

Paget's Disease of the Breast

Paget's Disease



Uncommon and distinctive skin cancer characterized by eczema-like rash involving the nipple with spread to surrounding areola and skin

Extramammary Paget's disease involves skin of female and male genitalia

Historical Aspects of Paget's Disease

- 1874, Sir James Paget described in 15 women chronic eczematous changes in the nipple-areola region associated with carcinoma of the breast within one year
- 1889, H.R. Crocker described lesions on scrotum and penis that were histologically similar to Paget's Disease of the breast
- 1901, Dubreuilh described Paget's Disease involving the vulva



Paget's Disease of the Vulva



Paget's Disease of the Axilla

Incidence of Mammary Paget's Disease (PD)

- 0.5-5% of carcinoma of the breast
- Post-menopausal women (mean age of 54 years, average age is older by 5-10 years compared to women with breast cancer without Paget's Disease)
- Rare in men
- ~ 62% of women with Paget's Disease have detectable breast tumor at presentation
- When palpable mass present, it is invasive ductal carcinoma of the breast in 90-94% of the cases
- When palpable mass absent but underlying lesion is present, 66-86% of PD patients have ductal carcinoma *in situ* (DCIS)

Clinical History of Paget's Disease

- Itching and burning most common complaints
- Long history of eczematous changes of the nipple and areola region of the breast without improvement on topical corticosteroids (delay of diagnosis on average 10-12 mo)
- Usually unilateral, can be bilateral
- Symptoms and signs: pain, itching, burning sensation, excoriation from itching, small vesicles that resolve and recur, discharge, ulceration, nipple inversion
- Lesion is typically red, crusty, thickened, and irregular sharply demarcated plaque

Mammary Paget's Disease



Extensive Paget's Disease



Nipple Invagination



Paget's Disease in male



Paget's Disease – 56-year-old woman who presented with erythematous, swollen, enlarged nipple with focal ulceration and oozing. Complained of serosanguinous discharge and bleeding. Found to have palpable breast mass and subareolar microcalcification by mammography. No lymphadenopathy.

Differential for Changes Associated with Paget's Disease

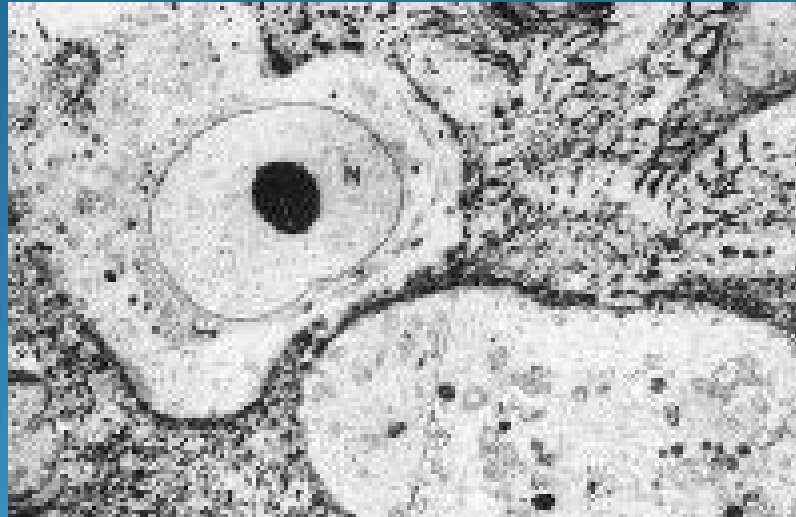
- Chronic Eczema
- Contact Dermatitis
- Psoriasis
- Benign Intraductal Papilloma
- Squamous Cell Cancer
- Basal Cell Cancer
- Superficial Spreading Malignant Melanoma
- Mammary Duct Ectasia
- Leiomyoma
- Toker cells – hyperplasia of mammary gland-related cells

Work-up for Paget's Disease

- Skin biopsy for diagnosis
- Imaging studies:
 - Bilateral Mammography
 - Breast Ultrasonography
 - MRI
 - ^{99m}Tc MIBI prone scinti-mammography

Histopathology of Paget's Disease

Paget's Cell



Paget cell containing ovoid nucleus (N), scanty nuclear chromatin, a large nucleolus, and abundant pale-staining cytoplasm with smooth and rough endoplasmic reticulum (arrow), scattered enlarged mitochondria, free ribosomes, and lysosomes. No desmosomal attachments are seen between Paget cells and adjacent keratinocytes. Tonofilaments are seen in the keratinocytes (uranyl acetate and lead citrate, original magnification X5,500). eMedicine, GF Kao.

Variants of Paget Cells

- Adenocarcinoma-like cell type – arranged in a columnar fashion
- Spindle cell type – angular and elongated shape, arranged in a nested pattern, and grow in compact masses
- Anaplastic cell type – can be confused with Bowen disease cell type. Pleomorphic cells with necrotic and mitotic/multinucleated features. Positive stain for CEA and EMA by immunoperoxidase favors Paget's Disease over Bowen disease.
- Acantholytic cell type – overlaps with anaplastic cell type. Prominent acantholysis seen.
- Pigmented cell type – occurs when melanin pigment is transferred from melanocytes into malignant Paget cell. Paget cells are DOPA-negative.

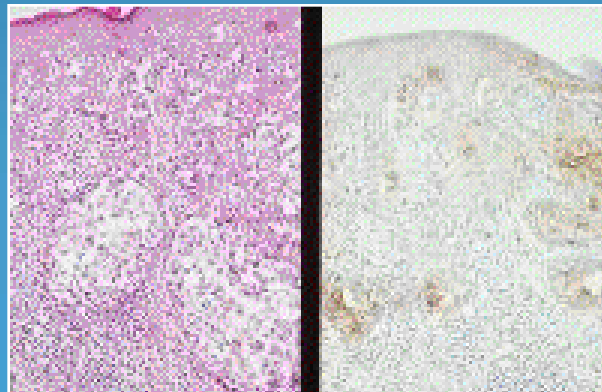
Histopathology of Paget's Disease



Nests of malignant Paget cells predominantly involving the lower layers of the epidermis. The cytoplasm of the tumor cells contains abundant pale staining, granular, mucinous material. Occasional small glandular structures can be seen within the malignant cell nests (hematoxylin and eosin [H&E], original magnification X100).

Markers for Paget's Disease

- PR and ER negative, although underlying breast tumor may be positive
- Negative for lysozyme, k-casein, and alpha-lactalbumin, which will be positive in breast tumor cells
- Positive for low-molecular-weight keratins, EMA, CEA, and PAS staining
- Positive for erbB-2 (>90%) - role of erbB2 in migration



H&E

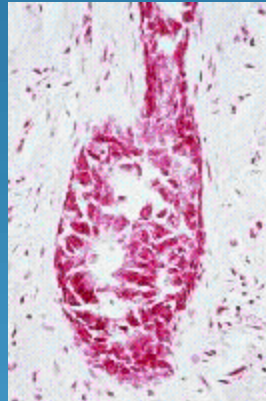
Anti-CEA

Histopathology Differentiation

- Expect histologic features of inflammation in irritant or contact dermatitis
- Melanoma cells are located in the basal layer, but can be found in all layers of the epidermis, as well as invade into dermis
- Melanoma cells will be positive for S100 and homotropine methylbromide (HMB-45) (monoclonal antibody to melanoma cells)
- In Bowen's Disease, keratinocytes will not stain for CEA
- In Benign Toker cells, CEA and S100 are both negative. Also, Toker cells are clear cells without epithelial mucin and are not associated with underlying malignancy

Pathogenesis of Paget's Disease

1. Epidermotropic theory - most commonly accepted. Theory where Paget cells originate from duct cancer cells that have migrated along basement membrane of ducts to the epidermis of the nipple.
 - supported by underlying intraductal or invasive carcinoma



Intraductal carcinoma of the breast underlying a Paget's disease of the nipple.
Cribriform pattern, dilated duct

2. In-situ Malignant Transformation - independent process of the nipple epidermis degenerating on its own. Supported in cases where histology shows no dermal invasion or connection to underlying breast carcinoma.

Management of Paget's Disease

- Mastectomy standard of care
- May receive chemotherapy and/or radiation therapy
- Controversy for appropriateness of breast conservation - no prospective randomized controlled trials to measure for recurrence compared to mastectomy
- Breast conserving therapy may include:
 - central mastectomy involving nipple-areola complex and suspicious lesion with postop XRT
 - central segmentectomy if no breast lesion identified clinically or radiographically
 - XRT alone
 - may be appropriate for early localized disease

Prognosis of Paget's Disease

- Prognosis affected by presence or absence of palpable tumor at presentation
- Survival rate with palpable tumor is 38-40% at 5 yrs and 22-33% at 10 yrs
- Without tumor is 92-94% at 5 yrs and 82-91% at 10 yrs
- Men have worse prognosis compared to women, likely due to delay in diagnosis
- Positive ErbB2 marker is associated with more aggressive disease process
- Solid/comedo large cell size subtype of DCIS is very aggressive

Paget's Disease



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References

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