

## **EXTRAMAMMARY PAGET'S DISEASE**

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Extramammary Paget's disease (EMPD) was first described in 1889 by Crocker in a paper entitled "Paget's disease affecting the scrotum and penis". Since then lesions of EMPD have also been reported on the vulva, perianal skin, perineum, groin, buttocks, pubis and other distant sites such as axilla, scalp, ear canal and eyelid. It usually affects areas with numerous apocrine glands.

### **Clinical presentation:**

EMPD usually presents as a slowly growing erythematous patch or plaque with a scaly or eroded surface. The lesions measure from a few to several centimeters in diameter. However, they can evolve to very large lesions that involve the entire vulva or perianal area. The lesions are commonly pruritic. In addition to EMPD, the clinical diagnoses include: squamous cell carcinoma in situ, leukoplakia, eczema, psoriasis and tinea. Because some lesions can be pigmented, the clinical differential diagnosis includes melanoma. EMPD is classified as primary if only the skin is involved and secondary when associated with an underlying adenocarcinoma from the rectum, vagina, cervix, urethra, bladder or prostate (approximately 25% of cases). In rare cases, there is an associated apocrine gland carcinoma.

### **Histopathologic findings:**

The typical Paget cells are large and round with pleomorphic vesicular nuclei, prominent nucleoli and abundant pale staining, sometimes vacuolated cytoplasm. Some cells may have hyperchromatic nuclei. Typical and atypical mitotic figures are present. The nucleus can be displaced to the periphery of the cell, which acquires a signet-ring appearance. The pattern of distribution is usually as single cells or small clusters of cells between epidermal keratinocytes at all levels of the epidermis, and they may reach the cornified layer. In some cases the cells form glandular structures. Very often the Paget cells are above the basal layer and compress the basal keratinocytes. The PAS-diastase and mucicarmine stains often show that the Paget cells contain cytoplasmic mucin. Even when the Paget cells extend down the epithelium of the adnexa, the disease is still considered *in situ*. In approximately 21% of vulvar EMPD the Paget cells infiltrate from the epidermis into the dermis. In cases of secondary EMPD with an underlying cervical or rectal adenocarcinoma, the skin is involved by irregularly shaped glands lined with atypical columnar cells.

**Immunohistochemistry:**

Immunohistochemistry is important for establishing a definitive diagnosis and for evaluating the possibility of an associated underlying adenocarcinoma in some cases. The Paget cells stain positively for CK7, carcinoembryonic antigen and epithelial membrane antigen. Cutaneous cases are positive for gross cystic disease fluid protein (GCDFP). Approximately 50% of cases are androgen receptor positive. EMPD lacks progesterone and estrogen receptors. Secondary EMPD is CK7+, CK20+ and GCDFP15-. Positive reaction for uroplakin III distinguishes EMPD secondary to urothelial carcinoma from primary EMPD. Ki-67 and cyclin D1 expression have been reported at significant higher levels in invasive lesions than in situ cases. Contrary to Paget's disease of the breast, which demonstrates HER-2 gene amplification in almost all cases, various studies report that EMPD shows HER-2 gene amplification from 0% to 43% of cases. HER2 oncogene amplification appears to be more common in recurrent EMPD.

**Pathogenesis:**

Approximately 25% of EMPD are secondary to an underlying adenocarcinoma. The pathogenesis of the primary EMPD which comprise the majority of the cases is unclear. Probably most of the primary EMPD originate in the epidermis from a pluripotential stem cell, pre-existing Toker cells or the epithelial cells of the intraepidermal apocrine duct.

**Differential Diagnosis:**

Pagetoid squamous cell carcinoma  
Malignant melanoma pigmented and amelanotic  
Mycosis fungoides (Pagetoid reticulosis or Woringer-Kolopp disease)  
Langerhan's cell histiocytosis

**Prognosis:**

EMPD *in situ* has a good prognosis. However, because EMPD can be multifocal, local recurrences are commonly seen. Invasive EMPD and EMPD secondary to an underlying adenocarcinoma have a poor prognosis with 50% mortality.

**Treatment:**

Wide local excision.  
Mohs' micrographic surgery.  
Recurrent primary EMPD: radiotherapy, CO2 laser ablation and photodynamic therapy.

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