Case Report

Keratolytic Winter Erythema: a misdiagnosed palmoplantar dermatosis

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INTRODUCTION

Keratolytic winter erythema is a rare genetic disorder of keratinization, characterized by palmoplantar erythema and recurrent skin peeling, originally described as Erythrokeratolysis Hiemalis in 1977. It is a dermatological rarity, frequently underdiagnosed and hence under reported. An interesting feature is its exacerbation ascribed to specific environmental and physiological triggers, for example, that it is worse in the winter months, hence its name. Other triggers include febrile illness, surgery, stress and menstruation. It is an autosomal dominant disorder with variable penetrance and linkage to chromosome 8p22-23 but cases that did not show linkage to chromosome 8p22-23 have been reported, suggesting genetic heterogeneity. Until now, no pathogenic mutations have been found in candidate genes within the disease region, cathepsin B (CTSB) and farnesyl-diphosphate farnesyltransferase-1 (FDFT1). The mutation, in fact, is not in a gene or coding sequence, but an intergenic region upstream of Cathepsin B (CTSB). It is a segmental duplication that includes an enhancer element that is active in keratinocyte development. In the presence of the duplication, CTSB gene expression is elevated in the stratum granulosum of affected individuals. It is therefore believed that the duplication of the non-coding enhancer element is the cause of the upregulation of cathepsin B and is likely modulated by specific environmental and physiological triggers. We report the case of an 18-year-old female with recurrent palmoplantar erythema and skin peeling with winter exacerbation.

CASE REPORT

An 18 years old female presented with complaints of asymptomatic redness of palms and soles associated with intermittent scaling and peeling of palmoplantar skin which started when she was 14 years old, described as episodes of hyperhidrosis followed by development of red base over skin of palms, soles.
and interdigital spaces. The episodes specifically exacerbated during cold and dry weather with near total remission in non-winter months.

The cycles repeated every 15 days. There was no history of any similar lesions elsewhere in extremities or anywhere over body. There was no history of exacerbation with menstruation, emotional stress or physical illness. The girl was born of a non-consanguineous marriage. Similar complaints were reported in her brother. No other family members were affected. No ancestors from the endemic region were traced. There was no history of itching, oozing, exacerbation with wet work, fluid filled vesicles. The patient was able to perform her daily activities with no restriction. On examination, she had diffused macular erythema over bilateral palms and soles associated with fine peeling of skin in few areas over lateral border of bilateral soles and interdigital skin of hands and feet (Figure 1 and 2). Hyperhidrosis was evident on palms. Rubbing of normal appearing skin caused easy and superficial peeling with no bleeding, oozing or underlying erythema. Mucous membranes were uninvolved. Teeth and nails appeared normal.

General and systemic examination revealed no abnormality. Routine hemogram and urine analysis were normal. Mutational analysis could not be done due to cost issues. Biopsy from erythematous patch from right foot showed mild epidermal hyperplasia with compact stratum corneum with preserved granular layer and focal spongiosis mild epidermal along sparse superficial perivascular inflammatory infiltrate.

Figure 1: (A) Diffuse macular erythema on both arms; (B) Preceding generalized hyperhidrosis.

Figure 2: Fine peeling of skin over lateral border of bilateral soles and interdigital skin of hands and feet that tends to arrest at skin creases.

Few scattered eosinophils were also present in upper dermis. (Figure 3-5). Based on clinic-histopathologic correlation, diagnosis of keratolytic winter erythema was made. She was treated with emollients and topical coal tar, educated about her disease and counselled to avoid exacerbating factors and wear gloves, with significant improvement in lesions within a week.

Figure 3: H and E 4X magnification shows compact stratum corneum with mild epidermal hyperplasia and sparse superficial perivascular inflammatory infiltrate.

Figure 4: H and E 4X magnification showing mild focal spongiosis.
The mutation was found to be in an intergenic region between CTSB and DPP12, suggesting that the genetic alteration has been traced back to a single founder, the mariner François Renier Duminy (born 1747 in France), who in later life settled in the Cape of Good Hope, leaving many descendants with KWE now living in South Africa. Cases have since been identified in several other countries.3

It is an autosomal dominant disorder with variable penetrance, therefore a family history of affected first degree relatives is significant, as in this case, though the level of clinical involvement may vary from person to person, even within a single family. The search for the genetic mutation started from the localisation of the genetic position of the trait to chromosome 8p23.1–p22. The mutation was found to be in an intergenic region upstream of cathepsin B (CTSB). It is a segmental duplication that includes an enhancer element that is active in keratinocyte development. There are two different duplications, one found in South African families (a 7.67-kb duplication) and the other in Norwegian families (a 15.93-kb duplication). In the presence of the duplication, CTSB gene expression is elevated in the stratum granulosum of affected individuals. A Norwegian family with four affected members did not show linkage to chromosome 8p22–p23, suggesting genetic heterogeneity.3 A striking feature is the element of exacerbation to specific environmental and physiological triggers, although these remain poorly understood. A frequent precipitant is cold dry weather, hence the seasonal variation, though it may be perennial in temperate climates. Other triggers include febrile illness, surgery, physical or emotional stress and menstruation. There is often an improvement in the condition during pregnancy and beyond the age of 30 years.3

It is therefore understood that the duplication of the non-coding enhancer element is the cause of the upregulation of cathepsin B and is likely modulated by specific environmental and physiological triggers.

The onset may be at any age from infancy to early adult life but it is not usually present at birth. The condition usually manifests in the first 5 years of life, with the most severely affected individuals already showing signs of the condition during infancy.3 It is thought to affect males and females equally. Cyclical centrifugal peeling at several sites on the palms and soles is a constant feature, and may spread to the dorsal hands and feet, and the interdigital spaces. The peeling is multifocal but tends to become arrested at the skin creases.3 Episodes may be preceded by itch and hyperhidrosis and sometimes preceded by erythema multiforme-like papules. Palmoplantar erythema develops in 80-99% affected cases, and is followed by the evolution of painless superficial opaque dry blebs, which peel or can be pulled away, leaving a red base with intact markings. Lesions may be associated with pustulation and hyperhidrosis in 5-29% cases. A second wave may begin at the centre of a lesion, resulting in gyrate and polycyclic annular erythema, which eventually resolves. The most severe cases have a history of onset in infancy, show year-round persistence of lesions and/or extension of the disease process onto the dorsal aspects of the hands and feet. Cycles repeat every few weeks and the palms and soles appear normal between attacks. Involvement of the lower legs and knees is sometimes seen. Buttock or thigh lesions, however, are relatively uncommon.3 Truncal lesions have been reported in one patient, and facial involvement in another. Most patients experience only mild discomfort, although associated palmoplantar sweating and a pungent odour are frequently encountered.

Differential diagnosis includes familial Peeling Skin Syndromes, annular erythema, erythema multiforme, Hailey–Hailey disease, erythrokeratoderma, epidermolysis bullosa simplex of hands and feet (Weber–Cockayne) and keratolysis exfoliativa. The condition is often misdiagnosed as Keratolysis exfoliativa, but presence of a relevant family history, winter exacerbation and preceding hyperhidrosis with interdigital involvement differentiate it from the former. A similar phenotype affecting the palms, more active in summertime, was reported in two siblings (British) who had atypical autosomal recessive erythropoietic protoporphyria.

Biopsy of the advancing edge of a lesion shows hyperplasia, spongiosis and, in the upper stratum

Figure 4: H and E 4X magnification showing compact stratum corneum with preserved granular layer and focal area of spongiosis with few scattered eosinophils in upper dermis.

DISCUSSION

Keratolytic Winter Erythema (Erythrokeratolysis hiemalis, Oudtshoorn disease) is a rare genetic disorder of keratinization, characterized by palmoplantar erythema and recurrent intermittent skin peeling at palms and soles, originally described in 1977. It is an orphan disease rarely seen and not always diagnosed.3 Seasonal manifestation in winter-time and a characteristic multi-form histology distinguish this dermatosis from other childhood scaling erythemas.2

It originated in South Africa among White and Coloured (or admixed) communities. The incidence in this population is 1/7000. It has been observed in at least 35 South African families of European descent originating from the Oudtshoorn district of Cape Provence. The genetic alteration has been traced back to a single founder, the mariner François Renier Duminy (born 1747 in France), who later in life settled in the Cape of Good Hope, leaving many descendants with KWE now living in South Africa. Cases have since been identified in several other countries.3

A striking feature is the element of exacerbation to specific environmental and physiological triggers, although these remain poorly understood. A frequent precipitant is cold dry weather, hence the seasonal variation, though it may be perennial in temperate climates. Other triggers include febrile illness, surgery, physical or emotional stress and menstruation. There is often an improvement in the condition during pregnancy and beyond the age of 30 years.3

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Biopsy of the advancing edge of a lesion shows hyperplasia, spongiosis and, in the upper stratum
spinosum, keratinocytes with pale cytoplasm, perinuclear vacuolization and pycnotic nuclei. Skin histology in a few cases was non-specific. There is a minimal inflammatory reaction, with only occasional lymphocytes observed in the superficial dermis. Therapy is symptomatic and focuses on diminishing the build-up of skin (hyperkeratosis). Bland emollients can be used. Urea and tar compounds, antiperspirants, oral retinoids and photodynamic therapy have been tried without much success. In our case, topical tar produced significant improvement in lesions. Topical keratolytics, retinoids and steroids may aggravate the condition. Topical calcipotriol might have minimal effect. Patients should be reminded that the disease may be aggravated by stress, a cold environment, or after a febrile illness and it would be best to avoid these conditions. Avoiding mechanical irritation of the skin can be beneficial. Genetic counseling is warranted.

**CONCLUSION**

Keratolytic Winter Erythema is a rare palmoplantar dermatosis, often misdiagnosed as Keratolysis exfoliativa, but presence of a relevant family history, winter exacerbation and preceding hyperhidrosis with interdigital involvement differentiate it from the former. The case presented adds a humble contribution to the very few anecdotal cases worldwide.

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