recovery of CD4+ T-cells by highly active antiretroviral therapy (HAART) in human immunodeficiency virus (HIV) patients. Recently, a similar concept, which implies that discontinuation or abrupt tapering of systemic corticosteroids and/or immunosuppressants increases the risk of opportunistic infection in non-HIV patients, has been proposed.\textsuperscript{4,5} DIHS is suggested to be a manifestation of the newly reported IRS.\textsuperscript{4} Kano et al. reported that three out of 28 patients with DIHS in their institute developed herpes zoster within 6 months after resolution.\textsuperscript{6} They speculate that the administration of systemic corticosteroids may alter the pathomechanisms of DIHS and lead to the later occurrence of herpes zoster. Herpes zoster usually occurs 2–3 months after the resolution of DIHS and is often associated with the reduction of corticosteroids. In contrast, it is unlikely that treatment with systemic corticosteroids was associated with the reactivation of VZV, because such treatment was not performed in the present case. The causative drugs of DIHS have immunosuppressive properties,\textsuperscript{4} and it was reported that a decrease in immunoglobulin levels and B-cell counts was induced by such drugs,\textsuperscript{7} which may primarily contribute to the reactivation of VZV. In contrast, CD4+ T-cell numbers initially increase, which subsequently decrease coincident with clinical outcome. Unfortunately, we could not examine CD4 T-cell counts during the course. Moreover, dysfunction of regulatory T cells at the resolution phase contributes to opportunistic infection,\textsuperscript{8} which also may have played an important role in VZV reactivation in the present case.

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References

Skin fragility, woolly hair syndrome with a desmoplakin mutation – a case from India

We report a case of skin fragility woolly hair syndrome (SFWH; OMIM 607655), an autosomal recessive disorder caused by mutations in desmoplakin (DSP).

A 23-year-old woman born of third degree consanguineous marriage from south India presented with short curly hair and thickening of nails since birth. She complained of recurrent blisters with secondary infection from infancy. The skin blistering occurred more during the summer season and frequently over the feet. She had observed that the degree of blistering had reduced with age. There were no symptoms suggestive of cardiac involvement. There was a family history of a similar skin condition in her 12-year-old nephew (own sister’s son). No other family members were affected. At presentation, she had coarse woolly hair with few erosions on the scalp, crusted erosions over the infranasal region, blisters on the dorsa of toes, and hyperkeratotic papules all over the body (Figs. 1 and 2a). There was diffuse thickening of the palms with focal hyperkeratosis over the thenar and volar aspects of metacarpophalangeal joints and diffuse thickening of the soles with a bulla over the dorsum of the first toe. There was thickening of nail plates of the left first, second, and third fingernails and all the toenails (Figs. 2a and b).

Clinical differential diagnoses considered were Naxos disease (due to plakoglobin mutations) and Carvajal syndrome (due to desmoplakin mutations), both having woolly hair, palmoplantar keratoderma, and cardiomyopathy. Pachyonychia congenita, a keratin disorder, was also considered in view of thickened nail plate, keratoderma, and hyperkeratotic papules.

Her routine blood investigations were within normal limits. Her cardiac evaluation with electrocardiogram and echocardiogram were normal. Histopathological examination of the skin from the dorsa of feet adjacent to an erosion showed a prominent granular layer with intraepidermal clefting (Fig. 2c). Direct
DNA sequencing revealed a homozygous mutation, DSP p.Arg2366Cys; c.7096C>T, in exon 24. Her affected nephew was also homozygous for p.Arg2366Cys. His parents (whose mother is her unaffected sister) were both heterozygous carriers of the mutation.

Thus, a diagnosis of skin fragility woolly hair syndrome (SFWHS) was made based on the clinical features of recurrent blisters, woolly hair, palmoplantar keratoderma, and nail changes in the absence of cardiomyopathy, and genetic analysis identifying a homozygous mutation in desmoplakin.

SFWHS caused by DSP mutations is a rare autosomal recessive disorder. The complexity of the structure of desmosomes and the large number of proteins involved partly explain the genetic and clinical heterogeneity of desmosomal disorders.

Desmoplakin is a large desmosomal plaque protein that belongs to the plakin family of cytoskeletal linker proteins that is expressed in many tissues including skin. There are three alternative splice variants, DSP-I, DSP-II, and DSP-Ia; DSP-II and DSP-Ia both have a shorter central rod domain than DSP-I due to differing sizes of exon 23. Desmoplakin-I is the major...
isoform expressed in heart tissue. DSP-II is reportedly absent/present at very low levels in the heart and simple epithelia but plays a more significant role than DSP-I in maintaining robust adhesion in keratinocytes. Desmoplakin-Ia is evident in both heart and skin but at considerably lower levels than DSP-I and DSP-II.4

The p.Arg2366Cys mutation in exon 24 is present in all isoforms of DSP. It is within the carboxy B domain of the inner desmosomal plaque region at the C-terminal of DSP. The C-terminal region of DSP is involved in interactions with intermediate filament proteins, and it is predicted this missense mutation will alter the tertiary structure of the carboxy domain and interfere with binding of DSP to keratin filaments.3

The clinical heterogeneity demonstrated by DSP mutations is due to the position and type of mutation together with different expression and functional properties of the DSP isoforms, particularly in the heart.5 Mutations in DSP are associated with several distinct clinical phenotypes affecting skin, nails, hair, and/or heart which are inherited as either autosomal recessive or dominant traits. Autosomal recessive forms include SFWSH, Carvajal syndrome, and lethal acantholytic epidermolysis bullosa. Autosomal dominant disorders include arrhythmogenic right ventricular dysplasia and keratoderma palmoplantaris striata II.1

SFWSH caused by mutations in DSP presents with woolly hair with varying degree of alopecia, recurrent blisters especially during summertime, palmoplantar keratoderma, and nail dystrophy.1,3,5 Reportedly there is absence of cardiomyopathy, but with only a small number of cases reported, it is wise to monitor patients regularly. Genetic testing confirms both the clinical diagnosis and mode of inheritance, which is important to determine the risk for future offspring. Interestingly, of the four cases described in the literature with SFWSHS, due to DSP mutations, three have mutations at p.Arg2366; two are compound heterozygotes where one mutation is p.Arg2366Cys,3,5 and the third case is homozygous for p.Arg2366His.1 The family reported here has a similar phenotype, and affected individuals are homozygous for p.Arg2366Cys.

Skin fragility syndrome can also be caused by mutations in plakophilin 1 where individuals present with widespread superficial scaling and erosions on the face, lips, palms, and soles as well as absence of eyebrows, eyelashes, and scalp hair.6,7 Hence, genetic analysis including desmoplakin, plakophilin, and plakoglobin should be considered for individuals with complex symptoms of skin fragility, woolly hair/hypotrichosis, palmoplantar keratoderma, follicular hyperkeratosis, and nail dystrophy to confirm the clinical diagnosis.8

Skin fragility woolly hair syndrome is an autosomal recessive disorder of DSP with no cardiac involvement; this is the first case with a DSP gene mutation reported from India.

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