Spectrum of orocutaneous disease associations

Genodermatoses and inflammatory conditions

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Learning objectives
After completing this learning activity, participants should be able to recognize the important relationship between the skin and the oral cavity with respect to genodermatoses.

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The oral cavity and cutaneous organ systems share a close embryologic origin. Therefore, there are numerous dermatologic conditions presenting with concomitant oral findings of which the dermatologist must be aware. The second article in this continuing medical education series reviews inflammatory orocutaneous conditions and a number of genodermatoses. It is essential for dermatologists to be familiar with oral cavity manifestations associated with dermatologic diseases for prompt diagnosis, management, and appropriate referral to stomatology and dentistry. (J Am Acad Dermatol 2017;77:809-30.)

Key words: amyloidosis; Behcet disease; burning mouth syndrome; cutaneous manifestations; Darier disease; genodermatoses; inflammatory; lichen planus; nevoid basal cell carcinoma syndrome; oral cavity; orocutaneous diseases; Peutz-Jeghers syndrome; sarcoidosis; sclerosis complex; tuberous erythema multiforme.

GENODERMATOSES

The genodermatoses are a group of rare, inherited, single-gene skin disorders that are often associated with a variety of other medical abnormalities. The epidermis of the skin and the enamel and dentine components of the teeth share a common

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embryologic origin. As such, many genodermatoses frequently present with preceding or concomitant manifestations of the oral cavity.[1,2] It is therefore imperative for the dermatologist to identify and recognize lesions of the oral mucosa for prompt diagnosis and treatment of these often multisystemic diseases. Table I shows the genodermatoses associated with both cutaneous and oral findings, highlighting the pertinent clinical findings, pattern of inheritance, and implicated gene.

INFLAMMATORY CONDITIONS

Darier disease

Key points

- **Darier disease is an autosomal dominant keratinization disorder associated with mutations of the *ATP2A2* gene**
- **Cases can be hereditary or sporadic**
- **Topical retinoids are effective treatments**

Background

Darier disease (DD) is an autosomal dominantly inherited keratinization disorder affecting the skin, nails, and mucous membranes. It is caused by mutations of the *ATP2A2* gene, which encodes a sarco/endoplasmic reticulum adenosine triphosphatase type 2 calcium pump located within the endoplasmic reticulum.[26,27] Sporadic mutations occur in up to two-thirds of cases.[28] Prevalence rates range from 1 in 30,000 to 1 in 100,000 individuals.[29,30]

Clinical

Skin. DD has a peak onset around puberty and is characterized by yellow to brown, greasy, keratotic papules involving the seborrheic areas of the face, scalp, and chest (Fig 5). Known trigger factors include excessive sweating, ultraviolet light exposure, mechanical trauma, humidity, high temperatures, pregnancy, and friction.[27,28]

Oral cavity. The hard palate is the most commonly affected oral site, followed by the gingiva, buccal mucosa, and tongue. Lesions include whitish papules with a central depression with aggregation to form nodular plaques. The palate often exhibits a fine to coarse "pebbly" appearance resembling nicotinic stomatitis. More severe forms are similar to papillary palatal hyperplasia.[6] Obstructive sialadenitis has been reported in ≤30% of cases and often involves the parotid gland.[31]

Systemic. DD may be associated with neuropsychiatric disorders, including bipolar affective disorder, mental retardation, epilepsy, encephalopathy, and schizophrenia.[27] Moreover, urogenital abnormalities, such as polycystic kidneys, hypoplastic gonads, and renal and testicular agenesis, are occasionally reported.[32]

Therapy

Treatment of DD includes removal of exacerbating factors. Topical retinoids are effective, and in combination with a mid-potency steroid or emollient can decrease irritation. Oral retinoids are indicated for more severe forms. In addition, topical antibiotics, salicylic acid, and antifungals can reduce infection and the associated foul odor.[27,28,33]

TUBEROUS SCLEROSIS COMPLEX

Key points

- **Tuberous sclerosis complex is an autosomal dominant neurocutaneous disease caused by mutation of the hamartin or tuberin genes**
- **Facial adenoma sebaceum, epilepsy, and mental retardation are the classic clinical triad**
- **The skin and oral cavity are involved in most cases**
- **Baseline management involves neurologic, cardiac, renal, ophthalmic, dermatologic, and dental evaluation**

Background

Tuberous sclerosis complex (TSC) is an autosomal dominant, multisystemic, neurocutaneous disease caused by mutations of the *TSC1* or *TSC2* genes or hamartin and tuberin, respectively.[34] The incidence is approximately 1 in 5000 to 1 in 10,000 births and is classically characterized by the clinical triad of facial adenoma sebaceum, epilepsy, and mental retardation.[35] Seven percent to 37% of patients have a positive family history, and de novo mutations are common.[36]

Clinical

Skin. TSC is associated with numerous skin findings, with hypomelanotic macules being the most common (90-98%). These lesions often involve the trunk and buttocks, and are best observed under a Wood's lamp.[37] Hypomelanotic macules presenting with infantile focal seizures should raise suspicion for TSC.[36] Bilateral facial angiofibromas are hamartomatous nodules often distributed in a butterfly pattern over the malar eminences and nasolabial folds, giving a ruddy appearance to the cheeks (Fig 6).[38] The shagreen patch presents as irregularly shaped, thickened patches with a roughened surface. In addition, yellow-brown to flesh-colored forehead fibrous plaques are present in approximately 36% of patients.[35,36,38]