Original paper

Extramammary Paget's disease: evaluation of the adnexal status of 53 cases

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Extramammary Paget's disease (EMPD) is a distinct form of malignant skin neoplasm. The clinicopathological significance of cutaneous adnexal involvement in EMPD has not been investigated in detail. Surgical specimens were obtained from 53 patients with primary EMPD. Tumor involvement of cutaneous adnexal structures was evaluated using histological parameters. The degree of involvement was scored on a scale of 0–2: 0, no involvement; 1, involvement of the upper portion of the adnexa; 2, involvement of the lower portion of the adnexa. A score of 2 was regarded as significant. The presence of comedo necrosis was also examined. Adnexal involvement was identified in 46 cases (86.8%). Comedo necrosis was observed in 6 cases (11.3%). The proportions of each parameter in *in situ* cases were as follows: significant adnexal involvement (score 2) in 15/26 (57.7%), and comedo necrosis in 3/26 (11.5%). The corresponding proportions in cases with invasion were 21/27 (77.8%) and 3/27 (11.1%), respectively. No significant differences in adnexal involvement and comedo necrosis were detected between *in situ* EMPD and invasive EMPD ($p > 0.05$). The current study suggests that the degree of adnexal involvement and the presence of comedo necrosis are not associated with tumor progression in EMPD.

Key words: extramammary Paget's disease, adnexal involvement, comedo necrosis, invasion, progression.

Introduction

Extramammary Paget's disease (EMPD) is a distinct form of a rare malignant skin neoplasm of unknown histogenesis [1] that was first described by Crocker in 1889 [2]. It usually affects older patients [3], and the lesions commonly develop in the vulva, penis, scrotum, perineum, perianal area, umbilicus, and axilla [4]. Early lesions clinically present as red or brown plaques, which later become erosive and infiltrative, with advanced lesions eventually forming nodules [3]. Histopathologically, the tumor cells (Paget cells) in EMPD are characterized by large nuclei, prominent nucleoli, and abundant pale to amphophilic cytoplasm [5], with features of adenocarcinoma [6]. The tumor cells in early lesions are arranged singly or in small groups in the epidermis [7], and the epithelium of the cutaneous adnexal structures and the entire thickness of the epidermis subsequently become involved [7]. At advanced stages, tumor cells invade the dermis and may metastasize [8]; lymph node metastasis is related to prognosis [9].

We have previously described the relationship between the histopathological pattern of the epidermis and dermal invasion, and tumor progression [10, 11]. However, the clinicopathological significance of cutaneous adnexal involvement has not been investigated in detail. The aims of this study were therefore

to examine adnexal status and to assess its relationship with EMPD progression.

Material and methods

Surgical specimens were derived from 53 patients with primary EMPD not associated with any underlying neoplasm. These cases were treated between 1995 and 2010, details of which were obtained from the archives of our institution. Clinical data were retrieved from the patients' medical records. All materials were fixed in 10% formalin, processed routinely, and embedded in paraffin.

One representative histologic section stained with hematoxylin and eosin (HE) was selected and analyzed for each case. Tumor involvement of cutaneous adnexal structures such as the hair follicle and sweat gland was evaluated using histological parameters. The degree of involvement was scored on a scale of 0–2: 0, no involvement; 1, involvement of the upper portion of the adnexa; 2, involvement of the lower portion of the adnexa (Fig. 1. A, B). An immunohistochemical study, for e.g. cytokeratin 7 (CK7) or CEA, was performed when it was difficult to evaluate based only on HE section (Fig. 1C). A score of 2 was regarded as significant. Central necrosis associated with adnexal involvement, equivalent to comedo necrosis in breast cancer (Fig. 2), was also examined. The relationships between histopathological parameters and invasion were analyzed statistically using χ^2 tests. A p value < 0.05 was considered to be statistically significant.

Results

The clinicopathological features of the 53 cases are summarized in Table I. Patient age at the time of surgery ranged from 55 to 94 years. There were 38 males and 15 females. The lesion was located on the scrotum in 37 cases, the vulva in 14 cases, the perianal area in 1 case, and the axilla in 1 case. Of the 53 cases, 26 were *in situ* EMPD and 27 were invasive EMPD. Of the 27 cases of invasive EMPD, 22 had dermal invasion ≤ 1 mm below the basement membrane of the epidermis (minimal invasion), and 5 had dermal invasion > 1 mm in depth (frank invasion).

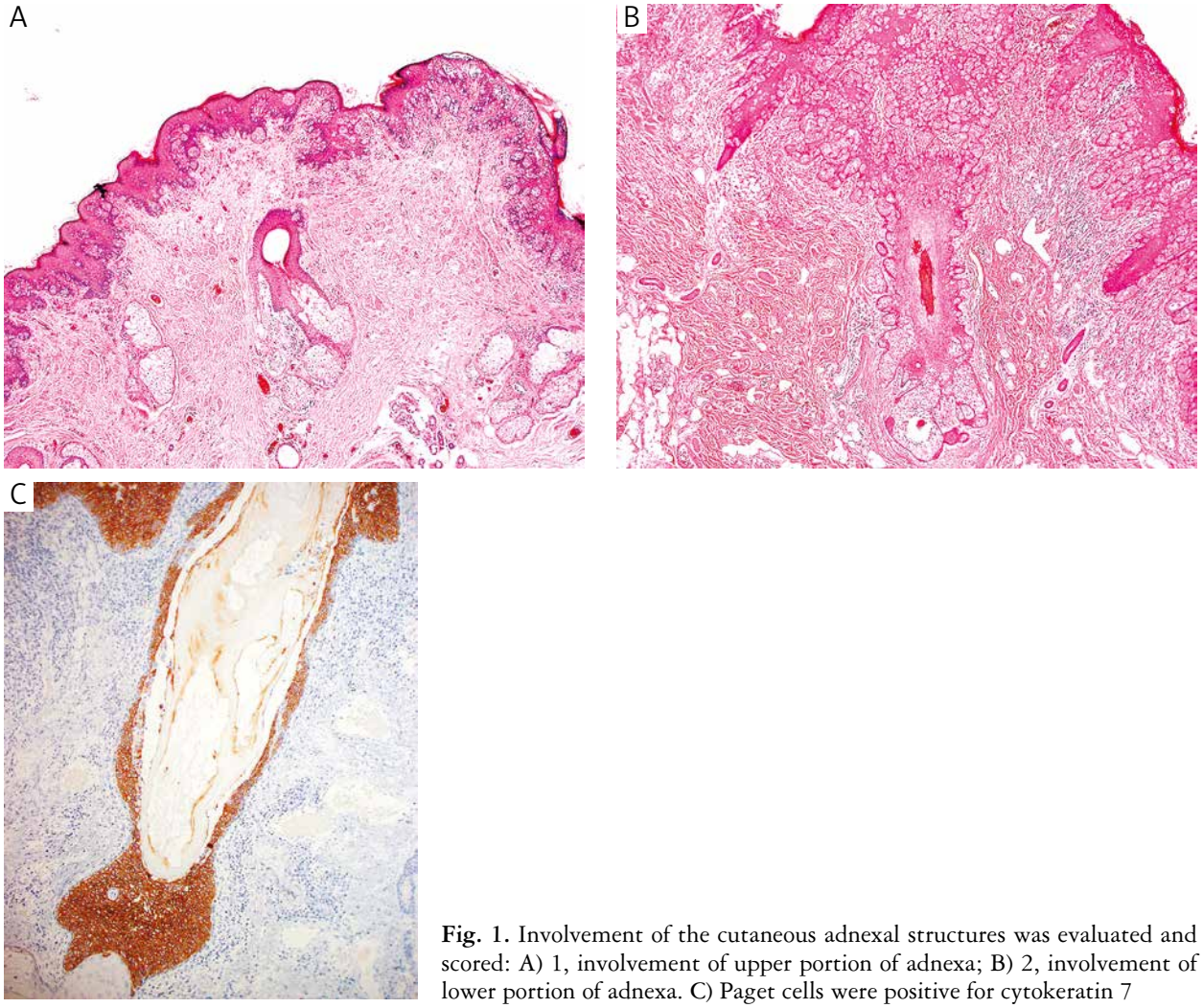

Fig. 1. Involvement of the cutaneous adnexal structures was evaluated and scored: A) 1, involvement of upper portion of adnexa; B) 2, involvement of lower portion of adnexa. C) Paget cells were positive for cytokeratin 7

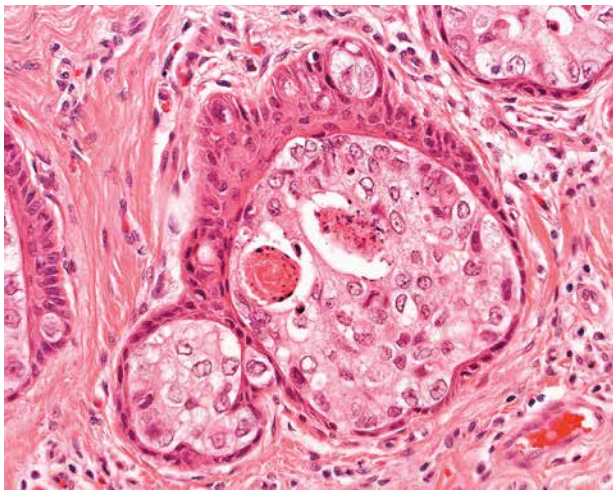

Fig. 2. Comedo necrosis was observed in the adnexal structure (hair follicle)

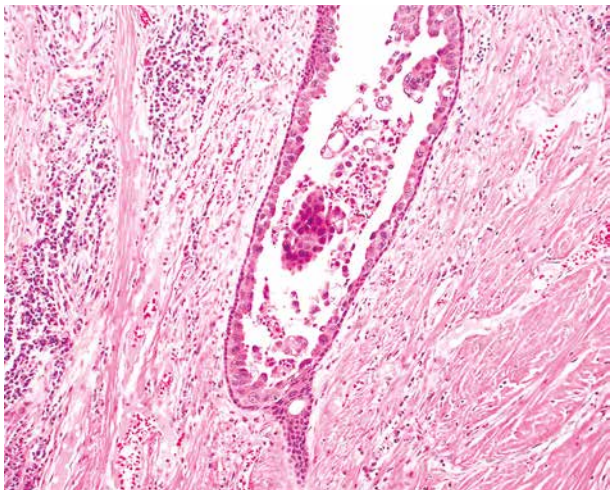

Fig. 3. The sweat gland was involved by Paget cells

Adnexal involvement was identified in 46 cases (86.8%) (hair follicle only, 4 cases; sweat gland only, 5 cases; both, 37 cases) (Fig. 3). Comedo necrosis was observed in 6 cases (11.3%) (hair follicle only, 1 case; sweat gland only, 5 cases). The proportions of each parameter in *in situ* cases were as follows: significant adnexal involvement (score 2) in 15/26 (57.7%) and comedo necrosis in 3/26 (11.5%). The corresponding proportions in cases with invasion were 21/27 (77.8%) and 3/27 (11.1%), respectively. No significant differences in adnexal involvement and comedo necrosis were detected between *in situ* EMPD and invasive EMPD ($p > 0.05$) (Table II). Tumor cells in the dermis were distributed mainly around the adnexa in 1 case of invasive EMPD. The remaining cases revealed that dermal invasion was more prominent beneath the interadnexal epidermis and showed a top-heavy distribution.

Discussion

Extra mammary Paget's disease is a distinct form of a relatively rare malignant skin neoplasm of unknown histogenesis [1]. Histologically, it is characterized by intraepidermal proliferation of neoplastic cells identical to those seen in classical mammary Paget's disease [12]. Although adnexal involvement was a common finding in the report by Shaco-Levy *et al.* and it did not affect the recurrence rate [13], its association with tumor progression has not been investigated in detail. In this study, adnexal involvement was identified in 46 cases (86.8%) and comedo

Table I. Summary of clinicopathological characteristics of study cases

Characteristics		Number
Age (years)	55–94	
Gender	male	38
	female	15
Site	scrotum	37
	vulva	14
	perianal lesion	1
	axilla	1
Diagnosis	*in situ*	26
	dermal invasion ≤ 1 mm	22
	dermal invasion > 1 mm	5

Table II. Relationship between adnexal status and dermal invasion

Status		Total, n (%)	*In situ* EMPD, n (%)	Invasive EMPD, n (%)	P-value
Score 2					
	present	36 (67.9)	15 (57.7)	21 (77.8)	0.117
	absent	17 (32.1)	11 (42.3)	6 (22.2)	
Comedo necrosis					
	present	6 (11.3)	3 (11.5)	3 (11.1)	0.961
	absent	47 (88.7)	23 (88.5)	24 (88.9)	

EMPD – extramammary Paget's disease

necrosis was present in 6 cases (11.3%). The proportion of cases with adnexal involvement showing a score of 2 was not significantly different between *in situ* EMPD (57.7%) and invasive EMPD (77.8%). Comedo necrosis in breast ductal carcinoma *in situ* has been associated with an increased risk of local recurrence and progression to invasive cancer [14]. In the present study, no significant difference was observed in the proportion of *in situ* EMPD and invasive EMPD cases with comedo necrosis, which occurred in 3/26 (11.5%) and 3/27 (11.1%) patients, respectively. These results suggest that the degree of adnexal involvement and the presence of comedo necrosis are not associated with EMPD progression.

Extra mammary Paget's disease is generally considered to be an adenocarcinoma of unknown origin [15]. In our study, dermal invasion was more prominent beneath the interfollicular epidermis than around the adnexa in most cases of invasive EMPD. Although the origin could not be clarified, we speculate that Paget cells initially develop in the epidermis and subsequently spread to the cutaneous adnexal structures, and dermal invasion mainly originates from the epidermal component and not the adnexal structures.

There were some limitations to the current study. First, we did not investigate lymph node status or patient outcome. Second, we only examined one representative section for each case. The evaluation of more sections by immunohistochemistry would have been beneficial because the lesion of EMPD is wide and the histopathological appearance may vary at different sites.

In conclusion, we evaluated the adnexal status of EMPD by examining clinicopathological features. Although further studies are necessary, the current study suggests that the degree of adnexal involvement and the presence of comedo necrosis are not associated with tumor progression in EMPD.

The authors declare no conflicts of interest.

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