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We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.
dermatomyositis muscle, myofibre injury is apparent in two forms: large areas of apparent infarction visible as the loss of myofibrillar uptake of multiple histochemical stains, seen occasionally in juvenile dermatomyositis and rarely in adult dermatomyositis, and the presence of perifascicular atrophy (PFA). PFA is a term used to describe small, basophilic myofibres around the edges of muscle fascicles. PFA does not generally affect all myofibres around the edge of the fascicle, but rather usually affects the specific myofibres that border the loose connective tissue (the perimysium), sparing myofibres that border other myofibres in neighbouring fascicles. The lesion is better described by the term perimysial PFA, or even perimysial myofibre atrophy.

In dermatomyositis skin, the characteristic pathology is an interface dermatitis, in which abnormalities are most prominent at the boundary between the epidermis and dermis. It is characterized by the presence of dying keratinocytes centred mostly on those in the basal layer, in opposition to the underlying basement membrane. The more differentiated cells that are located higher in the stratum spinosum or stratum granulosum are rarely affected. This cell death is manifested by cells with pyknotic nuclei and eosinophilic cytoplasm as well as by vacuolization of the basal layer. Curiously, the dying cells are often not confluent, and are present in patchy foci often in association with infiltrating mononuclear cells. Epidermal atrophy is also seen in long-standing lesions.

We point out here that the topology of the injury to both myofibres and keratinocytes is similar in dermatomyositis muscle and skin (Fig. 1). In both cases, injury preferentially affects the cells that border the loose connective tissue adjacent to them, with relative sparing of cells that are entirely surrounded by other cells. In cases with greater severity of changes, the pathology extends into deeper regions of muscle fascicles and more superficial layers of keratinocytes. Why such muscle and skin cells bordering loose connective tissue are more susceptible to injury is unknown. One speculative possibility is that these bordering cells are closer to cells of the immune system and their secreted products. It is possible that the pattern of muscle inflammation in dermatomyositis represents the ‘muscle equivalent’ of a lichenoid tissue reaction in the skin. Indeed, in this disease the inflammatory cells are usually much more abundant in muscle in the perimysial connective tissue than within fascicles, as they are more commonly seen in the papillary dermis and dermoepidermal junction than within the more superficial keratinocyte layers.

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References

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Morphological and genetic analysis of steatocystoma multiplex in an Asian family with pachyonychia congenita type 2 harbouring a KRT17 missense mutation

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Sir, Pachyonychia congenita (PC) is a rare, autosomal dominant keratin disorder. PC can be classified into two main clinical subtypes: PC type 1 (PC-1, OMIM 167200) and PC type 2

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Almost all mutations detected in patients with PC-2 (OMIM 167210). PC-1 is associated with mutations in KRT6A or KRT16, and PC-2 corresponds to mutations in KRT6B or KRT17.1,2 Almost all mutations detected in patients with PC occur in the helix boundary motifs of each keratin gene.3 Common clinical features of both PC subtypes are hypertrophic nail dystrophy, and focal hyperkeratosis of the palms, soles, knees and elbows.4 Among clinical manifestations in patients with PC, the development of steatocystoma multiplex is one of the most characteristic features for differentiating PC-2 from PC-1. Typically, patients with PC-2 exhibit 100–2000 round or oval cysts widely distributed on the back, anterior trunk, arms, scrotum and thighs.

We report an Asian PC-2 family with a missense mutation in KRT17. In this study, we present histological and ultrastructural features of a steatocystoma from the proband. Furthermore, comparative analysis of genomic DNA (gDNA) extracted from steatocystomas and peripheral blood of the family was performed. These observations could provide significant information for understanding the pathomechanisms of cyst formation in patients with PC-2.

The proband was a 36-year-old Asian woman with the chief complaint of nail dystrophy. Natal teeth were observed at birth. During childhood, nail hypertrophy was seen on the toenails and fingernails (Fig. 1a). Follicular hyperkeratosis on the knees and elbows was also noted at puberty, although the symptom disappeared as she grew older. She also complained of focal hyperkeratosis on the soles. The proband’s 3-year-old daughter had follicular keratosis on the knees, nail deformity, pilosebaceous cysts on the face, and focal hyperkeratosis on the soles. The proband’s 62-year-old father had had nail dystrophy, numerous steatocystomas on the trunk and hyperkeratosis on the soles since his adolescence. The family has a strong genetic background of nail hypertrophy and steatocystoma multiplex (Fig. 1c).

gDNA was extracted from whole blood samples of the proband, her father and her daughter. KRT6B and KRT17 were amplified from their gDNA by polymerase chain reaction (PCR) using specific primers to amplify the helix boundary motifs of each gene without coamplification of the pseudogenes and isogenes.5,6 Mutation analysis for KRT6B showed no mutations of the gDNA, and analysis of KRT17 indicated that the proband was a heterozygote for a recurrent mutation of c.296T>C transition (p.Leu99Pro) in KRT17 (Fig. 1d). The father and daughter were also heterozygotes for the same mutation in KRT17. Restriction enzyme digestion of PCR products by NcoI was carried out to confirm the mutation (data not shown). The mutation was not found in 50 normal control individuals. This mutation was previously reported elsewhere.1,7

Histopathological findings of skin specimens from a steatocystoma of the proband showed that the cyst wall consisted of several thin epithelial cell layers without granular layers (Fig. 2a,b). There were sebaceous glands near the cyst wall (Fig. 2b). Large basophilic granules were scattered in the cytoplasm of the uppermost-layer cells in the cyst walls (Fig. 2c). Immunohistochemically, upper layer cells in the cyst wall expressed keratin 17 (Fig. 2d). Ultrastructural observation revealed keratin clumps in the cytoplasm of epithelial cells in the cyst wall (Fig. 2e). The keratin clumps were large and irregularly shaped (Fig. 2f).

We excised one steatocystoma and overlying epidermis from the proband and three steatocystomas from the proband’s father, and we removed the normal tissue of the steatocystomas and intracystic materials as much as possible. DNA was extracted from both the cyst wall of steatocystomas and the overlying epidermis. Direct sequencing of gDNA from all

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**Fig 1.** Clinical features of the proband, pedigree of the present family and mutation analysis of KRT17. (a) The proband’s toenails showed severe dystrophy. (b) There were several steatocystomas on the proband’s axillae (arrows). (c) The family history indicated strong penetration. Squares indicate males, and circles, females. Blackened symbols are individuals with pachyonychia congenita type 2. The proband is indicated by an arrow. The asterisks indicate individuals who underwent mutation analysis. (d) Direct DNA sequence analysis of the helix initiation motif in KRT17; the c.296T>C transition mutation (p.Leu99Pro) in one allele of KRT17 was found in the proband’s blood.
samples identified the same KRT17 mutation in one allele as seen in the family’s peripheral blood (data not shown). Comparative sequence analyses for helix boundary motifs of KRT6B and KRT17 on gDNA extracted from the cyst wall and overlying epidermis vs. gDNA isolated from whole blood samples revealed neither sequence deviations indicative of loss of heterozygosity (LOH) nor second-hit mutations (data not shown).

Our results for four steatocystomas from patients with PC-2 suggest that cyst formation does not require a complete functional loss of keratin. The absence of LOH or second-hit mutations indicates that steatocystoma multiplex comprises benign cysts rather than tumours. Notably, the cyst wall of the steatocystoma from the proband had large basophilic granules. Ultrastructural observation confirmed that the granules were keratin clumps, which resulted from the conformational change in keratin filaments due to the KRT17 mutation. Dominant negative effects from a mutation in KRT17 may be sufficient to cause steatocystomas in patients with PC, although the exact mechanisms of steatocystoma formation remain unclear.
Metastatic prostate cancer presenting as paraneoplastic pemphigus: a favourable clinical response to combined androgen blockade and conventional immunosuppressive therapy

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Sin, Paraneoplastic pemphigus (PNP), first described in 1990, is an autoimmune mucocutaneous blistering disease which is associated with an underlying malignancy and is characterized by polymorphic clinical signs. Pathogenesis is due to an aberrant autoimmune response against the proteins of the plakin family such as plectin, envoplakin, periplakin, desmoplakin I and II, and bullous pemphigoid antigen I (BP230), although several cases of PNP with antibodies to desmoglein (Dsg) 1 and 3 have been described.

A 77-year-old man was admitted to our Oral Medicine Unit because of recalcitrant severe oral bullous/erosive mucositis with crusting lesions of the lips (Fig. 1a), accompanied by marked conjunctivitis of both eyes (Fig. 1b), with cutaneous bullous lesions of the abdomen and bilaterally of the hip and inguinal area (Fig. 1c). Nikolsky’s sign, performed on the oral mucosa and skin, was positive.

Oral biopsy revealed suprabasal epithelial detachment with an eosinophilic and neutrophilic infiltrate. Direct immunofluorescence showed positive fluorescence in the intercellular cement substance (ICS) of IgG and complement 3c, while IgA and IgM were negative. Indirect immunofluorescence, using normal human skin as substrate, showed an intercellular signal confined to the ICS with a titre of 1 : 360. Enzyme-linked immunosorbent assay gave a value of 54 U mL\(^{-1}\) for Dsg1 (normal 0–14) and a value of 162 U mL\(^{-1}\) for Dsg3 (normal 0–14), confirming a diagnosis of pemphigus vulgaris.

PNP was suspected due to the severe and polymorphic mucocutaneous involvement, in particular of the conjunctiva and labial mucosa, which resembled erythema multiforme-like lesions. Routine haematological tests, serum tumour markers [\(\beta_2\)-microglobulin, prostate-specific antigen (PSA), alpha-fetoprotein, carcinoembryonic antigen, Ca 19-9, Ca 72-4, Ca 125, acid phosphatase, Bence-Jones proteinuria], chest X-ray, echocardiogram, colonoscopy and oesophagogastroduodenoscopy were negative except for microhaematuria and an elevated level of PSA (49·1 ng mL\(^{-1}\); normal 0–4). A total body computed tomography (CT) scan revealed enlargement of the prostate, while bone scintigraphy revealed multiple foci of increased uptake (L2–L3, D8–D10). An ultrasound-guided needle biopsy of the prostate revealed a diffuse infiltration of adenocarcinoma. The prostate cancer grading (Gleason scale) was 8 (4 + 4). Immunohistological analysis revealed the presence of antibodies to 250-, 210-, 190-, 160- and 130-kDa proteins (Fig. 2). So, in line with the criteria previously proposed, a diagnosis of PNP was confirmed. Investigations by an internist and an otorhinolaryngologist were negative. High-resolution CT scan and tests for pulmonary function ruled out bronchiolitis obliterans.

The patient received conventional immunosuppressive therapy (CIST) comprising prednisone 100 mg daily and azathioprine 150 mg daily, and, at the same time, was referred to a nearby urological unit where he received combined androgen blockade (CAB) therapy comprising bicalutamide 150 mg and tamoxifin chlorohydrate 0·4 mg daily, goserelin acetate 10·8 mg every 75 days, alendronic acid 70 mg once weekly, and calcium carbonate/cholecalciferol 500 mg/440 IU every other day.

After 6 months, he was in complete clinical (Fig. 1d–f) and immunological remission on therapy (prednisone 50 mg twice weekly and azathioprine 50 mg daily), although still taking CAB, alendronic acid and calcium carbonate/cholecalciferol. The PSA level was 0·446 ng mL\(^{-1}\) and bone scintigraphy revealed only two foci with weak hypercaptaion (areas of increased uptake).

It has been postulated that the autoimmune response in PNP may be twofold: (i) humoral, via cross-reaction of foreign tumour antigens to epidermal antigens, or production of plakin proteins induced by the tumour, or an epitope spreading phenomenon, and (ii) cell mediated, via activation of CD8+ cytotoxic T lymphocytes, CD56+ natural killer...