Extramammary Paget Disease of the Scrotum: A Contemporary Clinicopathologic Analysis of 20 Cases in the United States

Maryam Shabihkhani, MD, Pallavi Patil, MBBS,† Belkiss Murati Amador, MD,* Jose A. Plaza, MD,‡ Adeboye O. Osunkoya, MD,§|| Kara A. Lombardo, BS,* Jonathan I. Epstein, MD,*¶# and Andres Matoso, MD*¶#*

Abstract: Extramammary Paget disease (EMPD) often involves apocrine gland-bearing locations including vulva and perianal area. EMPD of the scrotum is rare. Twenty patients were identified from the pathology files of 4 institutions between 2000 and 2018. Patients were 63- to 87-year-old (mean: 73 y) with a history of symptoms of between 4 months and 10 years. Two patients had a history of prostate cancer. Follow-up was available in 11 patients for a median of 71 months (range: 8 to 126 mo). Nine of 11 patients (82%) had positive margins, and 73% required reexcisions. Three patients had a focal dermal invasion, 1 of whom reportedly died of another etiology 25 months post diagnosis and 2 were disease-free at 24 and 68 months. No patient had inguinal lymphadenopathy. Two patients were alive with disease. Immunohistochemically, GATA3 and GCDFP15 were expressed in 6/6 cases, CK7 in 8/8 cases, and androgen receptor in 13/13 cases. HER2 was positive in 5/12 cases. PSA was positive in 1 patient who had a history of prostate cancer, whereas other prostate markers (NKX3.1 and prostein) were negative, and CK7 and GCDFP15 were positive, rendering primary EMPD diagnosis. Twelve other cases were negative for PSA and NKX3.1. In conclusion, EMPD of the scrotum has an insidious onset and its nonspecific symptoms can be misdiagnosed as dermatitis or fungal infection. Although localized EMPD has a favorable prognosis, the invasive disease is rare and did not predict metastasis or progression. Margins are frequently positive requiring reexcision. Occasionally, cases can be positive for PSA leading to diagnostic pitfalls.

Received for publication May 24, 2019; accepted June 4, 2019.
From the Departments of *Pathology; ¶Urology; #Oncology, Johns Hopkins University, Baltimore, MD; †Department of Pathology, Rhode Island Hospital and Alpert Medical School of Brown University, Providence, RI; ‡Inform Diagnostics, Irving, TX; Departments of §Pathology; and ||Urology, Emory University School of Medicine, Atlanta, GA.
M.S. and P.P.: contributed equally.
Partially supported by the Department of Pathology of Johns Hopkins University.
This work has been accepted as an abstract at the USCAP 2019 Annual Meeting in National Harbor, MD.
The authors declare no conflict of interest.
Reprints: Andres Matoso, MD, Department of Pathology, Johns Hopkins Hospital, 401 N. Broadway, Weinberg 2242, Baltimore, MD 21231 (e-mail: amatoso1@jhmi.edu).

Key Words: Paget, scrotum, GATA3, PSA, GCDFP15

(*Appl Immunohistochem Mol Morphol* 2020;28:524–531)

Extramammary Paget disease (EMPD) is a rare, slow-growing intraepithelial malignant neoplasm. EMPD can arise either as a primary cutaneous lesion or as secondary to visceral malignancies. The cell of origin for primary cutaneous EMPD is controversial. Although some cases of EMPD represent an epidermal extension of an adenocarcinoma arising from underlying apocrine or eccrine glands, EMPD may also arise from pluripotent stem cells.[1,2] EMPD predominantly involves apocrine gland-bearing sites, especially the vulva, scrotum, and perianal areas, axilla, groin, thigh, eyelid, external ear, umbilicus, and nose. The vulva is the most common site of EMPD, accounting for ~65% of cases, followed by the perianal region. EMPD of the scrotum or penis is less commonly reported. In the Netherlands, EMPD has an incidence of 1/3.7 million males annually.[3] Here in the United States, only 100 cases of primary scrotal EMPD were identified between 1973 and 2002 in a national registry-based study by Wright et al.[4]

EMPD onset is typically insidious and diagnosis is often significantly delayed, as the clinical presentation may resemble common benign dermatoses with nonspecific symptoms like eczema and pruritus. In the literature, there are small series or case reports of EMPD affecting the scrotum with most cases described from Asia; therefore, our knowledge of its clinical and histopathologic characteristics remains very limited in the United States. The purpose of this study is to review the clinicopathologic and immunohistochemical (IHC) features of patients with EMPD of the scrotum in the United States.

MATERIALS AND METHODS

Patients Selection

A retrospective, multicenter study of cases with EMPD was performed after approval by each Institutional Board Review. An electronic search of the institutional databases for patients who were diagnosed with EMPD was

conducted from 2000 to 2018. Age, sex, ethnicity, time elapse between onset of symptoms and diagnosis, treatment, follow-up, and survival were recorded. Survival was calculated from the date of diagnosis until the last follow-up or death.

Histologic Features

Hematoxylin and eosin stained slides were reviewed by 1 pathologist (A.M.) to confirm the diagnosis and detailed morphologic description. Histopathologic features including invasion, inflammation, pigmentation, the architecture of involved epidermis and margins were recorded for all cases.

IHC

IHC was performed in cases with available material. Table 1 summarizes the IHC staining methods and antibodies used in cases performed at the Johns Hopkins Hospital. Briefly, stains were performed on 4-μm formalin-fixed paraffin-embedded tissue sections and run on a Ventana Benchmark Ultra (Ventana Medical Systems, Tucson, AZ) using Ventana reagents for deparaffinization, antigen retrieval, and detection. Separate positive and negative external controls were also used. The IHC results were recorded positive when at least focal but definitive staining was present. Only nuclear staining was scored for GATA3, NKX3.1, and androgen receptor (AR), whereas cytoplasmic staining was recorded for cytokeratins, gross cystic disease fluid protein 15 (GCDFP15), carcinoembryonic antigen (CEA), prostate-specific antigen (PSA). Human epidermal growth receptor 2 (HER2) immunostaining was observed in a membranous pattern. The intensity of staining was recorded as weak, moderate, and strong.

RESULTS

General Clinical Characteristics

A total of 20 cases with EMPD of scrotum were identified from 4 participating institutions (Table 2). The mean age at the time of diagnosis was 73 years (range: 63 to 87 y). Ethnicity information was available for 17 patients. 88% of patients were Caucasian, 6% African American, and 6% Asian. Erythema or/and itching were the most common clinical presentations. A clinical diagnosis of fungal infection before the biopsy was noted in 2/20 (10%) patients. Time-lapse from symptom onset to definitive diagnosis ranged from 4 months to 10 years. Three patients (12%) had a prior history of cancer; 1 patient had renal cell carcinoma and 2 patients had prostate cancer. One patient was diagnosed with prostate cancer 4 years after EMPD diagnosis. Colonoscopy was performed in 11 patients (55%) and was negative for any malignant lesions in all cases. Perianal skin involvement was noted in 6 patients (30%) and the penis was involved in 2 cases (10%). No patient had inguinal lymphadenopathy.

Histopathology and IHC

All cases had epidermis with large pale tumor cells with a moderate amount of cytoplasm and occasional vacuoles. There was marked verrucous hyperplasia in 3 cases. Chronic inflammation was present in 11 patients (55%).

TABLE 1. Summary of Antibodies and Staining Methods Used in Immunohistochemistry

Antibody	Source	Host	Antigen Retrieval	Dilution	Detection Method
Pan Keratin	Ventana Medical Systems, Tucson, AZ	Mouse monoclonal, clone AE1/AE3/PCK26	CC1 (EDTA, pH 9) 95°C, 36 min	Predilute	iVIEW DAB
CK7	Agilent, Santa Clara, CA	Mouse monoclonal, clone OV-TL 12/30	CC1 (EDTA, pH 9) 95°C, 36 min	1:500	iVIEW DAB
CK20	Cell Marque, Rocklin, CA	Mouse monoclonal, clone Ks20.8	CC1 (EDTA, pH 9) 95°C, 64 min	Predilute	UltraView DAB
GATA3	BioCare, Pacheco, CA	Mouse monoclonal L50-823	CC1 (EDTA, pH 9) 95°C, 64 min	Predilute	UltraView DAB
GCDFP15	BioLegend, San Diego, CA	Mouse monoclonal clone D6	CC1 (EDTA, pH 9) 100°C, 32 min	1:200	OptiView DAB
NKX3.1	BioCare, Pacheco, CA	Rabbit polyclonal	CC1 (EDTA, pH 9) 95°C, 36 min	Predilute	UltraView DAB
PSA	Ventana Medical Systems, Tucson, AZ	Rabbit polyclonal	CC1 (EDTA, pH 9) 100°C, 4 min	Predilute	OptiView DAB
CEA	Agilent, Santa Clara, CA	Rabbit polyclonal	No antigen retrieval	1:15,000	UltraView DAB
AR	Cell Marque, Rocklin, CA	Rabbit monoclonal clone SP107	CCI (EDTA, pH 9) 95°C, 64 min	Predilute	UltraView DAB
HER2	Ventana Medical Systems, Tucson, AZ	Rabbit monoclonal clone 4B5	CC1 (EDTA, pH 9) 95°C, 36 min	Predilute	UltraView DAB

AR indicates androgen receptor; CEA, carcinoembryonic antigen; CK7, cytokeratin 7; CK20, cytokeratin 20; GCDFP15, gross cystic disease fluid protein 15; HER2, human epidermal growth receptor 2; PSA, prostate-specific antigen.

TABLE 2. Clinicopathologic Characteristics of Patients

Patient No.	Age (y)	Race	Primary Treatment	Margin Status at Last Treatment	Invasion	Total No. Recurrence	Lymph Node Dissection	LVI*	Other Therapy	Survival (mo)
1	72	White	WLE	Positive	Yes, 1 mm	3	No	No	No	Died (25)
2	63	Unknown*	Unknown	Unknown	No	Unknown	Unknown	Unknown	Unknown	No follow-up
3	78	White	WLE	Positive	No	1	No	No	No	Disease (125)
4	79	Asian	WLE	Negative	No	0	No	No	No	Died of cardiac event (95)
5	73	White	WLE	Positive	No	5	No	No	No	NED (14)
6	76	White	WLE	Negative	No	2	No	No	No	NED (108)
7	73	White	Biopsy†	Negative	No	4	No	No	Yes†	NED (79)
8	65	White	WLE	Negative	Yes, 1 mm	1	No	No	No	NED (68)
9	72	White	Biopsy	Negative	No	3	No	No	Yes, local chemoradiation	NED (70)
10	70	White	Biopsy	Negative	No	3	No	No	Yes‡	Disease (68)
11	76	White	WLE	Positive	No	2	No	No	No	NED (3)
12	73	White	WLE	Positive	Yes, 1.5 mm	3	No	Yes	No	NED (24)
13	75	Unknown	Unknown*	Unknown	No	Unknown	Unknown	No	Unknown	No follow-up
14	70	White	WLE	Unknown, but positive at first WLE	No	Unknown	No	Yes	Unknown	No follow-up
15	75	White	Unknown	Unknown	No	Unknown	No	No	Unknown	No follow-up
16	76	Black	WLE	Unknown, but positive at first WLE	No	Unknown	No	No	Unknown	No follow-up
17	87	White	WLE	Unknown, but negative at first WLE	No	Unknown	No	No	Unknown	No follow-up
18	55	White	WLE	Unknown, but negative at first WLE	No	Unknown	No	No	Unknown	No follow-up
19	66	White	WLE	Unknown, but positive at first WLE	No	Unknown	No	No	Unknown	No follow-up
20	78	Unknown†	Unknown	Unknown	No	Unknown	Unknown	No	Unknown	No follow-up

*Cases that subsequent treatment following initial diagnostic biopsy is unknown.
†Received local neoadjuvant chemotherapy following initial biopsy and then WLE 5 years after.
‡He received local chemoradiation following pertuzumab and trastuzumab.
LVI indicates lymphovascular invasion; NED, no evidence of disease; WLE, wide local excision.

None of the specimens presented hyperpigmentation compared with the uninvolved epidermis (Fig. 1). Three patients (15%) showed dermal invasion including 1 case with lymphovascular invasion (Fig. 2). The focus of invasion was 1 mm in 2 patients and 1.5 mm in the other patient. By IHC, GATA3 and GCDFP15 were positive in 6/6 (100%) cases and CK7 was positive in 8/8 (100%) cases. Focal strong expression of CK20 was noted in 1/20 (5%) case. Polyclonal CEA was expressed in 3/3 (100%) cases. Thirteen cases (13/13;100%) were positive for AR. HER2 was positive in 5/13 cases (38%). PSA was positive in only 1 patient who had a history of prostate cancer; however, other prostate markers (NKX3.1 and prostein-p501s) were negative. Despite positive PSA expression, this case showed all other morphologic features of EPMD including positive immunostaining for CK7, GCDFP15, and HER2 (Fig. 3).

Treatment and Follow-Up

Available information showed that treatment included wide excision (n = 14), local chemotherapy (n = 3) and radiotherapy (n = 2). One patient refused any kind of treatment. Follow-up information was available in 11 patients for a median period of 71 months (range: 8 to 126 mo). Ten of 16 patients with known margin status (62.5%) had a positive microscopic margin on at least 1 resection, requiring >1 procedure (reexcision) as part of their treatment. One patient who had longer follow-up received local chemoradiation following neratinib, pertuzumab, and trastuzumab without any wide excisional surgery (patient #10). None of the patients underwent inguinal lymph node dissection. Seven of the 11 patients (64%) demonstrated no evidence of disease (NED) at last follow-up (patients were NED at 3, 14, 24, 68, 70, 79, and 108 mo of follow-up). However, all of them had local recurrences or residual disease after the first excision, thereby requiring multiple procedures to achieve a NED status. Two patients were alive with disease and undergoing topical therapy. None of the patients died of the disease.

DISCUSSION

EMPD is an uncommon epidermal malignant neoplasm and is estimated to have an incidence of 0.11 in 100,000 people.[3] Many cases go undiagnosed due to the nonspecific symptoms, slow progression, and insidious onset. The symptoms include itching and burning pain, which over time may turn into an eczematoid, crusted, ulcerated, or papillary lesion.[5] The main clinical differential diagnoses include fungal infections, psoriasis, lichen

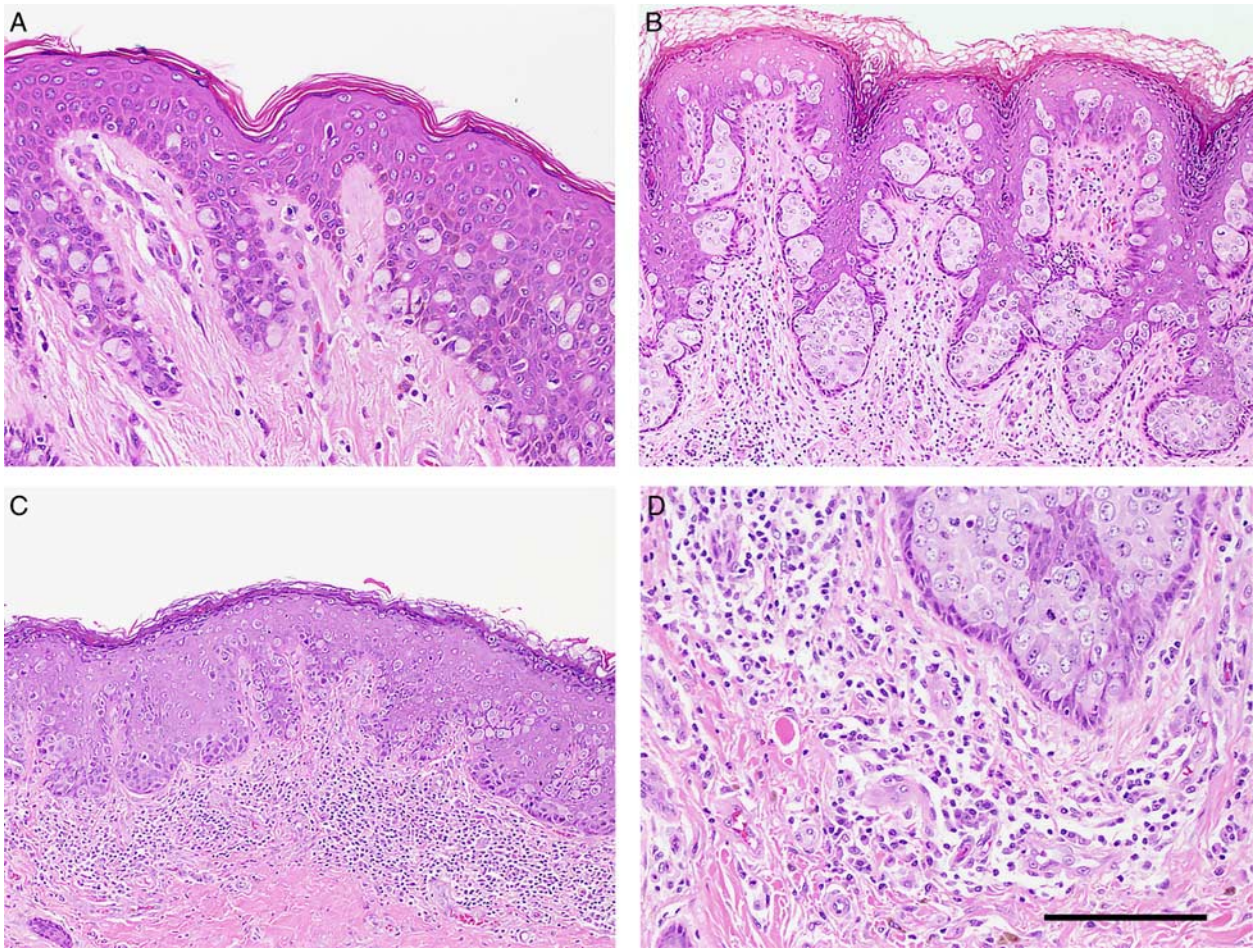

FIGURE 1. Histopathologic features of Paget disease of the scrotum. A, Paget cells spreading within the epidermis as single cells with pale cytoplasm and excentric nuclei, some of them show a signet-ring cell appearance. B, In contrast to "A," this case shows Paget cells clusters located towards the base of the epidermis as solid nests. Similar to "A," the neoplastic cells show the characteristic pale cytoplasm. C, A subset of cases demonstrate prominent dermal inflammation in a "lichenoid" (band-like) distribution. D, High power view of the dermal-epidermal junction with an inflammatory infiltrate composed predominantly of lymphocytes and plasma cells. The calibration bar is 100 μm in (A) and (B); 50 μm in (C); 200 μm in (D).

sclerosis, seborrheic dermatitis, Bowen disease, and basal cell carcinoma. A biopsy is essential for diagnosis.

Paget cells are recognized by the characteristic round, pale, vacuolated cytoplasm that stains strongly for mucin, with a large reticular nucleus located within the epidermis.[5] The epidermis can be hyperplastic with overlying hyperkeratosis and parakeratosis.[5] Mitotic figures may occasionally be identified. A chronic inflammatory cell infiltrate may present in the upper dermis. Rarely, EMPD can be depigmented[6] or pigmented.[7,8] Pigmented EMPD is characterized either by the conspicuous intracytoplasmic melanin pigment in the tumor cells or by increased dendritic melanocytes scattered among the tumor cells giving the lesion a pigmented appearance.[9,10] In our series, we did not observe any pigmentation variations between the area affected by Paget disease and the unaffected area.

Approximately 25% of the cases of EMPD have an underlying cutaneous adnexal carcinoma, mostly of apocrine type.[11,12] It is particularly important to note that EPMD also may represent an epidermotropic spread from a distant malignant neoplasm, such as carcinoma of the rectum, bladder, urethra, prostate, endometrium, endocervix, or stomach.[13,14] It has been reported that 10% to 15% of patients have an internal carcinoma involving the rectum. The anatomic location of EMPD plays a role in predicting the risk of associated carcinoma. The genital disease is associated with carcinoma in about 4% to 7% of patients.[15] Previous studies suggested that perianal disease in with an associated rectal adenocarcinoma is present in as many as one third of cases.[13] In our study, we did not find any colorectal malignancy in cases with perianal skin involvement. This is similar to other series, in which investigating the gastrointestinal tract in patients with penoscrotal EMPD did not show any underlying malignancies.[16,17]

Immunohistochemically, Paget cells are usually positive for low molecular weight cytokeratins such as CK7, CAM5.2, and AE1/AE3.[18] CK7 can also be positive in pagetoid Bowen disease and because of that, it has been

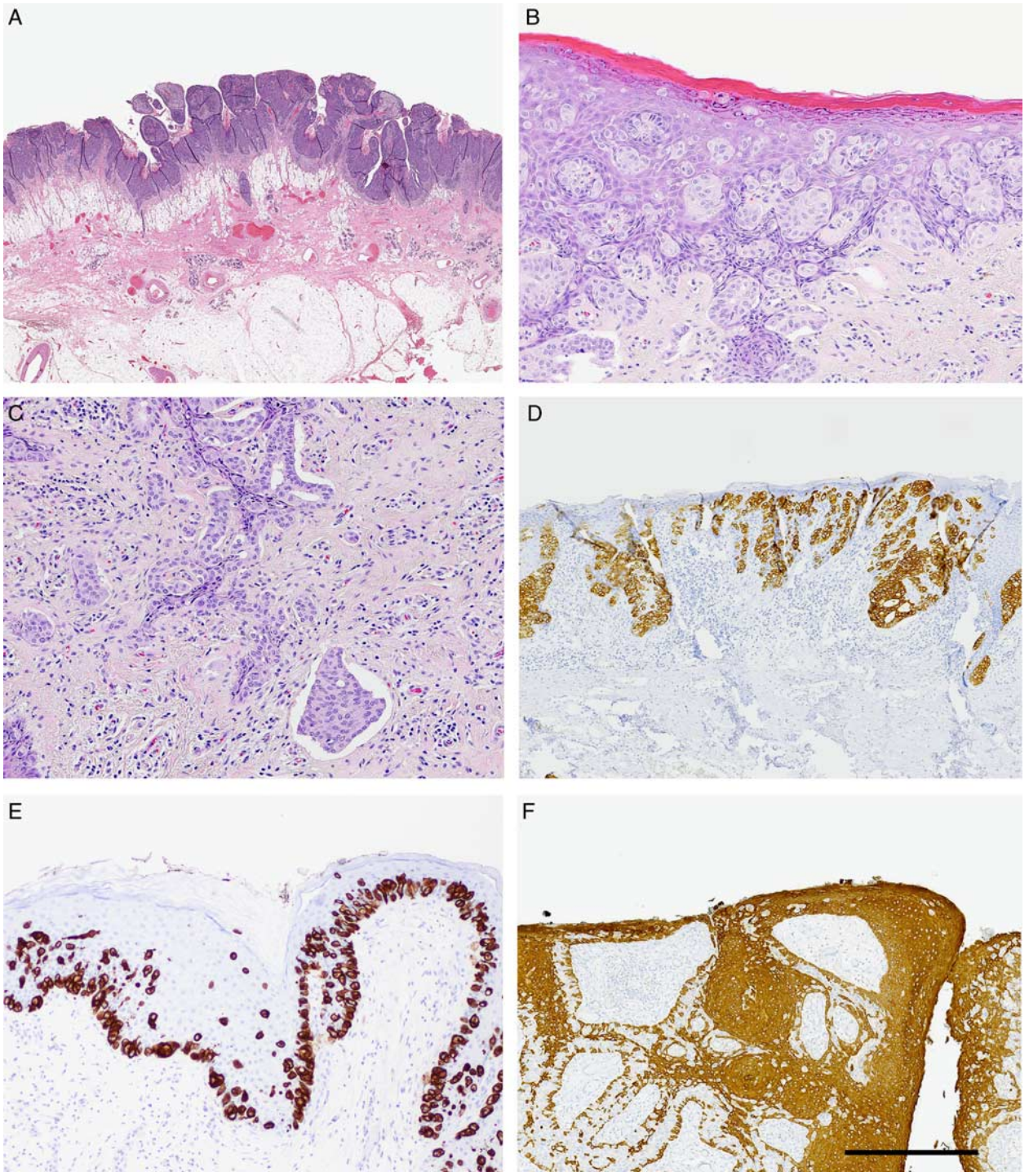

FIGURE 2. Histopathologic features and immunohistochemistry for cytokeratins of Paget disease of the scrotum. A, Epidermal hyperplasia in the area of skin affected by Paget disease. B, High power view demonstrates the nests of tumor cells with abundant pale cytoplasm. C, Focus of dermal invasion characterized by small nests of tumor cells surrounded by retraction artifact. D, Paget cells are consistently positive for cytokeratin 7 (CK7), whereas the squamous cells of the epidermis are negative. E, Similar to CK7, cytokeratin CAM5.2 is consistently positive in Paget cells, whereas the epidermis is negative. F, In contrast to CK7 and CAM5.2, cytokeratin 5/6 can be used to highlight epidermal cells, whereas it is negative in Paget cells. This stain is helpful to differentiate the tangential section of the epidermis versus invasion of the dermis, as highlighted in the image. The calibration bar is 200 μm in (A) and (D); 100 μm in (B), (E), and (F); 50 μm in (C).

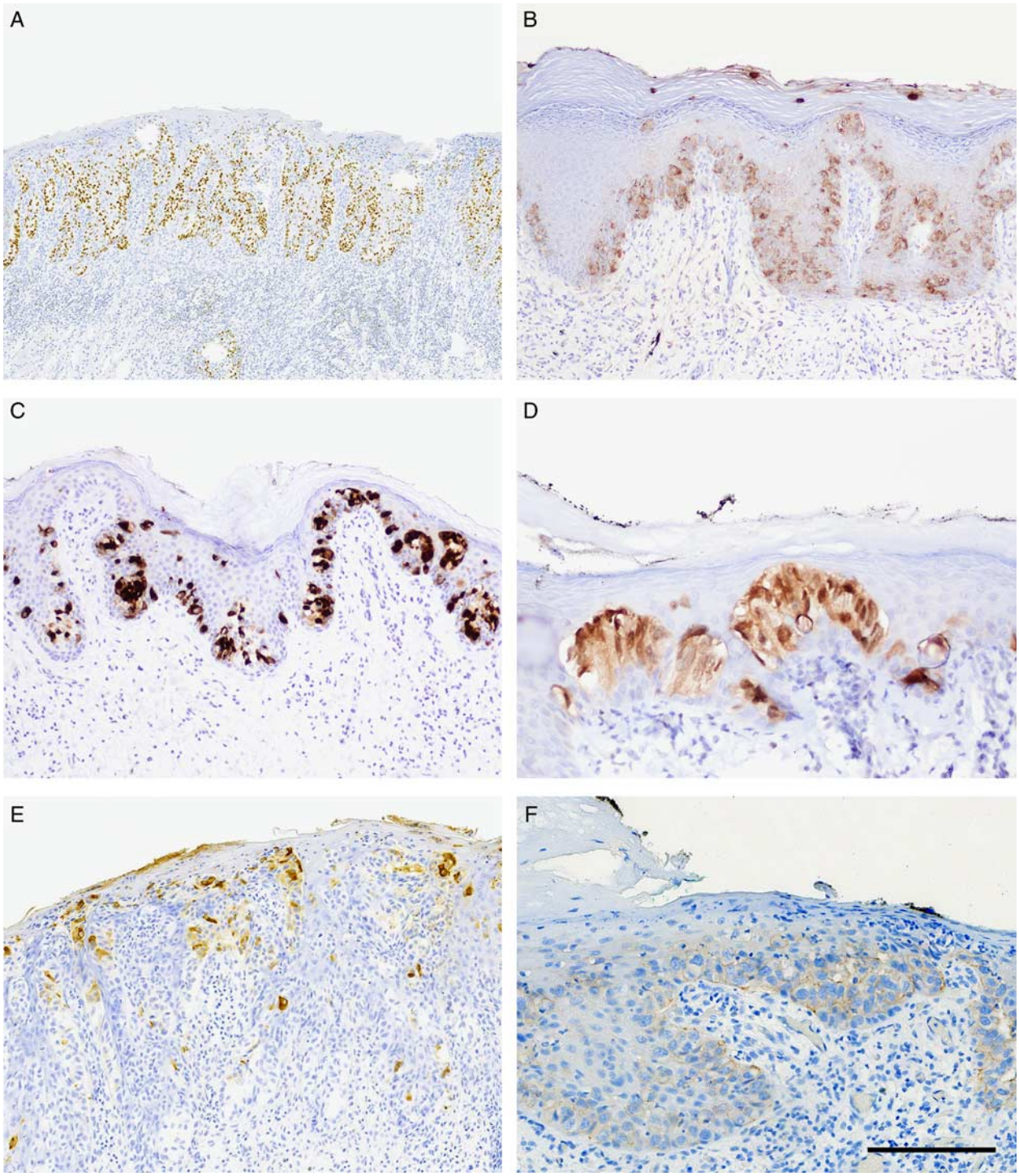

FIGURE 3. Immunohistochemistry findings. A, Paget cells are diffusely positive for GATA3. B, Polyclonal carcinoembryonic antigen and therefore other intestinal markers including CK20 or CDX2 should be used to exclude secondary involvement from the colon. C, Prostate-specific antigen is rarely positive in primary Paget disease and should not be used in isolation to diagnose metastatic prostate cancer. D, Androgen receptor (AR) is positive in Paget cells. E, Gross cystic disease fluid protein 15 (GCDFP15) is also frequently positive. Together with positive AR, expression of GCDFP15 is consistent with the apocrine origin of the cells. F, Expression of membranous human epidermal growth receptor 2 is weak and present in a minority of cases of Paget of the scrotum. Calibration bar 100 μm for (A) and 50 μm for (B–F).

suggested that Ber-EP4 should be added to the panel of markers as it labels all cases of EMPD but none of the other pagetoid neoplasms.[19] There is a variable expression for polyclonal CEA by Paget cells.[20] GCDFP15 is expressed in apocrine glands and metaplastic apocrine cells and is negative in eccrine glands.[20] GCDFP15 has been reported in ~50% of EMPD and is typically positive in primary EMPD and negative in secondary disease.[18,21] In our study, 6/6 cases were positive for GCDFP15 and GATA3. Given the frequent positivity in urothelial carcinoma, GATA3 could not be helpful in distinguishing between primary cutaneous EMPD and secondary form due to urothelial carcinoma, although this possibility is extremely rare.[22]

S-100 protein, HMB-45, and MART-1 are usually negative in EMPD; however, in pigmented Paget disease, the dendritic cells can stain for both S-100 protein and HMB-45 and may lead to confusion with malignant melanoma.[23] Hence, a useful IHC diagnostic panel may include both epithelial and melanocytic markers when malignant melanoma is in the differential diagnosis.

PSA is expressed in the pagetoid cells of many cases associated with an underlying adenocarcinoma of the prostate.[24] It may also be expressed in cases without any associated carcinoma of the prostate; however, the frequency of this finding was unknown because it had not been previously formally tested.[25] In the present study, PSA was positive in only 1 patient who had a history of prostate cancer, whereas other prostate markers (NKX3.1 and prostein) were negative, and CK7 and GCDFP15 were positive, rendering a primary EMPD diagnosis. Since many elderly men have a clinical history of prostate cancer, this is a potential pitfall if the pathologist is not aware of this phenomenon, which we have shown it is infrequent.

EMPD is negative for progesterone and estrogen receptors. In contrast, in approximately half the cases, ARs are expressed.[25] In our study, all 13 cases that had AR staining, showed strong immunoreactivity. Expression of AR by tumor cells has led to suggestions that treatment may be based on hormonal therapy such as that given in prostatic cancer.[26] Similarly, reports of overexpression of HER2 protein and HER2/neu amplification by fluorescence in situ hybridization in cases of Paget disease also suggest the possibility of clinical use of molecular targeted therapy against the HER2 pathway.[27,28] Although expression of HER2 has been used to diagnose Paget disease of the breast, our findings indicate that this is not frequently expressed in scrotal EMPD.[29]

The standard of care for EMPD includes excisional biopsy with wide margins or Mohs micrographic surgery. Subclinical extension and the multifocal feature may contribute to the high rate of recurrence with excision. We noted that achieving clear margins is essential to control the disease, similar to the other studies that show positive margins were associated with local recurrence.[17] Local therapies such as 5-fluorouracil, imiquimod, paclitaxel, and trastuzumab may provide additional therapeutic benefit for some patients.[30,31] In our study, 3 patients received imiquimod as part of their treatment, albeit all 3 had recurrent disease post therapy. Because of the rarity of scrotal EMPD, sufficient data is not available to establish the superiority of any specific chemotherapy over another.

Poor prognostic features in EMPD cohorts include invasive disease/underlying dermal adenocarcinoma, internal carcinoma, lymphovascular invasion, lymph node, and distant metastasis.[17] Studies have shown that EMPD with dermal invasion has higher rates of metastasis and mortality in contrast to lesions restricted to the epidermis that remain in situ for many years. In the current study, we had 3 cases with 1 focus of dermal invasion. One patient was lost to follow-up a year after his initial diagnosis and reportedly died 25 months post diagnosis (patient #1). Two other patients were alive at the end date of this study (patient #8 and #12). These 2 patients, including 1 case with lymphovascular invasion achieved NED at their last follow-up (at 24 and 68 mo postlast treatment). This data may suggest that the disease is slowly progressive, even in patients with dermal invasion or lymphovascular invasion, and these are not independent poor prognostic factors.

CONCLUSIONS

EMPD of the scrotum is mainly observed in elderly patients and is a rare disease that is often delayed for a long time before diagnosis. Biopsy should be performed in patients with suspicious lesions, including those with persistent pruritic eczematous lesions that fail to resolve after appropriate treatment. Patient with EMPD should also be evaluated for the possibility of synchronous neoplasms, although this is rare. Rarely, positive immunolabeling for PSA in primary EMPD could lead to diagnostic confusion, especially in a patient with a clinical history of prostate adenocarcinoma. Similarly, positive stain for GATA3 could suggest a urothelial origin in a patient with such clinical history. Wide local excision or Mohs micrographic surgery is the standard of care. A positive margin is one of the most important risk factors for local recurrence. High frequency of positive margins suggests that the disease extends beyond clinically visible lesions.

REFERENCES

1. Jones JR, Austin C, Ackerman AB. Extramammary Paget's disease. A critical reexamination. *Am J Dermatopathol*. 1979;1:101–132.
2. Regauer S. Extramammary Paget's disease—a proliferation of adnexal origin? *Histopathology*. 2006;48:723–729.
3. Siesling S, Elferink M, van Dijck J, et al. Epidemiology and treatment of extramammary Paget disease in the Netherlands. *Eur J Surg Oncol*. 2007;33:951–955.
4. Wright JL, Morgan TM, Lin DW. Primary scrotal cancer: disease characteristics and increasing incidence. *Urology*. 2008;72:1139–1143.
5. Kanitakis J. Mammary and extramammary Paget's disease. *J Eur Acad Dermatol Venereol*. 2007;21:581–590.
6. Yang CC, Lee JY, Wong TW. Depigmented extramammary Paget's disease. *Br J Dermatol*. 2004;151:1049–1053.
7. Pimentel C, Barnadas M, Dalmau J, et al. Pigmented Paget's disease in a man previously treated with mammaplasty reduction for gynecomastia. *J Am Acad Dermatol*. 2006;55:S62–S63.
8. Requena L, Sangueza M, Sangueza OP, et al. Pigmented mammary Paget disease and pigmented epidermotropic metastases from breast carcinoma. *Am J Dermatopathol*. 2002;24:189–198.
9. De la Garza Bravo MM, Curry JL, Torres-Cabala CA, et al. Pigmented extramammary Paget disease of the thigh mimicking a

melanocytic tumor: report of a case and review of the literature. *J Cutan Pathol*. 2014;41:529–535.
10. Hilliard NJ, Huang C, Andea A. Pigmented extramammary Paget's disease of the axilla mimicking melanoma: case report and review of the literature. *J Cutan Pathol*. 2009;36:995–1000.
11. Castelli E, Wollina U, Anzarone A, et al. Extramammary Paget disease of the axilla associated with comedo-like apocrine carcinoma in situ. *Am J Dermatopathol*. 2002;24:351–357.
12. Piura B, Zirkin HJ. Vulvar Paget's disease with an underlying sweat gland adenocarcinoma. *J Dermatol Surg Oncol*. 1988;14:533–537.
13. Chanda JJ. Extramammary Paget's disease: prognosis and relationship to internal malignancy. *J Am Acad Dermatol*. 1985;13:1009–1014.
14. Koh K, Nazarina A. Paget's disease of the scrotum: report of a case with underlying carcinoma of the prostate. *Br J Dermatol*. 1995;133: 306–307.
15. Parker LP, Parker JR, Bodurka-Bevers D, et al. Paget's disease of the vulva: pathology, pattern of involvement, and prognosis. *Gynecol Oncol*. 2000;77:183–189.
16. Park S, Grossfeld GD, Mcaninch JW, et al. Extramammary Paget's disease of the penis and scrotum: excision, reconstruction and evaluation of occult malignancy. *J Urol*. 2001;166:2112–2117.
17. Hegarty PK, Suh J, Fisher MB, et al. Penoscrotal extramammary Paget's disease: the University of Texas MD Anderson Cancer Center contemporary experience. *J Urol*. 2011;186:97–102.
18. Guarner J, Cohen C, DeRose PB. Histogenesis of extramammary and mammary Paget cells. An immunohistochemical study. *Am J Dermatopathol*. 1989;11:313–318.
19. Sellheyer K, Krahl D. Ber-EP4 enhances the differential diagnostic accuracy of cytokeratin 7 in pagetoid cutaneous neoplasms. *J Cutan Pathol*. 2008;35:366–372.
20. Eugene Battles O, Page DL, Johnson JE. Cytokeratins, CEA, and mucin histochemistry in the diagnosis and characterization of extramammary Paget's disease. *Am J Clin Pathol*. 1997;108:6–12.
21. Reed W, Oppedal B, Larsen TE. Immunohistology is valuable in distinguishing between Paget's disease, Bowen's disease and superficial spreading malignant melanoma. *Histopathology*. 1990;16:583–588.
22. Morbeck D, Tregnago AC, Netto GB, et al. GATA 3 expression in primary vulvar Paget disease: a potential pitfall leading to misdiagnosis of pagetoid urothelial intraepithelial neoplasia. *Histopathology*. 2017;70: 435–441.
23. Chiba H, Kazama T, Takenouchi T, et al. Two cases of vulval pigmented extramammary Paget's disease: histochemical and immunohistochemical studies. *Br J Dermatol*. 2000;142:1190–1194.
24. Allan S, McLaren K, Aldridge R. Paget's disease of the scrotum: a case exhibiting positive prostate-specific antigen staining and associated prostatic adenocarcinoma. *Br J Dermatol*. 1998;138: 689–691.
25. Inoguchi N, Matsumura Y, Kanazawa N, et al. Expression of prostate-specific antigen and androgen receptor in extramammary Paget's disease and carcinoma. *Clin Exp Dermatol*. 2007;32:91–94.
26. Fujimoto A, Takata M, Hatta N, et al. Expression of structurally unaltered androgen receptor in extramammary Paget's disease. *Lab Invest*. 2000;80:1465.
27. Ichiyama T, Gomi D, Fukushima T, et al. Successful and long-term response to trastuzumab plus paclitaxel combination therapy in human epidermal growth factor receptor 2-positive extramammary Paget's disease: a case report and review of the literature. *Mol Clin Oncol*. 2017;7:763–766.
28. Plaza JA, Torres-Cabala C, Ivan D, et al. HER-2/neu expression in extramammary Paget disease: a clinicopathologic and immunohistochemistry study of 47 cases with and without underlying malignancy. *J Cutan Pathol*. 2009;36:729–733.
29. Wachter DL, Wachter PW, Fasching PA, et al. Characterization of molecular subtypes of Paget disease of the breast using immunohistochemistry and in situ hybridization. *Arch Pathol Lab Med*. 2019;143: 206–211.
30. Bauman TM, Rosman IS, Sheinbein DM. Extramammary Paget's disease of the scrotum with complete response to imiquimod and photodynamic therapy. *BMJ Case Rep*. 2018;2018:bcr-2017-221696.
31. Beleznay K, Levesque M, 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.