

What Is Your Diagnosis?



A previously healthy 59-year-old white woman presented with a pruritic inflamed lesion on the left nipple of 2 years' duration. The irritation worsened with friction from contact with clothing and improved with use of lotions and emollients. The patient had no constitutional symptoms, history of trauma, or family history of breast or ovarian cancer. Physical examination revealed an erythematous scaling plaque measuring 3 cm in diameter overlying the left nipple. The right breast and nipple were unaffected. The contours of both breasts and nipples were bilaterally symmetric. No cervical, supraclavicular, or axillary lymphadenopathy was appreciated. There was no mammographic abnormality.

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The Diagnosis: Paget Disease of the Nipple

Histologic examination of the skin biopsy specimen taken from the nipple (Figure 1) demonstrated parakeratosis and neutrophilic debris in the stratum corneum. Large, atypical, epithelioid cells within the epidermis and prominent nucleoli were present within some of the atypical cells (Figure 2A). There also was chronic perivascular inflammation in the upper dermis. The atypical epithelioid cells stained positive for cytokeratin 7 (Figure 2B) and negative for carcinoembryogenic antigen, mucicarmine, and S100 protein. The histopathologic features were consistent with the diagnosis of Paget disease (PD) of the nipple. The patient subsequently underwent a modified radical mastectomy of the left breast and was found to have an underlying ductal carcinoma in situ.

Paget disease of the nipple, also called PD of the breast, was first described by Sir James Paget in 1874.¹ Paget disease is a rare malignancy of the nipple-areola complex, comprising less than 5% of all breast cancers and often associated with an underlying in situ or invasive carcinoma in the breast parenchyma.^{2,3} Clinically, PD is manifested by chronic eczematous changes with malignant crusting or ulceration of the nipple-areola complex and persistent soreness or itching. There may be an associated breast mass or mammographic abnormality.³ The pathologic hallmark is the presence of malignant, intraepithelial, adenocarcinoma cells. Paget cells and underlying ductal carcinoma cells have been shown to be positive for the v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, *ERBB2* (formerly *HER2* or *HER2/neu*), suggesting common genetic alterations for both the epidermal and breast tumor cells.⁴

There are 2 main theories regarding the pathogenesis of the disease: the epidermotropic and the in situ transformation.⁵ The first theory suggests that the Paget cells are ductal cells that have migrated from an underlying adenocarcinoma of the breast parenchyma to the epidermis of the nipple.⁶ The second theory postulates that nipple keratinocytes undergo transformation into malignant cells independent from any pathology within the breast parenchyma.⁷ The implication of the more widely accepted epidermotropic theory is consistent with the current standard of treatment, which has been mastectomy. The transformation theory suggests that treatment can be limited to the nipple-areola complex.



Figure 1. An erythematous scaling plaque measuring 3 cm in diameter overlying the left nipple.

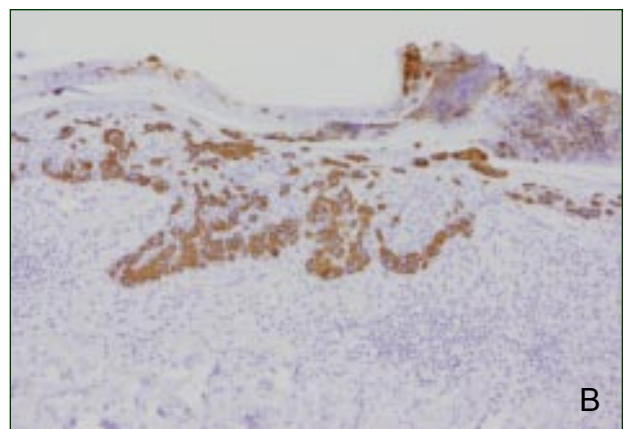
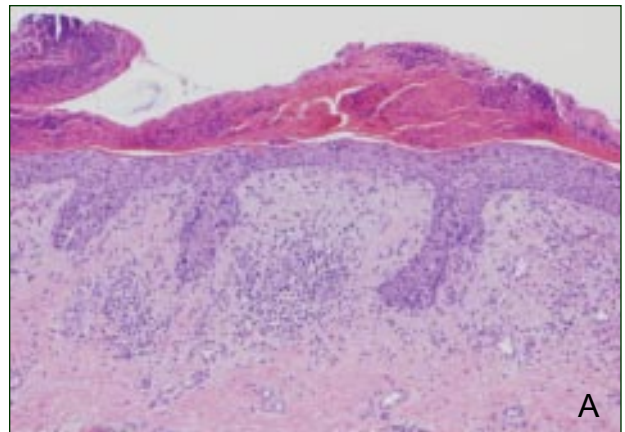


Figure 2. Dermatohistopathology revealed large, atypical, epithelioid cells within the epidermis and prominent nucleoli within some of the atypical cells (A)(H&E, original magnification $\times 20$). The atypical epithelioid cells in the epidermis stained positive for cytokeratin 7 (B) (original magnification $\times 20$).

Most cases of PD present in middle-aged women ($\approx 99\%$), with a mean age at diagnosis of 55 years.³ Clinical symptoms include erythema, itching, a burning sensation, thickening of the skin, inversion of the nipple, and serosanguineous nipple discharge. Symptoms usually are present for 6 months or more prior to the detection of an underlying breast cancer.³ The primary differential diagnoses are nipple eczema, psoriasis, and irritant contact dermatitis. Uncommon mimics of PD include nodular localized cutaneous amyloidosis, Bowen disease, drug eruptions, nevoid hyperkeratosis of the nipple, and malignant melanoma.⁸

Prognosis is related to the presence or absence of a palpable invasive breast tumor or axillary node metastases. Surgery with or without adjuvant therapy is the most common treatment of PD.⁹

REFERENCES

1. Paget J. On disease of the mammary areola preceding cancer of the mammary gland. *St Bartholomew Hosp Research London*. 1874;10:87-89.
2. Nance FC, DeLoach DH, Welsh RA, et al. Paget's disease of the breast. *Ann Surg*. 1970;171:864-874.
3. Valdes EK, Feldman SM. Paget's disease of the breast. *Breast J*. 2006;12:83.
4. Fu W, Loboocki CA, Silberberg BK, et al. Molecular markers in Paget disease of the breast. *J Surg Oncol*. 2001;77:171-178.
5. Paone JF, Baker RR. Pathogenesis and treatment of Paget's disease of the breast. *Cancer*. 1981;48:825-829.
6. Ashikari R, Park K, Huvos AG, et al. Paget's disease of the breast. *Cancer*. 1970;26:680-685.
7. Jamali FR, Ricci A Jr, Deckers PJ. Paget's disease of the nipple-areola complex. *Surg Clin North Am*. 1996;76:365-381.
8. Pizzichetta MA, Canzonieri V, Massarut S, et al. Pigmented mammary Paget's disease mimicking melanoma. *Melanoma Res*. 2004;14:S13-S15.
9. Marcus E. The management of Paget's disease of the breast. *Curr Treat Options Oncol*. 2004;5:153-160.