

## CLINICAL REPORT

# Ectopic Extramammary Paget's Disease: Case Report and Literature Review

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**Extramammary Paget's disease that occurs in non-apocrine-bearing regions is referred to as ectopic and has been rarely reported. A 62-year-old man presented with a slowly progressive, asymptomatic light-brown plaque on his back. Histopathological examination revealed the presence of large pale cells with prominent nuclei, which proliferated diffusely and focally in the epidermis. Immunohistochemically the tumour cells were positive for CK7, GCDFP-15, CEA, and p63. Based on these findings, we diagnosed the tumour as ectopic extramammary Paget's disease. We reviewed the English and Japanese literature and found 29 previously reported cases of ectopic extramammary Paget's disease, including our case, with a predominance of occurrence in the Asian population. The germinative milk line is known to be a possible site where extramammary Paget's disease occurs. Likewise, some germinative apocrine-differentiating cells might exist on the trunk preferentially in Asians. Attention should be paid to the development of ectopic as well as triple or quadruple EMPD in Asians. Key words: extramammary Paget's disease; ectopic; back; Asian.**

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The origin of extramammary Paget's disease (EMPD) remains unresolved and controversial. Nevertheless, the apocrine gland has been generally estimated as its origin, because most cases of EMPD occur mainly in the genital, axillary or perianal regions, where apocrine glands predominate. Immunohistochemical studies support this concept, as represented by the positive immunoreactivity for gross cystic disease fluid protein (GCDFP)-15 as well as carcinoembryonic antigen (CEA) and cytokeratin (CK) 7, which are present in apocrine glands (1). EMPD has been rarely observed in the non-apocrine-bearing regions, and such cases are referred to as "ectopic" EMPD (2). We report here a case of primary, ectopic EMPD arising on the back. We reviewed the literature extensively, focusing on the ethnic preponderance and predilection sites.

## CASE REPORT

A 62-year-old man who was native Japanese and an Asian presented with an asymptomatic erythematous lesion on his back, which had been present for 3 years. It slowly enlarged, and became partially elevated. He was referred to us for evaluation of the lesion in July 2008. On examination, the patient had a 4.6 × 3.2-cm, variably pigmented dark-brown and erythematous plaque on the left paravertebral skin (Fig. 1A). There was some surface scale with a more palpable lower pole (Fig. 1B). No other skin lesion was observed in the axilla, groin, genital or perianal area, or umbilicus. Lymph nodes were not pal-

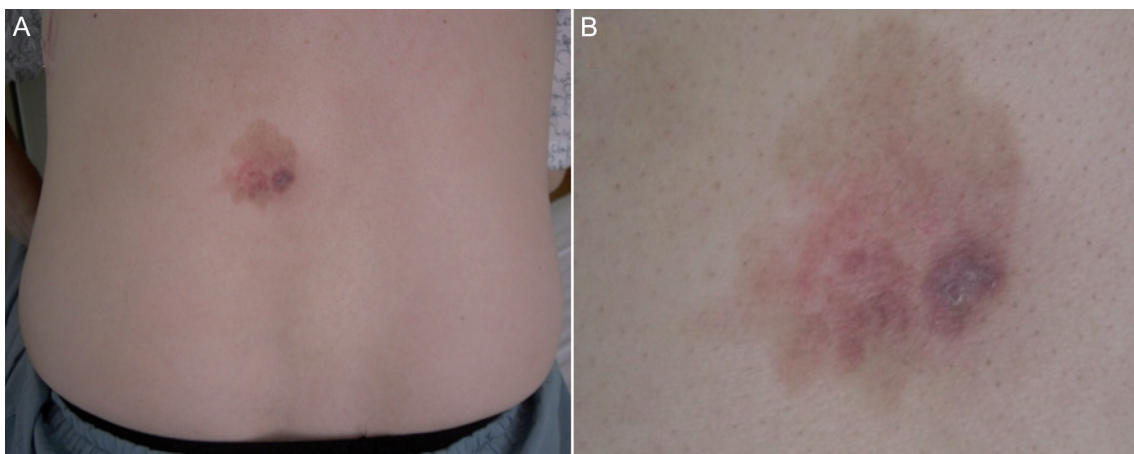


Fig. 1. Clinical appearance. (A) A dark-brown, erythematous plaque on the left paravertebral skin. (B) Higher magnification reveals some crust and scale.

pable in the cervical, axillary or inguinal area. His past medical and family histories were unremarkable.

Histopathological examination of biopsy specimens from the lesion revealed the presence of large pale cells with prominent nuclei, which proliferated diffusely and focally in the epidermis (Fig. 2A). Notably, the cells formed prominent duct-like nests in the basal or suprabasal layers. The tumour cells showed nuclear atypia, and the decapitation secretion into the lumina was partly seen in the inner cells of ductal structures (Fig. 2B). No tumour cell invasion was found in the dermis. Immunohistochemically, the tumour cells were positive for CK7, GCDFP-15, CEA and p63, but negative for periodic acid-Schiff (PAS), CK20, S-100 protein, and HMB-45. No involvement of the other organs was detected on various examinations, such as abdominal ultrasound, computed tomography, chest X-ray, and upper and lower endoscopic analyses.

Based on these clinical and pathological findings, we diagnosed the tumour as ectopic EMPD. Secondary EMPD to direct cutaneous invasion of an adjacent carcinoma could be excluded by GCDFP-15 positivity and CK20 negativity (3). In addition, other sweat gland tumours, such as malignant hidroacanthoma simplex, were excluded by its prominent ductal formation and immunostaining pattern.

The lesion was resected with a 1-cm safety margin from the surrounding subtle pigmentation, and was covered with a split skin graft from the patient's thigh skin. Currently, 8 months post-surgery, the patient is free from recurrence.

## DISCUSSION

EMPD is a malignant neoplasm with a predilection for the apocrine-rich anogenital skin. EMPD is classified into primary EMPD and secondary EMPD, which is a

direct spreading malignant tumour from internal malignancy such as rectal carcinoma or perianal carcinoma (4). The germinative milk line is defined as a narrow band-like thickening of the ectoderm extending over each side of the ventral surface of the embryo, from the upper limb buds to the posterior limb buds (5). The breast is usually restricted to the chest wall in humans; however, supernumerary or accessory breasts occur in 1–5% of the population in this milk line (6). The existence of apocrine glands is indicated on the milk line. Ectopic EMPD is defined as EMPD arising on non-apocrine-bearing areas. The milk line is included in this concept by its apocrine-possessing areas. We classified the ectopic area as non-germinative milk line, as shown in Table I. Ectopic EMPD does not have any characteristic features that differentiate it from the non-ectopic variant. They share immunostaining for CEA, CK7 and GCDFP-15 (7). Furthermore, there is no difference in the prognosis between ectopic and ordinary EMPD. There have been no reports, to our knowledge, regarding the association of EMPD and other diseases. Since ectopic EMPD occurs on the apocrine-poor or lacking regions, one cannot easily assume that the ectopic type is derived from apocrine glands. Although immunohistochemical analyses are useful to differentiate the apocrine gland from the eccrine gland, precise determination of tumour origin is still difficult in sweat gland neoplasms. For example, the GCDFP-15 positivity is one of the hallmarks of apocrine origin, but a recent immunostaining study has shown that GCDFP-15-positive cells are present even in eccrine glands depending on the body site (8). This provides a possibility that ectopic EMPD originate potentially not only from the apocrine gland, but also from the eccrine gland. Alternatively, the pluripotential germinative cell might be the origin of ectopic EMPD (9). This immature cell might be changed into the malignant tumour of apocrine glands.

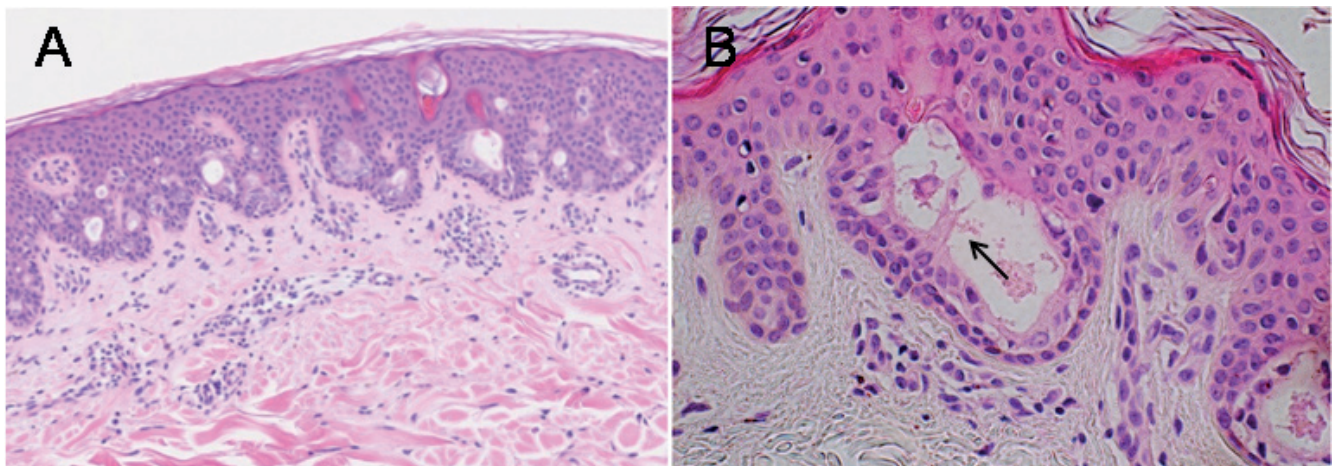


Fig. 2. Histopathological picture. (A) Pagetoid cells with prominent nuclei and pale cytoplasm are present diffusely and focally in the epidermis (arrow), forming ductal structures (haematoxylin and eosin (H&E); original magnification,  $\times 200$ ). (B) Decapitation secretion into the lumina is observed in the ductal nests (H&E; original magnification,  $\times 400$ ).

We reviewed the English and Japanese reported cases of ectopic EMPD (Table I) (2, 5, 9–33). According to the initial definition of ectopic EMPD (2), cases occurring on the germinative milk line as well as the anogenital region were excluded. There have been 29 reported cases of ectopic EMPD including our case. The male:female ratio is 1.6:1, and the mean age is 67.9 years. The tumour sites are as follows: trunk, 79.3%; face and head, 13.8%; and extremities, 6.9%. The Asian/non-Asian ratio is approximately 3:1, as there were 23 Asian cases and 6 non-Asian (mostly European) cases, suggesting that ectopic EMPD occurs preferentially in the Asian population. The Asian and non-Asian male:female ratios are 2.1:1 and 0.75:1, respectively, indicating the male dominance of the Asian cases. The predilection site of Asian ectopic EMPD is trunk 95.5%, whereas those of non-Asian are face, head and extremities 71.4% with fewer trunk cases 28.6%. Our patient is the third case of ectopic EMPD arising on the back (the first case in the English literature). Inada et al. (7) reported that ductal formation of tumour cells in the epidermis is a characteristic of ectopic EMPD on the back, as seen in our case.

Thus, there are apparent racial differences in the incidence, gender, and sites of ectopic EMPD. Several epidemiological studies have been performed on the relationship between race and incidence of EMPD. In

Table I. Reported cases of ectopic extramammary Paget's disease

Case	Authors (Ref.)	Age (years)/sex	Sites
1	Kojima (10)	68/M	Sternal region
2	Jones et al. (9)	78/F	Buttock
3	de Blois et al. (11)	60/F	Left knee
4	Inada et al. (7)	69/F	Back
5	Sitakalin & Ackerman (12)	88/F	Thigh
6	Saida et al. (2)	54/M	Lower anterior chest
7	Taniyama et al. (5)	67/F	Buttock
8	Kitahara et al. (13)	54/M	Lateral chest, medial site of nipple
9	Urabe et al. (14)	79/M	Lateral chest
10	Ohara et al. (15)	57/M	Upper abdomen
11	Sai et al. (16)	81/M	Scalp
12	Susaki et al. (17)	79/M	Hypochondrium
13	Minagawa (18)	78/M	Back and upper abdomen
14	Onishi & Ohara (19)	57/M	Upper abdomen
15	Tonegawa et al. (20)	73/F	Lower abdomen
16	Hotta et al. (21)	51/F	Frontal chest
17	Chilukuri et al. (22)	67/M	Cheek
18	Matsuura et al. (23)	76/F	Lower abdomen
19	Kubota et al. (24)	72/F	Upper abdomen
20	Ito et al. (25)	66/M	Frontal chest
21	Cohen et al. (26)	61/M	Face
22	Nagai et al. (27)	79/M	Abdomen
23	Hanakawa et al. (28)	51/M	Left chest
24	Yeh & Hu (29)	75/M	Bilateral chest
25	Syoji et al. (30)	81/F	Upper abdomen
26	Kamei & Tonegawa (31)	63/M	Lower abdomen
27	Kiyohara et al. (32)	65/M	Upper abdomen
28	Iwenofu et al. (33)	57/F	Scalp
29	Our case	62/M	Back

Table II. Compilation of published cases of extramammary Paget's disease with respect to race, sex and site

Race (n)	Mean age (range)	Sex (n)	Site (n)
Asian (22)	67.4 (51–82)	Male (15)	Trunk (21)
		Female (7)	Scalp (1)
Non-Asian (7)	69.4 (57–88)	Male (3)	Trunk (2)
		Female (4)	Face (2)
			Scalp (1)
			Extremities (2)

Asian countries, men have EMPD twice as often as women (15, 34), whereas in western countries women are predominantly affected (35). Ectopic EMPD has the same gender tendency as non-ectopic EMPD. More interestingly, there have been 68 reported Japanese cases of triple or quadruple EMPD, whereas only one case of triple EMPD has been reported outside of Japan (36). This is in accordance with the ethnic difference found in ectopic EMPD. The reason for this racial difference is speculative. It is known that the germinative milk line is a possible site where EMPD occurs. Likewise, some germinative apocrine-differentiating cells might preferentially exist on the trunk in the Asian population. Attention should be paid to the development of ectopic as well as triple or quadruple EMPD in Asians.

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