

PERIANAL PAGET'S DISEASE

Definition:

- 1874 Sir James Paget first described mammary Paget's: intraepidermal neoplasm limited to the nipple, caused by underlying breast carcinoma.
- 1889 Crocker: 1st pt. with extramammary Paget's disease (EMPD) involving penis and scrotum.
- Perianal Paget's disease (PPD) was described 4 years later in 1893 by Drier and Couillaud.
- PPD is a rare cutaneous intraepithelial adenocarcinoma, usually of epidermal apocrine gland origin, with glandular differentiation.
- Paget's has classically been described as affecting the breast. EMPD reported in the perineum, vulva, scrotum, penis, groin, thigh, buttock, and axilla.

Histopathology:

- Red erythematous or whitish gray, elevated, crusty, scaly eczematoid lesion.
- Large round clear staining cells with abundant pale-staining cytoplasm. Large nuclei in periphery of cells, which are confined to the epidermis. Hyperkeratosis, parakeratosis, acanthosis can be seen.
- PAS+ stain identifies sialomucin. (mucoprotein not present in Bowen's)
- Most stain negative for a marker for colorectal goblet cells.
- Thought to be relatively benign disease. EMPD arises as a primary intraepidermal neoplasm in most cases, and underlying neoplasm is only found in a small number of cases.
- Some cases start benign, can eventually become invasive resulting in adenocarcinoma.
- Immunohistochemical studies:
 - Marker of choice for EMPD cells: cytokeratin (CK) 7
 - +CK7/-CK20 indicates a primary cutaneous intraepithelial neoplasia.
 - +CK20 stain (or -CK7), indicates underlying regional or internal malignancy.
- Goldblum & Hart (recently confirmed by Liu et al.), support the theory of 2 types of PPD:
 - Primary cutaneous intraepithelial neoplasm, in which cells display sweat gland differentiation and +GCDFP15 (gross cystic disease fluid protein 15 = marker for apocrine cells).
 - Patients with assoc rectal adenocarcinoma have endodermal differentiation with gastrointestinal-type glands, +CK20 and -GCDFP15. This implies direct intraepithelial Pagetoid spread of anorectal adenocarcinoma.

Epidemiology:

- The true incidence of EMPD is difficult to estimate because of its rarity.
- 96 cases reported in the literature by 1988.
- M=F from cases reported.
- Mean age of onset reported 59-65

Clinical Presentation:

- Perianal eczema or pruritis followed by bleeding, ulceration or discharge and occasionally pain.
- Median duration of symptoms prior to diagnosis was 3 years (range 2-8).
- Typical presenting symptoms are nonspecific and most lesions are first treated as benign dermatologic conditions, thus duration of Sx prior to Dx can be long.

Differential Diagnosis:

- Idiopathic pruritis ani, hidradentitis suppurativa, condyloma acuminatum, perianal Crohn's involvement, Bowen's disease (SCC in situ), melanoma, descending spread of signet ring cell carcinoma of rectum, epidermoid carcinoma. Derm: contact dermatitis, psoriasis, tinea cruris, erythrasma, lichen simplex chronicus, SCC, superficial basal cell carcinoma, and mycosis fungoides

Diagnosis:

- Biopsy and identification of Paget's cells. - must exclude malignant conditions.
- Recommended that clinicians carefully examine the anus, rectum and colon in the presence of PPD to R/O associated carcinoma.

Associated Conditions:

- Unlike mammary Paget's disease, EMPD is not commonly associated with an underlying neoplasm.
- Adnexal adenocarcinoma in 7-24% of cases.
- Internal malignancy, mainly gastrointestinal carcinoma, in 12-14% (quoted up to 50%).

Treatment:

- Surgical wide local excision with or without skin grafting is considered the standard treatment.
- Beck and Fazio recommend multiple punch biopsies 1 cm from edge of lesion in 4 quadrants including dentate line, anal verge, and perineum for mapping extent of involvement, as Paget's cells may extend beyond the grossly visible margins of the lesion.
- Alternatively, margins can be examined intraoperatively by frozen section.
 - Besa et al., and Pierie et al., found positive surgical margins in 53% and 56% of patients with PPD, respectively.
- Surgery may have significant morbidity and discomfort.
- Skin coverage: use of local sliding or rotation grafts, muscle flaps, and mucocutaneous skin flaps have been successful. Split-thickness skin grafts are used most often, and more recently, according to St. Peter et al., stage grafting is being used with 4-day interval between resection and grafting.
- Although skin grafts are used frequently, reliable graft take in the perianal area poses a challenge.

Nonsurgical Approaches:

- External radiation therapy and photodynamic therapy (PDT) may be reasonable alternatives to surgery in cases such as patients who are unfit for surgery, those who wish to avoid radical surgery, or have multifocal widespread disease.
- PDT uses light energy to destroy tumor, with enhancement of a photosensitive drug. Light is focused to the tumor site, and the excess energy creates oxygen free radicals, which causes tissue damage.
- Shieh et al., treated 16 lesions of EMPD with PDT: 8 (50%) had complete response. Functional and cosmetic outcome were excellent in all pts.
- XRT has been associated with high rate of local complications.
- Recently, topical immunomodulation with imiquimod 5% cream (Aldara) [antiviral for use on anal and genital warts] has been reported in 2 cases with clinical and histologic resolution of the lesion at 3 mo. F/U. The mechanism of action is thought to be mediated by induction of mRNA encoding for inflammatory cytokines including IFN- α and TNF- α locally.

Advanced Disease:

- Tumor cells infiltrate into the dermis and advance to Paget's carcinoma, it is referred to as adenocarcinoma of the skin.
 - Poor prognosis as most cases already have micrometastases or distant metastases at time of diagnosis.
- Metastatic sites in order of frequency: inguinal and pelvic lymph nodes, liver, bone, lung, brain, bladder, prostate, and adrenal.
- No standard treatment with a significant effect has yet been established. Some have recommended APR with inguinal lymph node dissection for advanced lesions with underlying cancer.
- Chemotherapy is controversial. Limited studies have had success, while others have not; overall there is insufficient data available.

Recurrence:

- Recurrence is common with wide local excision: estimated 31-61% rate of recurrence
- Long-term follow up is needed in all patients to exclude local recurrence and development of associated cancer
- In general, the prognosis of primary PPD confined to the epidermis is considered good, with most patients being long-term survivors.

Largest Long-Term Study to Date: McCarter et al., Memorial Sloan Kettering, 2003.

- All patients between 1950-2000, 27 patients with median age of 63.
- Most treated with wide excision. 22% (6/27) required colostomy (5/27 had APR and 1 had wide excision with diverting colostomy.)
- 33% (9/27) had positive margins. 44% (12/27) had invasive disease identified by final pathology.
- 37% had local recurrence, and 44% required >1 procedure (most reexcision).
- Adjuvant chemo used in 22% of patients as they had more aggressive disease.

- At median follow-up of 67 months: 56% (15/27) had no evidence of disease; 2/27 had metastatic disease; overall survival at 5 years: 59% & 10 years: 33%; Disease free survival at 5 years: 64% & 10 years: 39%.
- Favor frozen section for negative margins, and using local skin flaps/secondary intention for large wounds rather than grafting because experienced high graft loss rates (unspecified #).
- Adjuvant therapy not found to be associated with local improvement or increased survival.

References:

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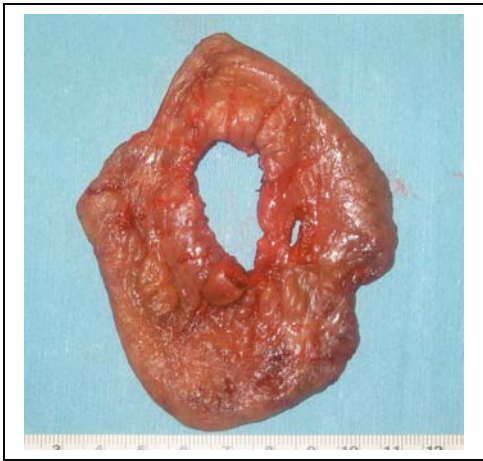
Perianal Paget's Disease – 86 yo female



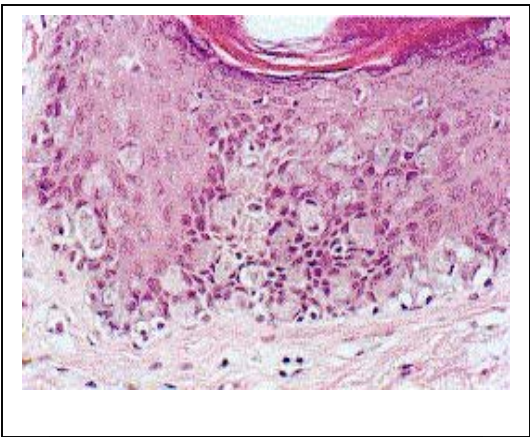
Planned excision



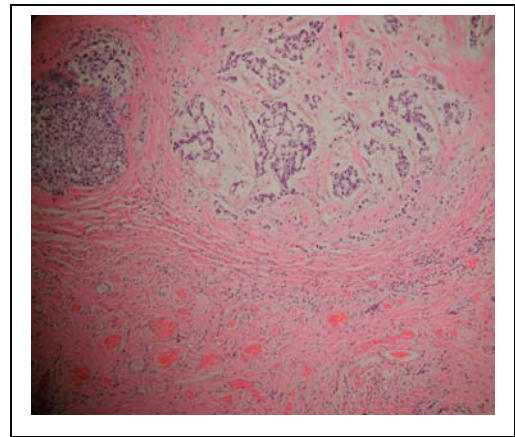
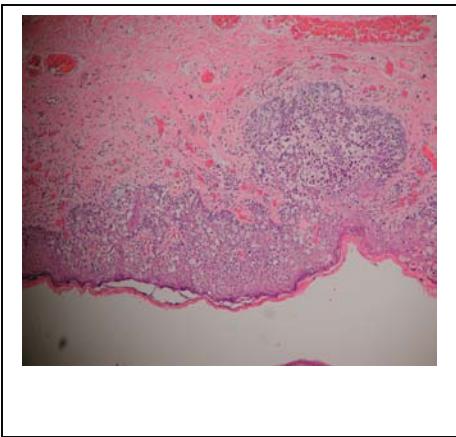
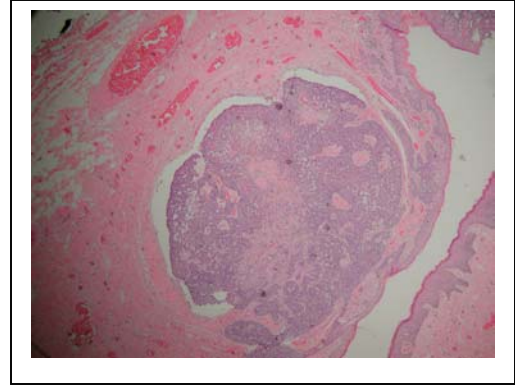
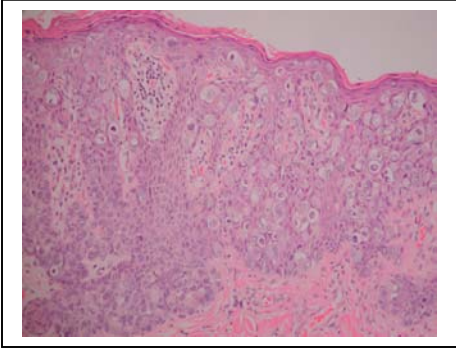
Completed repair



Surgical specimen



H & E stain of perianal Paget's Disease



Microscopic pathology from case of 86 year old female with perianal Paget's Disease – invasive cancer is seen