Chapter 21
Calcification and Ossification

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Key Points

- Cutaneous calcification or ossification is the result of a disruption of the normal calcium regulatory pathway in the skin by local or systemic events.
- Calcifying disorders of the skin can be divided into four groups: dystrophic calcinosis secondary to localized or diffuse tissue alterations; metastatic calcinosis, including calciphylaxis, due to impaired calcium-phosphate metabolism; idiopathic calcinosis, and iatrogenic calcinosis.
- Cutaneous ossifications are characterized by heterotopic lamellar bone deposits in the skin and can be divided into two main groups: primary osteomas (localized or diffuse) and secondary ossifications.
- Treatment of localized forms of cutaneous calcinosis or ossification is mainly surgical while treatment of the diffuse forms remains disappointing. Drugs modifying the calcium metabolism are used with variable results. Therapy of the underlying or associated problems such as connective tissue disease or hyperparathyroidism is mandatory to prevent further calcification and tissue damage.

Keywords Dystrophic calcinosis • Metastatic calcinosis • Calciphylaxis • Idiopathic calcinosis • Iatrogenic calcinosis • Osteomas • Secondary ossifications

21.1 Introduction

Cutaneous calcification or cutaneous calcinosis consists in deposits of hydroxyapatite and calcium phosphate crystals in the skin. Two intertwined mechanisms are implicated in the development of cutaneous calcinosis in humans: (1) abnormal plasmatic rates of calcium, phosphate, or vitamin D, which are regulated by a complex hormonal, enzymatic, and environmental network (Fig. 21.1) and (2) various local tissue alterations allowing initiation of crystal formation in the skin.

Ossification is a more complex phenomenon. The initial phase also requires hydroxyapatite crystallization but, unlike calcification, hydroxyapatite crystals are tightly packed and precisely organized in a lamellar haversian bone pattern. Cutaneous ossification is a dynamic process, with continuous bone formation and destruction by osteoblasts and osteoclasts.

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21.2 Clinical and Pathological Aspects of Skin Manifestations

21.2.1 Cutaneous Calcinosis

Clinically, cutaneous calcinosis consists of firm, yellow-whitish, infiltrated papules, nodules, or plaques. Hydroxyapatite deposits in the skin are radio-opaque and can be fortuitously discovered on X-rays. They can also be discovered by chance on histopathological sections when they are relatively small and not clinically suspected. Not infrequently, cutaneous calcinosis can be spontaneously eliminated through the epidermis. A chalky, whitish, more or less liquid material extrudes from the lesions. Most lesions develop gradually and are asymptomatic, although they may occasionally be tender. The distribution of the lesions varies according to the causal disorder. Radiographic examination may demonstrate the extent of tissue calcification. On histopathological grounds, calcium presents with monomorphous basophilic purple-blue deposits of various size and shape, stained deep blue to violet in H&E stained tissue sections (Fig. 21.2), black with the von Kossa stain, and red with Alizarin red. A foreign-body granulomatous reaction and/or peripheral dermal fibrosis are frequently associated.

Cutaneous calcinoses are classified according to their predominant pathogenic mechanism (1). (1) dystrophic calcinosis secondary to localized or diffuse tissue alterations; (2) metastatic calcinosis due to impaired calcium-phosphate

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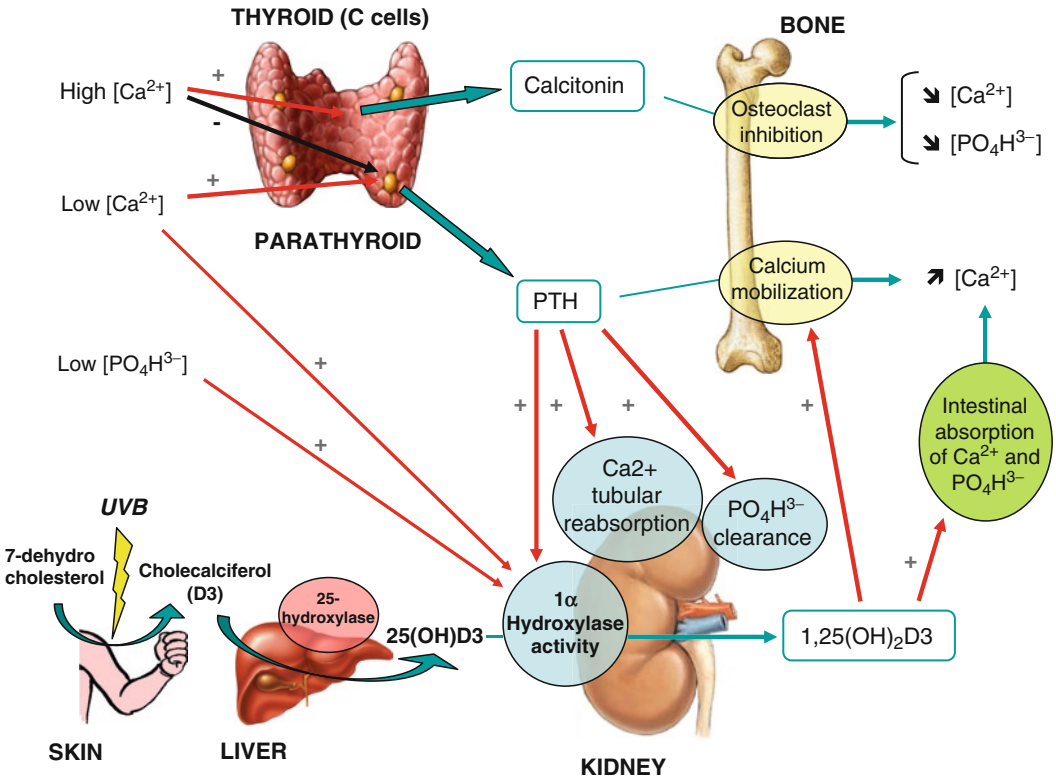

Fig. 21.1 Regulation network of calcium and phosphate plasmatic rates

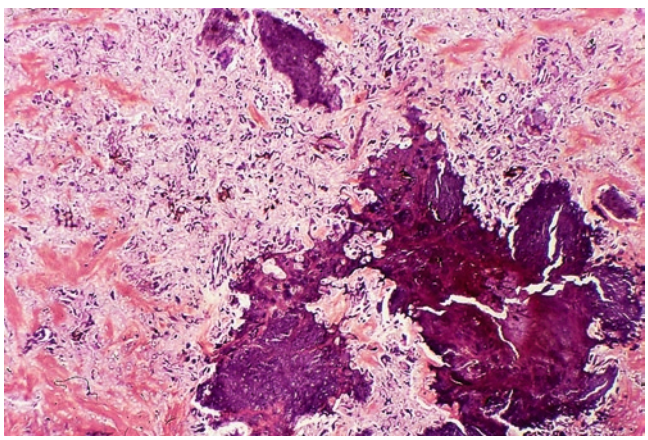

Fig. 21.2 Cutaneous calcinosis (HE stain)

metabolism, including calciphylaxis; (3) idiopathic calcinosis; and (4) iatrogenic calcinosis.

21.2.2 Dystrophic Calcinosis

Dystrophic calcinoses related to localized tissue alterations (1, 2) are summarized in Table 21.1. One of the most frequent causes of localized cutaneous calcification is probably *venous insufficiency* (Fig. 21.3). Calcinosis related to diffuse tissue alterations is seen in the setting of systemic diseases, especially in *connective tissue diseases* (3). It is a frequent feature in systemic sclerosis, especially in the context of CREST syndrome, mainly affecting the pulp of the fingers, but also the periarticular areas, the rachidian axis, and the skin overlying the iliac crests (Fig. 21.4a). Calcification appears in sclerotic skin as well as in uninvolved skin. X-ray examination leads to the discovery of cutaneous calcifications in almost 40% of patients with systemic sclerosis (Fig. 21.4b). Calcification is also seen in morphea, both localized, linear and generalized.

Calcifications occurring in dermatomyositis are larger and more diffuse than in systemic sclerosis. They can affect the skin, the muscles, and the tendons leading to limitations in the mobility of the joints (3). Calcinosis is present in two-thirds of cases of juvenile dermatomyositis and in 20% of adult form. The areas typically involved are those around the joints, the thighs, the arms, and the trunk. Calcinosis is often complicated by painful inflammatory reactions, transepidermal elimination, and cutaneous necrosis in the pressure areas. Severe forms are named "calcinosis universalis" (4).

Calcinosis has been reported in every clinical form of LE (3), although its frequency is lower than in systemic sclerosis or dermatomyositis patients. Asymptomatic cutaneous calcifications can be discovered in as many as 40% of patients

Table 21.1 Exogenous calcinosis and calcinosis related to localized tissue alterations

Transepidermal calcium salts absorption	Calcium gluconate or calcium chloride intravenous injection
	Calcium-containing electrode paste
	Professional exposure to calcium salts or saltpetre
Posttraumatic calcinosis	Heel puncture in neonates
	Intramuscular injections
	Traumatic wounds; lichenification
	Burn scars
	Surgical scars (laparotomy)
	Electrical burns
	Post-radiotherapy
Calcinosis related to vascular alterations	Venous insufficiency
	Phleboliths
	Haematomas
Calcifications related to tissue inflammation	Chronic osteomyelitis
	Chronic adenitis
	Frostbites and ear traumatisms
Post-infectious calcifications	Parasites: cysticercosis, dracunculosis, loa loa filariasis, Bancroft's filariasis, onchocercosis, hydatid cyst
	Leprosy
	Herpes, herpes zoster
Calcifications of cysts and tumors	Follicular tumors: trichoepithelioma, pilomatricoma, basal cell carcinoma, trichoblastic carcinoma
	Sweat gland tumors: syringoma, mixed tumor (chondroid syringoma)
	Epidermal and trichilemmal cyst
	Other tumors: lipoma, dermatofibroma, leiomyoma...
	Cutaneous meningeal heterotopia

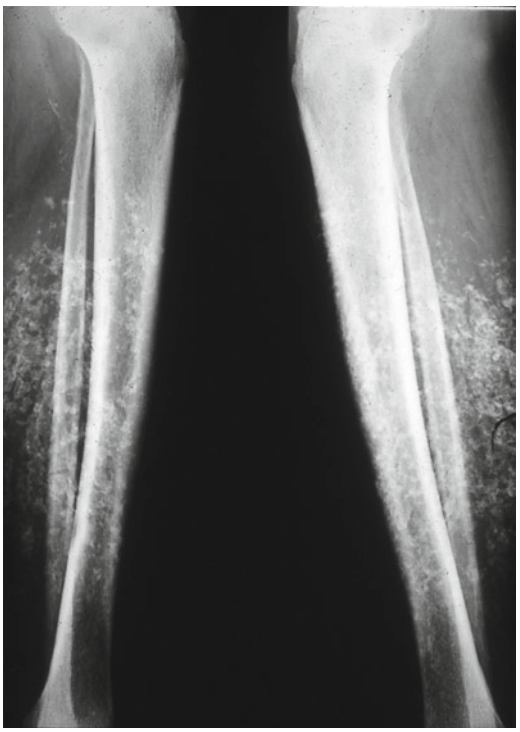

Fig. 21.3 Radiological aspect of cutaneous calcinosis in venous insufficiency

with systemic LE, mainly in the periarticular areas by radiographic examination. Rarely, dermal or subcutaneous calcifications can appear in long-lasting lesions of chronic LE, in subacute LE skin lesions, and lupus panniculitis (5). A form of calcinosis universalis similar to dermatomyositis has been reported in patients suffering from systemic LE (6).

Calcifications have been reported less frequently in many other systemic diseases including porphyria cutanea tarda (7), mixed connective tissue disease (8), nephrogenic systemic fibrosis (9), polyarteritis nodosa and in some inherited diseases such as *pseudoxanthoma elasticum (PXE)* (10), Ehlers–Danlos syndrome, gravis type, Werner syndrome (premature aging with possible soft tissue calcification of the ligaments, tendons, synovial, vasculature, and/or subcutaneous tissue), and Rothmund–Thomson syndrome (small papules on the extremities with dermal calcification; diffuse calcinosis). In PXE, elastic fibers are fragmented, swollen, and clumped in the middle and deep reticular dermis. They appear basophilic because of calcium deposition (Fig. 21.5). Similar calcification is noted in the media and intima of blood vessels.

Anecdotal cutaneous calcinosis has been reported in the context of leukemia (11) and following solid-organ transplantation, bone-marrow transplantation, and especially, liver transplantation (12).

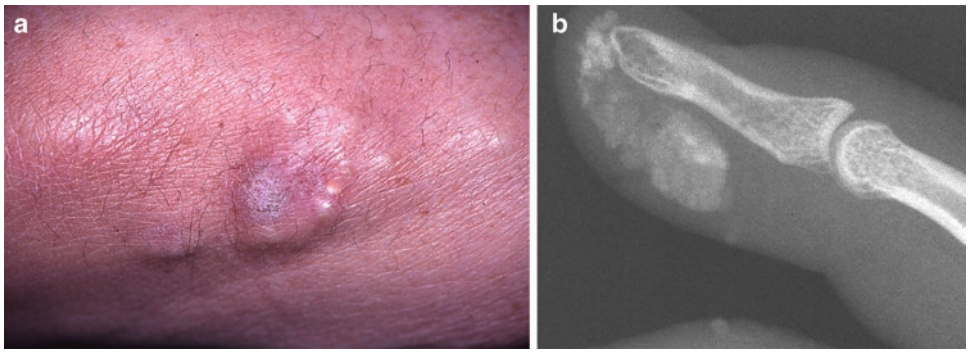

Fig. 21.4 (**a**) Clinical aspect of cutaneous calcification in systemic sclerosis; (**b**) Radiological aspect of calcification of the pulp of the finger in systemic sclerosis

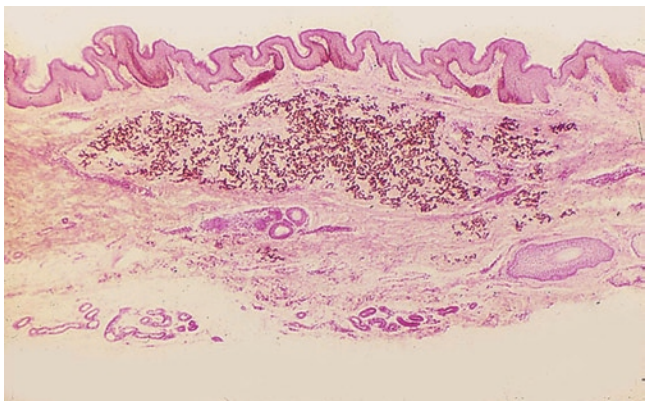

Fig. 21.5 Pseudo-xanthoma elasticum. Histopathological aspect (Orcein stain)

21.2.3 Metastatic Calcinosis

Metastatic calcinoses are related to alterations of calcium-phosphate metabolism. Hyperphosphatemia, indeed, is the major factor implicated in the development of cutaneous calcinosis in the context of hypercalcemia, independently of the blood calcium rate (13).

Cutaneous calcinosis associated with hypercalcemia has been reported in various pathological conditions including sarcoidosis, osteolytic diseases (especially bone metastases), and infectious diseases with granuloma formation (histoplasmosis, tuberculosis). Histiocytes of sarcoidal or infectious granulomas are able to synthesize vitamin D, inducing therefore hypercalcemia. Rarer causes of hypercalcemia with occasional cutaneous calcinosis are seen in vitamin D intoxication and milk alkali syndrome in which calcifications involve the muscles, the eyes, and the visceral organs more often than the skin.

The most frequent clinical manifestations of cutaneous calcinosis develop in the setting of hyperparathyroidism secondary to renal failure. Renal insufficiency leads to a decrease in the 1α hydroxylation of 25(0H)D3 to 1,25$(OH)_2$D3 that is the active form of vitamin D. Its deficiency leads to hypocalcemia and hyperphosphatemia, triggering secondary hyperparathyroidism (13). Bone resorption is increased by the high parathormone (PTH) rate, normalizing calcemia, but worsening hyperphosphatemia. Hydroxyapatite crystallization is triggered locally by various tissue alterations, initiating the cutaneous calcification process. A peculiar clinical manifestation of calcinosis in renal failure patients is *calcific uremic arteriolopathy (calciphylaxis)* (14) characterized by painful necrotic livedo of the limbs with escharotic plaques and mutilating necrosis due to arterial calcifications (Fig. 21.6a). Preexisting protein S or protein C deficiency could favor the development of the lesions. Both imaging study and histopathological examination of the lesions reveal multiple calcifications of the small cutaneous arterioles (Fig. 21.6b).

Calcifying panniculitis results in painful firm nodules, sometimes necrotic, in areas of thick subcutaneous fat tissue (15). Histopathological features show a diffuse calcification of the subcutis without arterial calcification. Calcium deposits decorated with Von Kossa staining underline the cell membranes of the adipocytes, in a way called *en cadre* calcification. Calcifying panniculitis may be triggered by injections and local trauma or may be a complication of infection or gangrene.

A disturbance of the calcium and phosphate metabolism/balance is also seen *in tumoral calcinosis (lipocalcinogranulomatosis, Teutschländer disease)*, a very rare benign condition presenting with massive subcutaneous soft tissue deposits of calcium phosphate near the large joints (16) and in *familial tumoral calcinosis*, which are a heterogeneous group of inherited disorders characterized by the occurrence of cutaneous and subcutaneous calcified masses. Two major forms of the disease are now recognized: hyperphosphatemic and normophosphatemic familial tumoral calcinosis (17). X-rays show enormous subcutaneous radio-opaque masses (Fig. 21.7). Pathological examination reveals irregular subcutaneous round calcifications surrounded by epithelioid histiocytes.

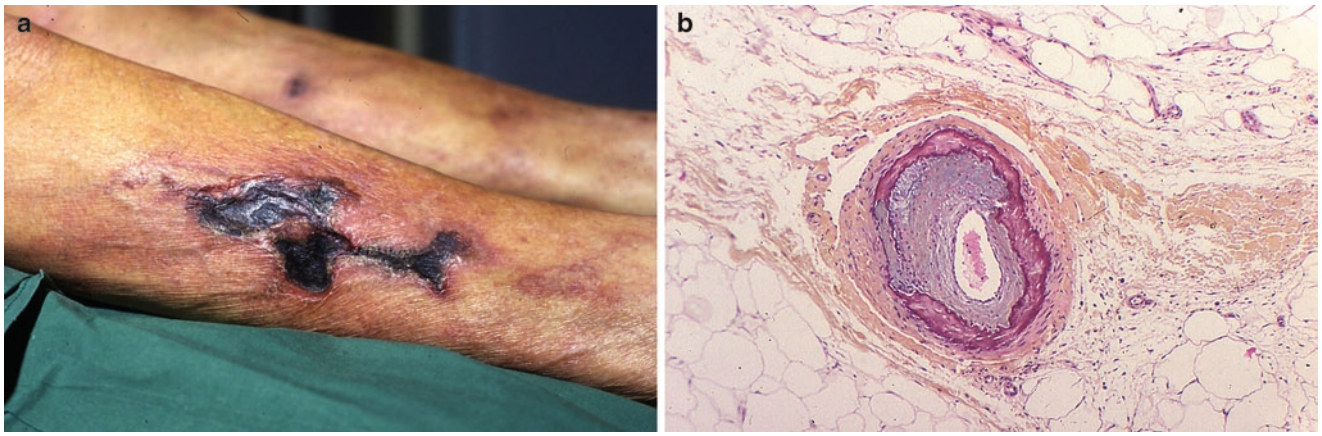

Fig. 21.6 Calciphylaxis in a patient with end-stage renal failure. (**a**) Clinical aspect; (**b**) Calcification of a small cutaneous artery (HE stain)

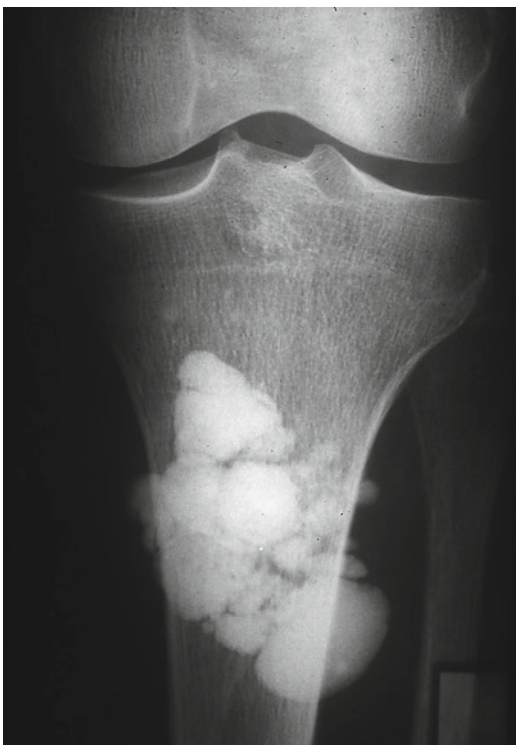

Fig. 21.7 Tumoral calcinosis (Teutschländer disease). Bulky subcutaneous calcified masses in the periarticular area of the knee

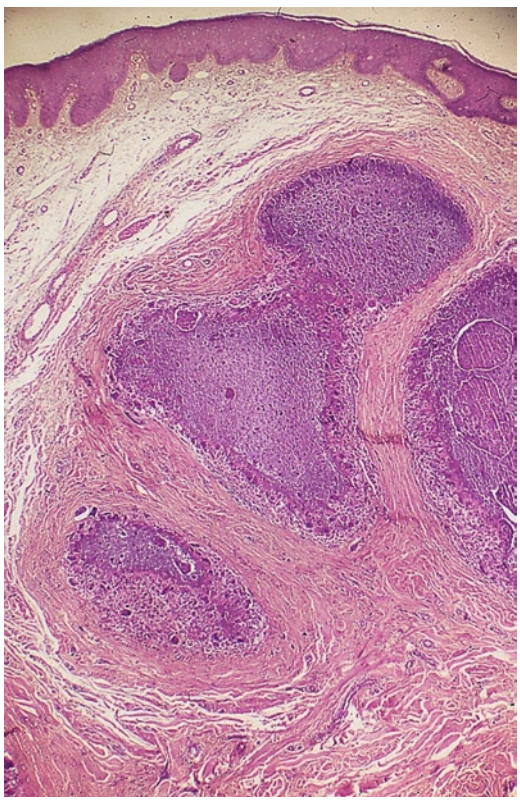

Fig. 21.8 Scrotal calcinosis. Histopathological aspect (HE stain)

21.2.4 Idiopathic Calcinosis

Idiopathic calcinosis is characterized by isolated or multiple papular to nodular lesions, arising in the absence of previous alteration of the skin and of metabolic disorders, including *genital and mammary calcinoses, Winer's solitary calcified nodule, idiopathic calcinosis of the extremities, and extensive idiopathic calcinosis*.

The most frequent condition is *scrotal calcinosis* (18). Vulvar and penile calcinoses have also been described. The lesions are firm and yellow nodules of the skin of the scrotum, the labia majora or the penile shaft, and are often asymptomatic. They display a peculiar histopathologic aspect, showing large dermal calcified masses surrounded by a large granulomatous area containing macrophages and foreign body giant cells (Fig. 21.8). The clinical differential diagnosis is with scrotal or vulvar epidermal cyst.

Mammary calcinosis is often deeply localized in the breast tissue and rarely presents as a dermatological lesion. Idiopathic calcinosis of the areola has exceptionally been reported (19).

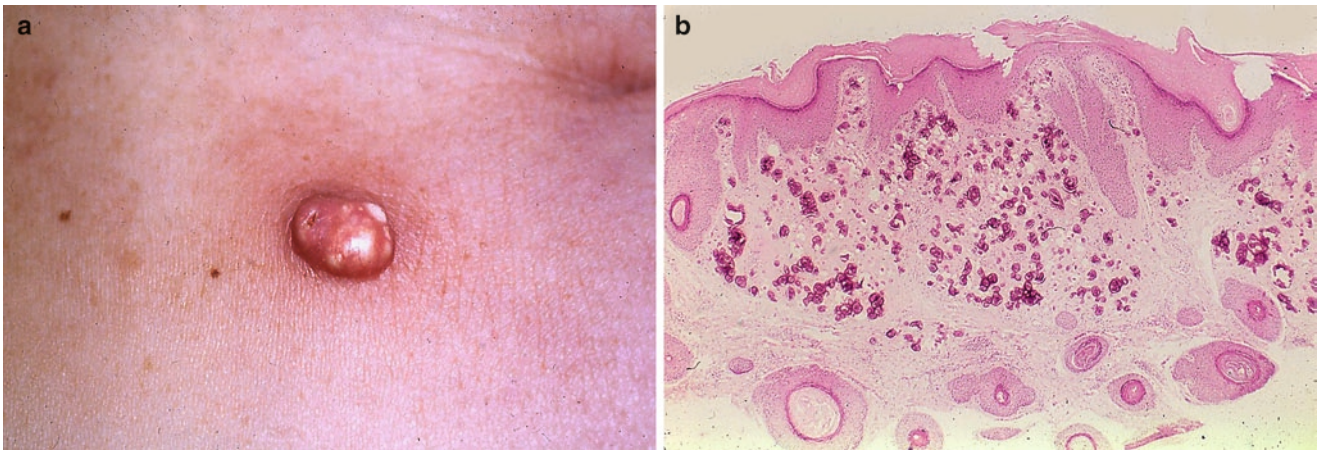

Fig. 21.9 Winer's solitary calcified nodule. (**a**) Clinical aspect. (**b**) Histopathological aspect (HE stain)

Winer's solitary calcified nodule is a solitary small, hard, yellow lesion on the head and neck area, presenting at birth or occurring in early childhood (Fig. 21.9a) (20). Histopathology shows multiple small calcified masses in the upper dermis, surrounded by fibrosis, with absent or very mild inflammatory infiltrate (Fig. 21.9b).

Idiopathic calcinosis of the extremities also named calcinosis circumscripta or subepidermal calcified nodules is characterized by multiple small white papules predominating on the volar aspect of the hands and feet. It has been reported in patients suffering from Down's syndrome (trisomy 21) (21).

Extensive idiopathic calcinosis has often been reported as calcinosis universalis, a term that should be restricted to diffuse calcinosis in dermatomyositis patients. Patients exhibit a diffuse calcification of the skin, the tendons, and the aponeuroses, in the absence of systemic sclerosis or dermatomyositis. The clinical picture and the functional prognosis are close to those of myositis ossificans in children.

21.2.5 Iatrogenic Calcinosis

The cutaneous lesions of iatrogenic calcinosis cutis are typically described as white-yellow papules, plaques, and nodules. They are often multiple and may be associated with erythema, necrosis, or ulceration. *Cutaneous calcinosis secondary to subcutaneous injection of calcium-containing heparin* occurs in patients with renal failure (22). The clinical lesions are characterized by erythematous firm nodules in the areas of subcutaneous injections of low-molecular-weight-calcium-containing heparin in patients with end-stage renal failure and high calcium-phosphate product. Calcified material is transepidermally eliminated. Skin lesions always heal gradually after a few weeks of cessation of the treatment. The biopsy typically shows important calcium deposits in the whole dermis and subcutis, around collagen and elastic fibers, in vessel walls and decorating lipocytes.

Iatrogenic calcinosis cutis has been reported after the *extravasation of calcium-containing intravenous solutions* and following electroencephalographic and electromyographic examinations with electrodes containing calcium chloride paste (23).

21.2.6 Cutaneous Ossification

Cutaneous ossifications have traditionally been divided into primary ossifications (osteoma cutis) and secondary ossifications (2, 24). The latter are related to localized or diffuse tissue alteration and to impaired calcium-phosphate metabolism.

Primary osteomas of the skin (osteoma cutis) may be solitary or multiple.

Solitary osteoma of the skin is often a congenital lesion on the scalp, presenting as a hard radio-opaque nodule of variable size that can ulcerate. Histopathologic examination reveals a well-limited dermal ossified structure, without any associated inflammation (Fig. 21.10). Plaque-like variants, usually on the forehead, have been described in infants (25).

Multiple osteomas cutis are acquired lesions of small size. *Multiple miliary osteomas on the face* (26), or Arzt's disease, consist in multiple tiny, firm yellowish papules on the face of elderly women without any previous history of acne (Fig. 21.11). Another presentation includes disseminated miliary osteomatosis, in which the lesions can be distributed on the whole integument without any relationship with Albright hereditary osteodystrophy.

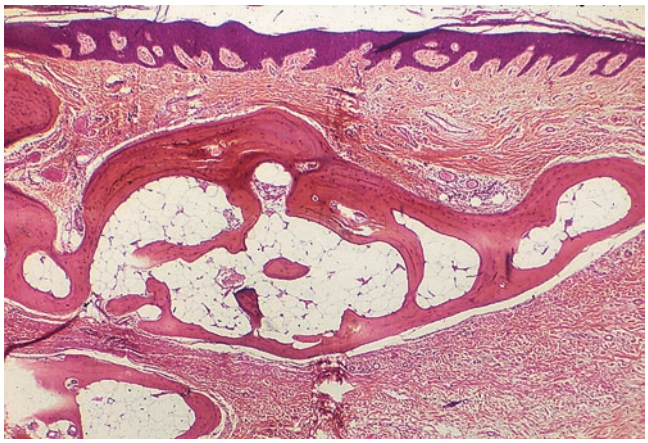

Fig. 21.10 Solitary osteoma cutis. Histopathological aspect (HE stain)

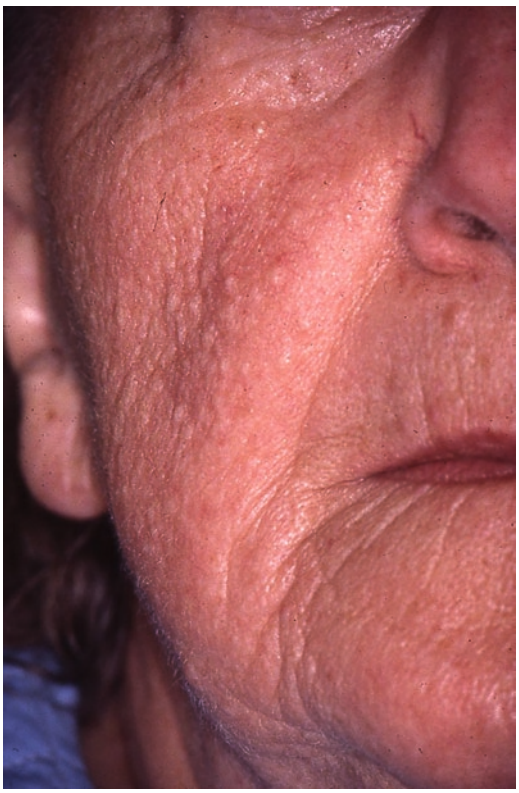

Fig. 21.11 Multiple miliary osteomas on the face

Secondary cutaneous ossifications include ossifications due to tissue alterations and ossifications related to *GNAS* gene alterations.

The former condition is seen in many cutaneous tumors such as benign melanocytic nevus (27), the so-called *osteonevus of Nanta* (1–2% of total melanocytic nevi) whose histopathology shows a small focus of ossification, often situated along a hair follicle among the dermal melanocytic proliferation. Osteomas have also been reported in blue nevus and Spitz nevus and rarely in melanoma. Other tumors exhibiting ossification include follicular tumors (pilomatricoma, basal cell carcinoma, trichoepithelioma), chondroid syringoma (mixed tumor) epidermoid cyst, trichilemmal cyst, dermatofibroma, atypical fibroxanthoma, and hemangioma. *Pilomatricoma* is the most frequent ossifying tumor (10–20% of cases).

Secondary ossification is also found in inflammatory lesions such as postacne facial osteomas that should be distinguished from idiopathic multiple miliary osteomas on the face (28). They appear in the scarring process of acne lesions and may assume a bluish color after prolonged minocyclin treatment. Secondary cutaneous ossification may be encountered in chronic venous insufficiency, surgical scars, intravenous injection sites and in systemic diseases such as diffuse scleroderma, systemic sclerosis, chronic discoid LE, nephrogenic systemic fibrosis, and dermatomyositis.

Ossifications related to GNAS gene alterations include rare inherited ossifying diseases such as progressive osseous heteroplasia (POH), Albright hereditary osteodystrophy (AHO), pseudohypoparathyroidism 1a and 1c (PHP1a/c), and pseudopseudo-hypoparathyroidism (PPHP) (29).

21.3 Treatment and Prognosis

The treatment of primary or secondary localized calcinosis is based on surgical excision of the lesions (30). There is no specific complication due to localized calcinosis, except for transepidermal elimination, which can be painful, but which rarely shows secondary infection.

In diffuse cutaneous calcinosis associated with systemic diseases (scleroderma, dermatomyositis, etc.) and in idiopathic diffuse cutaneous calcinosis, the prognosis relies mainly on possible functional disabilities. Pressure ulcers and secondary infections may arise, portending a worse prognosis. The treatment is quite disappointing. Aluminum hydroxide, biphosphonates, systemic steroids, warfarin, diltiazem hydrochloride, and probenecid have been tried with variable results (31, 32). Sodium etidronate seems more efficient in calcinosis associated with systemic sclerosis than in other diffuse calcinoses. Recently, intravenous immunoglobulin (IVIG) therapy has been offered to patients with diffuse calcifications in systemic sclerosis and dermatomyositis (33). Electric shock wave lithotripsy has seldom been employed to treat calcinosis in dermatomyositis and CREST syndrome (34).

The control of blood phosphate rate is a major objective in the management of patients with renal failure. It allows diminishing the frequency of periarticular and conjunctival hydroxyapatite deposits, but not of vascular deposits.

Calcific uremic arteriolopathy (calciphylaxis) in the context of renal failure carries a poor prognosis. Cutaneous lesions never regress spontaneously. They frequently lead to the death of the patient, through secondary infection and sepsis. The treatment of choice is early parathyroidectomy. Low-calcium dialysis may be of some help, as well as sodium thiosulfate treatment (35). Hyperbaric oxygen therapy has also been proposed in association with other treatments (36).

The other forms of calcinosis in the context of renal failure can be treated with aluminum hydroxide (2 g per day) and low-phosphate diet regimen.

Surgical resection may be the sole treatment option when calcinosis is complicated by infection, nerve compression, or nonhealing ulcer. It is often employed in dermatomyositis patients and in tumoral calcinosis. In the latter condition, recurrence after surgery is observed in as much as 90% of cases.

The treatment of cutaneous ossification relies on surgical excision, if the lesions are esthetically or functionally annoying. Disseminated osteomatosis and miliary osteomas of the face are benign conditions, but they can be disfigurating. Miliary osteomas on the face may be improved by topical 0.05% tretinoin. Physical treatments (37) are the most effective ones including needle microincisions followed by mechanical extirpation of the bony formation, dermabrasion, erbium:YAG laser, or curettage followed by carbon dioxide laser.

Among ossifications related to GNAS mutations, progressive osseous heteroplasia (POH) and rarer progressive forms of PPHP or PHP portend poor functional prognosis, due to progressive ossification of tendons and deep connective tissue. Surgical resection of diffuse lesions tends to lead to recurrence or complications (38). Treatment with pamidronate (biphosphonate) does not resolve preexisting bony formation, but may decrease the occurrence of new ossification, and therefore slow the rate of progressive disability.

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