*** no patient handout*

Darier disease in

Synopsis

Darier disease, also known as keratosis follicularis or Darier-White disease, is an autosomal dominantly inherited disease caused by mutations in the *ATP2A2* gene, which encodes a sarco / endoplasmic reticulum calcium-ATPase pump (SERCA2). Although disease penetrance is high, expression is variable, and sporadic mutations may occur. There is no sex predilection.

Darier disease presents in early adolescence to mid-adult life, with peak onset in the second decade of life. The disease manifests with greasy, hyperkeratotic papules in a seborrheic distribution, along with palmoplantar pits, acrokeratosis verruciformis-like papules, and characteristic nail findings (candy-cane nails). Leukodermic macules are a rarely reported finding. These small macules occur most frequently on the ventral aspect of limbs and trunk. Their onset is prior to puberty. They have been recognized and reported most frequently in individuals with darker skin phototypes.

In additional to cutaneous findings, 15%-50% of patients present with oral involvement, including cobblestoning of the oral mucosa, gingival hypertrophy, and sialadenitis. Esophageal involvement with erosions has been described. The severity of oral disease may parallel that of the cutaneous disease.

After onset, the disease is lifelong. It may be accentuated or only prominent in the spring and summer, when exposures to heat, perspiration, and ultraviolet (UV) light are increased. Other exacerbating conditions / factors may include trauma, menstruation, and certain drugs (eg, lithium, oral corticosteroids).

The lesions of Darier disease may be pruritic, painful, or malodorous. Along with the appearance, these symptoms may lead to significant psychosocial distress. Patients are at an increased risk of bacterial or viral skin infections.

Linear, segmental, or unilateral presentations are uncommon variants of the disease caused by mutations in the same gene.

For more information, see **OMIM**.

Codes

ICD10CM:
Q82.8 – Other specified congenital malformations of skin

SNOMEDCT:
48611009 – Darier's disease

Look For

Cutaneous findings – Small, symmetrical, skin-colored or yellow-brown papules, most frequently on the chest and face in a so-called "seborrheic distribution," including the scalp and the retroauricular folds. Intertriginous lesions are also seen. Pits may be seen on the palms and soles. Papules (usually 0.5-1.0 cm in size) can be crusted, eroded, or verrucous in texture. Lesions are frequently described as greasy.

Acrokeratosis verruciformis-like papules on the dorsal hands may be seen.

Leukodermic macules are hypopigmented, confetti-like, discrete and confluent 2-3 mm macules that are seen most frequently on the front of the thighs, the backs of the arms, and the anterior trunk, especially in individuals with darker skin phototypes.

Variant presentations include an acral hemorrhagic presentation with acral purpuric vesicles and a predominant intertriginous presentation with vegetating plaques in the groin folds. The segmental variant displays typical findings that follow Blaschko's lines. Rarely, lesions have a unilateral or herpes zoster-like distribution.

Nail findings – Nail plates are thin, with chips and cracks along the nail margin, and often have parallel white or red bands in the nail bed (candy-cane nails). A V-shaped notch in the free edge of a nail is characteristic.

Oral findings – Tiny white to mucosal-colored asymptomatic papules that can coalesce and cause a cobblestoning appearance of the hard palate and alveolar mucosa. The tongue and buccal mucosa may be involved as well. Obstructive sialadenitis is another manifestation secondary to blockage of salivary glands, and it can cause intermittent swelling, pruritus, malodor, and pain.

Diagnostic Pearls

The papules have a rough surface, which, upon gentle palpation, feels like the surface of very coarse sandpaper or a fine grater.

The constellation of classic cutaneous, nail, and oral findings should raise suspicion for Darier disease, especially if there is a family history of similar findings.

Differential Diagnosis & Pitfalls

- **Confluent and reticulated papillomatosis**
- **Seborrheic dermatitis**
- **Grover disease** (transient acantholytic disease) has a similar biopsy but has a different age of onset (eg, fourth or fifth decade).
- Follicular **atopic dermatitis** (eczema) has a similar distribution, as do follicular occlusion syndromes, **perforating disorders**, **granuloma annulare**, and some tumors of the appendages.

- **Hailey-Hailey disease** is more erosive and is more common in intertriginous areas.
- **Pemphigus foliaceus**
- **Acne**
- **Acanthosis nigricans**

Oral manifestations:

- Drug-induced **gingival hypertrophy**
- **Denture-induced hyperplasia**
- **Condyloma**
- **Oral squamous cell carcinoma**
- **Oral leukemic infiltration**
- **Granulomatosis with polyangiitis**
- **Kaposi sarcoma**

Acrokeratosis verruciformis-like papules:

- **Acrokeratosis verruciformis of Hopf** – An isolated finding in the absence of Darier disease; conditions are allelic.
- **Flat warts**
- **Epidermodysplasia verruciformis**

Leukodermic macules:

- Confetti-like macules of **tuberous sclerosis**
- **Flat warts**
- **Vitiligo ponctué**
- **Arsenic toxicity**
- Extragenital **lichen sclerosus**
- **Epidermodysplasia verruciformis**
- **Pityriasis versicolor**

Best Tests

Skin biopsy is usually characteristic. Biopsy of oral lesions demonstrates similar characteristic findings.

Perform a skin swab for bacterial or viral culture if infection is suspected.

Consider endoscopic studies for patients who report esophageal symptoms.

Histopathology Findings:
Common features

- Hyperkeratosis with parakeratosis
- Suprabasal acantholysis induces the formation of intraepidermal lacunar space
- Corp ronds (dyskeratotic cells with round pyknotic nuclei, perinuclear clear halo and eosinophilic cytoplasm) in the stratum corneum and stratum granulosum
- Corp grains (dyskeratotic cells with elongated pyknotic nuclei and basophilic or eosinophilic cytoplasm) in the stratum corneum or as acantholytic cells within the lacunae
- Villi-like projections of papillary dermis lined by a single layer of basal keratinocytes extend into the lumen of the lacunae
- Mild chronic inflammatory infiltrate in the underlying dermis

Occasional features

- Papillomatosis

Management Pearls

Basic measures for all patients with Darier disease include sun protection and the use of cool cotton clothing, soap substitutes (eg, Cetaphil), emollients, and mild keratolytics (urea or lactic acid moisturizers). Oral hygiene is important.

Treat any complicating infection aggressively, and adjust systemic retinoid dosages to find the optimum therapeutic window. Patients may be able to stop retinoids during the winter, but exacerbations off therapy are common. Because therapy with retinoids is long term, the avoidance of pregnancy in females is essential. It is important to discuss with and follow patients for the long-term, bony side effects of retinoids.

Superinfection with herpes simplex virus (HSV), a well-characterized complication termed Kaposi varicelliform eruption, is treated with appropriate antiviral agents. If suspicion is high,

treatment is merited despite a negative viral culture.

Therapy

Topical retinoids (tretinoin 0.025%-0.1%, adapalene 0.1%, or tazarotene 0.05% nightly) can be useful, although the dosage needs to be closely adjusted, as irritation is frequent and can lead to erosion. The concomitant use of low-potency topical corticosteroids may help control irritation.

Darier disease responds well to systemic retinoids such as isotretinoin (starting dose 0.5 mg/kg/day in 2 divided doses) or acitretin (starting dose of 10-25 mg daily), both of which have teratogenetic potential. Women of childbearing potential should use 2 different birth control measures to avoid pregnancy on isotretinoin. Do not use acitretin in women of childbearing age. These drugs should be used by those familiar with them and their side effects.

Other therapies with purported success in case reports include topical 5-fluorouracil, topical tacrolimus, oral contraceptives, dermabrasion, laser treatment (carbon dioxide and erbium:YAG), and photodynamic therapy. Treatment of hyperhidrosis with injections of botulinum toxin A may be useful in selected patients.

Impetiginized lesions can be treated locally with mupirocin or, if extensive, with the appropriate systemic antibiotics (eg, dicloxacillin or cephalexin).

Acyclovir (or one of its congeners) is indicated in the case of HSV superinfection. (See **Kaposi varicelliform eruption**.)

Oral mucosal manifestations:

- The oral lesions in Darier disease are asymptomatic and do not necessitate treatment.
- Dilatation of salivary ducts may lead to symptomatic improvement of obstructive sialadenitis.
- Systemic retinoids are ineffective for oral lesions.