inflammatory background with squamae and dyskaryotic cells (Papanicolaou x400).*



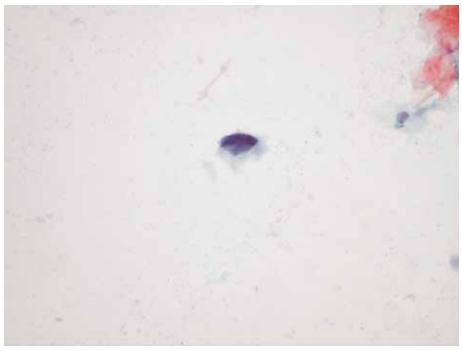


*Fig. 3 and 4. Paget's cell (Papanicolaou x1000).*

flammatory background, in the clusters of squamae the small dyskaryotic cells were found, predominantly single with nuclear hyperchromasia, irregular nuclear membrane and distinctly reduced cytoplasm with abnormal keratinization (Figure 1, 2) along with the large, tumor single cells. Tumor cells (Figure 3, 4) were large, with a high nuclear:cytoplasmic ratio and possessed a central or eccentric, large nucleus. Nucleoli were rare. Cytoplasm varied from small densely basophilic to pale and abound. Cytological diagnosis of vulvar intraepithelial neoplasia III (VIN III) was established and further procedure was recommended. After the positive Collins' test the biopsy was done. Histologically, surface was covered by squamae, the epithelium and basal layer was full of large,

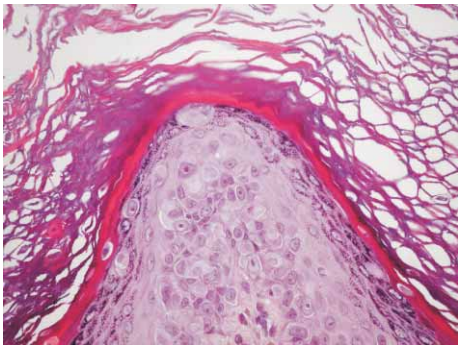


*Fig. 5. Paget's cells extending into the upper epithelium (HE – hemalaun eosin x400).*

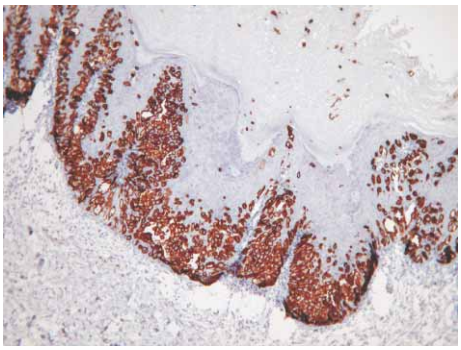


*Fig. 6. Cytokeratin 7 positive Paget's cells (x100).*

anaplastic – Paget's cells, single or in small clusters (Figure 5). Immunohistochemically the tumor cells were CK 7 and EMA strongly positive (Figure 6) and CEA and GCDFP-15 scanty positive. CK 20, Estrogen, Ca-125, PAS and alcian-blue were negative. Histopathological evaluation with immunohistochemical features and clinical data gave us the definitive diagnosis of the Paget disease type III and an evaluation of bladder was suggested.

## Discussion

Vulvar Morbus Paget appears as either an erythematous or an eczematous lesion like red to pink area with

white islands of hyperkeratosis, most often in postmenopausal women around 65 years of age[10], predominantly on the labia major, the labia minor and in the areas of the perineum. The most common clinical symptom is pruritus. Because of its clinical resemblance to dermatosis, these patients may be treated with various topical medications for some time before the diagnosis is made by biopsy[11]. Based upon the origin of the neoplastic cells the disease has been recently subclassified into three distinct types: type I is primary vulvar cutaneous Paget's disease; type II is Paget's disease as a manifestation of an associated adjacent primary anal, rectal or other-non-cutaneous adenocarcinoma and type III is pagetoid urothelial intraepithelial neoplasia (PUIN), as a manifestation of bladder neoplasia. Type I can be further subclassified as type 1a, 1b and 1c. Type 1a is primary vulvar intraepithelial Paget's disease – as adenocarcinoma in situ where the Paget's cells can be identified by scraping from attached areas. Type 1b is MP as primary vulvar intraepithelial Paget's disease with invasion. Type 1c is vulvar Paget's disease presenting as a manifestation of primary underlying vulvar adenocarcinoma (adenocarcinoma of the Bartholin's gland, specialized anogenital glands, or other vulvar glandular structures[12]). The distinction between these subtypes can be made by immunohistochemistry panel of the antibodies. The Paget's cells are positive for low weight cytokeratins 7 (CK7), carcinoembryonic antigen (CEA), antiepithelial membrane antigen (EMA), grosses cystic disease fluid protein-15 (GCDFP-15) and show PAS positive material[13]. Primary perianal Paget's disease (type II) is usually immunoreactive for cytokeratin 20 and negative for GCDFP-15[14]. Cervical adenocarcinoma manifesting as vulvar Paget's disease could be HPV positive especially for oncogenic types 16 or 18. Typically Paget's cells are HPV negative. Paget's disease – type III does not contain mucin, PAS-positive material, CEA, or GCDFP-15. The cells of PUIN are immunoreactive for CK 7 and may be cytokeratin 20 positive and uroplakin III positive. Melanoma cells, in contrast, are negative for these markers, but positive for S-100 polyclonal antibody and antihuman melanoma HMB-45[15]. The treatment and prognosis of vulvar Paget's disease depends on the type of disease and of the underlying carcinoma. Because of the possible reappearance of the disease close cytological follow-up for a longer period of time is essential before excluding recurrence. MP with its pathognomonic Paget's cells is similar wherever it occurs. The preliminary cytological diagnosis of vulvar Paget's disease is possible only if the cell sample is representative.

Adequate sample for correct diagnosis of vulvar Paget's disease must include two different types of the cells: squamous cells along with squamae with or without abnormality of nuclei and the Paget's cells. Sometimes these cells are scanty and mixed with squamous cells, and are hard to be noticed, so that careful and skilled analysis is required to avoid misdiagnosis. So knowledge of the cytologic features of MP could provide a highly probable cytologic diagnosis of the disease and should alert the clinician to the need for immediate biopsy[2]. Of course, clinical history and anamnestic data of patients are crucial in helping make an accurate cytological diagnosis. However, the correct diagnosis can be made only by biopsy with the use of the immunohistochemical panel of the antibodies. Therapy for vulvar PUIN is directed toward the bladder urothelial neoplasm while the vulvar pagetoid intraepithelial neoplastic process is treated conservatively. Paget's disease of the vulva is a rare neoplasm but it should be considered, especially in older women, and vulvar smears should be taken whenever symptoms are present.

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## PAGETOVA BOLEST STIDNICE – PRIKAZ SLUČAJA


### S A Ž E T A K

Pagetova bolest (PB) vulve predstavlja rijedak oblik intraepitelnog adenokarcinoma. Obuhvaća manje od 1% svih zloćudnih neoplazma vulve. Javlja se češće u postmenopauzi a histološki je istovjetan Pagetovoj bolesti dojke. Vulva je najčešća ekstramamarna lokalizacija. Klinički se vidi ograničeno eritematozno uzdignuće s otocima hiperkeratoze. Prikazan je slučaj 49-godišnje transplantirane pacijentice (multiorganska transplantacija: bubrega i jetre) sa simptomima svrbeži i nelagodnog peckanja u području velikih usana i perineuma. Prilikom pregleda uzeo se i obrisak stidnice za citološku analizu. U oskudnom materijalu na upalno promijenjenoj pozadini preparata uz mnoštvo bakterija i skvama nađene su dvije vrste stanica: pločaste diskariotične stanice iz dubljeg sloja epitela te pojedinačne anaplastične stanice u kojima dominira poremećen odnos jezgre i citoplazme, s ekscentričnom i hiperkromatskom jezgrom, ponegdje istaknutijim nukleolima te nešto obilnijom bazofilnom citoplazmom. Citološki nalaz je uputio na vulvarnu neoplaziju (VIN III) uz diferencijalnu dijagnozu Pagetove bolesti. Nakon pozitivnog Collins-ovog testa učinila se ekscizija lezije te je patološka verifikacija potvrdila Pagetovu bolest a imunohistokemijski panel uputio na tip III Pagetove bolesti.