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# CONTINUING MEDICAL EDUCATION

## Cutaneous deposition diseases. Part II

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Part II of the cutaneous deposition disorders focuses on cutaneous calcification and ossification, alkaptonuria and ochronosis, and gout. These disorders have in common the deposition of materials in the dermis or subcutis and often involve metabolic defects in hormonal and enzymatic regulation. The pathogenesis, clinical findings, and treatment of these diseases are discussed. Both the histologic and ultrastructural findings are reviewed. (J Am Acad Dermatol 1998;39:527-44.)

***Learning objective:*** After reading this review, the practitioner should be familiar with both the cutaneous and systemic manifestations of these disorders.

The cutaneous deposition disorders often involve metabolic diseases that result in the accumulation of abnormal materials in the internal organs and within the skin. Not infrequently the skin manifestations precede the systemic. The dermatologist may be critical in the detection of these diseases by early recognition of these cutaneous manifestations.

### CUTANEOUS CALCIFICATION

Cutaneous deposition of calcium salts (calcinosis cutis) in the skin and subcutaneous tissue occurs in a variety of clinical settings. It begins as a calcium phosphate nidus and progresses to hydroxyapatite crystal formation within a collagen matrix. Four subsets occur: metastatic calcinosis, dystrophic calcinosis, idiopathic calcinosis, and iatrogenic calcification.

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**Pathogenesis**

The pathogenesis is not well understood, but apparently involves abnormally high mitochondrial calcium phosphate levels resulting in crystal deposition and cell death. In metastatic calcinosis, high levels of serum calcium or phosphate occur, with precipitation of crystals in soft tissue. In dystrophic calcinosis, tissue damage allows increased intracellular calcium influx.[1] Idiopathic calcinosis occurs in the absence of an abnormal serum calcium level or antecedent trauma.

The ultrastructural morphology of calcinosis cutis has been studied, but numerous technical difficulties have arisen because of the mineralization of the tissue.[2] One case of dystrophic calcinosis cutis revealed mineralization of only elastic fibers,[3] whereas another showed mineralization of both collagen and elastic fibers.[2] Pleomorphic hydroxyapatite crystals were arranged around thick type I collagen fibrils in a “flower-like” arrangement. Elastic fibers appeared speckled from the deposition of star-shaped crystals around the microfibrils. The excessively mineralized fibers were filled with needle-shaped crystals. The ground substance did not contain crystals, but had either a reticulate or globular structure at the periphery of the calcified material. Scattered

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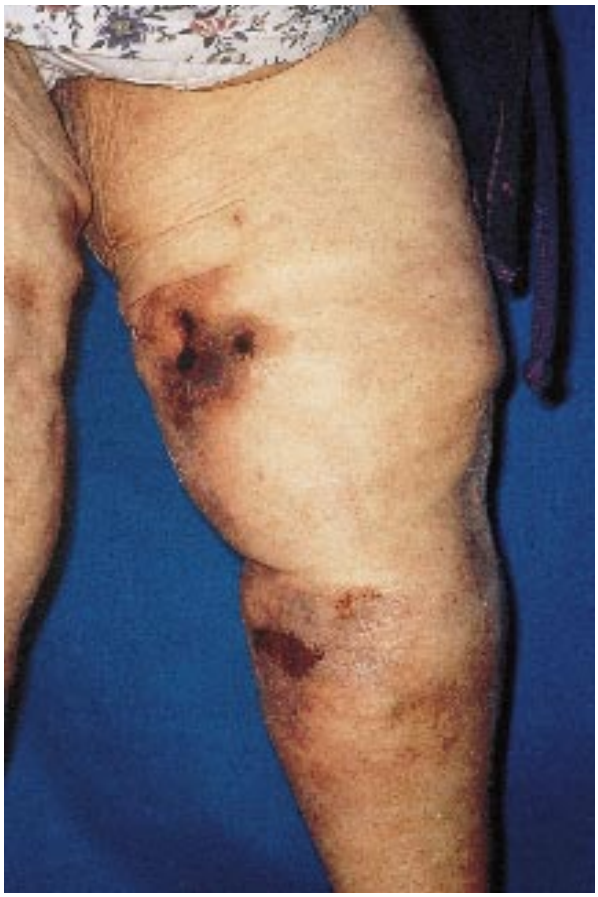

**Fig 1.** Calciphylaxis. Livedoid necrosis caused by vascular calcification.

fibroblasts and macrophages were present with no evidence of intracellular calcified material.[2] Mineral crystal deposits were noted on the collagen fibrils and within the cytoplasm of fibroblasts in a separate study of scrotal calcinosis.[4] The initial site of mineralization (whether collagen, elastic fibers, or ground substance) remains controversial.[2] The electron-dense mineral crystals were found to consist of calcium and phosphate by energy dispersive x-ray spectrometry[4,5] in several studies.

**Metastatic calcification.** Metastatic calcification occurs in a variety of conditions in which the final metabolic defect results in elevated serum calcium or phosphate levels. It is generally a systemic disease with multiorgan involvement, but can occasionally present as calcinosis cutis. It affects predominantly the kidneys, lungs, stomach, and the media of arteries. Cutaneous lesions may present as papules, plaques, and nodules. It most commonly occurs in patients with chronic renal failure in whom poor renal clearance of phosphate results in hyperphosphatemia. Renal spilling of calcium triggers parathyroid hormone release, which raises both calcium and phosphorus at the expense of bone. Markedly high phosphate levels then occur with resultant nodular subcutaneous calcifications or calciphylaxis. The nodules often occur in a periarticular distribution and are reversible with correction of the calcium and phosphate abnormalities.

Calciphylaxis involves mural calcification of small and medium sized vessels. Patients present with painful, violaceous, mottled skin lesions with a livedoid pattern involving the breasts, buttocks, and extremities (Fig 1). The lesions become necrotic and result in nonhealing ulcers and gangrene. They frequently lead to uncontrollable sepsis and death.[1,6,7] The pathogenesis is multifactorial, often involving either primary or secondary hyperparathyroidism with resultant calcium-phosphate dysregulation and an elevated calcium-phosphate product. In patients with a normal calcium-phosphate product, it is speculated that parathyroid hormone sensitizes the vasculature, and subsequent challenges (ie, trauma, albumin, metal salts) result in calcification.[6] Parathyroidectomy may be curative in these patients,[8] because of ablation of the sensitizing effect of parathyroid hormone on the vasculature preceding the calcification. Reduced functional protein C may be important in the pathogenesis, resulting in a hypercoagulable state and contributing to thrombosis in the presence of vascular damage that leads to ischemic skin necrosis.[9] Calciphylaxis has been reported in patients with AIDS. Factors that may lead to calciphylaxis in these patients include coexistent renal disease, immunosuppression, excess ingestion of vitamin A and D or calcium, associated lymphoma or granulomatous disease, immobilization, multiple blood transfusion, and skin trauma.[10]

Renal disease with hyperparathyroidism has also been associated with calcifying panniculitis[11,12] in addition to small vessel calcifications.[13] Hypercalcemia and hyperphosphatemia may result from parathyroid-like hormones secreted by various malignant neoplasms, especially those of squamous origin.[1] Other clinical situations such as hypervitaminosis D or milk-alkali syndrome can result in metastatic calcification caused by elevated calcium or phosphate levels.

**Dystrophic calcification.** Dystrophic calcifica-

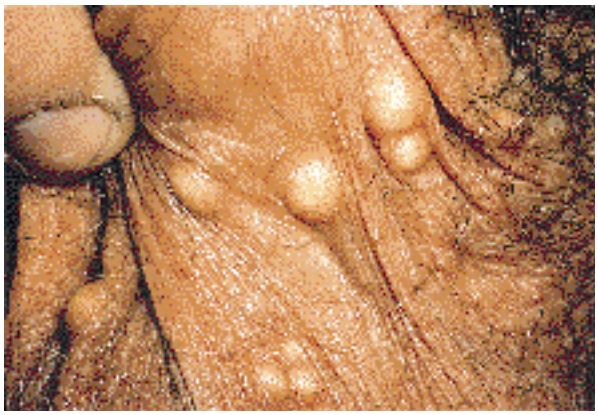

**Fig 2.** Calcinosis cutis of scrotum.

tion, the most common type of calcinosis cutis, occurs in previously damaged or diseased tissue. It occurs in localized or generalized forms without visceral involvement or serum calcium/phosphate abnormalities.

Localized involvement occurs in many inflammatory lesions such as acne, stasis ulcers, and granulomas, as well as benign and malignant neoplasms. Calcinosis circumscripta usually presents as small deposits around the fingers or elbows in patients with scleroderma, or more commonly, CREST syndrome. It has also been reported in patients with systemic lupus erythematosus.[14] The deposits may ulcerate and extrude a thick, white granular material.

Calcinosis universalis presents clinically with multiple, large calcium deposits in skin, muscle, and tendons.[1] It is most commonly seen in patients with childhood dermatomyositis. Smaller calcified nodules may be seen on the elbows, knees, shoulders, and buttocks.[1] A diffuse "exoskeleton" picture can also occur in these patients, with fascial plane calcification.[1]

Inherited diseases such as Ehlers-Danlos syndrome and pseudoxanthoma elasticum can be associated with calcinosis cutis. Various panniculitides of diverse causes such as pancreatic disease and lupus erythematosus may also be associated with dystrophic calcification of the fat.[15]

**Idiopathic calcification.** Idiopathic calcification of normal skin has been described in the scrotum,[16] penis,[17] vulva,[18] and breast.[19,20] The serum calcium level is normal. Debate continues concerning the origin of scrotal calcinosis[16] (Fig 2). Benign dermal breast calcifications can be distinguished from malignant microcalcifications radiographically[19,20] to avoid unnecessary needle biopsies.

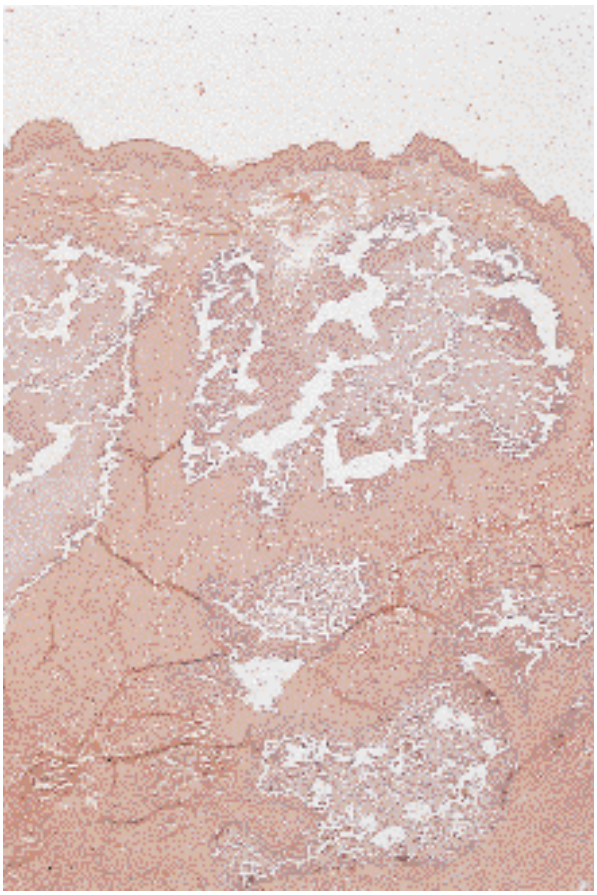

**Fig 3.** Calcinosis cutis. Basophilic irregular masses in dermis. (Hematoxylin-eosin stain; original magnification ×50.)

The subepidermal calcified nodule presents as a congenital or acquired hard, verrucous nodule on the head or extremities of a child.[1] A case of gingival calcified nodules was recently reported.[21] The cause is unclear.

Tumoral calcinosis is a familial disorder associated with hyperphosphatemia.[22] Healthy adolescents present with large calcified masses within the subcutaneous tissue or muscle of large joints.[1] It occasionally affects the skin and causes ulceration. The internal organs are not involved.

**Iatrogenic calcinosis cutis.** Iatrogenic calcinosis cutis has been reported after intravenous extravasation of calcium chloride[23] and phosphate,[24] as well as with calcium salt exposure from electroencephalography[25] and electromyographic[26] electrode compounds. Pentazocine[27] and pitressin[28]

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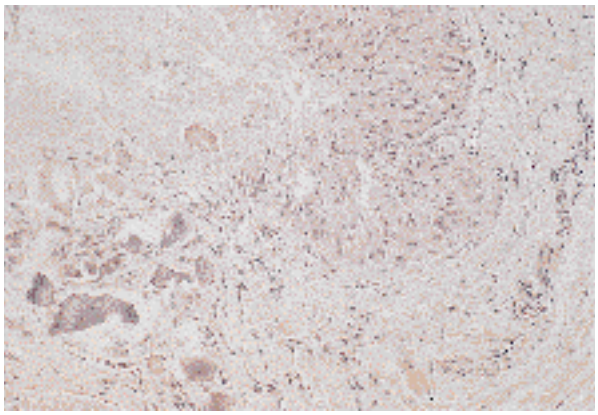

**Fig 4.** Calcinosis cutis with granuloma formation and foreign body reaction. (Hematoxylin-eosin stain; original magnification × 66.)

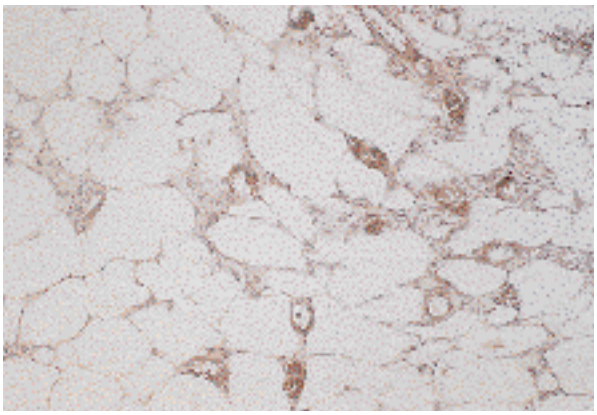

**Fig 5.** Calciphylaxis. Calcified blood vessel walls within subcutis. (Hematoxylin-eosin stain; original magnification ×50.)

can also cause deep soft tissue calcifications. Calcified nodules of the heels have been described after numerous heel sticks in neonates.[29,30] The mechanism likely involves both local elevation of calcium levels and tissue damage.[1]

### Histology

In both metastatic and dystrophic calcinosis cutis, calcium deposits stain dark blue with hematoxylin and eosin, and black with the von Kossa stain. The calcium appears as fine granules in the dermis and as large irregular masses in the subcutis[31] (Fig 3). One case involved only the sweat ducts.[32] A foreign body reaction can often be seen around larger calcium masses, along with inflammation and fibrosis (Fig 4). Intravascular fibrosis may be seen in biopsy specimens of leg ulcers from patients receiving dialysis because of renal failure. Calciphylaxis is characterized by wedge-shaped ulcers extending to the subcutis, with calcium deposition in the walls of small vessels at the base of the ulcers (Fig 5). Thrombotic occlusion of the vessels may also be noted. Inflammatory cells, particularly neutrophils, may extend into the subcutaneous fat mimicking a lobular panniculitis.[13] Less commonly, vessels are not calcified, but there is calcifying panniculitis characterized by interstitial deposition of calcium in the subcutaneous tissue, affecting mainly the septa and elastic fibers.[33]

In dystrophic calcinosis cutis, calcium deposits are often localized to areas of damaged tissue or a neoplasm, and vascular involvement is not a feature.[31] Idiopathic calcinosis generally displays homogeneous, discrete areas of calcification with well-demarcated borders.[34] Subepidermal calcified nodule reveals an acanthotic epidermis with occasional calcium granules indicating transepidermal elimination. The calcium deposits are in the upper dermis arranged in globular aggregates.[31] Tumoral calcinosis may display the architecture of a multiloculated cystlike structure with a milky fluid containing calcium granules.[1]

### Treatment

Various treatments of calcinosis cutis have been attempted with varying degrees of success. The underlying mechanism of cutaneous calcification remains unknown, although high levels of γ-carboxyglutamic acid (Gla) have been found in the calcified tissue and urine of patients with calcinosis.[35] Gla is a unique amino acid normally found in bones and teeth.[35,36] It has calcium and phospholipid binding properties that may trigger ectopic soft tissue calcification if produced de novo at these sites.[36]

The enzyme responsible for producing Gla is inhibited by warfarin at doses of 1 mg/kg per day.[35,37] Early, limited calcinosis has responded clinically and radiographically to this treatment; extensive disease has shown no response. The duration of treatment needed is unknown but is likely to be prolonged. Although warfarin appears to be a promising and safe treatment associated with decreased Gla urinary excretion, spontaneous clearing of the deposits may have occurred.

Previous studies of other treatments have been limited by small numbers of patients and difficulties in evaluating responses to treatment because

of the possibility of spontaneous clearing. Steroids,[38,39] and the chelating agent diphosphonate[38,40] along with many others, have not been uniformly successful. Colchicine (0.5 mg twice daily) was successful in healing skin ulcers associated with calcinosis cutis in two patients with connective tissue diseases.[41] In one of the patients, regression of calcium deposits was evident radiographically. Aluminum hydroxide has been reported to reduce or prevent calcification in patients with juvenile dermatomyositis[42,43] but again, spontaneous clearing may have occurred. Dystrophic calcification has been reported to clear spontaneously with transepidermal elimination of calcium.[44] Studies in rats given the anticalcifying agent phosphocitrate in a liposomal delivery system have shown promise in inhibiting dystrophic calcification.[45]

Recently, diltiazem has been used to treat calcinosis cutis. Dramatic improvement with regression of calcinosis has been described in a patient with diffuse systemic scleroderma. The calcinosis, which had previously been unchanged for several years, improved despite persistent disease activity.[46] Striking regression of the exoskeleton type of calcification in a patient with juvenile dermatomyositis[47] and in another patient with CREST syndrome[48] associated with widespread calcinosis has been reported after prolonged diltiazem treatment. Palmieri et al[49] described 4 patients with idiopathic (3 patients) or CREST-related (1 patient) calcinosis of 1 to 2 years' duration. Three of these had been treated with diltiazem, and one had received verapamil for 18 months. All patients treated with diltiazem had disappearance of calcific lesions but verapamil was ineffective.

Diltiazem may stop the progression of calcium deposition by reducing cellular calcium influx in the affected tissue. It is conceivable that after the growth of the calcific deposit ceases, scavenging by macrophages at the periphery might contribute to its remission.[46,48]

Correction of the underlying disease can help reverse metastatic calcification. Treatment of calciphylaxis is primarily supportive. Skin lesions should be kept clean, debrided as necessary, and treated with antibiotics on the basis of culture and sensitivity studies.[10,33] Hyperparathyroidism or any other metabolic or phosphate aberration must be promptly corrected. If any precipitating or challenging agent is suspected, an attempt should be made to eliminate it. In cases of primary hyperparathyroidism, surgical resection of a solitary parathyroid adenoma may cause subsequent normalization of calcium metabolism and clearing of skin lesions. Several reports describe a total parathyroidectomy with autotransplantation of 1 gland in the forearm[1,33] or subtotal parathyroidectomy[7] as definitive treatment for calciphylaxis in patients with chronic renal failure and secondary hyperparathyroidism. However, the response of the skin lesions to parathyroidectomy in these patients has been found to be inconsistent and unpredictable by others.[8,10,12]

Reducing dialysate calcium levels in patients on hemodialysis can significantly decrease the rate of progression of vascular calcification.[50] Low calcium dialysis caused regression of ectopic calcification and stopped progression of necrotic areas in 1 patient with calciphylaxis.[51]

Indications for surgical treatment of calcinosis cutis include painful masses, recurrent infection, ulcerations, functional impairment, and cosmetic concerns.[52] Conflicting reports of efficacy exist.[40,52,53] Overall, it appears to offer temporary palliative relief. Local wound care and antibiotics often hasten the spontaneous healing of calcified ulcers.[40] Surgical risks include tissue damage, especially to digital neurovascular bundles, recurrence of the masses, and wound complications such as infection and hematoma.[40]

## CUTANEOUS OSSIFICATION

Cutaneous ossification (osteoma cutis) involves bone deposition in the skin via osteoblastic organization of new type I collagen fibers.[1] Both membranous and enchondral bone formation may be seen.[34] It usually occurs in the connective tissue adjacent to a preexisting neoplasm.[1] Less commonly it occurs as a result of inflammatory or metabolic disease, or in calcified tissue. Primary osteoma cutis occurs within normal tissue. All are termed metaplastic ossification. Osteoma cutis is also a feature of Albright's hereditary osteodystrophy,[54] characterized by hyperphosphatemia, hypocalcemia, and various somatic abnormalities.

### Pathogenesis

The pathogenesis of cutaneous ossification remains unclear. Mesenchymal tumor cell or fibroblastic transformation into osteoblasts has been suggested.[55,56] Bone morphogenic proteins

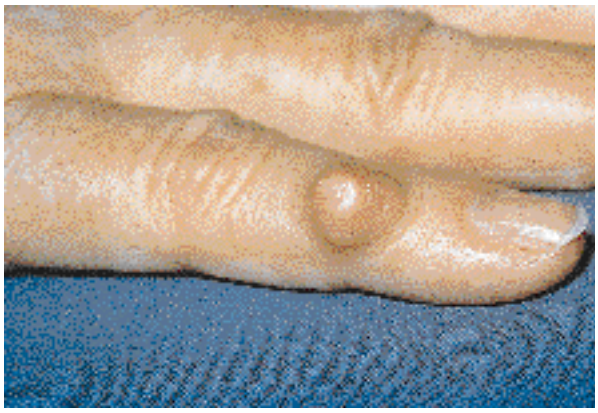

**Fig 6.** Cutaneous osteoma.

are growth factors of the transforming growth factor–β supergene family, shown experimentally to induce enchondral bone formation after injection into skin.[57] A recent ultrastructural study was performed on a case of primary osteoma cutis.[56] Macrocalcified areas of lamellar bone on electron microscopy showed osteocyte-like cells with an elongated nucleus, rough endoplasmic reticulum, and mitochondria with traces of granular calcium deposits. The connective tissue matrix contained globular or needlelike deposits corresponding to calcium phosphate and hydroxyapatite crystals, respectively. Collagen fibrils were arranged in lamellae with thin elastic fibers between them.

Microcalcified areas were noted in the adjacent, apparently normal dermis. These areas contained hydroxyapatite crystals and osteoblast-like cells with random collagen fibrils suggestive of osteoid bone. It is believed that the osteoblasts have differentiated from local skin fibroblasts under the influence of bone-inducing factors secreted from the osteoma.[56]

**Primary cutaneous ossification.** Primary ossification of the skin occurs in 4 major clinical settings in the absence of preexisting skin lesions.[31] The first is characterized by generalized neonatal nodules extending into the subcutaneous tissue (without evidence of Albright's hereditary osteodystrophy). A second group includes patients with a single, platelike osteoma[58] of the scalp or extremities appearing in the neonatal period without evidence of antecedent trauma or infection. The third group involves a small osteoma, presenting later in life, anywhere on the body (Fig 6); transepidermal elimination of chalky bone may occur.[56] Finally, women can present with multiple miliary facial osteomas often occurring in acne lesions or scars.[31]

Not all osteoma cutis cases can be clearly categorized, and several clinical situations are associated with the disorder. A thorough review is beyond the scope of this article, but 2 situations will be mentioned. Progressive osseous heteroplasia is a recently identified, rare form of calcinosis cutis and deep fascial ossification in infants.[1,59,60] Although the cause remains unclear, the serum alkaline phosphatase level is sometimes elevated, reflecting the ossification. In infants between birth and 6 months of age skin-colored, "rice grain" papules or nodules[60] appear at calcified sites. Heterotopic bone formation of soft tissues occurs, with immature membranous bone, enchondral bone, and mature cancellous bone. Cancellous bone has revealed well-differentiated hematopoietic marrow elements.[59] Because of the rarity of the disease, the prognosis remains uncertain. A review by Rodriguez-Jurudo, Gonzalez-Crussi, and Poznanski[59] described several serious complications in these children, including ulceration, infection, and painful muscular spasms of involved limbs. One case resulted in amputation of a lower extremity for pain relief; when this failed, chordotomy was performed. The pathogenesis is unknown, although some familial cases have occurred, suggesting a genetic influence. No known treatment exists; supportive management is recommended. Surgical excision of lesions is controversial.[59] Biopsy specimens should always include subcutaneous fat[60] because the ossification begins in the dermis and spreads to fat and muscles, as well as overlying skin. No dysmorphic features are present as are seen in Albright's hereditary osteodystrophy (AHO).

AHO is characterized by generalized osteomas of the skin, subcutis, and occasionally fascial planes.[54] They may occur in any area and may present at birth or later in life. The syndrome is characterized by short stature, round facies, decreased intellect and numerous skeletal anomalies, including shortened metacarpals (Fig 7). The Albright dimpling sign refers to the depression seen at the site of knuckles when patients clench their fists (Fig 8). Both pseudohypoparathyroidism (with hypocalcemia) and pseudopseudohypoparathyroidism (with normal calcium levels) can be present. The osteomas have no area of predilection

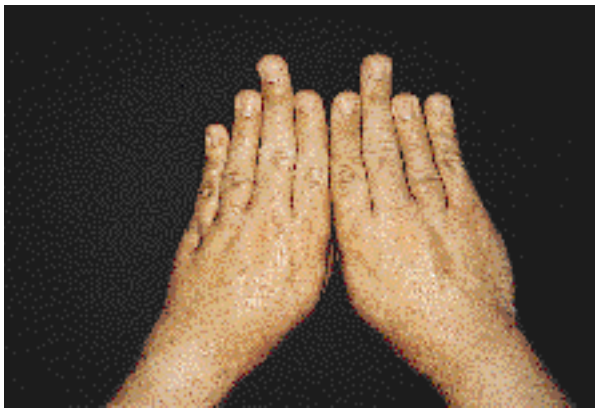

**Fig 7.** Albright's hereditary osteodystrophy; characteristic shortening of fourth and fifth metacarpals.

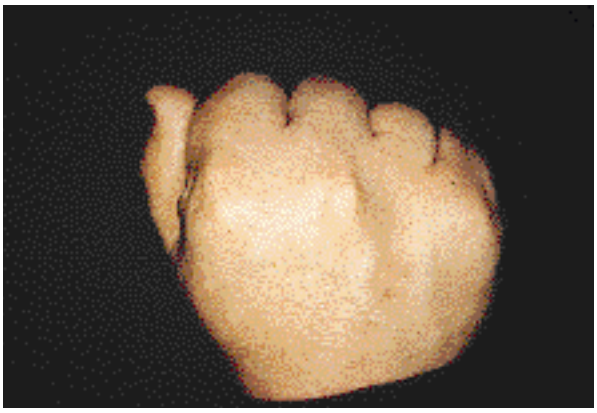

**Fig 8.** Albright's dimpling sign: depressions at site of knuckles while clenching fist.

and are variable in size. The inheritance pattern is not well established.[54] Cutaneous calcification can occur as well as osteomas.

**Secondary cutaneous ossification.** Secondary ossification of the skin is bone deposition in a neoplasm, scar, or various dermatitides and is often associated with connective tissue disease. The most common lesion displaying ossification is the pilomatricoma, which can also show extramedullary hematopoiesis.[61] Basal cell carcinomas, nevi, and chondroid syringomas may also show ossification. Posttraumatic soft tissue ossification is best exemplified in patients with spinal cord injury, although the mechanism remains unclear.[59]

Myositis ossificans[62] is a confusing term describing ossification of soft tissues, including digital soft tissues or subcutaneous fat.[59] It is a benign, self-limiting condition, often seen posttraumatically in young adults; it has an excellent prognosis. The lesions consist of mature lamellar bone without cellular atypia. Surgical excision is curative.[59] This disorder should be distinguished from fibrodysplasia ossificans progressiva, an inherited disorder resulting in soft tissue ossification as well as skeletal abnormalities, especially of the great toe.[62]

### Histology

Primary osteoma cutis, including the ossification seen in AHO, reveals bone spicules in the dermis and subcutaneous tissue on hematoxylin-and-eosin staining[31,55] (Fig 9). Sheets of bone have also been reported.[55] Haversian canals containing vessels and connective tissue are often seen.

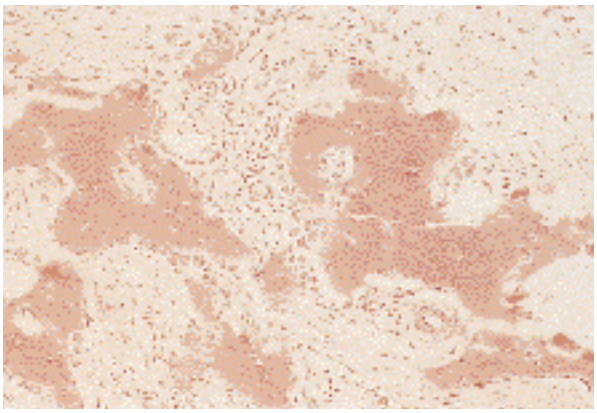

**Fig 9.** Osteoma cutis. Bone spicules are seen in dermis. (Hematoxylin-eosin stain; original magnification ×50.)

Osteoblasts with an elongated nucleus can be seen at the periphery of bony deposits. Deep invaginations of the bone (Howship's lacunae) house the multinucleate osteoclasts.[31]

The osteocytes differentiate from mesenchymal cells and form only membranous bone.[55] Cement lines may be seen with polarized light. Hematopoiesis can occasionally be seen in the central marrow space. Ulceration and epidermal elimination can occur.[56] Microcalcifications (mineralized matrix) containing osteoblast-like cells surrounding the lamellar bone deposits have been noted.[56]

Secondary ossification is the formation of membranous bone in a preexisting lesion or, less commonly, in association with an inflammatory process. The only exception to the formation of

membranous bone in skin is the enchondral bone formation that occurs in chondroid syringomas.[31] The ossification in a pilomatricoma occurs within the adjacent connective tissue rather than within the tumor itself.[55] The tumor cells may also transform into osteocytes.[55] Loose, fibrous connective tissue and capillaries can be seen between bone spicules, but overall the histologic features resemble a primary osteoma.[55]

### Treatment

Treatment of osteoma cutis primarily involves surgical excision. Excellent cosmetic results have occurred in cases of acne-induced osteoma cutis after full-face dermabrasion and punch excisions of individual osteomas.[63]

The evaluation of all patients with calcification or ossification should include serum calcium and phosphorus levels, 24-hour urinary calcium, parathyroid hormone and vitamin D levels, and protein C activity if calciphylaxis is a concern.[1] Roentgenography can often distinguish bone in cutaneous ossification from radio-dense deposits in calcinosis. Computed tomography can detect early soft tissue calcification in dermatomyositis before roentgenograms.[64] Small or deep lesions may be localized by means of sonography and may assist in surgical planning.[65]

The differential diagnosis is fairly limited, but cutaneous calcium oxalate[66] and subcutaneous cholesterol crystals[67] should also be considered.

## ALKAPTONURIA AND OCHRONOSIS

Alkaptonuria is a rare autosomal recessive disorder of homogentisic acid (HGA) catabolism. Its incidence is estimated at 1 in 1 million births,[68] with a higher frequency in Eastern Europe and Santo Domingo.[69] The human gene responsible for alkaptonuria has recently been localized to chromosome 3q[70,71] but has not been mapped or cloned. The underlying defect is a lack of renal and hepatic HGA oxidase (HGAO) activity.

### Pathogenesis

The enzyme HGAO cleaves HGA to its end product, maloylacetoacetic acid.[72] Because of the enzymatic block, HGA is oxidized and polymerized by the enzyme polyphenol oxidase, present in skin and cartilage, to the reactive product benzoquinone acetic acid. This melanin-like product is believed to bind irreversibly to collagen.[31,69] The exact chemical composition of the pigment has not been determined.[73] The collagen bound may be damaged by the pigment deposition; alternatively, preferential deposition may occur on previously damaged collagen. HGA metabolites inhibit the enzyme lysyl hydroxylase with resultant poor collagen cross-linking in experimental models.[74] The pathogenesis of alkaptonuria involves high levels of HGA, an intermediate in the catabolism of phenylalanine and tyrosine. As mentioned previously, the enzyme disorder results in a high level of HGA in the urine, with no known adverse effects attributed to the lack of the normal end product. The pigment products in connective tissue and urine are indistinguishable. It is believed that more than one pigment product may be formed by the oxidation of the HGA,[73] complicating attempts at identifying the pigment. Characterization of the pigment by means of electron spin resonance signals and absorption spectra data suggest some similarity to the eumelanins.[75] Histochemical staining also reveals findings similar to melanin.[76] However, it differs from melanin by being more resistant to bleaching with hydrogen peroxide.[77] The function of trace metals such as zinc in the formation of free radical components of melanin with subsequent tissue damage has been addressed.[75,78]

The pigment product has an affinity for fibrillary collagens, especially those rich in the mucopolysaccharides of ground substance.[76,79] It may be that pigment forms on collagen at the sites of highest activity of polyphenol oxidase, the skin and cartilage.

An ultrastructural study of ochronotic skin has been performed by Attwood, Clifton, and Mitchell.[77] On staining of thick sections with toluidine blue, non-membrane-bound granular black pigment was observed in macrophages and in the adjacent ochronotic fibers. Round deposits of ochronotic pigment were seen within the amorphous masses of degenerated collagen.

Electron microscopy revealed both normal collagen and extensive masses of degraded collagen consistent with actinically damaged collagen. Prominent electron-dense masses could be seen within large, scalloped ochronotic fibers.[77]

Electron-dense rounded bodies were found in the macrophages near ochronotic fibers. These could not be morphologically distinguished from melanin, however, because of similar electron den-

sities. Basal keratinocytes contained increased melanin and prominent Golgi zones suggesting increased melanosome production. Melanin was also noted in the papillary epidermis. Numerous cytoplasmic cystic spaces were noted within the basal cell cytoplasm.

Overall, the ultrastructural findings in this study support the view that damaged collagen results in the preferential deposition of HGA, which is then oxidized and polymerized to ochronotic pigment. It remains unsettled, however, whether pigment deposition occurs in the previously damaged collagen or whether collagen is damaged by the pigment deposition; both are likely to be involved in the pathogenesis of this disorder.

The pathogenesis of the joint destruction remains unclear. Pigment precursors are transported to the joints from the circulation via the subchondral blood flow and are stored in the synovial fluid.[80] The split and fragmented articular surfaces are believed to occur, in part, because of lysyl hydroxylase inhibition by HGA,[74] with poor collagen cross-linking. Extensive chondrocalcinosis also occurs, contributing further to cartilage degeneration.[73,81] The cartilage fragments may contribute to a nonspecific synovitis,[79] and oxygen radical generation may also be involved.[78]

**Clinical features**

Alkaptonuria is characterized by the triad of urinary HGA, ochronosis, and, eventually, ochronotic arthropathy. The HGA or "alkapton" is 2,5-hydroquinone acetic acid and is excreted into the urine (alkaptonuria); with oxygen exposure or alkalinization, discoloration of the urine occurs. Ochronosis refers to the systemic deposition of ochre-colored pigment in collagen-rich connective tissue.[82] Grossly, the tissues appear blue-black, partly because of the Tyndall effect. Approximately half of alkaptonuria patients have clinical evidence of ochronosis.[83] Because of effective renal excretion of HGA, the signs and symptoms of systemic ochronosis, including arthropathy, urinary calculi, cardiovascular involvement, and cutaneous pigmentation, rarely occur before the third or fourth decade. Dark or pink-staining diapers may be noted in infancy, however.[70,84,85] With advancing age, a decrease in renal function results in elevated HGA levels and clinically evident disease.

The most important clinical manifestation of alkaptonuria is the disabling ochronotic arthritis that occurs to some degree eventually in all patients.[76] The arthritis affects the spine and the large weight-bearing joints. The hands and feet are spared.[76] In the spine, darkly pigmented ochronotic cartilage and intervertebral discs are present, but the bones are spared.[76] The spine can become ankylosed with fractures through the ankylosed disc space.[86] Pathognomonic x-ray findings include degeneration of discs with narrowing of the disc spaces and calcification of the residual disc material.[87] The large joints reveal marked pigmentation of the articular surfaces and synovia in degenerated areas arthroscopically.[80] The knees are often affected and reveal articular degeneration and calcification, often leading to a crippling disability in patients in their forties.[76]

Although the classic renal association with alkaptonuria is the black discoloration of urine, patients with acidic urine may never notice their urine being dark.[69] In general, urinary ochronosis involves the incidental finding of prostatic and renal stones,[88] although in a recent case report, ureteral obstruction resulted in nephrectomy.[88] Prostatic ochronotic stones are believed to occur in nearly every case of alkaptonuria, because of the gland's alkaline secretions.[89] One report described the unmasking of occult alkaptonuric ochronosis in a 19-year-old woman after the onset of renal failure.[73]

Cardiovascular involvement occurs in approximately half of the patients.[90] It usually involves extensive valvular pigment deposits and calcification[91] of the aortic valve with subsequent aortic stenosis.[91] The intima of coronary arteries and the aorta were noted to be stained black by ochronotic pigment in an undiagnosed patient during coronary bypass surgery.[92] A diagnosis of alkaptonuria was made after confirmatory testing.[92] Pigment may be found within macrophages in atherosclerotic plaques,[92] but no clear evidence exists for the occurrence of premature atherosclerosis in these patients.[91]

Pigmentation of connective tissue is common in alkaptonuria and focal pigmentation is commonly seen in thin-skinned areas such as the auricle.[73] Diffuse cutaneous pigmentation is uncommon except in cases of renal failure.[93] However, a patchy hyperpigmentation eventually occurs in patients because of pigment accumulation in the dermis over many years.[31] Sun-exposed areas and

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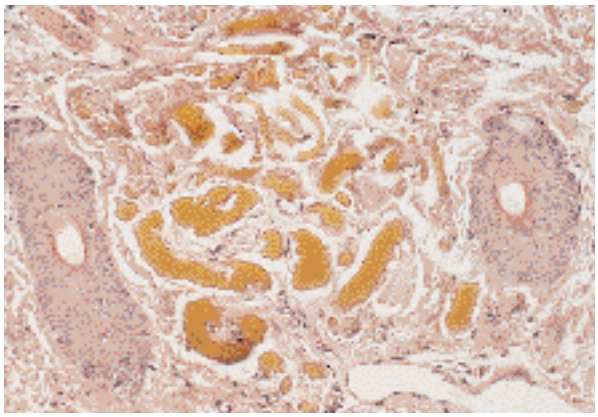

**Fig 10.** Ochronosis. Yellow-brown pigment is deposited on collagen fibers. (Hematoxylin-eosin stain; original magnification ×66.)

areas with numerous sweat glands are commonly affected[94]; dark brown sweat may stain clothing.[82] The ear cartilage is usually the first affected site.[94] Scleral deposits of ochronotic pigment occur in up to 70% of patients[94] and are referred to as Osler's sign. Vision is not affected.[94] Black cerumen and pigmented tympanic membranes and ossicles may result in hearing deficits or tinnitus.[79] The upper respiratory tract is often involved, although the patients are asymptomatic.[84] Autopsies have revealed pigment deposition in the breasts, thyroid, lymph nodes, and bone marrow.[73] Unusual sites of involvement include the teeth,[95] central nervous system,[96] and endocrine organs.[97]

Patients may present with palmoplantar hyperpigmentation or gray nail plate discoloration.[68] The axillae, groin, and ears are the most common sites of pigmentation; the neck, nose, and dorsum of the hands are also affected. All are areas of either thin or actinically damaged skin that may overlie pigmented cartilage or tendons.

### Histology

Biopsy specimens reveal dermal yellow-brown crescentic masses (Fig 10) often in association with solar elastosis.[77] The pigment is deposited within swollen collagen fibers that appear rigid, fractured, and with jagged edges.[98] Degenerated collagen appears as amorphous brown clumps often associated with foreign-body giant cells.[31] Fine granular pigment can be seen lying free in the dermis and within macrophages.[77] Blood vessel endothelial cells and sweat glands may also contain fine granules of pigment.[31,99] Elastic fibers may also contain pigment.[31] A mild increase in basal layer melanin may also be seen.[77] The dermal pigment stains black with cresyl violet and methylene blue stains; silver nitrate stains for melanin are negative,[100] as are stains for iron and lipofuscin.[77]

### Diagnosis

The diagnosis of alkaptonuria is often based on clinical findings and family history. The characteristic histologic features can confirm the diagnosis. Quantitative urinary and serum HGA levels can be performed by means of spectrophotometry.[69] Dark urine on standing or with alkalinization is characteristic of alkaptonuria. Benedict's reagent containing copper is used in routine testing for sugar. HGA reduces copper, yielding a yellow-orange precipitate in Benedict's test, which may be misinterpreted as indicating glucosuria. However, the color of the supernatant is brown-black in alkaptonuria.[89] A positive Benedict test giving a yellow-orange precipitate and a brown-black supernatant,[85] combined with a negative glucose oxidase test, strongly suggests alkaptonuria.[69,85] Characteristic x-ray findings may support the diagnosis if ochronotic arthropathy exists. A recent report described a useful screening test for alkaptonuria in infants, similar to that used for neuroblastoma screening, by means of high-performance liquid chromatography.[101] A rapid assay for detecting alkaptonuria has been described by means of nuclear magnetic resonance spectroscopy to quantify urinary HGA levels.[102]

The differential diagnosis of ocular ochronosis includes melanoma. Localized cutaneous pigmentation can occur with the use of tetracycline, phenothiazines, or heavy metals.[103] The differential diagnosis of ochronotic arthropathy includes ankylosing spondylitis,[95] calcium pyrophosphate dihydrate deposition,[104] herniated disc,[83] and idiopathic atrophic osteoarthritis.[105]

**Treatment.** The disease is compatible with a normal life span.[69] No cure exists for alkaptonuria. A low phenylalanine and tyrosine diet does not alter the course of the disease.[81] The long-term use of ascorbic acid reduces the excretion of HGA,[106] but its efficacy has not been established. Prevention of the long-term sequelae of this disease may warrant its use in the neonatal period, however.[85] Its mechanism of action appears to

involve inhibition of oxidation and polymerization[85] and also binding[94] of HGA to collagen. A dose of 100 mg/kg daily is advocated.[107,108] Corticosteroids may be used in arthritic patients[85] but may aggravate the osteoporosis in these patients.[94] Intralesional steroids[109] to affected joints may be helpful. Future agents may involve protection of lysyl hydroxylase from inhibition.[76] Joint[109] and valve replacement may be necessary.

## EXOGENOUS OCHRONOSIS

Exogenous ochronosis refers to focal darkening of the skin most commonly seen after hydroquinone application to lighten the skin (Fig 11). It typically occurs in dark-skinned patients who use high-strength preparations, but even over-the-counter low concentrations (<2%) may result in this paradoxical darkening of the skin.[110] Hydroquinone is available in concentrations of 2% to 10%.[111] The hyperpigmentation generally occurs after 6 months of use of a bleaching cream[112] and is usually limited to areas exposed to the agent. It is irreversible[84] and difficult to treat. Topical agents containing mercury, phenol, resorcinol, and antimalarials may also be responsible.[110,113]

Systemic absorption of topical phenol may result in pigmentation of skin and cartilage because of its oxidation to hydroquinone.[114] Antimalarial pigmentation presents with facial, pretibial, mucosal, and subungual pigmentation.[115] It may be partially reversible after discontinuation of the medication.[84] Although the mechanism of pigmentation remains unclear, the pigment may be melanin rather than a melanin-like precursor,[113] as in the other exogenous forms.

### Pathogenesis

The cause of exogenous ochronosis is unclear. It may be caused by local inhibition of HGAO by hydroquinone, resulting in polymerized pigment.[116] Whether deposition of hydroquinone or indole acetic acid polymers on collagen occurs, with subsequent collagen degeneration, is unknown.[98] Another hypothesis involves increased tyrosinase activity by hydroquinone.[117] Hull and Procter[118] described exogenous ochronosis in a black patient with vitiligo. In an attempt to lighten normal, remaining skin on the face, the patient applied 2% hydroquinone. The vitiliginous areas remained white, whereas normal skin darkened dramatically. A biopsy specimen of the dark area revealed ochronotic pigment and pigment incontinence. Vitiliginous skin revealed a lack of melanocytes and only a trace of ochronotic pigment. This implies that functional melanocytes are important in the pathogenesis of ochronosis. Sun exposure may activate melanocytes and explain the distribution of ochronosis as well. Whether a melanin-hydroquinone complex forms in the dermis has not been established. Common to both endogenous and exogenous ochronosis are phenolic intermediates that can be converted into melanin-like precursors.[113]

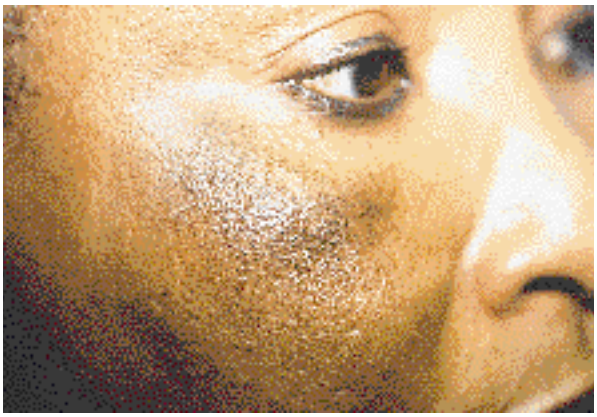

**Fig 11.** Exogenous ochronosis resulting from hydroquinone use.

### Clinical features

Three clinical stages have been identified in exogenous ochronosis.[119] The first displays erythema and mild macular pigmentation, followed by darker pigmentation associated with dark "caviar-like" papules and atrophy. Exogenous ochronosis can simulate melasma. Progression to papulonodular lesions occurs in the third stage. Annular, granulomatous lesions may occur in this late stage.[120] A sarcoidal reaction is seen histologically, with phagocytosis of ochronotic fibers. It may represent an atypical variant of sarcoidosis and should prompt an evaluation to rule out the sarcoidosis.[120]

### Histology

Exogenous ochronosis shows histologic findings similar to those seen in alkaptonuria early in its course. As the disorder progresses to papules and nodules, the ochronotic collagen fibers degen-

erate into amorphous eosinophilic material termed *ochronotic colloid milium*.[111] A granulomatous infiltrate has been described, with sarcoidlike granuloma formation surrounding ochronotic material.[120] Pseudoepitheliomatous hyperplasia[111] and transepidermal elimination of pigment[120] have been described, as well as transfollicular elimination associated with a lichenoid infiltrate.[111] Antimalarial pigmentation contains increased melanin and hemosiderin in addition to ochronotic pigment.[115]

### Treatment

Treatment of exogenous ochronosis involves discontinuing the offending agent.[121] Usually the process is irreversible. Dermabrasion[122] and carbon dioxide laser[123] have been tried with varying degrees of success. One case of tetracycline-responsive, sarcoidal, exogenous ochronosis has also been reported.[124] A case of exogenous ochronosis and allergic contact dermatitis associated with hydroquinone responded well to topical retinoic acid 0.05% and a sunscreen with a high sun protection factor.[125]

## GOUT

Gout is a metabolic disease resulting from tissue deposition of monosodium urate crystals from supersaturated extracellular fluids. The clinical manifestations include acute gouty arthritis, aggregates of crystal in connective tissues (tophi), urate urolithiasis, and, rarely, gouty nephropathy. The cutaneous manifestations of gout will be discussed. They occur in patients with acute gouty arthritis or tophaceous deposits.

### Pathogenesis

The pathogenesis of gouty arthritis and tophi involves urate crystals precipitating from supersaturated body fluids and depositing in joint spaces and cutaneous structures. The crystals stimulate the production of interleukin-1 by monocytes and macrophages. As an endogenous pyrogen, interleukin-1 mediates inflammation and fever.[126] It is believed to be of central importance in the pathogenesis of both acute and chronic gouty inflammation, in part by activating neutrophils with subsequent phagocytosis, chemotaxis, and complement activation. The ingestion of crystals by neutrophils triggers cell damage, rupture of lysosomes, and the leakage of lysozymes, inciting further inflammation and tissue damage. The lack of marked inflammation in tophi of the subcutaneous and dermal layers of the skin has not been clearly explained, however.

The ultrastructure of urate crystals from an olecranon bursa tophus was studied by means of scanning and transmission electron microscopy.[127] On scanning electron microscopy, rod-shaped crystals 5 to 20 μm in length were seen, with irregular deposits on their surfaces. The deposits were believed to be immunoglobulins or other proteins adsorbed onto the crystal surface. With transmission electron microscopy, the crystals appeared as either (artifactual) tubular networks or elongated rods with electron-lucent spaces. The electron-lucent areas were believed to represent the nidus, around which the crystals precipitated, or to represent remnants of proteoglycans or hyaluronic acid.

### Clinical features

The typical patient with gout is a middle-aged or older man, often with a family history of gout. Genetic factors influence renal clearance of uric acid and may be involved in the familial incidence of hyperuricemia and gout.[128] Gout is being seen more frequently in elderly women, however, especially those taking diuretics and who have impaired renal function.[129] The prevalence of gout increases with age and is higher in black patients than white.[130] A high incidence occurs in US Filipinos and South Pacific Islanders, in whom it is associated with obesity. Other risk factors include alcohol use, lead exposure, diuretic use, hypertension, and renal insufficiency.

The first acute attack of gout is preceded by hyperuricemia for many years. The hyperuricemia may be caused by overproduction of urate, underexcretion of urate, or a combination of these. Secondary hyperuricemia may be caused by myeloproliferative disorder,[131] medications such as thiazide diuretics that interfere with urate excretion, or renal failure. Diseases with high tissue nucleic acid turnover, such as psoriasis, are also associated with hyperuricemia. Rare defects of purine overproduction have also been described.[132]

The natural history of gout involves 4 clinical stages.[133] The first is asymptomatic hyperuricemia. Only a minority of patients with elevated uric acid levels actually experience gout; the reasons for this remain unclear. The second stage is acute gouty

arthritis. More than 50% of initial episodes present as podagra, an acute inflammation of the first metatarsophalangeal joint. The ankles, knees, and feet can also be affected. Up to 39% of initial attacks may be polyarticular,[134] but the classic description is oligoarticular pain, swelling, and redness. The third stage refers to intervals between attacks, termed intercritical gout. In most patients, repeat attacks occur within 6 months to 2 years, and if left untreated, become more frequent and severe. The fourth stage is chronic tophaceous gout. The tophi usually occur 10 or more years after the onset of gout. A more rapid onset can be seen in tophi associated with myeloproliferative disorders and tophi in infants with deficiencies of enzymes involved in purine metabolism. The prevalence of tophi has decreased recently, because of improved diagnosis and treatment[132]; they are present in less than 10% of gout patients.

The acute gouty arthritis generally presents with the rapid onset of incapacitating, throbbing pain in the affected joint.[135] The overlying skin is tender, warm, and erythematous and may be confused with a sprain, septic joint, or cellulitis. Fever and systemic symptoms may occur. If untreated, it clears after days to weeks. As the swelling subsides, the skin takes on a violaceous hue and desquamation occurs. The predilection of the acute attack for the first metatarsophalangeal joint may be because of its weight-bearing stresses with subsequent joint damage; the exact initiating event remains unclear.[126]

The differential diagnosis includes chondrocalcinosis (pseudogout),[136] osteoarthritis, Reiter's disease, and psoriatic arthritis.[137]

Laboratory abnormalities include hyperuricemia (a serum urate level above 7 mg/dL) although an acute attack may be associated with a normal value. Leukocytosis and an elevated erythrocyte sedimentation rate are also seen. Hemolytic anemia, abnormal calcium levels, and hypothyroidism may also be associated.[135] The diagnosis of gout depends on identification of urate crystals within the joint fluid or within tophi under polarized light. Negatively birefringent, needle-shaped crystals are diagnostic of gout. The presence of hyperuricemia and a clinical response of the arthritis to colchicine within 48 hours help to confirm the diagnosis.[135]

The incidence of chronic tophaceous gout increases with increasing severity of the gout. The

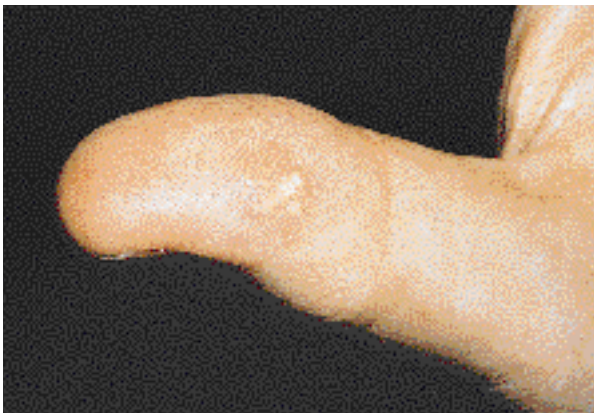

**Fig 12.** Gout. A gouty tophus is seen on finger pad.

crystals usually occur in the subcutaneous tissue overlying joints, tendons, or cartilage. They appear as firm pink nodules or fusiform swellings (Fig 12); the overlying skin may be yellow, erythematous, or ulcerated.[133] It may drain a clear fluid with white flakes of urate, or a thick chalky material. Unusual clinical presentations of tophi include an ulcerative fungating mass of the toe,[138] bullous tophi of the fingers,[139] and the sparing of hemiplegic limbs from tophaceous deposits,[140] possibly from disuse of the limbs. Unusual locations for tophi include the heart valve,[141] eyes,[142] finger pads,[143] larynx,[144] nose,[145] and breast.[146] Tophi have been reported to involve the cervical spine with subsequent myelopathy,[147] and the sacroiliac joint.[148] Rarely, tophi may be the initial manifestation of gout.[149-151] This occurs predominantly in older women with renal insufficiency and affects the fingers rather than the lower extremities. If left untreated, tophaceous articular deposits can erode into bone cartilage and tendons, causing significant structural damage.

The differential diagnosis includes rheumatoid nodules, xanthomas, and calcinosis cutis. Ultrasound examination[152] can distinguish tophi from rheumatoid nodules; tophi reveal central clear spaces (non-sonotransmitting), whereas rheumatoid nodules reveal central echodense areas. Other diseases associated with subcutaneous depositions include calcium pyrophosphate dihydrate, hydroxyapatite, calcium oxalate, and cholesterol[153] deposits.

Radiographic changes seen in gout[154,155] include soft tissue or bony tophi with or without calcification; an erosive arthropathy with central

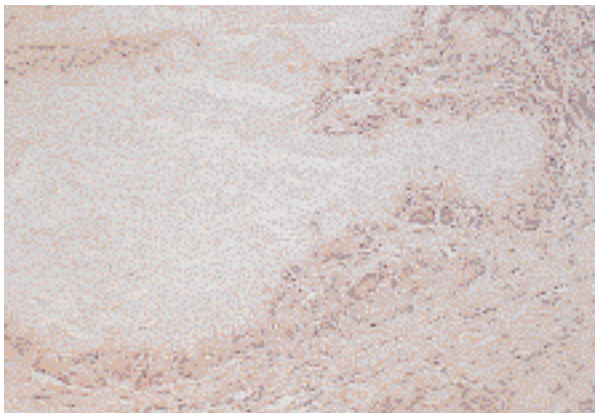

**Fig 13.** Gout. Amorphous material with empty clefts representing dissolved urate crystals. Foreign body giant cell reaction is present peripherally. (Hematoxylin-eosin stain; original magnification ×50.)

"punched out" erosions with sclerotic "overhanging" margins, and a lack of osteophytes. Both the lytic lesions and tophi are reversible with lowering of the serum uric acid level.

### Histology

Gouty deposits in subcutaneous tissue consist of amorphous, amphophilic material with stellate empty spaces surrounded by giant cells, lymphocytes, and occasionally plasma cells (Fig 13). The empty spaces represent dissolved urate crystals. The macrophage nuclei may be distorted by crystals and may appear malignant.[128] On occasion, these may be the only cells present. With alcohol fixation and polarization, brightly refractile brown sheaths of fine, needlelike crystals can be seen. Adding a red compensator results in yellow crystals when parallel to the direction of the compensator, and blue crystals when perpendicular to that plane.[156]

Secondary calcification or even ossification may occasionally be seen.[31] The best fixative to preserve crystals is an ethanol-based fixative, such as Carnoy's fluid.[31] A fibrous capsule may surround the tophi,[157] and collagen and mucopolysaccharides may be abundant. The De Galantha stain may be used to stain the crystals brown/black.

### Treatment

The treatment of acute gouty arthritis often includes the initial use of narcotic analgesics to allay the severe pain. Control of the acute attack must be achieved before beginning drugs that lower the serum urate. Colchicine, nonsteroidal anti-inflammatory drugs (NSAIDS) and, less commonly, corticosteroids, are also used in acute gout. The primary benefit of colchicine is its inhibition of neutrophilic phagocytosis of urate crystals by binding to microtubules and blocking transport of phagocytized crystals to lysosomes. It is an antimitotic agent that also interferes with leukocyte migration, chemotaxis, and adhesion. Indomethacin and most other potent NSAIDS are effective in reducing the pain and inflammation of acute gout. Side effects, including renal insufficiency, are greatest in the elderly patients. Diagnostic aspiration of joint fluid can greatly reduce the pain of gout,[158] and subsequent intra-articular injection of corticosteroids can be administered in patients with monoarticular gout.[159,160] When colchicine and NSAIDS are ineffective or contraindicated, systemic corticosteroid therapy can be used, with the dose tapered over 1 to 3 weeks.[161] Other treatments include corticotropin,[162,163] the parenteral NSAID ketorolac tromethamine,[164] intravenous urate oxydase,[165] and phenylbutazone.[135] Colchicine should be given concurrently to prevent acute, rebound attacks.[135]

The treatment of acute gout does not affect the underlying hyperuricemia that can cause joint, soft tissue, and kidney disease. Hyperuricemia occurs because of decreased renal elimination of urate or, less commonly, increased production of urate. These can be differentiated by measuring 24-hour urine urate excretion. Asymptomatic hyperuricemia is usually benign and rarely needs treatment.[166] Most symptomatic patients have both factors present.[158]

The uricosuric agents sulfinpyrazone and probenecid prevent reabsorption of uric acid, and are used in underexcretors of uric acid. In 10% to 15% of gout patients, the enzymes involved in purine synthesis are abnormal resulting in overproduction of uric acid.[167] Enzymes that are abnormal include deficient glucose-6-phosphatase and hypoxanthine-guanine phosphoribosyl transferase, and increased activity of phosphoribosyl pyrophosphate synthetase. Increased cell turnover, as occurs in myeloproliferative disorders, is associated with elevated purine levels and often results in secondary gout. Allopurinol, a xanthine oxidase inhibitor, decreases uric acid production, and is used in this subgroup of overproducers.

Other indications for allopurinol include urate nephrolithiasis[158] and severe tophaceous deposits.[133] Tophi usually clear within 6 to 12 months after normalization of the hyperuricemia.[133] Tophi have also been reported to clear within 18 months of using the uricosuric agent benzbromarone.[168]

Serum urate-lowering drugs are taken lifelong. Prophylactic colchicine must be used during the first 3 months of therapy with serum urate-lowering drugs to avoid acute flares. Weight control, a high fluid intake, decreased alcohol intake, and a low purine diet are advised in all gout patients. Surgical management is rarely indicated.[169]

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# CME examination

Identification No. 898-110

Instructions for Category I CME credit appear in the front advertising section. See last page of Contents for page number.

Questions 1-31, Touart DM, Sau P. J Am Acad Dermatol 1998;39:527-44.

*Directions for questions 1-16: Give single best response.*

1. The most common cause of metastatic calcification is
   a. parathyroid adenoma
   b. chronic renal failure
   c. hyperthyroidism
   d. hypervitaminosis D
   e. milk-alkali syndrome

2. Metastatic calcification predominantly affects each of the following *except*
   a. lungs
   b. kidney
   c. pancreas
   d. stomach
   e. media of arteries

3. Patients with calciphylaxis typically present with
   a. erythematous papules
   b. palpable purpura
   c. indurated painless cutaneous plaques
   d. painful violaceous skin lesions with livedoid pattern
   e. none of the above

4. Pathogenesis of calciphylaxis involves
   a. primary or secondary hyperparathyroidism
   b. elevated calcium-phosphate product
   c. sensitization of tissue by parathyroid hormone
   d. all of the above

5. Factors that may result in calciphylaxis in patients with AIDS include
   a. renal failure
   b. immobilization
   c. granulomatous disease
   d. multiple blood transfusion
   e. all of the above

6. Each of the following statements is true regarding dystrophic calcification *except*
   a. it is the most common type of calcinosis cutis.
   b. calcification commonly occurs in normal tissue.
   c. visceral involvement is absent.
   d. serum calcium and phosphate levels are normal.
   e. it may occur as localized or generalized forms.

7. Calcinosis circumscripta more commonly occurs in
   a. chronic renal failure
   b. systemic lupus erythematosus
   c. CREST syndrome
   d. hyperparathyroidism
   e. none of the above

8. Calcinosis universalis is most commonly seen in patients with
   a. CREST syndrome
   b. morphea
   c. lupus erythematosus
   d. childhood dermatomyositis
   e. malignant neoplasms

9. Calcium deposits stain black with which of the following special stains?
   a. Verhoeff–van Gieson
   b. Masson trichrome
   c. Periodic acid–Schiff
   d. Fontana-Masson
   e. None of the above

10. Each of the following characteristics is present in Albright's hereditary osteodystrophy *except*
    a. short stature
    b. shortened metacarpals
    c. round facies
    d. decreased intellect
    e. hypercalcemia

11. Secondary cutaneous ossification characterized by enchondral bone formation occurs in which of the following pathologic processes?
    a. Chondroid syringoma
    b. Pilomatricoma
    c. Basal cell carcinoma
    d. Nevi
    e. Scar

12. Exogenous ochronosis is most commonly caused by topical application of which of the following agents?
    a. Mercury compounds
    b. Phenol
    c. Hydroquinone
    d. Resorcinol
    e. Antimalarials

13. The most important clinical manifestation of alkaptonuria is
    a. black discoloration of urine
    b. cutaneous pigmentation
    c. prostatic calculi
    d. cardiovascular involvement
    e. ochronotic arthritis

14. A high incidence of gout occurs in
    a. white persons
    b. black persons
    c. US Filipinos

d. American Indians
e. Middle Easterners

15. Risk factors of gout include
    a. alcohol use
    b. exposure to lead
    c. diuretic use
    d. hypertension
    e. all of the above

16. Diltiazem has been used in the treatment of which of the following diseases?
    a. Gout
    b. Ochronosis
    c. Dystrophic calcinosis
    d. Pseudohypoparathyroidism
    e. None of the above

*Directions for questions 17-21: For each numbered item, choose the appropriate lettered item.*
    a. Hypercalcemia
    b. Acne
    c. "Rice grain" papules at calcified site
    d. Short stature
    e. Podagra

17. Progressive osseous heteroplasia
18. Albright's hereditary osteodystrophy
19. Calciphylaxis
20. Gout
21. Dystrophic calcification

*Directions for questions 22-26: For each numbered item, choose the appropriate lettered item.*
    a. Methylene blue stain
    b. von Kossa stain
    c. De Galantha stain
    d. Howship's lacuna

22. Gout
23. Metastatic calcification
24. Osteoma cutis
25. Dystrophic calcification
26. Exogenous ochronosis

*Directions for questions 27-31: For each numbered item, choose the appropriate lettered item.*
    a. Alkaptonuria
    b. Pseudohypoparathyroidism
    c. Gout

27. Osler's sign
28. Benedict's test
29. Carnoy's fluid fixative
30. Homogentisic acid oxidase
31. Hypocalcemia

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## Answers to CME examination

Identification No 898-109

September 1998 issue of the Journal of the American Academy of Dermatology

Questions 1-32, Manders SM. J Am Acad Dermatol 1998;39:383-98.

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|---|---|---|---|
| 1. b | 9. b | 17. d | 25. b |
| 2. d | 10. a | 18. e | 26. a |
| 3. a | 11. a | 19. c | 27. c |
| 4. e | 12. b | 20. b | 28. c |
| 5. c | 13. a | 21. a | 29. a |
| 6. c | 14. b | 22. b | 30. b |
| 7. e | 15. e | 23. a | 31. c |
| 8. b | 16. a | 24. a | 32. b |