Depigmented genital extramammary Paget’s disease: A possible histogenetic link to Toker’s clear cells and clear cell papulosis

Background: The histogenesis of extramammary Paget’s disease (EMPD) is still controversial. Benign pagetoid cells of the nipple first described by Toker and the similar clear cells found in white maculo-papules of clear cell papulosis (CCP) have been proposed to be potential precursor cells giving rise to EMPD and primary intraepidermal Paget’s disease in the nipple. The observation of a rare case of depigmented EMPD provided us with a chance to examine further the interesting Toker’s clear cell/CCP hypothesis.

Methods: We performed pathologic studies, including Fontana-Masson stain and immunostaining for AE1/AE3 and S100P, on a new case of depigmented EMPD manifesting a 4×3 cm hypopigmented-depigmented patch on the root of the penis.

Results: The lesion showed extensive intraepithelial proliferation of atypical pagetoid cells with markedly reduced epidermal melaninization but nearly normal numbers of melanocytes. The tumor cells were strongly positive for AE1/AE3 by immunostaining. Some tumor cells displayed tadpole-like morphology resembling the pagetoid cells of CCP. Such morphology was not observed in two random examples of non-depigmented genital EMPD.

Conclusions: The findings of tadpole-shaped pagetoid cells and depigmentation in the present case suggest that depigmented EMPD may be histogenetically related to CCP. Depigmented EMPD should be considered in the differential diagnosis of vitiligo, depigmented mycosis fungoides and lichen sclerosus located along the milk line.

Case report

A 69-year-old man was referred to our clinic for further management of a white patch in the genital where an erythematous plaque of EMPD of the scrotum had been excised 2 years ago. The patient denied any pre-existing depigmented macules or patches over the chest, lower abdomen or genital area since childhood. Examination revealed a 4×3 cm patch at the root of the penis (Fig. 1). The lesion was depigmented with sharp demarcation from the surrounding normal skin for the most part. There was no other depigmented lesions elsewhere. There was no regional lymphadenopathy or internal malignancy. Laboratory tests, including blood cell counts, PSA, stool hemoccult, urine cytology and abdominal sonography, were normal. Under the suspicion of depigmented EMPD, the lesion was excised with simple closure. The histopathology revealed an extensive proliferation of atypical pagetoid cells arranged as solitary units or in nests within the epidermis and follicular infundibula (Fig. 2). The nuclear atypia was less obvious toward the periphery of the lesion. There was no dermal invasion. The inflammatory infiltration in the dermis was focal and relatively sparse and there were no melanophages.

Fontana-Masson stain revealed reduced to absent pigmentation of keratinocytes in the lesion. The basal melanocytes were visible but appeared to be slightly reduced in number on hematoxylin and eosin (H&E)-stained sections, compared with the surrounding normal skin. Similar findings were observed with S-100 immunostaining (dilution 1:100; BioGenex), but the basal melanocytes in both lesional and adjacent normal skin were stained poorly despite strong staining of the dermal nerve fibers. The tumor cells were focally positive for mucicarmine, weakly positive for carcinoembryonic antigen (CEA) (dilution 1:750; Dako), but negative for S-100 protein, synaptophysin (dilution 1:50; Dako) and chromogranin A (dilution 1:100; BioGenex). Anti-human cytokeratin (AE1/AE3, dilution 1:50; Dako) stain was strongly positive in the tumor cells (Fig. 3), some of which displayed tadpole-like morphology resembling the pagetoid cells of CCP. The tadpole morphology was not observed in two random examples of typical genital non-depigmented EMPD, which showed normal melaninization with Fontana-Masson stain. A new hypo-pigmented patch, 3×2 cm, was noted on the other side of the root of the penis 6 months later at a follow-up examination. The lesion was excised and again revealed changes of EMPD.

Discussion

In our patient, two lesions of hypo- or de-pigmented EMPD appeared on the root of the penis sequentially...
after a typical erythematous plaque lesion was excised from the scrotum. Since these hypo- or depigmented lesions had been present for only a few months, they were presumed to be early lesions of EMPD. There have been 3 other patients, all male, with depigmented genital EMPD.1–3 Two had asymptomatic depigmented spots for 11 months and 4 years, respectively, and were diagnosed as EMPD after the lesions became erythematous or crusted.1,2 One case was reported to have depigmented macules as the sole manifestation of EMPD.3 Our patient could not recall whether the first erythematous lesion had been preceded by a white patch not. It is possible that many more early or non-inflamed lesions of EMPD are hypopigmented and remain ignored by patients and their doctors or are dismissed as benign processes until the lesions are more advanced or become inflamed, eroded or crusted.

The mechanism of depigmentation in EMPD is unknown. Physical replacement of keratinocytes or basal melanocytes and disturbed symbiosis between melanocytes and keratinocytes (including melanocyte destruction) have been suggested.2,3 Although the first hypothesis is plausible in advanced lesions where Paget’s cells are numerous, most cutaneous Paget’s disease and other neoplasms with intraepidermal pagetoid proliferation are not depigmented. Moreover, we have seen advanced EMPD in which the basal melanocytes are highly dendritic and heavily pigmented. In the present case, the Fontana-Masson stain revealed reduced production of melanin in the lesion. The basal melanocytes were easily detected but their numbers appeared to be slightly reduced. There were no melanophages to suggest postinflammatory pigmented alteration. Thus it is unlikely that the reduced or total loss of pigmentation in the EMPD under study was caused by obvious loss of basal melanocytes, blockage in melanosome transfer or post-inflammatory pigmentary alteration. Rather the hypo- or de-pigmentation could be attributed mainly to a reduced production of melanin, and possibly to a slight reduction of melanocyte density due to dilution or replacement effect by the tumor cells. The role of clear cells in the pathogenesis of this melanocytic alteration remains to be elucidated.

The histogenesis of EMPD is more controversial than that of mammary Paget’s disease where almost all cases originate from an underlying ductal carcinoma. Although the pagetoid cells in EMPD may arise from apocrine glands or from adenocarcinoma of an organ adjacent to the skin, as many as 90% of the cases have been reported to begin as an intraepidermal adenocarcinoma.11,12 Some authors have postulated that EMPD might arise within the epidermis, either from eccrine or apocrine glands.13–15 Others have suggested that ectopic mammary glands or pluripotential germinative cells in the epidermis are the potential precursor cells.16

Toker,7 who first reported a distinct but small population of benign pagetoid clear cells in normal nipples, suggested that these pagetoid clear cells might represent cells of abortive mammary differentiation within the basal layer during either embryonic or postnatal life. He further speculated that the clear cells could be potential precursor cells of primary intraepidermal Paget’s disease of the breast. This hypothesis may explain some instances where mammary Paget’s disease was not associated with an underlying ductal adenocarcinoma.10,17,18 The hypothesis is further supported by the finding of multifocal Toker’s clear cell hyperplasia in a lesion of mammary Paget’s disease confined to the epidermis.10 In 1987, Kuo8 described a new entity called “clear cell papulosis” occurring in young children. To date, only about 10 cases have been documented, including the 4 cases reported by us.8,9,19,20 Since then, we have seen three more patients, one boy and two girls. All 13 patients were children younger than 5 years. CCP is characterized by multiple small whitish maculopapules distributed along the milk lines clinically, and intraepidermal proliferation of benign pagetoid cells resembling Toker’s clear cells pathologically. The clear cells are best detected by immunostaining for AE1. With this new observation, Kuo extended Toker’s hypothesis and suggested that the clear cells identified in CCP might give rise to cutaneous Paget’s disease.8 Although this is an attractive hypothesis, particularly for EMPD, no direct evidence has been demonstrated so far.

In the white lesions of CCP, there was reduced or absence of epidermal melaninization and basal melanocytes appeared normal in number within the lesions.9 The findings suggest a dysfunction of melanocytes in CCP lesions. Since we have never seen CCP in adults, we believe it is possible that the lesions eventually become less obvious or invisible with age, due to either disappearance of the clear cells or normalization of the epidermal pigmentation. The lack of clinical evidence of a pre-existing CCP in patients with cutaneous Paget’s disease does not exclude the possibility that there might be CCP in early childhood and that residual clear cells might remain in the epidermis and later give rise to cutaneous Paget’s disease.

The other potential precursor cells for EMPD are Toker’s clear cells if they exist outside the nipple. Toker found that nipple clear cells occur in about 10% of normal nipples by examining H&E-stained sections.7 It is possible that Toker’s clear cells are a normal component of the epidermis along milk lines but in numbers so small that they are not readily recognized. Moreover, the clear cells may be dismissed as keratinocytes or melanocytes by observers who are not aware of their existence. In fact, a few CEA-posi-
tive clear cells have been detected in a normal appearing axillary skin specimen from a patient with genital Paget’s disease.\textsuperscript{21}

In search of further evidence to support the histogenetic link between CCP and EMPD, we are particularly impressed by two observations. The first is the rare case of multifocal Toker’s cell hyperplasia in association with primary intraepidermal mammary Paget’s disease in which the foci of Toker’s cell hyperplasia were depigmented clinically.\textsuperscript{10} The second is the documentation of depigmented EMPD.\textsuperscript{1–6} The present case gave us a chance to study the relationship between CCP and EMPD. We found tadpole-shaped clear cells, similar to the pagetoid cells of CCP, mainly at the periphery of the lesion where pagetoid cells were less numerous. We did not see such tadpole-shaped pagetoid cells in two other random examples of classical, non-depigmented EMPD examined with cytokeratin immunostaining. Furthermore, the nuclear atypia in these peripheral pagetoid cells seemed less prominent compared with other EMPD lesions in our file. Though preliminary, these findings provide a circumstantial evidence for possible histogenetic link between CCP and depigmented EMPD.

In conclusion, our observation suggests that EMPD, especially depigmented EMPD, might be histogenetically related to CCP and Toker’s clear cells. The recognition of hypopigmented or depigmented variant of EMPD is important in clinical practice. Clinicians should be alerted to this unusual manifestation of EMPD. Depigmented EMPD should be included in the differential diagnosis of hypopigmented or depigmented macules or patches, such as vitiligo, vitiligo-like mycosis fungoides and lichen sclerosus, along the milk line, especially on the axilla, breast, abdomen, suprapubic area and external genitalia.

References