SECTION EDITOR: MICHAEL E. MING, MD

Verrucous Plaques on the Face

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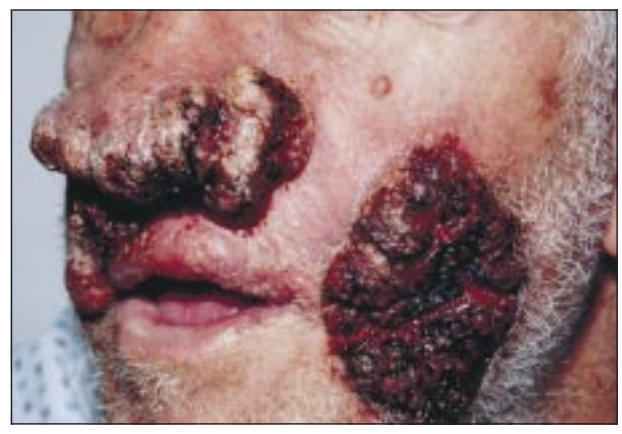
REPORT OF A CASE

A nonimmunosuppressed 67-year-old man was referred to our clinic for treatment of facial lesions previously given the microscopic diagnosis of keratoacanthoma. Eight months earlier, the patient noticed what he thought was a cold sore on his upper lip. The lesion was excised after it failed to resolve. Two months later, rapidly enlarging, massive verrucous plaques involving the upper lip, nasal tip, and right ala developed. Despite treatment with topical fluorouracil and isotretinoin (40 mg/d), the lesions continued to enlarge (Figure 1). An incisional biopsy specimen was obtained from the lip lesion (Figure 2). Purulent debris was stained with Gomori methenamine-silver (Figure 3).

What is your diagnosis?



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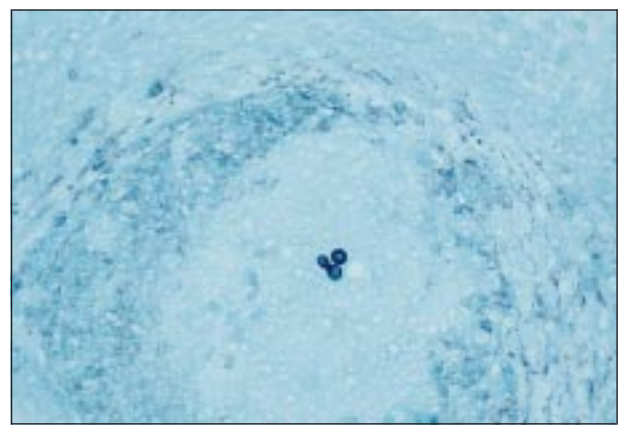

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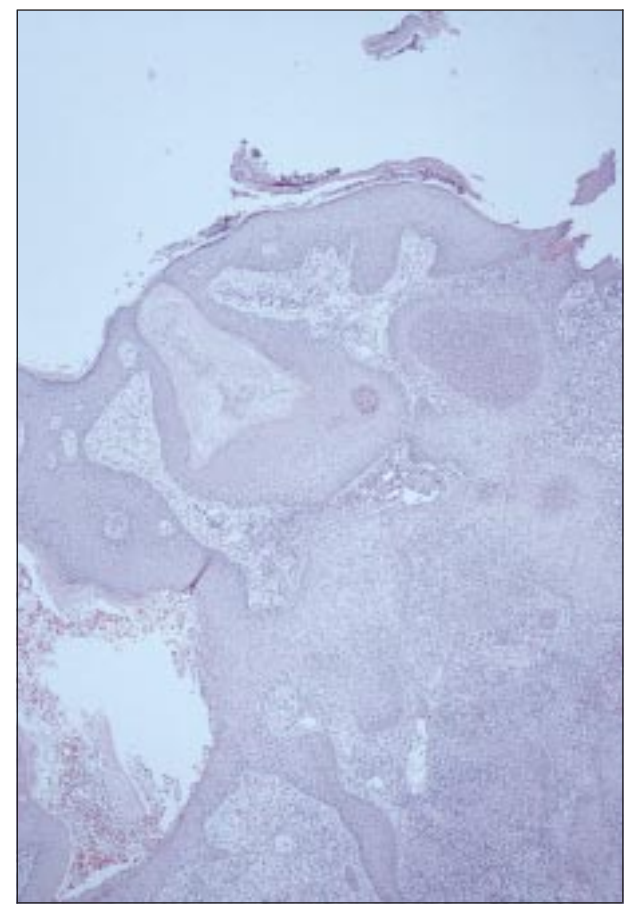


Figure 2.

An Ulcerating Verrucous Plaque on the Foot

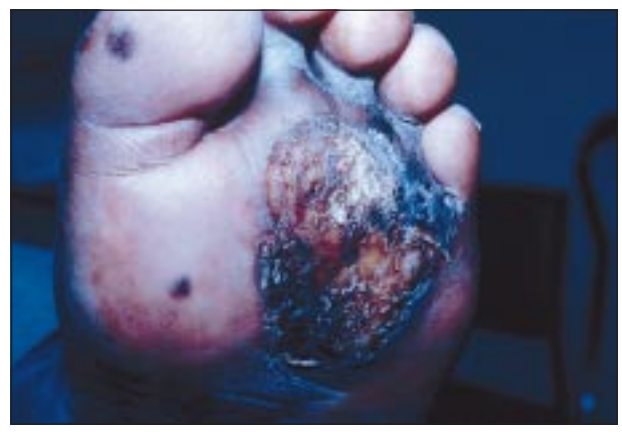
Julia Ho, MD; Dayna G. Diven, MD; Pamela J. Butler, MD; Stephen K. Tyring, MD, PhD; Duke University Medical Center, Durham, NC (Dr Ho), University of Texas Medical Branch, Galveston (Drs Diven and Tyring), and Milwaukee Medical Clinic, Milwaukee, Wis (Dr Butler)

REPORT OF A CASE

A 29-year-old African American man with long-standing type 1 diabetes mellitus, hypertension, retinopathy, nephropathy, and peripheral vascular disease that had resulted in leg amputation above the knee presented with a 4-year history of a verrucous lesion on his foot. It had been stable in size for 3 years but had intermittently ulcerated and healed. He had been seen by numerous physicians for what was thought to be a diabetic ulcer with a surrounding callus.

On physical examination, the patient was found to have a hyperkeratotic, partially ulcerated verrucous plaque on the plantar surface of his forefoot (Figure 1). No other verrucous lesions were noted. A podiatrist obtained a wedge biopsy specimen after attempts at healing were unsuccessful (Figure 2).

What is your diagnosis?



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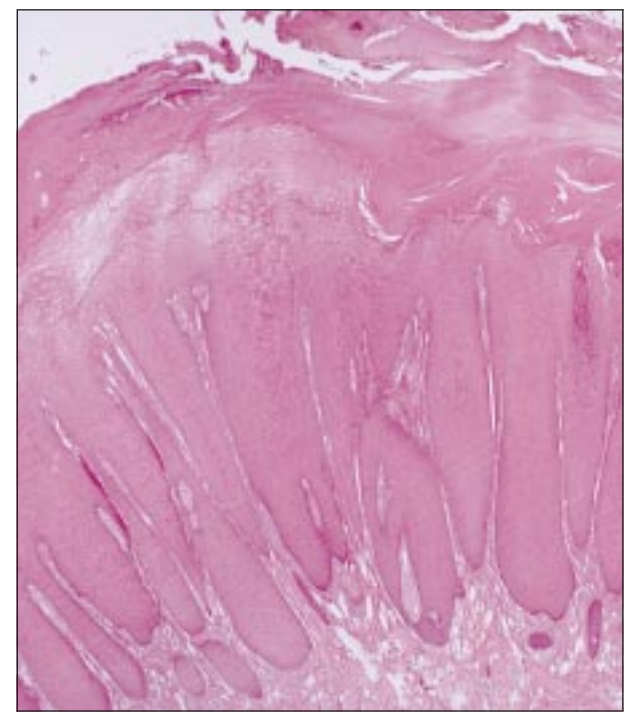

Figure 2.

Extensive Bluish Gray Skin Pigmentation and Severe Arthropathy

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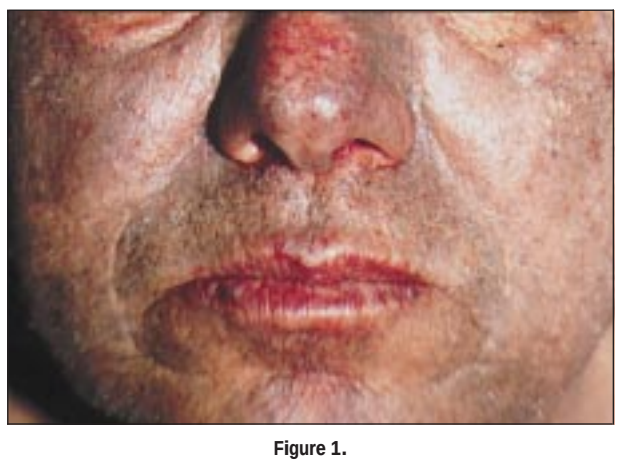
REPORT OF A CASE

A 65-year-old man presented with a 30-year history of slowly developing extensive bluish gray skin pigmentation. For about 2 decades, he had increasing pain in the lumbar region, hips, and knees. His mother, who had similar clinical signs, remembered that the patient's diapers had shown discoloration when he was a baby.

Physical examination revealed prominent bluish gray pigmentation of the face (Figure 1), hands, and cartilage of the ears and nose. Pigmentation of extensor tendons was prominent and could be seen through the skin of the hands (Figure 2). There were grayish axillary skin pigmentation, similar pigmentary changes of the nailbed, and black cerumen. On the right sclera, triangular brown pigmentation appeared laterally. A biopsy specimen was obtained from a pigmented area (Figure 3).

What is your diagnosis?



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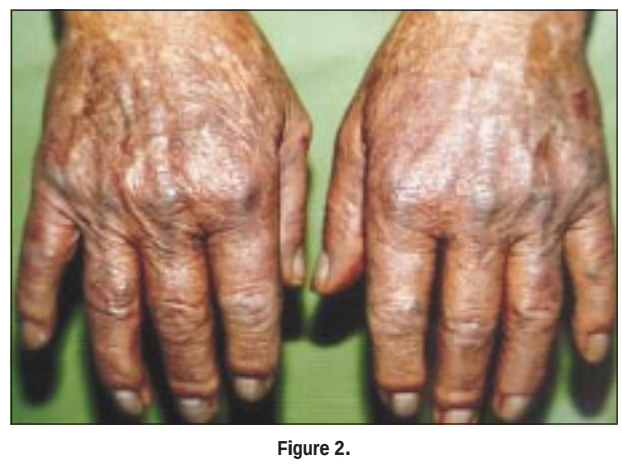

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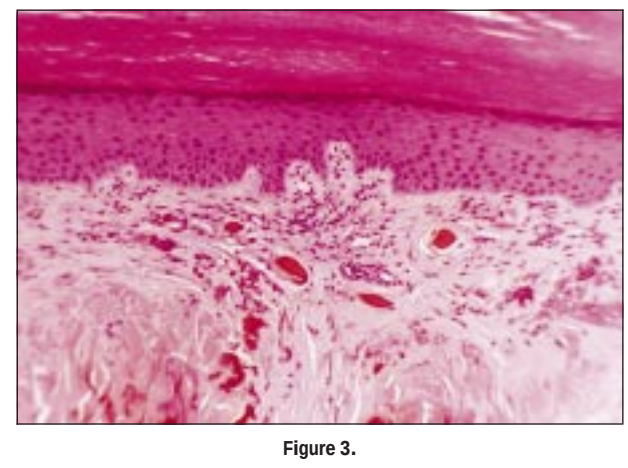


Figure 3.

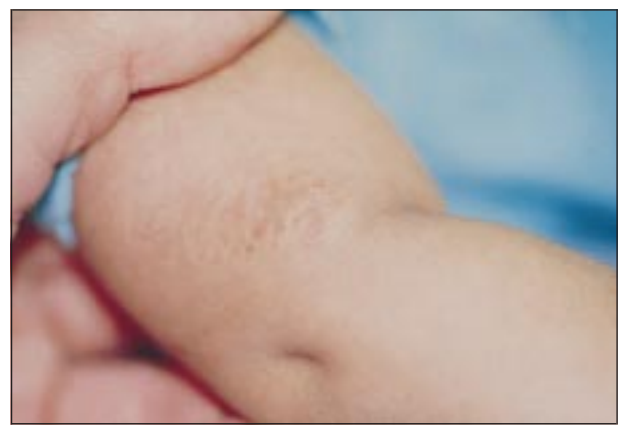
Grouped Papules on the Arm of an Infant

Elizabeth S. Morris; Monica M. Scheel, MD; Kurt F. Lundquist, MD; Sharon S. Raimer, MD; University of Texas Medical Branch, Galveston

REPORT OF A CASE

A 2½-month-old Hispanic girl was referred to the dermatology clinic for evaluation of flesh-colored to light-brown papules on her right arm that had been present since birth. The papules were arranged in 2 groups that were somewhat linear in distribution. One group consisted of flesh-colored papules on the right forearm, and the other consisted of light-brown verrucous papules on the upper part of the right arm, just above the elbow (Figure 1). The lesions had not changed since birth and appeared to be asymptomatic. The patient was healthy, and the findings of her physical examination were otherwise unremarkable. Her mother had no medical problems, and both the pregnancy and delivery were without complications. A 2-mm punch biopsy specimen was obtained from the right forearm (Figure 2).

What is your diagnosis?



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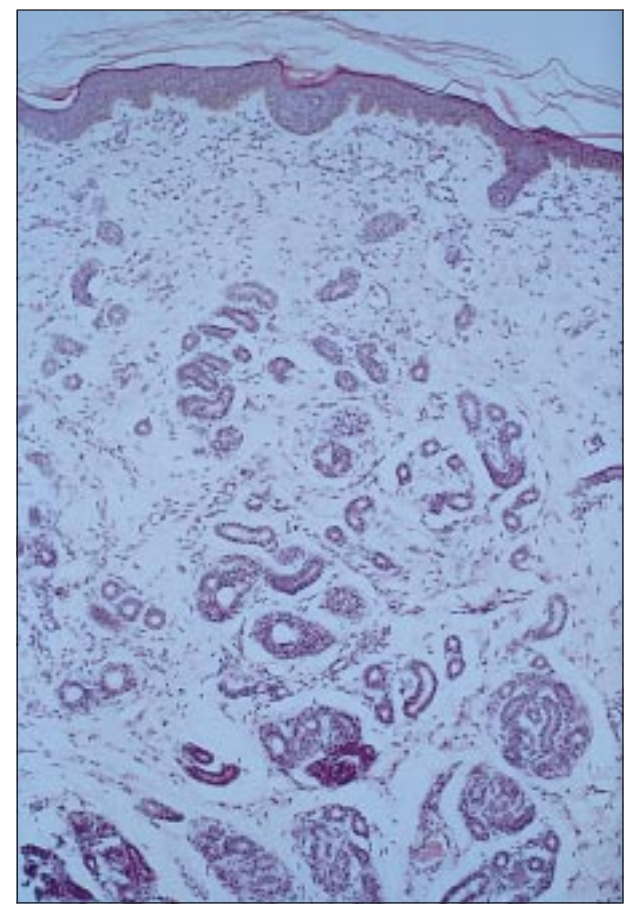

Figure 2.

Verrucous Plaques on the Face

Diagnosis: North American blastomycosis.

MICROSCOPIC FINDINGS AND CLINICAL COURSE

The biopsy specimen showed marked pseudoepitheliomatous hyperplasia with intraepidermal microabscess formation. The dermis showed a dense infiltrate of neutrophils, giant cells, and spores lying both extracellularly and within multinucleated giant cells. The Gomori methenamine-silver stain showed yeast forms with broad-based budding.

The patient's chest x-ray film revealed no abnormalities, and magnetic resonance imaging of his face showed ethmoidal sinus involvement. The patient was originally treated with intravenous amphotericin B, followed by oral itraconazole. After 6 months of oral itraconazole therapy, the lesions have resolved, leaving behind residual scarring. His nasal airway is patent.

DISCUSSION

Gilchrist described the first reported case of blastomycosis in 1894. He attributed the skin infection to a protozoan organism, but later refuted his own description when he isolated and named the fungus *Blastomyces dermatitidis*.[1] Blastomycosis is caused by an endemic, thermally dimorphic fungus found in the Ohio and Mississippi River areas. The fungus is an 8- to 15-µm, round, broad-based budding yeast with doubly refractile walls in infected tissue or culture at 37°C.

Almost all cases of blastomycosis begin as a primary pulmonary infection following inhalation of conidia.[1] The transformation from mycelia to the yeast phase is necessary for infection to occur. The primary infection may resolve spontaneously or progress to resemble an atypical pneumonia. Chronic pulmonary involvement may simulate tuberculosis, with cavitation, pleural fibrosis, and hilar adenopathy.[2] Challapalli and Cunningham[3] described an adolescent who had vertebral blastomycosis with associated patchy pulmonary infiltrates, apical pleural thickening, and loss of volume in the right upper lobe, simulating tuberculosis. Noncaseating granulomas occur as the result of developing immunity. Some cases of pneumonia spontaneously resolve, but endogenous reactivation may occur at either pulmonary or extrapulmonary sites.

Extrapulmonary sites of involvement most frequently occur in the skin, followed by bone and the urogenital and central nervous systems. The sites of predilection are the face, mucous membranes, and exposed areas.[2] Infection occurs most frequently in men and rarely in children. Unusual cases have included presentation as an ovarian tumor,[4] as an intraocular infection,[5] and as a primary inoculation in a lesion of bullous pemphigoid.[6] Primary or isolated cutaneous lesions are rare, with most thought to occur when the primary pulmonary focus has resolved prior to presentation. For unexplained reasons, infection with blastomycosis is uncommon among patients who have acquired immunodeficiency syndrome or who have undergone renal transplantation, including those living in the endemic areas.

Diagnosis is made by identification of the yeast phase on tissue biopsy specimens, potassium hydroxide preparations of expressed material, or cultures. Histopathologic studies show pseudoepitheliomatous hyperplasia, intraepidermal abscesses, and a polymorphous dermal infiltrate. Pseudoepitheliomatous hyperplasia can be mistaken for keratoacanthoma, as occurred in this case. If hyperplasia is present without pronounced nuclear atypia, a diligent search for microorganisms should be considered. The spores can be found within multinucleated giant cells scattered throughout the dermis or lying free among clusters of neutrophils. Periodic acid–Schiff and Gomori methenamine-silver stains may aid in visualization. The fungus grows readily on Sabaroud glucose agar at room temperature (25°C), producing a white fluffy colony. At 37°C, the colony is brown and wrinkled.

Many immunocompetent patients with acute pulmonary blastomycosis recover without therapy. Some physicians believe that observation is sufficient in an asymptomatic patient, while others will initiate treatment. The drug of choice for acute non–life-threatening blastomycosis is oral itraconazole (400 mg/d for at least 6 months).[7,8] Ketoconazole and fluconazole (400 to 800 mg/d for 6 months) are effective alternative therapies.[7] Amphotericin B therapy is effective for all types of blastomycosis. The immunocompromised patient with acute pulmonary blastomycosis should initially receive amphotericin B for a total of 1000 mg, followed by 400 mg of itraconazole daily for 6 months. In all patients, refractory or rapidly progressive disease should be treated with amphotericin B.[7,8]

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An Ulcerating Verrucous Plaque on the Foot

Diagnosis: Verrucous carcinoma (epithelioma cuniculatum).

MICROSCOPIC FINDINGS AND CLINICAL COURSE

Microscopic examination of the biopsy specimen showed epidermal acanthosis with blunt epidermal projections extending into the dermis. Koilocytes were present. Excision to subcutaneous tissue was performed with negative intraoperative margins by frozen as well as permanent sections. A split-thickness skin graft was used to cover the wound. There has been no recurrence at 4 years.

DISCUSSION

The term *verrucous carcinoma* was coined in 1948[1] to define a well-differentiated, slow-growing neoplasm with a tendency for local recurrence, but without a tendency to metastasize. Verrucous carcinoma was first described in the oral cavity. Subsequently, it has been reported in other stratified squamous surfaces, including mucous, mucocutaneous, and cutaneous sites. The 3 major locations of verrucous carcinoma are the oral cavity (oral florid papillomatosis), the anogenital region (giant condyloma of Buschke and Lowenstein), and the plantar surface of the foot (epithelioma cuniculatum).

Epithelioma cuniculatum, which more commonly affects males (79%-89% of patients), is found most often in patients in their 50s.[2] The tumor occurs predominantly on the soles, but may be found on the palms or other areas of the body. The cardinal manifestation of this disease is a fungating, exophytic mass with numerous keratin-filled sinuses.[2] These lesions usually occur on the anterior weight-bearing area of the sole of the foot.[3] Typically, the history is one of a recalcitrant plantar wart or epidermal hyperplasia with recurrence after local excision.[4] As the tumor grows, it invades locally and has been shown to involve the plantar fascia[5] or to advance toward the dorsal surface of the foot, with destruction of the metatarsal bones.[6]

Histologic diagnosis can be difficult. A deep biopsy specimen of the lesion is necessary, as superficial portions may resemble a verruca vulgaris with hyperkeratosis, parakeratosis, and acanthosis.[7] The pattern of invasion has been described as "bulldozing rather than stabbing."[8] Verrucous carcinoma is histologically characterized by blunt papillary projections of well-differentiated epithelium, supported by edematous, typically nonreactive stroma. The epithelium shows little atypia and is characterized by well-differentiated, lightly staining, and benign-appearing keratinocytes. Human papillomavirus types 1 through 4, 6, 11, and 18 have been implicated in the pathogenesis of verrucous carcinoma; however, their role is controversial.[9]

Epithelioma cuniculatum most often presents as a nonhealing wart on the soles, palms, or other location that fails treatment. Multiple biopsy specimens are often necessary to establish the diagnosis. Epithelioma cuniculatum rarely metastasizes to regional lymph nodes and has a low mortality rate compared with other subtypes of verrucous carcinoma. The differential diagnosis includes verruca vulgaris, reactive epidermal hyperplasia, dermatofibroma, drug eruption (bromoderma and ioderma), infundibular cyst, benign adnexal tumor, giant seborrheic keratosis, giant or subungal keratoacanthoma, pyogenic granuloma, eccrine poroma, hyperkeratotic basal cell epithelioma, verruciform xanthoma within a squamous cell carcinoma in situ, verrucous melanoma, and cutaneous squamous cell carcinoma with verrucoid clinical features.[2] The treatment is wide local excision. In more serious cases, amputation of a toe or even a foot may be necessary. Electrodesiccation, cryotherapy, and laser surgery often fail. Surgical curettage is sufficient in minor cases.[10]

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Extensive Bluish Gray Skin Pigmentation and Severe Arthropathy

Diagnosis: Endogenous ochronosis (alkaptonuria).

MICROSCOPIC FINDINGS AND CLINICAL COURSE

Hematoxylin-eosin–stained sections showed degeneration of collagen fibers and a deposition of round to oval, ochrelike amorphous substance within the dermis. Ultramicroscopic examination revealed both intact and partly degenerated collagen fibers and the deposition of an amorphous, electron-dense substance.

The patient was also noted to have urine that darkened on exposure to air. Radiography of the skeletal system demonstrated a characteristic picture of severe arthropathy with narrowing of the intervertebral, articular spaces and calcification of the disks. The clinical diagnosis was confirmed by the detection of homogentisic acid (HGA) in the urine specimen by thin-layer chromatography (excretion rate, 11.64 mmol/d). Some improvement in the patient's arthralgia was observed after administration of nonsteroidal anti-inflammatory drugs (eg, diclofenac, 50 mg 3 times a day) and physiotherapy.

DISCUSSION

Endogenous ochronosis, or alkaptonuria, is a rare (1: 25 000) genetic, metabolic disorder in which deficiency of the enzyme HGA oxidase causes pigment deposition in various tissues.[1-4] Lack of HGA oxidase prevents metabolism of HGA, which is an intermediate product of phenylalanine and tyrosine breakdown. Excessive amounts of HGA are excreted in the urine and are transformed into a brown pigment on exposure to air, darkening the urine. This phenomenon is thought to be the initial manifestation of endogenous ochronosis and is often noted in infancy by discoloration of diapers. However, at a pH of less than 7.0 or in the presence of reducing substances, such as ascorbic acid, the urine will not change color.[5] For this reason, diaper staining may be more prominent after the diaper is cleaned with soap, which alkalinizes the urine. Normally, the urine contains no HGA at all, so any amount is diagnostic.[1]

In the body, polymerized HGA accumulates in connective tissues, including the skin and cartilage, resulting in pigmentation[6] and degeneration. Extensive skin pigmentation has been described,[6,7] but only in adulthood. This may be the result of inhibition of the active tubular secretion of HGA in the kidney.[7] In tissue, HGA inhibits several enzymes that are important for the cross-linking of collagen fibers.[3] The most severe subjective symptoms (eg, arthralgia) develop from degeneration of cartilage, which usually begins in the third or fourth decade of life, but may begin earlier and be more severe in males.[8]

Alkaptonuria should be differentiated from the exogenous form of ochronosis, which can be caused by the use of certain medications, such as antimalarial agents and bleaching creams.[9,10] The metabolism of these medications results in an HGA polymer–like substance that differs from the polymer found in alkaptonuria. Also, discoloration and arthralgia do not occur in the exogenous form of ochronosis; its only manifestation is a reversible skin discoloration that disappears when the responsible medication is no longer used.[10] The exclusion of other conditions that cause skin pigmentation, such as Addison disease, hemochromatosis, and pellagra, or that result in dark urine, such as melanuria, porphyria cutanea tarda, and hematuria, is usually straightforward.

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Grouped Papules on the Arm of an Infant

Diagnosis: Eccrine nevus.

MICROSCOPIC FINDINGS

Histologic sections showed a proliferation of eccrine ducts with an organoid architecture. No vascular abnormalities were seen.

DISCUSSION

The eccrine nevus is a rare entity with varying clinical manifestations. Microscopically, it consists of an increase in the size or number of mature eccrine secretory coils,[1] as seen in our patient. This lesion is considered to be a hamartoma and must be differentiated from the eccrine angiomatous hamartoma, a similar lesion. Both show increased numbers of eccrine structures, but pure eccrine nevi lack the numerous capillary channels surrounding and intermingled with the eccrine structures that are found in eccrine angiomatous hamartomas.[1] Fewer than 20 cases of pure eccrine nevi have been reported in the literature. Clinically, the lesion often presents as a localized hyperhidrotic area without other distinctive clinical features.[2-9] There have been reports of lesions presenting as depressed brownish hyperhidrotic patches[10] and as brown hyperhidrotic plaques.[11] Eccrine nevi that result in hyperhidrosis have been called *localized unilateral hyperhidrosis*,[4,8,9] *nevus sudoriferous*,[5] and *sudoriferous hamartoma*.[11] Other cases have been asymptomatic and have presented as skin-colored to slightly brown papules,[12] depressed brownish patches,[13] and centrally depressed nodules surrounded by a slightly scaly border.[14] Our case is similar to that described by Imai and Nitto,[12] which had groups of asymptomatic flesh-colored to light-brown papules in a linear distribution. Interestingly, many reported cases of eccrine nevi have occurred on the forearm,[15] as did the lesion in our patient. Only 2 cases in the literature were reported to be congenital. Both involved areas of localized unilateral hyperhidrosis without other clinical features in adults who had had the lesions as long as they could remember.[4] Several previously reported cases occurred during childhood and adolescence,[3,5,10-12] with the youngest of the patients developing the nevus at the age of 1 month.[13] Our case is unusual in that, to the best of our knowledge, it is only the third case of a congenital eccrine nevus reported in the literature and the first of those to present with papules without hyperhidrosis. Eccrine nevi are harmless but may be surgically removed if so desired for cosmetic purposes.[16]

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