A Woman with Acantholytic Disease

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CASE SUMMARY

History

A 42-year-old woman had gradual onset of asymptomatic brown papules over upper chest, shoulder and neck for one year. The number of papules increased and extended to abdomen. The main exacerbating factors were sunlight and menstruation, and less often heat and sweating. There was no oral mucosal lesion, malodor or psychiatric symptom.

Her past health was good. Her family members, including her 12- and 18-year-old children, were apparently not affected.

Physical examination

There were multiple, discrete 2-3 mm keratotic brown papules over anterior trunk, shoulder and neck. They were more concentrated at abdomen (Figures 1 and 2). Palmar pits were present. Oral mucosa was normal. There was no significant nail change except mild onycholysis on left ring and little finger nails.

Investigations

Skin biopsy on right shoulder (Figures 3 and 4) showed focal area of suprabasal acantholysis, mild hyperkeratosis and occasional corps ronds at upper epidermis. There was mild perivascular mononuclear infiltrate in upper dermis. The histological features were consistent with Darier's disease.

Skin swab for culture gave heavy mixed growth of Acinetobacter species, Moraxella species, *Staphyloccous aureus* and *Enterobacter gergoviae*. Herpes culture was negative.

Diagnosis

The diagnosis is Darier's disease.

Management

She was given a course of erythromycin, topical emollient and mildly potent topical steroid. Despite these treatment there was increased extension of the disease. Topical tretinoin was then prescribed, and the patient noted significant improvement with flattening

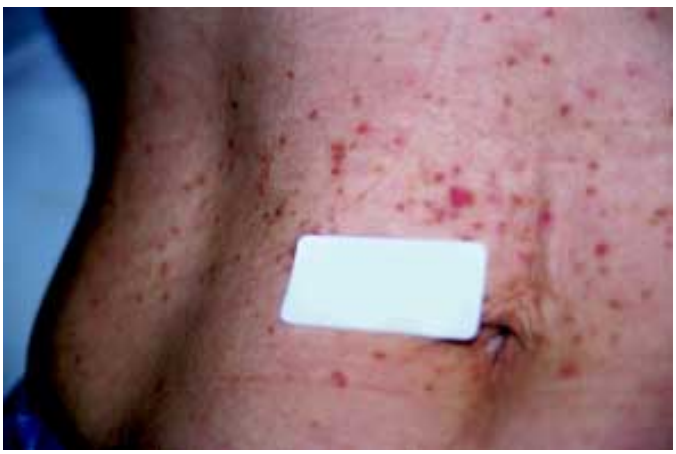

Figure 1: Discrete brown keratotic papules on abdomen

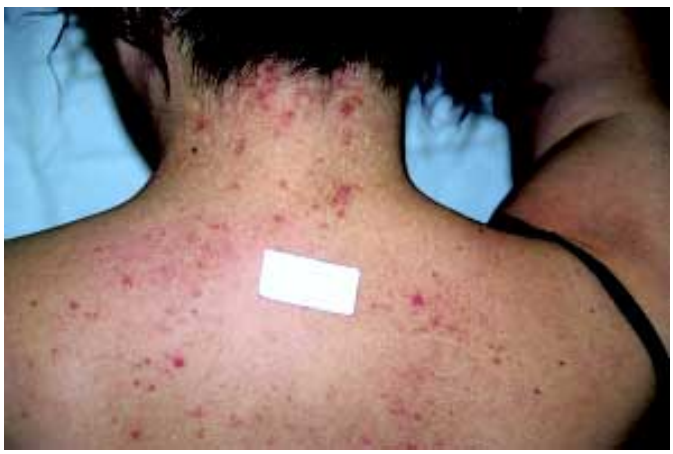

Figure 2: Discrete brown keratotic papules on upper back

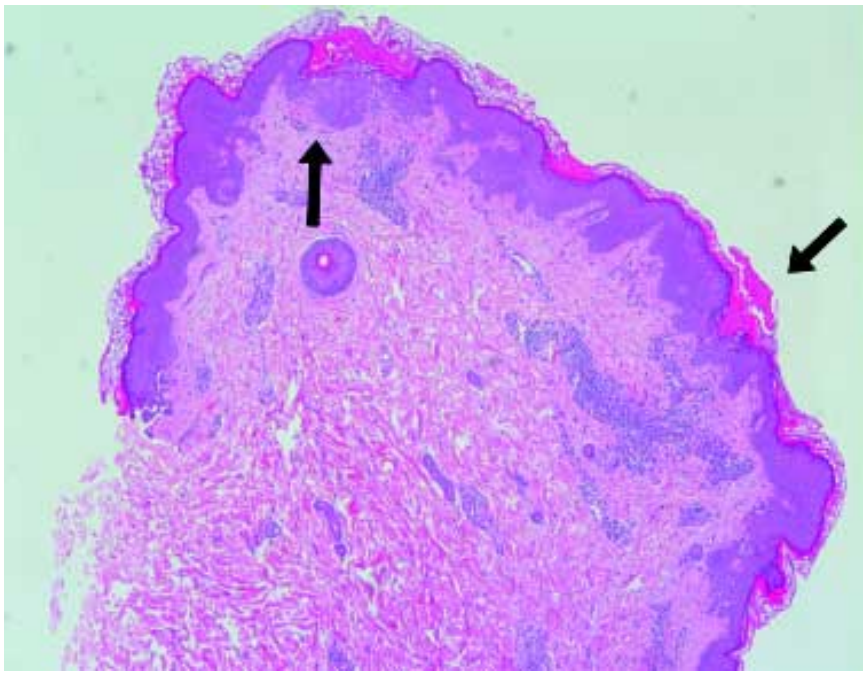

Figure 3: Low power picture showing superficial perivascular lymphocytic infiltrate with two discrete foci of acantholytic dyskeratosis (arrows). (By courtesy of Dr. K. C. Lee, Department of Pathology, PMH)

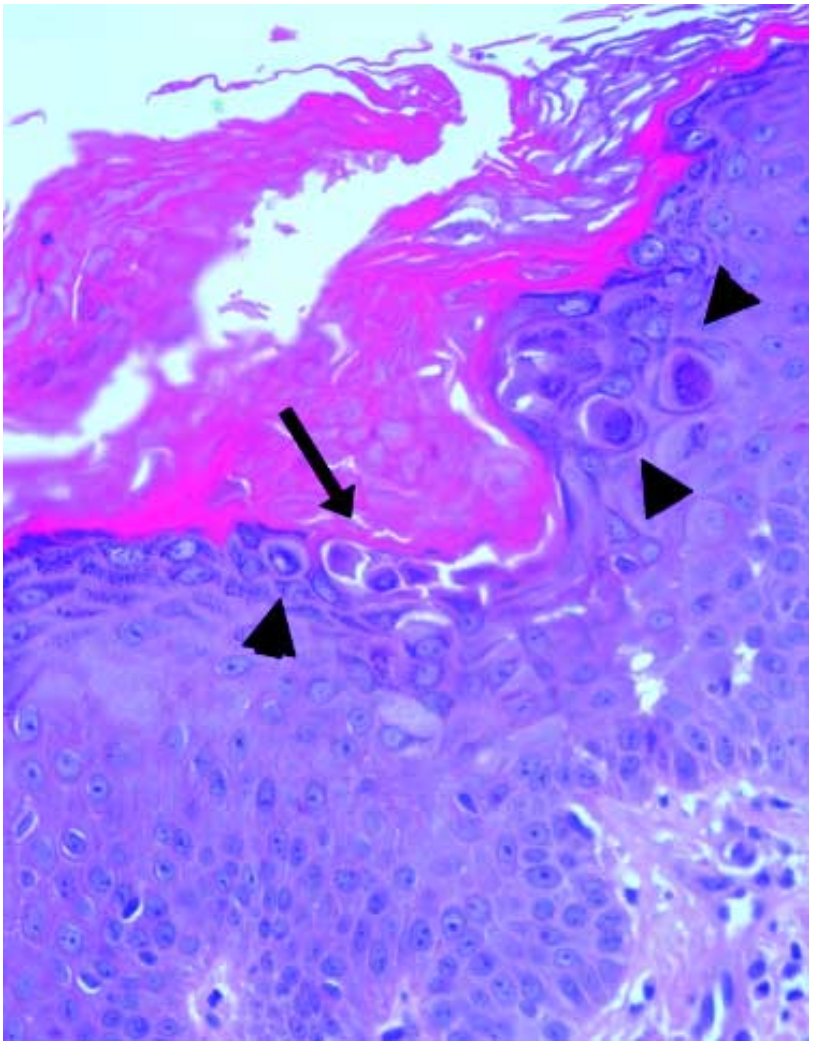

Figure 4: High power view showing prominent suprabasal acantholysis in association with dyskeratotic cells - the corps ronds (arrow heads) and grains (arrow), hypergranulosis, and hyperkeratosis. (By courtesy of Dr. K. C. Lee, Department of Pathology, PMH)

of the papules after two months' treatment. Thorough family screening was planned.

REVIEW ON DARIER'S DISEASE

Darier's disease is an uncommon hereditary acantholytic disease with an autosomal dominant inheritance.[1] The prevalence ranged from 1:55,000 to 1:100,000.[2] A study of family pedigrees found that skip generation was unusual and hence it was deduced that the penetrance was complete.[3] However, there was significant phenotypic variation between and within each generation. Nevertheless, 47% of the patients are sporadic cases as a result of new mutations.[2]

Clinical features

Darier's disease typically has its onset in second decade. There are warty, brown itchy papules and plaques affecting seborrhoeic areas (face, scalp, trunk and groin). Seborrhoeic pattern is the commonest (92%).[2] The other less common pattern are flexural (6%), nevoid and hand.[2] Ninety percent of the patients has mild to moderate severity and male patients tend to have more severe outcome than female patients.[2]

Palm, nails and oral mucosal involvement are common. Palmar pits and nail changes often occur early and precede the appearance of rash. "Sandwich sign" of nails is pathognomonic and it consists of longitudinal red alternating with white line.[2] Other nail changes include nail fragility, free edge V-shaped notch, longitudinal ridging and split. Oral mucosal lesions consist of white keratotic papules on hard palate (sandpaper appearance), cobblestone lesions on buccal mucosa and fissuring of tongue.

The disease tends to persist lifelong with periods of exacerbation related to sweating, minor cutaneous trauma, ultraviolet light exposure and menstruation.

Complication and association

In most severe condition, the patient may suffer from social embarrassment as a result of extensive and vegetative lesions with malodor. Affected patients are prone to widespread cutaneous herpes simplex and bacterial infection. However, there is no specific immune defect found in these patients.[4] Increased prevalence of neuropsychiatric disorders such as manic-depressive illness, epilepsy, mental retardation and schizophrenia was found.[1] It is possible that different gene mutations leading to Darier's disease and other psychiatric conditions might lie on the same chromosome. Furthermore, bone cyst, renal and testicular agenesis were rarely associated with Darier's disease.

Histology

The most distinguished histological feature of Darier's disease is acantholytic dyskeratosis.[5] Acantholysis is demonstrated as suprabasal cleft or rarely vesicular formation whereas dyskeratosis manifests as corps ronds and grains of Darier. Corps ronds are found in the granular layer. They have irregular eccentric and sometimes pyknotic nuclei, surrounded by a clear halo enclosed within a basophilic or eosinophilic "shell". There may be variable amount of highly irregular keratohyaline granules. Grains are located within the horny layer. They are flattened oval cells with elongated cigar-shaped nuclei and abundant keratohyaline granules.

Comparison with other acantholytic diseases

There are four groups of acantholytic disorders: autoimmune, hereditary, non-hereditary non-immunological and epidermal tumors with acantholysis (Table 1).[6]

Pemphigus is an autoimmune disease whereas the hereditary acantholytic diseases, namely Darier's disease and Hailey-Hailey disease, are inherited in an autosomal dominant fashion. The gene location of Darier's disease (chromosome 12q23-24.1) was mapped at different region from Hailey-Hailey disease (chromosome 3q21-24).[7] Grover's disease is a non-hereditary, non-immunological disorder and its pathogenesis is not fully understood.

There are also various distinguishing features in the clinical manifestations and histology among Darier's disease, Hailey-Hailey disease and pemphigus vulgaris, as shown in Table 2.

Pathogenesis

Keratinocyte adhesion is mediated by three major

Table 1. Types of acantholytic diseases

Groups	Diseases	Examples
Group 1	Autoimmune disease	Pemphigus group
Group 2	Hereditary disease	Darier's disease, Hailey-Hailey disease
Group 3	Non-hereditary and non-immunological disease	Grover's disease
Group 4	Epidermal tumours with acantholysis	adenoid squamous cell carcinoma, acantholytic actinic keratinosis

Table 2. Comparison of acantholytic diseases

	Non-autoimmune, hereditary		Autoimmune
Diseases	**Darier's disease**	**Hailey-Hailey disease**	**Pemphigus vulgaris/foliaceus**
Inheritance	AD	AD	--
Gene mapping	12q 23-24.1	3q 21-24	--
Age of onset	2nd decade	2nd to 4th decade	40-60
Site of lesions	mostly seborrheic	flexural	generalized or local
Clinical features			
1. Cutaneous features	greasy keratotic papules with crusting	blisters, erosions on erythematous base	blisters, erosions on erythematous base
2. Oral mucosa	+	--	+
3. Nail	+	+/-	--
Histology			
Site of cleft	suprabasal	intraepithelial	intraepithelial
Adjacent epithelium	intact	disintegrating	intact
Corps ronds/grain	+	rarely	--
Dermal infiltrate	mononuclear	mononuclear	mononuclear, eosinophils
Immuno-fluorescence	--	--	+
Pathogenesis			
Immuno-electro-microscopy	In acantholytic cells, intracellular (desmoplakin I/II, plakoglobin) and extracellular (desmoglein) portion of desmosomes dissolve into cytoplasm. Adherens junctions (E cadherin, *b* catenin) are partly dissolved. *These abnormalities are found in lesional and less severely in peri-lesional skin.*		In acantholytic cells, dissolution of desmoplakin and plakoglobin does not occur but there is partial or total dissolution of desmogleins. *No abnormality is found in peri-lesional skin.*

types of adhesive and communicative structures: desmosome (desmoglein, desmoplakin I/II, plakoglobin), adherens junction (plakoglobin, E cadherin, *b* catenin, vinculin) and gap junction. Acantholysis occurs as a result of breakdown of desmosome-keratin filament complexes between keratinocytes. Furthermore, desmosome may function as an attachment sites for tonofilament orientation which is important for keratinization.

The mechanism of acantholysis in Darier's disease is similar to Hailey-Hailey disease but different from that of pemphigus vulgaris. In the hereditary types, immunoelectro-microscopic studies of the acantholytic cells demonstrate dissolution of major desmosomal components and partly adherens junctions, into the cytoplasm.[6,8] The immuno-staining density of desmosome is also decreased in peri-lesional area. This suggests that there is an initial genetically determined

instability of the desmosome-keratin filament complex which finally leads to acantholysis.

On the other hand, similar studies in pemphigus vulgaris only demonstrate partial or total dissolution of desmogleins into the cytoplasm.[6,8] The desmoplakin and plakoglobin portion of the desmosomes were intact. Such abnormality could only be demonstrated in lesional skin. This suggested that acantholysis occurs as a result of disruption of desmosomes after the binding of autoimmune antibodies.

Management

General measures include good personal hygiene, avoiding precipitating factors and treating associated cutaneous infection. Mild disease usually responds to the following topical therapies: antiseptic, antibiotic, emollients, keratolytics, corticosteroid and retinoid. Low dose systemic retinoid is often required in severe patients. Dermabrasion or carbon dioxide laser can be considered for recalcitrant hypertrophic type. Screening of family members to pick up early sign and genetic counseling is mandatory.

Learning points:
Pathogenesis differs in hereditary acantholytic diseases and autoimmune pemphigus.

Patients with Darier's disease are prone to widespread cutaneous herpes simplex and bacterial infection, and have increased prevalence of neuropsychiatric disorders.

References

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