DOI: 10.1515/sjdv-2016-0017

Apocrine Adenocarcinoma with Extramammary Pagetoid Spread into the Groin: a Case Report and a Literature Review

Branislav LEKIĆ[1], Mirjana GAJIĆ-VELJIĆ[1,2], Dušan ŠKILJEVIĆ[1,2], Svetlana POPADIĆ[1,2], Ljiljana MEDENICA[1,2]

[1]Clinic of Dermatovenereology, Clinical Center of Serbia, Belgrade, Serbia
[2]Department of Dermatovenereology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia

*Correspondence: Dušan Škiljević, E-mail: dusanskiljevic@yahoo.com

DE GRUYTER OPEN

UDC 616.56-006.04:616.67-006.6]-092

Abstract

Apocrine adenocarcinoma is a rare form of sweat gland malignancy mostly affecting adults without evident prevalence for sex or race. Clinically, it presents as a single or a multi-nodular mass or plaque in the axillary or anogenital region, with no additional symptoms. This neoplasm is locally invasive, grows slowly and has an ability to metastasize to visceral organs, regional lymph nodes and bones. We report a case of infiltrating apocrine adenocarcinoma on the scrotum and pubic area with extramammary pagetoid spread into the groin. The immunohistological staining patterns suggested that both extramammary Paget's disease and apocrine adenocarcinoma derived from the apocrine gland, because the tumor cells were positive for cytokeratin (CK) 7 and gross cystic disease fluid protein-15 (GCDFP-15), but negative for CK20 and prostate-specific antigen (PSA). The results of this case study will facilitate the understanding of this malignant tumor.

Key words

Adenocarcinoma; Apocrine Glands; Sweat Gland Neoplasms; Paget Disease, Extramammary; Genital Neoplasms; Diagnosis; Case Reports

Apocrine adenocarcinoma is a very rare malignant sweat gland neoplasm with apocrine differentiation (1, 2). It is usually located in the axilla, scalp, anogenital region, eyelid, ear, chest or wrist (3). This neoplasm is locally invasive, grows slowly and has an ability to metastasize to visceral organs, regional lymph nodes and bones (4). In many cases, the lesions have been unrecognised for more than 10 years, and even up to 30 years before diagnosis (1). Until now, only a few cases of apocrine adenocarcinoma localized in the groin have been reported (5 – 8). In rare instances, apocrine adenocarcinoma is associated with extramammary Paget's disease (EMPD), because epidermal spread is uncommon in patients with apocrine adenocarcinoma (9). The immunohistological staining patterns suggest that both EMPD and apocrine adenocarcinoma are derived from the apocrine gland (8).

Case Report

An 82-year-old man was admitted to our Clinic with marked erythema and large, irregularly shaped, oozing ulcerations on the scrotum (Figure 1A), infiltrated erythematous plaques with numerous papules and nodules on the pubic area (Figure 1B), and well-defined erythematous plaques, 8 x 5 cm in diameter in the right groin (Figure 2). Edema of the right leg and bilateral inguinal lymphadenopathy were observed.

The lesions have been present for 6 years, and treated with topical antibiotics and corticosteroid therapy. The patient's family and personal history were unremarkable.

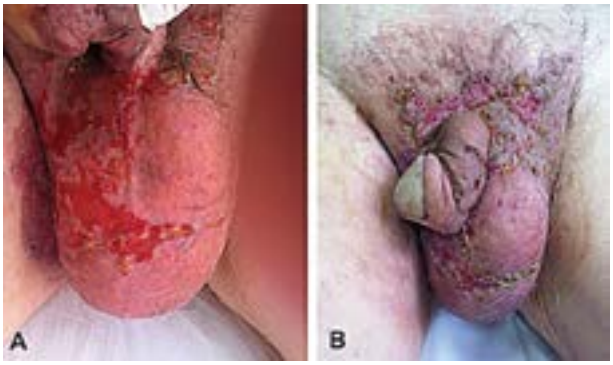

Figure 1. (A) Ulcerations on the scrotum and **(B)** numerous papules and nodules on the pubic area and penis

The skin biopsy obtained from nodule on the pubic area and erythematous plaques from the right groin were sent for histopathological and immunohistochemical examination. The nodular lesion on the pubic area showed a poorly differentiated invasive adenocarcinoma with a low mitotic rate. The tumor invaded the papillary,

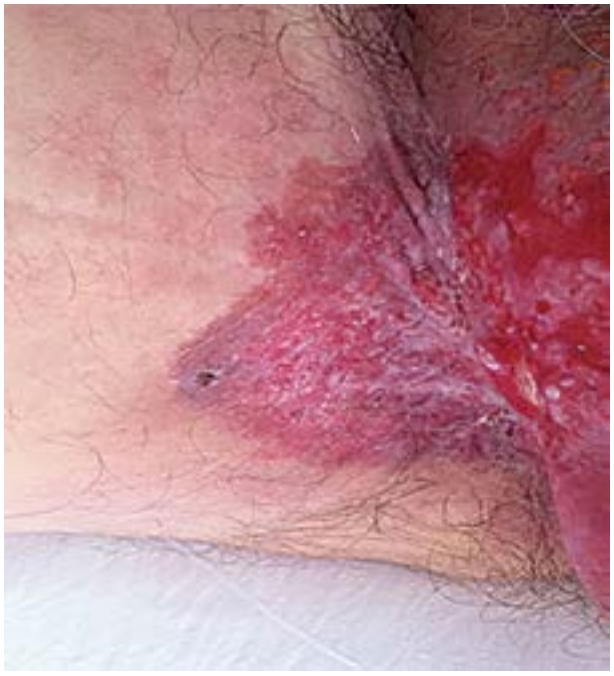

Figure 2. Well-defined erythematous plaque in the right groin

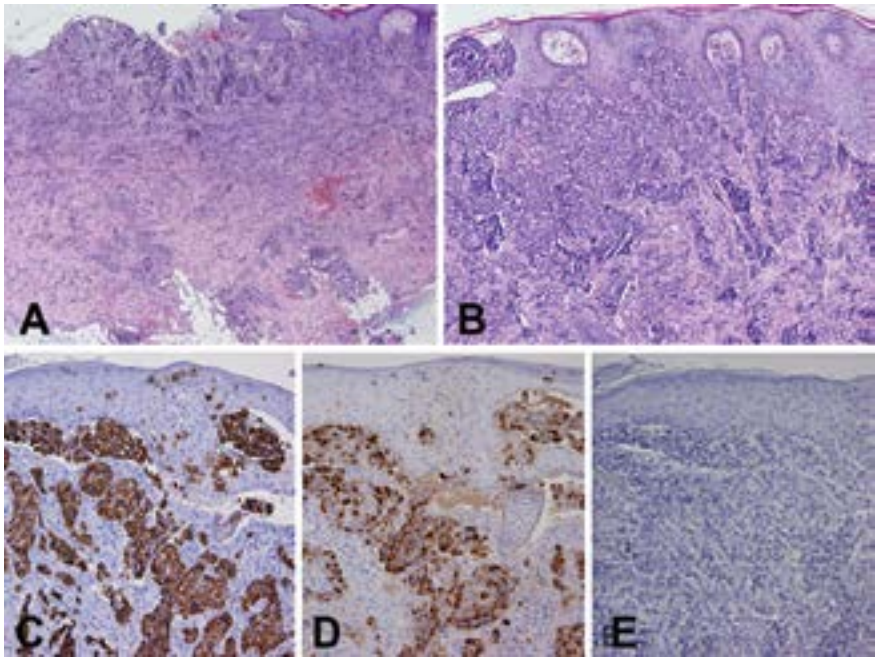

Figure 3. (A) The tumor tissue invaded the papillary and reticular dermis as well as in the subcutaneous tissue and ulcerated the epidermis (Hematoxylin and eosin; original magnification x 40). **(B)** Poorly differentiated invasive adenocarcinoma in the papilar and reticular dermis and infiltrating the epidermis. Micronodular and trabecular growth pattern with hardly any gland formation, hyaline stroma (Hematoxylin and eosin; original magnification x 100). **(C)** Tumor cells with positive immunostaining for cytokeratin 7 (CK7) and **(D)** gross cystic disease fluid protein-15 (GCDFP-15), but **(E)** negative immunostaining for CK20

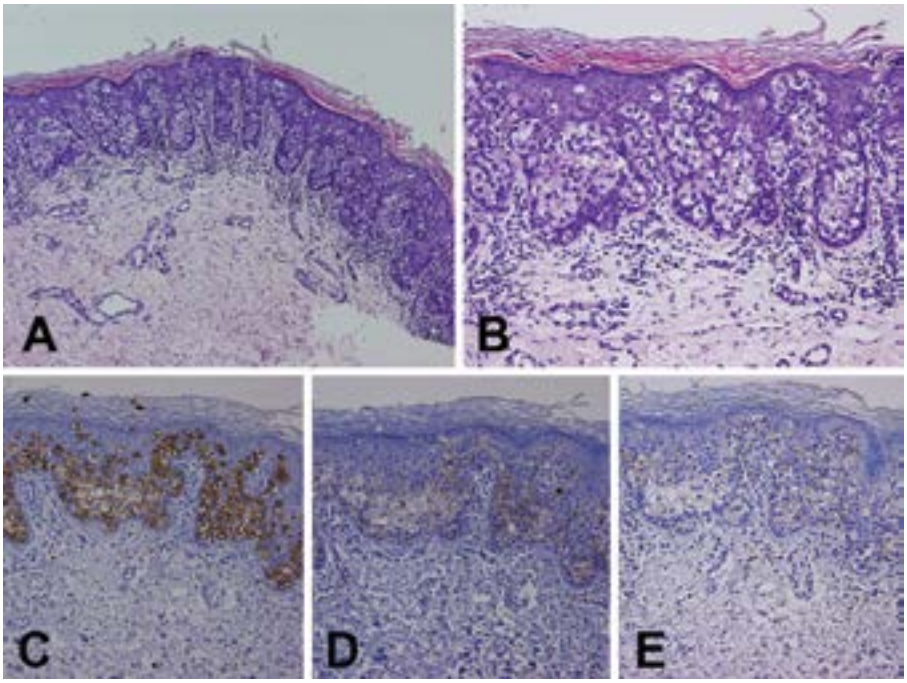

Figure 4. (A) Paget's cells located in the epidermis (Hematoxylin and eosin; original magnification x 100); **(B)** Characteristic Paget's cells within the epidermis (Hematoxylin and eosin; original magnification x 200); **(C)** Paget's cells with positive immunostaining for cytokeratin 7 (CK7) and **(D)** gross cystic disease fluid protein-15 (GCDFP-15), but **(E)** negative immunostaining for CK20

reticular dermis and the subcutaneous tissue with infiltrative ulceration of the epidermis (Figures 3A, B). The immunohistochemical study showed that the tumor cells were positive for epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA), cytokeratin (CK) 7 and gross cystic disease fluid protein-15 (GCDFP-15), and negative for CK20, prostate-specific antigen (PSA) and S-100 (Figures 3C, D).

The erythematous plaque on the right groin showed large cells with large nuclei and abundant pale cytoplasm (Figures 4A, B), single or in groups, suggestive of Paget's cells in the epidermis. The immunohistochemical study showed that the cells were positive for EMA, CEA, CK7 and GCDFP-15, and negative for CK20, PSA and S-100 (Figures 4C, D).

Routine laboratory test results were within the physiological limits. A series of exams: serum PSA, abdomino-pelvic computed tomography (CT), chest radiography, bone scintigraphy (99mTc DPD) failed to prove the presence of internal malignancy. Abdomino-pelvic CT confirmed enlarged lymph nodes in both inguinal regions; all the other tests were within normal limits.

The patient was presented to the consilium of surgical oncologists, and it was concluded that the patient was inoperable, and opted for conservative treatment.

After 8 months of follow-up, the disease showed progression with invasive local tumor growth.

Discussion

Apocrine adenocarcinoma is a rare form of sweat gland neoplasm of adults with no evident prevalence for sex or race [1, 3, 9]. The etiology of apocrine adenocarcinoma is unknown [1]. Clinically, it is asymptomatic presenting as a single or a multi-nodular mass or as a plaque in the axillary or anogenital region, without any additional symptoms [3, 9]. Pagetoid epidermal spread is uncommon in patients with apocrine adenocarcinoma [9]. Up to now, only four cases of the apocrine adenocarcinoma of the groin associated with EMPD, have been reported (Table 1).

EMPD is a rare clinical condition that generally appears between 50 and 80 years of age, more commonly in women, with female-to-male ratio of 1.4:1 [10, 11]. The most common site of involvement is the vulva; the second most common is the perianal

Table 1. Literature review of previous case reports of patients with apocrine adenocarcinoma with extramammary Paget's disease in the groin

Author	Year	Sex	Age	Location	History of lesion	Immunohistochemistry Apocrine adenocarcinoma	Immunohistochemistry EMPD	Metastases adenopathy	Treatment
Bowling et al.[5]	2005	Male	72	Right groin, scrotum	18 months	MNF 116(+), AE1/3(+), CK7(+), CAM5.2(+), S-100(-), CK20(-), PSA(-), PSAP(-), vimentin(-)	CK7 (+)	no	Complete local excision
Harnandez and Copeland[6]	2007	Male	77	Left groin, scrotum	Not noted	CEA(+), AE1/3(+), GCDFP-15(+), melan-A(-), S-100(-), CK20(-)	CEA(+), AE1/3(+), GCDFP-15(+), melan-A(-), S-100(-), CK20(-)	Lymph node infiltration	Wide excision, sentinel node biopsy
Pascual et al.[7]	2008	Male	79	Left groin, scrotum	1 year	CEA(+), CK7(+), CK20(+), GCDFP-15(+), mucin 1(+), mucin 2(+), HER2/neu (+), HMB-45(-), S100(-), CDX-2(-), PSA(-)	CEA(+), CK7(+), CK20(+), GCDFP-15(+), mucin 1(+), mucin 2(+), HER2/neu (+), HMB-45(-), S-100(-), CDX-2(-), PSA(-)	Metastases after surgical treatment	Local excision
Seo et al.[8]	2011	Male	71	Left groin, scrotum	6 months	CEA(+), EMA(+), CK7(+), GCDFP-15(+), S-100(-), melanin-A(-), CK-20 (-)	CEA(+), EMA(+), CK7(+), GCDFP-15(+), S-100(-), melanin-A(-), CK-20 (-)	Multiple lung, bone, and lymph node metastases	Conservative treatment
Our case	2012	Male	82	Right groin, scrotum, pubic area	6 years	CEA(+), EMA(+), CK7(+), GCDFP-15(+), CK-20(-), PSA(-), S-100 (-)	CEA(+), EMA(+), CK7(+), GCDFP-15(+), CK-20(-), PSA(-), S-100 (-)	Adenopathy	Conservative treatment

Legend: EMPD: extramammary Paget's disease, CK: cytokeratin, CEA: carcinoembryonic antigen, PSA: prostate-specific antigen, PSA: prostate-specific acid phosphatase, HER: human epidermal growth factor receptor, CDX: caudal-related homeobox, EMA: epithelial membrane antigen, GCDFP-15: gross cystic disease fluid protein-15

region, and then the perineum, scrotum, axilla, and eyelids [11, 12].

The histogenesis of EMPD is a controversial issue, but there are four hypotheses regarding its pathogenesis. The first hypothesis suggests that EMPD represents an apocrine adenocarcinoma that arises in glandular structures of the skin and extends to the epidermis [7, 8]. According to the second theory, the stem cells present in the basal cell layer of the epidermis transform into Paget's cells as a result of their faulty development in their attempt to mature into an apocrine structure [7, 8]. The third hypothesis implies that EMPD is the result of multiple foci of malignant transformation of a population of cells with a common embryological origin. This theory would account for the reportedly high incidence of "skip areas" between the subjacent invasive adenocarcinoma and the epidermal lesions [12]. The fourth hypothesis proposes that EMPD represents epidermotropic metastasis or a direct extension of an associated internal malignancy, especially of the genitourinary and gastrointestinal tract [7, 8, 11].

There are two hypotheses regarding the relationship between EMPD and apocrine adenocarcinoma. The first hypothesis postulated that invasive EMPD is the origin of apocrine adenocarcinoma. The second suggests that apocrine adenocarcinoma, involving the dermis, exhibits intra-epidermal pagetoid spread and deep invasion into subcutaneous tissue, identical to mammary ductal adenocarcinoma that exhibits epidermotropic growth in the case of mammary Paget's disease [8]. Based on the aforementioned theories, patients with EMPD should be divided into two subgroups: cutaneous (primary) subtype of EMPD, and endodermal (secondary) subtype of EMPD [7, 12].

The clinician should therefore search for an underlying malignancy in EMPD [12]. In our case, the imunohistochemical examination revealed a pattern similar to cutaneous EMPD, because the tumor cells were positive for CK7, and GCDFP-15 but negative for CK20 and PSA. Our results differ from those published on endodermal EMPD with other underlying internal malignant tumors [12]. The immunohistological staining patterns suggested that both EMPD and apocrine adenocarcinoma originated from the apocrine gland (Table 1). GCDFP-15 usually stains apocrine adnexal glands in axillary and anogenital skin and is considered as a very specific marker for apocrine differentiation [13].

In one case Paget and dermal tumor cells were positive for CK20. Pascual et al. [7] concluded that their case showed combined immunohistochemical findings suggestive of cutaneous and endodermal subtype of EMPD with no associated internal malignancy.

Conclusion

In conclusion, we presented a rare case of infiltrating apocrine adenocarcinoma with extramammary pagetoid spread into the groin. Early biopsy is very important to establish a correct diagnosis in patients who fail to respond to conventional topical therapy. The histopathological and immunohistochemical results of this case study will facilitate the understanding of this malignant tumor.

Abbreviations

EMPD - extramammary Paget's disease
EMA - epithelial membrane antigen
CEA - carcinoembryonic antigen
CK7 - cytokeratin 7
GCDFP-15 - gross cystic disease fluid protein-15
PSA - prostate-specific antigen
CT - computed tomography

References

1. Requena L, Kutzner H, Hurt MA, SantaCruz DJ, Mehregan DA, Mehregan DR, et al. Malignant tumours with apocrine and eccrine differentiation. In: LeBoit PE, Burg G, Weedon D, Sarasin A, editors. World Health Organization classification of tumours. Pathology and genetics of skin tumours. 3rd ed. Lyon: IARC Press; 2006. p. 125-38.
2. Hollowell KL, Agle SC, Zervos EE, Fitzgerald TL. Cutaneous apocrine adenocarcinoma: defining epidemiology, outcomes, and optimal therapy for a rare neoplasm. J Surg Oncol. 2012;105(4):415-9.
3. Paties C, Taccagni GL, Papotti M, Valente G, Zangrandi **A**, Aloi F. Apocrine carcinoma of the skin. A clinicopathologic, immunocytochemical, and ultrastructural study. Cancer. 1993;71(2):375-81.
4. Pai RR, Kini JR, Achar C, Rau **A**, Kini H. Apocrine (cutaneous) sweat gland carcinoma of axilla with signet ring cells. A diagnostic dilemma on fine-needle aspiration cytology. Diagn Cytopathol. 2008;36(10):739-41.
5. Bowling JC, Powles A, Nasiri N, Searle A, Bunker CB.

Spontaneous regression of extramammary Paget's disease after excision of primary apocrine carcinoma, in an immunosuppressed patient. Br J Dermatol. 2005;153(3):676-7.
6. Hernandez JM, Copeland EM 3rd. Infiltrating apocrine adenocarcinoma with extramammary pagetoid spread. Am Surg. 2007;73(3):307-9.
7. Pascual JC, Perez-Ramos M, Devesa JP, Kutzner H, Requena L. Extramammary Paget's disease of the groin with underlying carcinoma and fatal outcome. Clin Exp Dermatol. 2008;33(5):595-8.
8. Seo SH, Shin DH, Sung HW. Apocrine carcinoma of the groin possibly associated with extramammary Paget's disease. Ann Dermatol. 2011;23(4):519-22.
9. Robson A, Lazar AJ, Ben Nagi J, Hanby A, Grayson W, Feinmesser M, et al. Primary cutaneous apocrine carcinoma: a clinico-pathologic analysis of 24 cases. Am J Surg Pathol. 2008;32(5):682-90.
10. Zollo JD, Zeitouni NC. The Roswell Park Cancer Institute experience with extramammary Paget's disease. Br J Dermatol. 2000;142(1):59-65.
11. Payne WG, Wells KE. Extramammary Paget's disease of the scrotum. Ann Plast Surg. 1994;33(6):669-71.
12. Juang GD, Lin MY, Hwang TI. Extramammary Paget's disease of the scrotum. J Chin Med Assoc. 2011;74(7):325-8.
13. Fernandez-Flores A. Immunohistochemical and morphologic evaluation of primary cutaneous apocrine carcinomas and cutaneous metastases from ductal breast carcinoma. Rom J Morphol Embryol. 2012;53(4):879-92.

Apokrini adenokarcinom sa ekstramamarnim Pedžetovim širenjem u preponu − prikaz slučaja i pregled literature

Sažetak

Apokrini adenokarcinom predstavlja redak oblik malignog tumora znojnih žlezda koji se javlja kod odraslih osoba, bez jasne polne i rasne predilekcije. Klinički slika obuhvata pojedinačne ili multinodularne tumore ili plakove lokalizovane u aksilarnoj ili anogenatlnoj regiji, bez dodatnih simptoma. Neoplazma je lokalno invazivna, polako raste i ima sposobnost metastaziranja u visceralne organe, regionalne limfne noduse i kosti. Prikazujemo slučaj infiltrativnog apokrinog adenocarcinoma skrotuma i pubične regije sa ekstramamarnim „pedžetoidnim" širenjem u preponu. Imunohistohemijske metode pokazuju da su i ekstramamrna Pedžetova bolest i apokrini adenokarcinom istog porekla – apokrinih žlezda, zato što su tumorske ćelije bile pozitivne na citokeratin (CK) 7 i *gross cystic disease fluid protein*-15 (GCDFP-15), a negativne na CK20 i antigen specifičan za prostatu (PSA). Rezultati studije ovog slučaja mogu pomoći u razumevanju patogeneze i biološkog ponašanja ovog malignog tumora.

Ključne reči

Adenokarcinom; Apokrine žlezde; Neoplazme znojnih žlezda; Ekstramamarna Pedžetova bolest; Genitalne neoplazme; Dijagnoza; Prikazi slučajeva