

What Is Your Diagnosis?



A 70-year-old man presented with a nonpruritic erythematous scaly plaque in the left suprapubic region of 6 months' duration that had failed to respond to terbinafine cream 1% after 1 month of treatment of suspected tinea cruris. His medical history was remarkable for hypertension, hyperlipidemia, chronic obstructive pulmonary disease, benign prostatic hyperplasia, an abdominal aortic aneurysm, alcohol dependence, tobacco use disorder, and unintentional weight loss of 15 lb over the last year.

PLEASE TURN TO PAGE 135 FOR DISCUSSION

Sailesh Konda, MD; Wen Chen, MD; Harold R. Minus, MD

Dr. Konda is from the Department of Dermatology, Loma Linda University Medical Center, California. Dr. Chen is from the Department of Pathology and Dr. Minus is from the Department of Dermatology, both at the Washington DC VA Medical Center.

The authors report no conflict of interest.

Correspondence: Sailesh Konda, MD, Department of Dermatology, Loma Linda University Medical Center, 11370 Anderson St, Ste 2600, Loma Linda, CA 92354 (skonda@llu.edu).

The Diagnosis: Extramammary Paget Disease

A biopsy of the plaque revealed an intraepidermal proliferation of large cells with abundant clear cytoplasm and large vesicular nuclei distributed throughout the epidermis (Figure 1). The neoplastic cells stained positive for both periodic acid–Schiff stain (Figure 2) and CK7

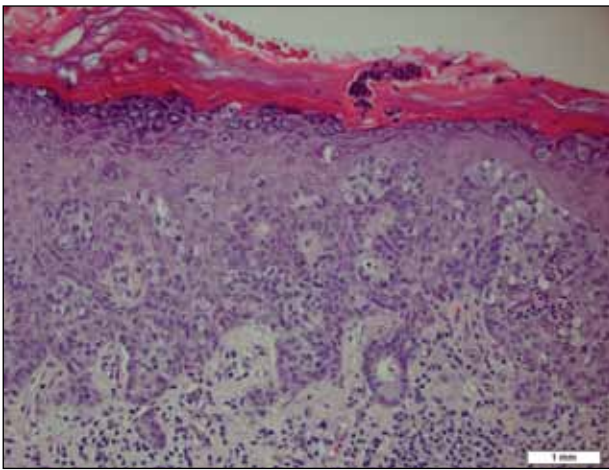


Figure 1. Intraepidermal proliferation of large cells with abundant clear cytoplasm and large vesicular nuclei distributed throughout the epidermis as individual cells and as variably sized aggregates of cells (H&E, original magnification $\times 200$). (Reference bar indicates 1 mm.)

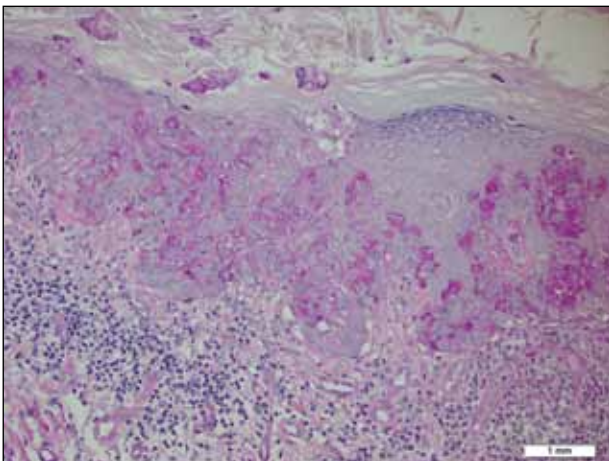


Figure 2. Granular cytoplasm was positive on periodic acid–Schiff staining (original magnification $\times 200$). (Reference bar indicates 1 mm.)

(Figure 3). Chemistry and liver function panel, urine analysis, carcinoembryonic antigen levels, and prostate-specific antigen levels were within reference range. A complete blood cell count revealed mild megaloblastic anemia. Subsequent computed tomography of the chest, abdomen, and pelvis revealed an abdominal aortic aneurysm and prostatic enlargement without any evidence of potential malignancies. Colonoscopy revealed multiple hyperplastic polyps and a tubular adenoma. Cystoscopy was normal, except for evidence of prostate enlargement. Urine cytology was unremarkable. The patient was referred for excision of the lesion with Mohs micrographic surgery. Follow-up was recommended every 3 months for the first 2 years following surgery and every 6 months thereafter to monitor for recurrence or secondary neoplasms.

Sir James Paget first described mammary Paget disease of the nipple in 1874 in his report of 15 women with skin eruptions of the nipple and areola and subsequent carcinoma of the underlying breast.¹ Paget also described a patient with a similar eruption on the glans penis and Crocker² described extramammary Paget disease (EMPD) of the scrotum and penis in 1889. The principle difference between mammary Paget disease and EMPD is the anatomic location.

Extramammary Paget disease is a rare condition that typically affects patients aged 50 to 80 years

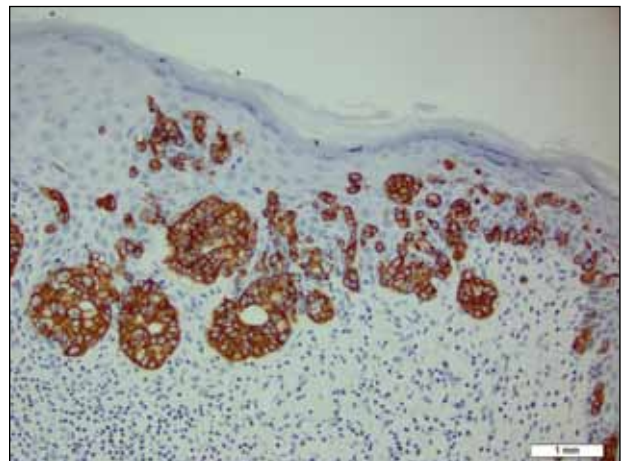


Figure 3. Neoplastic Paget cells were characteristically positive on staining for CK7 (original magnification $\times 200$). (Reference bar indicates 1 mm.)

and is more common in women and white-skinned races.³ Extramammary Paget disease frequently targets cutaneous sites that are rich in apocrine glands. The most commonly affected site is the vulva followed by perineal, perianal, scrotal, and penile skin. Less commonly, the axillae, buttocks, thighs, eyelids, and external auditory canals may be affected.⁴

Patients with EMPD typically present with well-demarcated, nonresolving, erythematous and eczematous plaques that may have associated crusting, scaling, papillomatous excrescences, lichenification, ulceration, or bleeding. The most common symptom is pruritus, followed by burning, irritation, pain, and tenderness.⁵ Ten percent of patients are asymptomatic. The average interval between symptom onset and diagnosis is 2 years.⁵

Histopathology reveals diffusely infiltrating, irregular, neoplastic Paget cells within the epidermis that are large and vacuolated with abundant pale bluish cytoplasm and large vesicular nuclei, which may be centrally or laterally compressed. The cells may be distributed singly or in groups as strands, nests, or glandular patterns within the lower epidermis, rete ridges, and adnexal structures. Hyperkeratosis, acanthosis, and parakeratosis may also be present. Paget cells stain for immunohistochemical markers of apocrine and eccrine derivation including low-molecular-weight cytokeratins, gross cystic disease fluid protein 15, periodic acid–Schiff stain, and carcinoembryonic antigen.⁵ Perrotto et al⁶ studied 98 specimens from 61 patients and found that CK7 was positive in all EMPD specimens, while CK20 and gross cystic disease fluid protein 15 were positive in large subsets of both primary and secondary EMPD. Cases of EMPD secondary to anorectal adenocarcinoma were largely *ERBB2* (formerly *HER2/neu*) negative and *CDX2* positive.⁶

Diagnosis of EMPD should be followed by a thorough investigation for underlying carcinomas. In a review of 197 cases of EMPD, 24% of patients with EMPD had an associated underlying in situ or invasive adnexal apocrine carcinoma, which was associated with a higher mortality rate than in patients without this underlying malignancy. Additionally, 12% of EMPD patients had an associated underlying internal malignancy.⁷ These malignancies may include carcinomas of the urethra, bladder, vagina, cervix, endometrium, prostate, colon, and rectum. Perianal EMPD has a higher frequency of associated malignancies than vulvar EMPD.⁵ The location of EMPD is related to the location of the underlying malignancy; for example, perianal EMPD is associated with colorectal adenocarcinomas, and EMPD of the penis, scrotum, and groin is associated with genitourinary malignancies. Investigations to search

for associated malignancies in patients with EMPD may include pelvic ultrasonography and/or magnetic resonance imaging, hysteroscopy, colonoscopy, sigmoidoscopy, cystoscopy, intravenous pyelogram, mammogram, and/or chest radiograph.

The most effective treatment of EMPD is margin-controlled surgical excision. High local recurrence rates may be due to irregular margins, multicentricity, and the tendency of EMPD to involve clinically normal-appearing skin. Hendi et al⁸ noted that EMPD may actually be unifocal with subclinical fingerlike projections extending beyond the main body of the tumor, requiring CK7 immunostaining for visualization to ensure complete margin control. The recurrence rate after standard surgical excision is 33% to 60%. The recurrence rate after excision via Mohs micrographic surgery is 16% for primary EMPD and 50% for recurrent EMPD.⁹ Other treatment modalities include radiotherapy, topical chemotherapy with 5-fluorouracil or imiquimod, and photodynamic therapy.¹⁰⁻¹³ Combined systemic chemotherapy with trastuzumab and paclitaxel can be considered for the treatment of *ERBB2*-positive EMPD.¹⁴

For patients with chronic genital or perianal lesions that are unresponsive to treatment, dermatologists should maintain a high index of suspicion for EMPD. If a patient is diagnosed with EMPD, a full-body skin examination should be performed with palpation of all lymph nodes. Imaging studies directed at the anatomic location of the involved skin should be utilized to search for an underlying internal malignancy.

REFERENCES

1. Paget J. On disease of the mammary areola preceding cancer of the mammary gland. *St Bartholomew Hosp Rep*. 1874;10:87-89.
2. Crocker H. Paget's disease affecting the scrotum and penis. *Trans Pathol Soc Lond*. 1889;40:187-191.
3. Zollo JD, Zeitouni NC. The Roswell Park Cancer Institute experience with extramammary Paget's disease. *Br J Dermatol*. 2000;142:59-65.
4. Heymann WR. Extramammary Paget's disease. *Clin Dermatol*. 1993;11:83-87.
5. Shepherd V, Davidson EJ, Davies-Humphreys J. Extramammary Paget's disease. *BJOG*. 2005;112:273-279.
6. Perrotto J, Abbott JJ, Ceilley RI, et al. The role of immunohistochemistry in discriminating primary from secondary extramammary Paget disease. *Am J Dermatopathol*. 2010;32:137-143.
7. Chanda JJ. Extramammary Paget's disease: prognosis and relationship to internal malignancy. *J Am Acad Dermatol*. 1985;13:1009-1014.

CONTINUED ON PAGE 142

CONTINUED FROM PAGE 136

8. Hendi A, Perdakis G, Snow JL. Unifocality of extramammary Paget disease. *J Am Acad Dermatol*. 2008;59:811-813.
9. Hendi A, Brodland DG, Zitelli JA. Extramammary Paget's disease: surgical treatment with mohs micrographic surgery. *J Am Acad Dermatol*. 2004;51:767-773.
10. Zampogna JC, Flowers FP, Roth WI, et al. Treatment of primary limited cutaneous extramammary Paget's disease with topical imiquimod monotherapy: two case reports. *J Am Acad Dermatol*. 2002;47:S229-S235.
11. Beleznyay KM, Levesque MA, Gill S. Response to 5-fluorouracil in metastatic extramammary Paget disease of the scrotum presenting as pancytopenia and back pain. *Curr Oncol*. 2009;16:81-83.
12. Kitagawa KH, Bogner P, Zeitouni NC. Photodynamic therapy with methyl-aminolevulinate for the treatment of double extramammary Paget's disease. *Dermatol Surg*. 2011;37:1043-1046.
13. Hata M, Omura M, Koike I, et al. Role of radiotherapy as curative treatment of extramammary Paget's disease. *Int J Radiat Oncol Biol Phys*. 2011;80:47-54.
14. Takahagi S, Noda H, Kamegashira A, et al. Metastatic extramammary Paget's disease treated with paclitaxel and trastuzumab combination chemotherapy. *J Dermatol*. 2009;36:457-461.