

Case Report

A young man with generalised hyperkeratotic papules: a case of Darier's disease

滿佈角化丘疹的年輕男性患者：毛囊角化病一案例

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Darier's disease (Keratosis follicularis) is an uncommon autosomal dominant genodermatosis. Patients present with hyperkeratotic papules in seborrhoeic areas with nail abnormalities. We describe a young gentleman with this disorder for more than three years. A brief review of its clinical features and treatment is also made in this report.

毛囊角化病為不常見的常染色體顯性遺傳性皮膚病，特徵為皮脂腺旺盛皮區有角化丘疹及指甲有多種異常。本文記述一例年輕男性患者患有此病愈三年。此病的臨牀表現及其治療也予簡述。

Keywords: Autosomal dominant, Darier's disease, genodermatosis

關鍵詞：常染色體顯性，毛囊角化病，遺傳性皮膚病

Introduction

Darier's disease is an uncommon inherited skin condition characterised by loss of adhesion between epidermal cells (acantholysis) and abnormal keratinization. The defect lies in the *ATP2A2* gene which encodes the sarco/endoplasmic reticulum Ca²⁺ ATPase. Severely affected patients may present with diffuse,

malodourous, greasy hyperkeratotic follicular papules over the seborrhoeic areas while mild cases may go unrecognised. The following is a case report of a 20-year-old Chinese gentleman with a generalised and typical presentation of such condition.

Case report

The patient was a 20-year-old Chinese gentleman who enjoyed good past health. He developed brownish, firm skin eruptions on the face and chest since age 17; the condition was progressive and spread to his back and limbs. Besides slightly itchy, the lesions were asymptomatic. He never had any systemic upset. The skin lesions would worsen and became mildly itchy in summer time. They were

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not malodorous. He also noted that his nails were dry and brittle. The family history was unremarkable. On physical examination, diffuse brownish hyperkeratotic papules were found on the seborrhoeic areas (face, chest and upper

back) but less on the limbs. The palms and soles appeared normal; there was no punctate keratosis or pits. Oral mucosa was normal (Figures 1 & 2). Clinical differential diagnoses included Darier's disease (Keratosis follicularis),



Figure 1. Diffuse greasy hyperkeratotic papules on the chest.



Figure 2. A close-up view of the forehead of the patient. Note the monomorphic hyperkeratotic lesions with mainly follicular distribution.

severe seborrhoeic dermatitis, plane warts, epidermodysplasia verruciformis, acrokeratosis verruciformis of Hopf, confluent reticulate papillomatosis, phrynoderma, Hailey-Hailey disease, Grover's disease of the persistent type and other follicular keratosis such as keratosis pilaris.

A skin biopsy was performed which showed irregular acanthosis and focal parakeratosis; multifocal dyskeratosis resulting in the formation of corps ronds & grains. There was also suprabasal acantholysis with clefts. Moderate perivascular lymphocytic infiltrate was found in the upper reticular dermis. These features were consistent with Darier's disease. Thus, the final diagnosis in this patient was Darier's disease.

Topical 0.025% fluocinolone acetonide cream and emollient were given initially for symptomatic control. Adapalene (0.1%) gel was also tried for the large and unsightly lesions but without much success. As the patient was rather frustrated with the unappealing appearance of the skin condition, systemic isotretinoin (0.5 mg/kg/day) was prescribed. The lesions appeared reduce in size and no new lesions developed after about a month of the treatment. The patient tolerated the systemic retinoid well and experienced no systemic complication. Further reduction of isotretinoin was planned.

Discussion

Darier's Disease (DD) or Darier-White disease, also known as keratosis follicularis, is an uncommon autosomal dominantly inherited genodermatosis that is characterised by hyperkeratotic papules in seborrhoeic regions with various nail abnormalities. The disease was first reported independently by Darier and White in 1889. The prevalence of DD has been estimated to be 1 in 55,000 in central United Kingdom. However, local data is lacking. Although this is an inheritable disease, spontaneous mutation is common. One study showed that up to 47% of

patients did not have a clear family history as in our patient.¹

Darier's disease affects both sexes equally. The onset may range from four to 70 years of age. However, the majority of patients like our case, present in their first and second decades of lives. Pruritus is a common feature. Heat, humidity, stress, sunlight and UVB rays may exacerbate this condition. Even though the severity of DD fluctuates over time, it is a chronic unremitting condition. Our patient had exemplified the classical clinical features in DD: the lesions first appear as skin-coloured papules, which soon become yellowish-brown, greasy, and warty; they are especially common in the seborrhoeic areas and often show a follicular distribution. About 80% of the patients have mild flexural involvement e.g. groin, axillae or submammary skin in women. These flexural lesions are especially bothersome to the patients because of their malodour. Hands involvement is very common, but can be very subtle sometimes, which include punctate keratosis, palmar pits and occasionally, haemorrhagic macules. Nail changes provide very important diagnostic clue which include white and red longitudinal bands, longitudinal nail ridges, splits, and a V-shaped nick at the free margin of the nail. Whitish papules with central depression are infrequently seen on mucosal surfaces.

As far as the pathophysiology is concerned, DD resulted from a defective gene, ATP2A2, which is located in chromosomal region 12q23-24.1. Mutation of this gene causes functional disruptions in all domains of sarco/endoplasmic reticulum (SERCA2, the calcium pump) and results in reduction of ATP affinity; loss of calcium affinity; decreasing phosphorylation of ATP and Pi; blocking of dephosphorylation and uncoupling of calcium transport from ATP hydrolysis. These defects disturb the cytosolic calcium level and, ultimately, influence adhesion between keratinocytes and cellular differentiation in the epidermis.²

The diagnosis of DD relies on clinical as well as

histological features. Acantholysis and dyskeratosis are the two main features of DD. Corps ronds and grains just represent two types of dyskeratotic cells. Corps ronds are predominantly located in stratum spinosum and stratum granulosum. They are characterised by an irregular eccentric and sometimes pyknotic nucleus, a clear perinuclear halo and a brightly eosinophilic cytoplasm. While grains are mostly located in stratum corneum and they consist of oval cells with elongated cigar-shaped nuclei with abundant keratohyaline granules. There is also loss of epidermal adhesion with acantholysis, results in the formation of suprabasal clefts (lacunae). In most cases, including our patient, sufficient histological evidence can readily be obtained with light microscopy, thus further investigation is not necessary. But electron microscopy can be helpful in difficult situations. In electron microscopy, because of the dissolution of desmosomal plaque proteins, specifically, desmoplakin I and II, plakoglobin, and desmoglein, the deficiency in the tonofilament/desmosome attachment results in the formation of basal cell vacuolisation, decreased numbers of desmosomes on the lateral borders of basal cells, separation of tonofilaments from their insertions on the cell membrane, and tonofilaments in large, circular aggregates around the nucleus, leading to tonofilament clumping (perinuclear aggregates of keratin intermediate filaments).

Patients with DD are more susceptible to cutaneous infections with herpes simplex virus, poxvirus and bacteria. Rarely DD is associated with disorders such as retinitis pigmentosa, bone cysts, renal agenesis, testicular agenesis, autoimmune thyroid disease and neuropsychiatric abnormalities (mood disorders, epilepsy and mental retardation). The mortality rate among DD patients is no greater than that of the general population. In fact, one-third of the patients improve with age; although, another one-third may deteriorate. Psychosocial consequences from the appearance of the lesions constitute the major morbidity of DD.

As general measures, patients with DD are recommended to use high protective factor sunscreens and to stay away from strong sunlight as much as possible. It is wise to keep cool and wearing cotton underwear. Treatment of superimposed infection is mandatory to prevent further complication and the development of malodour. Topical steroid and emollient are adequate for mild form. In general, topical retinoid is ineffective and irritating. Although tazarotene, a third generation retinoid, showed promising result, more clinical data is needed before it can be recommended as a standard treatment.³ Oral retinoids (both acitretin and isotretinoin) are the most effective medical treatment for DD. They work by affecting epidermal proliferation and differentiation. In one multicentre study, isotretinoin for four weeks resulted in symptomatic improvement in 70% of the patients; and 95% after 16 weeks of treatment.⁴ Our patient's response to isotretinoin seemed to concur with this finding. However, after the treatment was stopped, most of the symptoms worsened. Since prolonged remissions are not seen in DD, more chronic treatment with oral retinoids may be needed. Surgical treatment, including laser therapy, is mainly indicated for hypertrophic forms and localised plaques unresponsive to other treatments.⁵

References

1. Burge SM, Wilkinson JD. Darier-White disease: a review of the clinical features in 163 patients. *J Am Acad Dermatol* 1992;27:40-50.
2. Sakuntabhai A, Ruiz-Perez V, Carter S, Jacobsen N, Burge S, Monk S, et al. Mutations in ATP2A2, encoding a Ca²⁺ pump, cause Darier disease. *Nat Genet* 1999; 21:271-7.
3. Burkhart CG, Burkhart CN. Tazarotene gel for Darier's disease. *J Am Acad Dermatol* 1998;38(6 Pt 1):1001-2.
4. Dicken CH, Bauer EA, Hazen PG, Krueger GG, Marks JG Jr, McGuire JS, et al. Isotretinoin treatment of Darier's disease. *J Am Acad Dermatol* 1982;6(4 Pt 2 Suppl):721-6.
5. Wheeland RG, Gilmore WA. The surgical treatment of hypertrophic Darier's disease. *J Dermatol Surg Oncol* 1985;11:420-3.