

Extensive Darier disease accompanied by pterygium and scoliosis in a patient with a start codon mutation of the *ATP2A2* gene

Dear Editor,

Darier disease (OMIM 124200) is an inherited skin condition characterised by malodorous keratotic papules, primarily affecting the seborrheic areas on the upper trunk and scalp.¹ Mutations in the *ATP2A2* gene are identified as the causative factors for Darier disease.¹ Darier Disease is thought to be associated with extracutaneous conditions such as diabetes, heart failure and neuropsychiatric disorders.^{1,2} Here, we report a case of a severe Darier disease with pterygium and scoliosis, potentially linked to a start codon mutation in *ATP2A2*.

A 30-year-old Chinese man presented with generalised pruritic eruptions persisting for 16 years. These lesions

initially developed on his scalp at the age of 14, progressively involving the face, trunk and extremities. He had a history of recurrent bacterial infections and suicidal behaviour. On examination, multiple erythematous and hyperpigmented warty papules and plaques were widely distributed on the body, predominantly on the scalp, face, trunk and extensors of all the limbs [Figures 1a, 1b and 1c]. Nail and oral mucosa were unremarkable. Anterior segment photography unveiled the presence of blepharitis and pterygium in both eyes, and corneal epithelial defects were observed under corneal fluorescein staining [Figure 1d]. X-ray of the spine revealed significant scoliosis [Figure 2]. Importantly, he reported no history of long-term weight-bearing or trauma, common risk factors for scoliosis, suggesting an atypical aetiology in this



Figure 1a: Widespread warty papules predominantly involving the trunk.

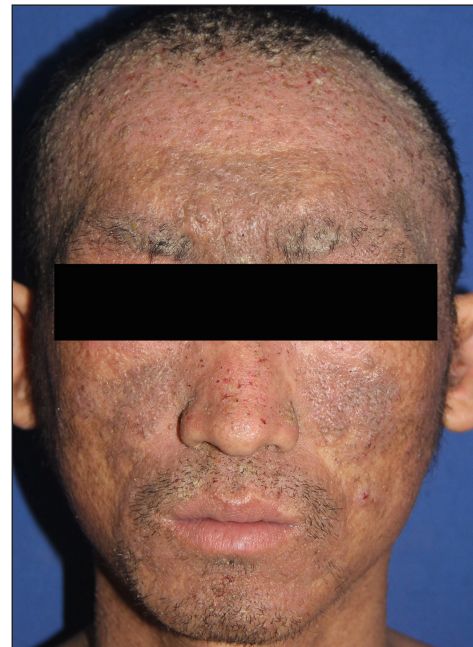


Figure 1b: Numerous greasy papules and plaques with crusts, as well as scars on the scalp and face.

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Figure 1c: Lesions involving the extensor surfaces of the extremities.

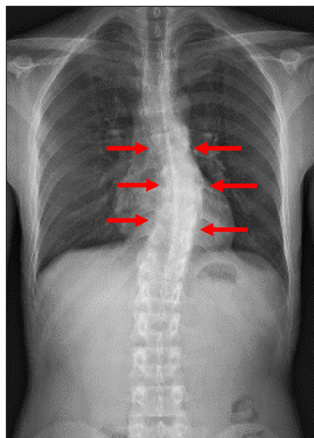


Figure 2: Spinal X-ray revealing significant scoliosis (red arrows).

case. Histopathological study indicated papillated epidermal hyperplasia, acantholytic cleft formation and dyskeratotic cells in the epidermis [Figures 3a and 3b], leading to a diagnosis of Darier disease.

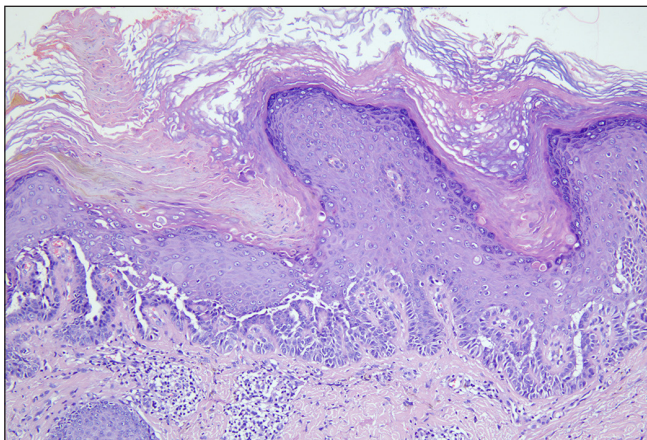


Figure 3a: Papillated epidermal hyperplasia, along with acantholytic cleft formation (Haematoxylin and eosin, 100x).

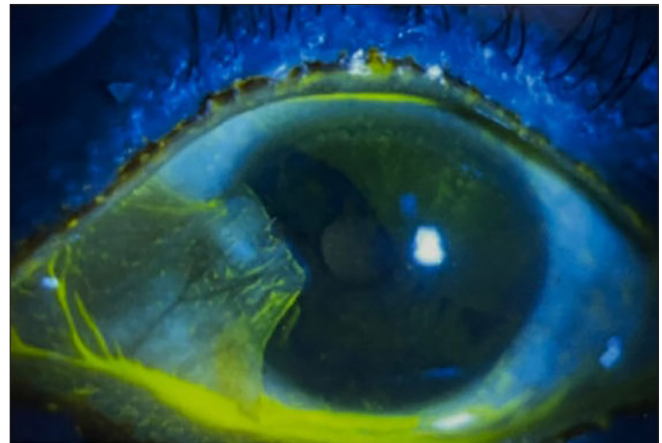


Figure 1d: Noteworthy pterygium and corneal epithelial defects observed under corneal fluorescein staining.

Genomic DNA isolated from the proband and parents revealed a recurrent heterozygous mutation (c.1A>G, p.Met1Val) in *ATP2A2*, confirmed by Sanger sequencing. This mutation was absent in his unaffected parents [Figure S1]. No pathogenic mutations associated with scoliosis were identified.

ATP2A2 encodes sarcoendoplasmic reticulum Ca²⁺-ATPase isoform 2 (SERCA2), which transports Ca²⁺ back into the lumen of the endoplasmic reticulum from the cytosol.¹ Therefore, inherited defects in *ATP2A2* occurring in Darier disease may lead to impaired regulation of the intracellular calcium signalling. Haploinsufficiency, resulting from the presence of a dysfunctional allele, is acknowledged as the molecular mechanism underpinning Darier disease.^{1,2} Although more than 200 *ATP2A2* mutations have been documented to be associated with Darier disease, no precise genotype–phenotype correlation has been recognised to date.^{1,2}

In this case, we describe a severe form of Darier disease with an *ATP2A2* c.1A>G mutation. Interestingly, two previous reported Darier disease cases with start codon mutation also presented with widespread severe lesions.^{3,4} This indicates that start codon mutations may contribute to

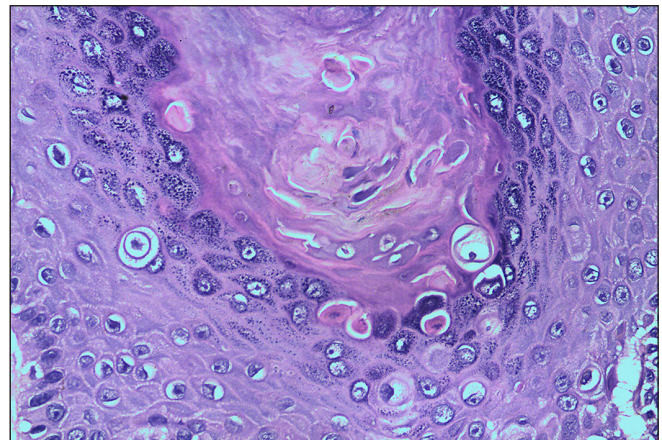


Figure 3b: The presence of dyskeratotic cells (Haematoxylin and eosin, 400x).

a complete haplo-insufficiency, potentially explaining severe phenotypes.

In addition to classical features, our case also presented with pterygium and scoliosis. To the best of our knowledge, these features have not been reported in Darier disease.^{1,2} Ophthalmic involvement in Darier disease may not be uncommon, with a survey reporting 39% of patients experiencing eye problems, predominantly manifesting as blepharitis and dry eye disease.⁵ Pterygium is an ocular surface disorder presenting as a raised, wedge-shaped lesion with potential implications for vision. In our case, potential mechanisms contributing to pterygium may include chronic inflammation affecting the ocular surface epithelium and the crusting of skin lesions, which could obstruct the Meibomian gland and disrupt its normal functioning.

Skeletal changes are rarely documented in Darier disease. Bone cysts and developmental retardation were found in a few cases.^{6,7} The aetiology of scoliosis in Darier disease remains elusive, potentially involving a spectrum of genetic and environmental factors. In our case, no known scoliosis-related mutations were found, and the patient's history lacked known risk factors. This suggests a possible link with SERCA2's role in calcium homeostasis affecting osteoclast survival in the skeleton, which may contribute to scoliosis.^{6,7} However, further experiments are needed to verify this hypothesis.

In conclusion, we identified a start codon variant in the *ATP2A2* gene in this case with severe Darier disease. Our case highlights the importance of ophthalmologic and orthopaedic evaluation in Darier disease patients. The potential associations of *ATP2A2* mutations with scoliosis and pterygium warrant further investigation.

Ethical approval

The research/study was approved by the Institutional Review Board at the Biomedical Ethics Committee, West China Hospital, Sichuan University, number 2021Y-Approval-11, dated 2021/1/11.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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