23.15 Skin and systemic diseases 5743 Clive B. Arc

23.15 Skin and systemic diseases 5743 Clive B. Archer and Charles M.G. Archer

ESSENTIALS Dermatology is most interesting where it overlaps with general in- ternal medicine. Skin lesions can be part of a systemic disease (e.g. in sarcoidosis or systemic lupus erythematosus), or they may be a manifestation of an underlying disease or process as in the case of acanthosis nigricans, which can be associated with either an underlying adenocarcinoma in older patients, or with insulin re- sistance and sometimes overt diabetes mellitus in younger obese patients. Sarcoid can affect the skin in numerous ways, including erythema nodosum, nodular sarcoid lesions, multiple papules, and larger plaques, particularly on thenose, a site at which the skin changes are frequently perniotic in appearance (lupus pernio, scar sarcoidosis, and rarely angiolupoid sarcoid). Diabetes mellitus can also affect the skin in a myriad of ways, with more common forms including granuloma annulare, necrobiosis lipoidica, diabetic dermopathy, cutaneous infections, and the con- sequences of neuropathy. Liver disease can affect the skin by causing pruritus, pigmenta- tion (grey or jaundice), vascular changes (spider naevi), porphyria cutanea tarda, dryness, and hair/nail alterations. Renal disease may affect the skin by causing pruritus, pigmentary changes, dryness, and calciphylaxis, and use of immunosuppression can lead to an increase in malignancy in some cases. Common associations of pyoderma gangrenosum include in- flammatory bowel diseases (ulcerative colitis and Crohn’s disease), rheumatoid arthritis, and other rheumatological disease, haemato- logical malignancies, and monoclonal gammopathies. The noninfectious granulomatous disorders of the skin in- clude sarcoidosis, granuloma annulare, and necrobiosis lipoidica. Granulomatous diseases caused by bacterial infections (e.g. tubercu- losis and leprosy) and fungal infections are discussed in Chapter 23.10 and Section 8. Sarcoidosis and the skin Sarcoidosis has been defined as ‘a disease characterized by the for- mation in all or

several affected organs or tissues of epithelial cell tubercles, without caseation, although fibrinoid necrosis may be pre- sent at the centre of a few, proceeding either to resolution or to the conversion of the epithelial cell tubercles into hyaline fibrous tissue'. Other changes present to a varying degree include partial or com- plete suppression of tuberculin and other intradermal cell-mediated immune responses, and an elevated serum calcium level. The Kveim test, which was positive in most active cases, is no longer available. Aetiology Many infectious agents have been put forward as the potential cause of sarcoidosis, but cultures have been negative and responses to anti- infective treatments have been disappointing. A polymerase chain reaction (PCR) study revealed the presence of various subtypes of mycobacterial DNA in 16 of 20 cases of cutaneous sarcoidosis, but the significance of these and other findings are unclear. Genetic fac- tors may be important, HLA type, for example, seeming to influence the pattern of the disease rather than determining its occurrence. The prevalence of sarcoidosis in developed countries is greater than 10 per 100 000 population, but an apparent increased inci- dence in the last 50 years is probably due to improved methods of detection. Clinical features Skin lesions occur in about 30% of patients with systemic sarcoid- osis, but cutaneous sarcoidosis can occur without systemic disease. Significant pulmonary disease can be asymptomatic and the extent of skin involvement does not correlate with the extent of systemic disease. The specific skin lesions of sarcoidosis arise from a dense accu- mulation of epithelioid granulomas in the dermis or subcutis and can be of variable morphology. Erythema nodosum (Fig. 23.15.1) is a nonspecific clinical feature of early or acute sarcoidosis without the characteristic sarcoidal granulomas (see Chapter 23.7). Nodular sarcoid lesions are often annular and reddish-brown or violaceous in colour. There may be multiple papules and larger plaques, par- ticularly on the nose, a site at which the skin changes are frequently perniotic in appearance (lupus pernio) (Fig. 23.15.2). Skin lesions can affect pre-existing scars (the Koebner or isomorphic phenom- enon), sometimes referred to as scar sarcoidosis. A rare but char-acteristic telangiectatic form of sarcoidosis, angiolupoid sarcoid, affects women, almost always on the sides of the nasal bridge, on 23.15 Skin and systemic diseases Clive B. Archer and Charles M.G. Archer

section 23 Disorders of the skin 5744 the adjacent cheek or below the eyebrows. Sometimes the nodular lesions are solely subcutaneous, and erythrodermic and lichenoid sarcoidosis are unusual morphological forms. Sarcoidosis is more common in black skin and in African- Americans; typical lesions include annular lesions on the nose (Fig. 23.15.3), hypopigmented macules and papules, keloid-like lesions, ulcerative, verrucous, and large nodular forms. Erythema nodosum is uncommon in black skin. In white skin the colour of the lesions ranges from yellowish to the livid violaceous colour which is most marked in lupus pernio. The epidermis is rarely affected and scarring is unusual except in the papular and annular forms. Differential diagnosis The differential diagnosis includes lupus vulgaris, a cutaneous form of tuberculosis, syphilis, and tuberculoid leprosy (see Chapter 23.10). These can usually be distinguished on histology. Other common disorders with granulomatous histology include granuloma annulare, rosacea, and Crohn's disease. Sarcoid-like reactions in a scar should be distinguished from a foreign body reaction.
A granulomatous sarcoidal reaction to any pigment of a tattoo may occur, either alone or accompanied by other signs of sarcoidosis. Clinical investigation A skin biopsy is usually required to show the characteristic granu- lomatous histology. However, a patient with erythema nodosum and bilateral hilar lymphadenopathy may not require histological con- firmation of the erythema nodosum (a form of panniculitis) for the diagnosis of acute sarcoidosis to be acceptable. A chest X-ray should be performed in all cases. Angiotensin- converting enzyme (ACE) is produced by

sarcoidal granulomas and serum ACE is raised in about 60% of patients with systemic Fig. 23.15.1 Erythema nodosum, with painful bruise-like lesions on the shins. Fig. 23.15.2 Sarcoidosis, showing the violaceous lesions of lupus pernio on the nose. Fig. 23.15.3 Sarcoidosis on the nose of a man of Afro-Caribbean origin.

23.15 Skin and systemic diseases 5745 sarcoidosis. However, serum ACE can be elevated in tuberculosis, diabetes mellitus and alcoholic liver disease, and is often normal in localized sarcoidosis of the skin. Serum calcium should be checked, as an increased level may lead to renal failure. Less spe- cifically, the erythrocyte sedimentation rate (ESR) is usually raised, with a slight anaemia, neutropenia or lymphopenia, and hypergammaglobulinaemia in over 50% of patients. An ECG is re- quired to exclude cardiac involvement. Pulmonary function tests might be indicated and computed tom- ography of the chest is helpful to define lung involvement. Hand radiographs may show cystic changes in chronic disease, usually when there are clinical abnormalities in the fingers. The most specific investigation was the Kveim test, in which sarcoidal tissue from the spleen of an affected individual was injected intradermally to produce an epithelioid cell granulomatous reaction. A positive response was the development of a reddish papule at two to three weeks. Excision at six weeks showed the confirmatory hist- ology. However, this test is no longer used because of the infective risk of injecting human tissue. See Chapter 18.12 for further details of investigation of the patient with suspected sarcoidosis. Treatment Limited cutaneous sarcoidosis can resolve spontaneously, so a con- servative approach to treatment is often adopted. Papular and sub- cutaneous skin lesions may settle spontaneously but lupus pernio tends to persist. Superpotent topical corticosteroids are usually tried and can be helpful. Intralesional triamcinolone is often effective, care being taken to inject deeply to avoid atrophy of the skin. In some types of cutaneous sarcoid (e.g. lupus pernio), cosmetic camouflage advice is useful. Other local therapies reported to be beneficial have included cryotherapy, radiotherapy, PUVA (psoralen ultraviolet A) in hypopigmented and erythrodermic sarcoidosis, pulsed dye laser in lupus pernio, and topical tacrolimus. Commonly used systemic therapies include oral corticosteroids, pulsed intravenous corticosteroids, methotrexate, and azathioprine. The most frequent indications for systemic treatment include symp- tomatic pulmonary disease, ocular disease not responding to local corticosteroids, disfiguring skin disease or lymphadenopathy, hypercalcaemia, liver disease with significant dysfunction or hep- atomegaly, other organ involvement such as myocardial disease, nervous system disease or renal disease, myopathy or myositis, and thrombocytopenia. See Chapter 18.12 for further details of treat- ment of the patient with sarcoidosis. Prednisolone is usually prescribed at 30–40 mg daily and re- duced over about two months to a maintenance dose of prednis- olone 15 mg on alternate mornings. Treatment may be necessary for about six months, and azathioprine is often introduced for its immunosuppressive and steroid-sparing effects. Intravenous pulsed methylprednisolone (e.g. 1 g/week for two months, has been ef- fective in patients with severe systemic disease). Methotrexate is often an effective systemic agent, usually pre- scribed as a weekly oral dose (e.g. 7.5–25 mg weekly), with careful monitoring. The response of sarcoidosis to other drugs has been vari- able, including ciclosporin, chlorambucil, allopurinol, isotretinoin, thalidomide, and minocycline. Diabetes mellitus and the skin Skin disorders in individuals with diabetes mellitus include dia- betic dermopathy, the most common skin disorder associated with diabetes, cutaneous infections, the consequences of diabetic neur- opathy, acanthosis nigricans (related to insulin resistance), necro- biosis lipoidica, and probably generalized granuloma annulare. Anogenital pruritus in diabetes mellitus may be caused by candid- iasis or streptococcal infection, but diabetes is not a proven cause of generalized pruritus. See

Chapter 13.9.1 for further discussion of diabetes. Diabetic dermopathy (diabetic shin spots) This occurs in about half of the patients with diabetes, men being more commonly affected than women. Diabetic dermopathy is thought to be due to microangiopathy and possible neuropathy. Reddish oval macules and slightly scaly plaques are seen on the shins, forearms, thighs, and over bony prominences, later evolving into brownish atrophic scars, the brown pigment being due to haemosiderin deposition. The presence of these lesions has been suggested to correlate with other internal complications of diabetes including retinopathy, nephropathy, and neuropathy. Granuloma annulare Granuloma annulare (GA) is a reaction pattern in the skin with a well-established morphology and natural history, although the aetiology and pathogenesis are unclear. Several potential antigenic trigger factors have been suggested. There is an association between granuloma annulare and diabetes mellitus but this is seen uncom- monly. Granuloma annulare can occur at any age but most patients are under 30 years old, women being affected more frequently than men. Localized granuloma annulare is the most common form and pre- sents as reddish collections of papules which form annular lesions, with palpable edges, often over the knuckles (Fig. 23.15.4) and on the elbows. Other areas of the skin may be involved and a diffuse or generalized pattern occurs uncommonly. In the generalized pat- tern, there are numerous skin-coloured or erythematous, slightly palpable coalescing papules, arranged symmetrically on the trunk and limbs. Annular lesions may be violaceous in colour and itching is often a feature of the generalized form. Perforating (referring to extrusion of material through the epidermis) and subcutaneous granuloma annulare are uncommon patterns, the latter sometimes being difficult to distinguish from rheumatoid nodules. It is reasonable to exclude diabetes mellitus in patients with granuloma annulare, but this probably occurs in only about 5% cases of localized GA, rising to about 20% in the generalized form. The association of granuloma annulare with diabetes mellitus is de- batable, however, and some relatively small studies have not shown a definite association. The distinction from necrobiosis lipoidica, more strongly associated with diabetes mellitus, is usually made histologically but granuloma annulare and necrobiosis lipoidica can occur in the same patient. The sporadic occurrence of granuloma annulare and its tendency to remit spontaneously makes it difficult to assess the efficacy of treatment and in many cases no treatment is needed. Spontaneous

 remission would occur in about 50% of patients within 2 years but recurrence, usually at the same sites, occurs in 40%. Potent topical corticosteroids might hasten resolution of localized granuloma annulare and intralesional triamcinolone can be effective if treatment is required. Cryotherapy has also been used. PUVA seems to be effective for generalized granuloma annulare. Other treatments reported to be of benefit include retinoids, ciclosporin, local injections of low-dose recombinant interferon-γ, and topical imiquimod or tacrolimus. However, better clinical studies are re- quired in what is a sporadic disorder. In one clinical trial of gener- alized granuloma annulare treated with oral potassium iodide, the active drug had no advantage over placebo. Necrobiosis lipoidica The precise pathogenesis of necrobiosis lipoidica is unknown, but impaired vascularity of the microcirculation is considered to play a role. Necrobiosis lipoidica has been reported in monozygotic twins. The occurrence of diabetes mellitus in up to 60% patients who have necrobiosis lipoidica was probably overestimated previously in ter- tiary referral populations. Necrobiosis lipoidica might precede the development of diabetes in about one in 10 individuals. However, it does not occur exclusively in diabetes, and the term necrobiosis lipoidica diabeticorum is no longer used. It can occur at any age but usually develops in young adults and in early middle age. There is a female to male ratio of 3:1. Only about 0.3% patients

with diabetes mellitus will have necrobiosis lipoidica. Necrobiosis lipoidica occurs as reddish-yellow shiny plaques on the shins, with atrophy and telangiectasia (Fig. 23.15.5), but early lesions are less obvious. Lesions may ulcerate and a chronic course is usual. In most cases, lesions are bilateral, and they are similar in appearance, whether occurring in diabetic or nondiabetic patients. The differential diagnosis includes granuloma annulare, in which there is less necrobiosis on histology. The yellowish appearance may resemble xanthomatous lesions but this will be distinguished on histology. Necrobiotic xanthogranuloma is a rare disease in which red-orange or yellowish indurated plaques occur on the trunk and periorbital regions, associated with systemic lesions and a mono- clonal gammopathy. Treatment with a superpotent topical corticosteroid under poly- thene occlusion is effective in settling the active inflammatory pro- cess of necrobiosis lipoidica, but the chronic atrophic changes are not reversible and the lesions persist. Early treatment is therefore re- commended. Intralesional triamcinolone has been used with good effect, and some dermatologists use perilesional triamcinolone to prevent extension of the process centrifugally. Short courses of pred- nisolone have been reported to arrest the process but are usually not required. Psoralen and ultraviolet A (PUVA) using a topical psoralen have been beneficial, as has excision and grafting in severe cases. Other treatments which have been tried in the past with limited success include nicotinamide, clofazimine, pentoxifylline, ciclosporin, mycophenolate mofetil and, more recently, infliximab. Promising results have been obtained with thalidomide, antimalarial drugs and, most recently, ultraviolet A1 phototherapy. Cutaneous infections in diabetes mellitus Skin infections due to Staphylococcus aureus and group A Streptococcus haemolyticus are common in diabetes mellitus. Infections with boils (furuncles), carbuncles (with multiple sinuses), and styes were more common before insulin and antibiotics became available, and good skin care, especially of the feet and lower legs, is essential to help prevent cellulitis. Uncommonly, diabetics are prone to soft tissue infections with a mixture of organisms, some- times referred to as nonclostridial gas gangrene or bacterial syner- gistic cellulitis/gangrene, probably a form of necrotizing fasciitis. Well demarcated red areas on the legs and feet of older diabetics do Fig. 23.15.5 Necrobiosis lipoidica, showing reddish-yellow atrophic plaques on the shins. Fig. 23.15.4 Granuloma annulare, showing an annular dermal lesion on the dorsum of the hand.

 not necessarily indicate cellulitis or erysipelas, and this is sometimes referred to as erysipelas-like erythema. Candida albicans infections of the mouth, nail folds, genitals, and intertriginous zones (skinfolds) are common in diabetes. A high glucose level in the saliva seems to be related to the increased preva- lence of oral candidosis. Recurring candida infection is thought to be the cause of an increased prevalence of phimosis in diabetic men. Diabetic neuropathy Older patients with diabetes mellitus are at risk of developing a peripheral neuropathy with mixed sensory and motor nerve in- volvement. Good foot care is essential to prevent the formation of indolent painless perforating ulcers, particularly at pressure points (e.g. from footwear or the bed). The ulcer is usually punched out and often occurs on the sole of the foot in the middle of a cal- losity. Diabetic ulcers are usually due to a combination of factors including microangiopathy, neuropathy, and an increased tendency to infection. Acanthosis nigricans and insulin resistance Acanthosis nigricans, in which there is hyperpigmentation and hyperkeratosis of the flexures (e.g. a velvety appearance in the ax- illae), exists in two forms. In the absence of obesity, acanthosis nigricans (Fig. 23.15.6) may be an important clinical sign of an underlying adenocarcinoma (e.g. carcinoma of the stomach). The changes of acanthosis nigricans in younger obese patients, in which the nape of the neck and antecubital fossae are often involved, are as- sociated with insulin resistance (hyperinsulinaemia) and sometimes overt diabetes mellitus. There

are considered to be two syndromes of insulin resistance, type A occurring in hyperandrogenic women due to a genetic defect affecting insulin receptor function, and type B in older women with signs of immunological dysfunction. Acanthosis nigricans has been reported in response to exogenous insulin. Other skin disorders associated with diabetes mellitus Diabetic bullae Various forms of diabetic blisters occur, presenting as appar- ently spontaneous lesions mostly on the feet and hands. A typ- ical subepidermal blister occurs on a noninflamed base and heals without scarring in a few weeks. Skin reactions to insulin (insulin allergy) Insulin may cause immediate or, more commonly, delayed reac- tions in the skin. A delayed reaction usually begins after two weeks as an itchy nodule at the site of the injection. It lasts for days before healing, with hyperpigmentation and sometimes scarring. Insulin lipodystrophy is rare. Atrophic lesions at the sites of in- sulin injections reflect localized fat atrophy which usually persists. Vitiligo Vitiligo occurs more frequently in patients with diabetes mellitus, a prevalence of about 5% being reported in late-onset diabetes. Wet gangrene of the foot This is a late manifestation of diabetic microangiopathy, non- diabetic atherosclerotic patients tending to develop a dry form of gangrene due to large vessel disease. Liver disease and the skin Numerous systemic diseases may affect the liver and some of these will have cutaneous features (e.g. as occurs in sarcoidosis). The predominant dermatological features and dermatoses associated with liver diseases are discussed here. For a full discussion of liver disease, see Section 15. Pruritus in liver disease Generalized pruritus is the most common symptom associated with liver disease. It may precede the onset of jaundice and may be a feature of hepatitis. Itching is most prominent in primary biliary cirrhosis, sclerosing cholangitis, and other forms of biliary tract obstruction, being less of a problem in alcoholic cirrhosis, autoimmune chronic active hepatitis, and haemochromatosis. Improvement in hepatic itching by drugs which block the action of opiates suggests that en- dogenous opiates may be important in the mechanism of itching. Treatment is directed at the underlying cause (e.g. drug with- drawal in drug-induced cholestasis, surgery for mechanical bil- iary obstruction). Antihistamines are usually ineffective. Other approaches have included cholestyramine, rifampicin, and various forms of phototherapy. Pigmentary changes in liver disease Jaundice is first seen in the sclerae before it becomes generalized. Carotenaemia and drugs, including mepacrine, can also cause yellowing of the skin. A grey hyperpigmentation may occur in chronic liver disease of any cause. There might be a yellowish tinge due to associated jaun- dice. The pigmentation is usually more prominent on sun-exposed sites, including the face with perioral and periorbital accentuation. Pigmentation sometimes localizes to the palmar creases, and men Fig. 23.15.6 Acanthosis nigricans, showing hyperpigmentation and hyperkeratosis of the axillary skin.

 sometimes have increased pigmentation of the areola in association with gynaecomastia. Vascular changes in liver disease Some of the recognized vascular changes in liver disease are non- specific, including spider naevi (spider telangiectases/spider angi-omas) and palmar erythema. Finger clubbing, thought to be due to increased digital pulp blood flow and dilation of arteriovenous anas- tomoses, occurs in about 15% of patients with cirrhosis. Hair, nail, and collagen changes in liver disease The body hair is often thinned and men tend to develop a female pubic hair pattern, due to increased production and decreased me- tabolism of oestrogens, associated with decreased production and increased metabolism of testosterone. Extensive loss of scalp hair might be due to zinc deficiency. Nail colour changes include diffuse white colour, proximal white colour, and distal reddish-pink colour, and white bands. Nail plate changes include clubbing, and flattened nails or koilonychia, associ- ated with poor nutrition or altered iron metabolism. Striae occur in both sexes, especially on the lower abdomen, thighs, and

buttocks. Porphyria cutanea tarda Porphyria cutanea tarda (PCT) is associated with chronic liver disease. In this form of porphyria, there is photosensitivity with blisters, scar- ring, milia (small epidermal cysts), and hyperpigmentation on sun- exposed areas (e.g. dorsa of hands and forearms) with hypertrichosis of the face (e.g. the temples). See Chapters 12.5 and 23.9. Lichen planus The cause of most cases of lichen planus is unknown but lichen planus has been reported in primary biliary cirrhosis, usually following treatment with penicillamine, and in chronic active hepatitis. Hepatitis C virus has also been associated with lichen planus. Uncommon skin disorders Capillaritis of the skin has also been reported in chronic active hepa- titis and primary biliary cirrhosis. Other skin disorders include pityriasis lichenoides, pyoderma gangrenosum, the Gianotti–Crosti syndrome, and the signs of zinc deficiency. Renal disease and the skin The skin and renal system may be affected by the same disease pro- cess. This occurs in various forms of collagen diseases and vasculitis (see Chapter 23.7), in hereditary syndromes such as Fabry's disease (angioma corporis diffusum) and nail-patella syndrome, and in metabolic diseases, including calcific arteriolopathy (calciphylaxis) and primary systemic amyloidosis. Here we concentrate on the cutaneous signs of chronic renal failure, with discussion of re- cent findings in calcific arteriolopathy and nephrogenic fibrosing dermopathy. Uraemic pruritus Generalized severe pruritus occurs in about one-third of pa- tients with renal failure, with many more patients experiencing less troublesome pruritus. In one study, up to 85% of patients on haemodialysis suffered from pruritus, the haemodialysis seeming to provoke the itching in two-thirds of them. There seems to be a correlation between pruritus and predialysis plasma urea levels, but a less obvious relationship between itching and dry skin (xerosis) and secondary hyperparathyroidism. The mechanism of pruritus is complicated, since a reduction in uraemia often does not improve the itching, and pruritus is unusual in acute renal failure. Uraemic neuropathy affects about 60% of patients with renal failure or on long-term haemodialysis and may play a role in uraemic pruritus. The incidence of uraemic pruritus has been reported to be decreasing, which in part may be due to the use of more sophisti- cated techniques and equipment for dialysis. In dialysis, lowering the magnesium concentration of the dialysate has been reported to be helpful. In intractable itching, emollients and ultraviolet B (UVB) radiation are reported to be the most effective therapy. Other treat- ments have included UVA (without psoralen), cholestyramine, acti- vated charcoal, and erythropoietin therapy. Pigmentary changes in chronic renal failure Anaemia presenting as pallor is an early and common sign of chronic renal failure, resulting from reduced haemopoiesis and in- creased haemolysis. A greyish-brown discolouration develops in many cases, due to deposition of melanin. Increased nail pigmen- tation, usually confined to the distal nail, occurs in a proportion of patients. This distal brown or reddish colour, combined with a prox- imal white appearance gives rise to the term 'half and half' nails, a distinctive pattern seen in about 10% of patients with renal failure. Purpura due to mild thrombocytopenia or more marked platelet dysfunction is common and may be partly corrected by dialysis. Urea frosting, in which crystalline urea is deposited on the skin, is now exceedingly rare. Renal transplantation and the incidence of skin cancer The incidence of skin cancers in patients who have received a renal transplant is above that of the general population, and patients often have numerous viral and dysplastic lesions on their skin, some of which will become malignant. The incidence of basal cell carcinomas (BCCs) rises in a linear fashion from the date of transplantation, but the increase in the incidence of squamous carcinomas (SCCs) rises in an exponential fashion. Sun exposure does play a major aetio- logical role in these immunosuppressed patients, as in the non- transplanted population. There is a high incidence in Australia with a mean nonmelanoma skin cancer (NMSC) incidence of 28.1%, with a maximum incidence of 47.1% in patients immunosuppressed for more than 20 years. The same group from

Queensland noted that white patients at highest risk for developing NMSC have blue or hazel eyes, have spent a longer time living in a hot climate, and are more likely to have a pretreatment SCC. See Chapter 23.14. Sun avoidance advice is important in all potential renal transplant patients and should be encouraged among the general population. Calcific arteriolopathy (calciphylaxis) Calcific arteriolopathy (calciphylaxis, calcific uraemic arteriolopathy or CUA) is a disorder in which patients, usually with renal failure, de- velop large painful areas of ulceration. These can be distal involving the limbs, or can be proximal causing large areas of ulceration on the breasts, abdomen, and buttocks.

23.15 Skin and systemic diseases 5749 Recent studies have shown that the calcification is not the same as that seen in patients with skin necrosis, and the term calciphylaxis is considered inaccurate. CUA indicates the site of the calcification and the usual clinical state of the patients. However, CUA has been reported in patients with minimal or no renal failure, hence the author's preferred use of the term calcific arteriolopathy. In addition to renal failure, the other major risk factors include female gender, white race, diabetes mellitus, obesity, and warfarin and the clotting disorders such as protein C and protein S deficiency. It has also been shown that the use of calcium salts and vitamin D in chronic renal failure is a risk factor. A direct role of hyperparathyr- oidism in the development of calcific arteriolopathy is not proven, the disease having been described in the presence of a normal parathormone level. The usual presentation of calcific arteriolopathy is of areas of ul- ceration on the legs, buttocks, abdomen, or breasts which are painful and may be extensive. Livedo reticularis around the ulcers may be present. Acral ulceration can also occur, causing autoamputation. The differential diagnosis is any cause of ulceration, especially vas- culitis, in which livedo reticularis may also be present. Increasing awareness of the condition is allowing the diagnosis of calcific arteriolopathy at an earlier nonulcerative stage, before the subcuta- neous indurated plaques develop into ulcers. The diagnosis of calcific arteriolopathy is usually by biopsy, the histology showing calcification of the media of small arterioles in the skin. This is associated with a brisk intimal proliferation, sometimes with fibrin thrombi visible in the lumen. Other types of vascular cal- cification are seen in chronic renal failure. The calcification seen in calcific arteriolopathy is no longer thought to be a passive process. The calcium deposited is hydroxyapatite, which is the same as seen in bone. This is different from the compounds found in other types of calcification. If calcific arteriolopathy is diagnosed at the nonulcerative stage there is some evidence for the use of oral prednisolone at a dose of 30–50 mg mane for up to eight weeks. If ulceration is already pre- sent, debridement of the necrotic tissue is sometimes recommended and use of antibiotics to prevent overwhelming sepsis is important. Adequate pain control is another important management measure. The outcome is poor, with a mortality of about 60% for proximal disease and about 20% for distal disease, usually from overwhelming sepsis. Since there is such a high mortality, the approach should be to aim for prevention. The control of the hyperphosphataemia is thought to be fundamental to this. Phosphate binders are used, with some evidence showing that the non-calcium-containing binders are better. Parathyroidectomy has been found to be useful in the control of calcific arteriolopathy in some series but not in others. Nephrogenic fibrosing dermopathy Nephrogenic fibrosing dermopathy (NFD) is a recently reported fi- brotic disease occurring in patients with renal disease. Nephrogenic fibrosing dermopathy was initially reported in patients with estab- lished renal failure, either on dialysis or having had a transplant, but it has since been reported in patients with chronic renal insuffi- ciency not requiring renal replacement therapy. An association with the intravenous injection of gadolinium-based radiocontrast media has been suggested. The clinical presentation of this rare disorder is of

plaques of indurated skin on the extensor surfaces of the limbs, and scleral involvement has been described. The limbs are affected in a sym- metrical manner with skin-coloured papules coalescing to form brawny plaques with a ‘peau d’orange’ appearance, occasionally with swelling of the hands and feet. Patients may complain of pain, prur- itus, and causalgia. Most patients do not have systemic involvement, but when this is present the disease may be rapidly fatal. The histology shows an increase in dermal collagen with a paucity of inflammatory cells. There is mucin deposition with abundant eo- sinophilic spindle cells in the upper dermis that stain for CD34. The disease that nephrogenic fibrosing dermopathy is most similar to is scleromyxedema, but the relative sparing of the face in nephrogenic fibrosing dermopathy and the lack of a paraprotein allows the dis- eases to be separated on clinical grounds. The mainstay of treatment is improvement of the renal function but transplantation is not guaranteed to cure the disease. Treatments such as plasmapheresis, topical calcipotriol under occlusion, PUVA, and oral steroids have been tried, but the results are difficult to as- sess, since an improvement in renal function is itself an effective form of therapy. Other systemic diseases and the skin Pyoderma gangrenosum Pyoderma gangrenosum (PG) is an uncommon, noninfectious neutrophilic dermatosis commonly associated with underlying sys- temic disease. Several clinical variants of pyoderma gangrenosum have been described, including ulcerative, pustular, bullous, and vegetative forms. An immune-mediated process is thought to play an important pathogenetic role, with about 50% of patients having an associ- ated systemic disease. Common associations include inflammatory bowel diseases (ulcerative colitis and Crohn’s disease), rheumatoid arthritis and other rheumatological disease, haematological malig- nancies, and monoclonal gammopathies. A characteristic presentation of pyoderma gangrenosum be- gins with small tender papules or pustules that evolve into painful ulceration with typical undermined violaceous edges (Fig. 23.15.7). Lesions can be solitary or multiple. Healing usu- ally occurs with an atrophic cribriform scar (i.e. having several small holes within it). Associated symptoms include fever, mal- aise, myalgia, and arthralgia. Bullous pyoderma gangrenosum is often associated with myeloproliferative disorders. Vegetative or superficial granulomatous pyoderma gangrenosum may have superficial and deep components and is not usually associated with any systemic disease. The diagnosis of pyoderma gangrenosum is made by recognizing the characteristic clinical features and by excluding other causes of ulceration. A biopsy across the edge of a lesion, depending on the type of pyoderma gangrenosum, will show a neutrophilic infiltrate, but at best the histology is ‘consistent with’ as opposed to ‘diagnostic of’ the condition. Many effective treatments for pyoderma gangrenosum have been reported, the precise choice depending on disease severity as well as on the presence of an underlying systemic disease. For early or mild disease, topical therapy with a superpotent corticosteroid or tacrolimus, along with good wound care, may be sufficient. Intralesional triamcinolone may also be effective.

 For more severe cases or PG resistant to topical therapy, oral pred- nisolone has been the mainstay of treatment. Other treatments in- clude pulsed intravenous corticosteroids, minocycline, dapsone, and immunosuppressants such as azathioprine or ciclosporin. Ciclosporin is usually effective at a dose of less than 5 mg/kg per day. Methotrexate has been used for patients with underlying in- flammatory bowel disease and, more recently, infliximab and other biological agents have been effective. Less commonly used treat- ments include plasmapheresis, intravenous immunoglobulin, and thalidomide. Behçet’s disease Behçet’s disease is a multisytem disease that is defined by the pres- ence of oral aphthosis with at least two of the following: genital aphthae, synovitis, posterior uveitis, cutaneous pustular vasculitis, or

meningoencephalitis, in the absence of inflammatory bowel dis- ease or autoimmune diseases. It typically affects young adults and is uncommon in northern Europe and the United States of America, but common in Middle Eastern and Japanese populations. Here we focus on cutaneous manifestations, but see Chapter 19.11.10 for a full discussion of Behçet's disease. Behçet's disease was named after the Turkish dermatologist who described the multisystem disease. The pathogenesis is unclear, but there may be a genetically determined response to an infec- tious agent. Biopsies of early aphthae or of lesions of pustular vas- culitis show a leukocytoclastic vasculitis, although late lesions are lymphocytic. The clinical course of Behçet's disease is variable, although patients typically have oral aphthae with any combination of genital aphthae, cutaneous pustular vasculitis, ocular lesions, or arthritis. Only pus- tular vasculitis and erythema nodosum-like nodules should be used to satisfy diagnostic criteria, although a variety of skin findings (e.g. pyoderma gangrenosum-like lesions) may be present in patients with Behçet's disease. Posterior uveitis is the only ocular criterion for the diagnosis of Behçet's disease, but there are other ophthal- mological manifestations. The posterior uveitis in Behçet's disease is due retinal vasculitis and may result in blindness. The musculoskel- etal involvement in Behçet's disease is an asymmetrical, migratory, nonerosive oligoarthritis, mimicking rheumatoid arthritis. Many neurological manifestations may occur, but only meningoencephal- itis is considered to be a diagnostic criterion. Vascular involvement in Behçet's disease may affect arteries and veins, leading to aneur- ysms or occlusions that are sometimes fatal. The diagnosis of Behçet's disease should be suspected in any pa- tient with recurrent and extensive oral aphthosis. Other causes of aphthosis such as inflammatory bowel disease, as well as lesions that mimic aphthae such as herpes simplex virus infection, must be ex- cluded. The diagnosis should also be considered in young patients with deep venous thrombosis, particularly in the absence of other risk factors or thrombophilia. A positive pathergy provocation test, read at 24–48 h, may further support the diagnosis. Aphthae may be treated with topical or intralesional cortico- steroids, topical tacrolimus, or with viscous lidocaine (lignocaine). Oral colchicine may also be used to treat mucocutaneous manifest- ations, although this option might be limited by gastrointestinal intolerance and requires monitoring for neutropenia. Dapsone in combination with colchicine has also been used successfully. Thalidomide may be effective in this situation but is becoming in- creasingly difficult to prescribe for women because of the risks to the fetus. Behçet's disease with manifestations other than mucocutaneous involvement may be treated with systemic corticosteroids, although this may not control severe ocular, neurological, or nonvasculitic vascular disease. Immunosuppressive agents such as ciclosporin, azathioprine, and methotrexate have been used for patients with se- vere Behçet's disease. Xanthomas There are different forms of xanthoma. Eruptive xanthomas of the skin, often on the buttocks and limbs, may develop in patients with hyperlipoproteinaemia in association with diabetes mellitus. Control of the hyperlipoproteinaemia and diabetes usually leads to resolution of the yellowish papules. See Chapter 12.6 for more de- tailed discussion. Crohn's disease and the skin Periorificial granulomatous lesions sometimes occur in Crohn's dis- ease. Perianal abscesses and multiple fissures with fistulae occur in about a quarter of patients. Anal tags which are oedematous or have granulomatous histology are common. Oral Crohn's disease pre- sents as a thickened corrugated appearance of the oral mucosa and lips. Granulomatous cheilitis may precede other features of Crohn's disease. Cutaneous Crohn's disease may also affect sites not in continuity with the bowel, and reactive dermatoses associated with Crohn's dis- ease include oral aphthae, erythema nodosum (see Chapter 23.7), and pyoderma gangrenosum (see next), a neutrophilic derma- tosis. Other skin diseases are rarely associated with Crohn's disease, and it can be difficult to distinguish perianal Crohn's disease from hidradenitis suppurativa. Fig. 23.15.7

Pyoderma gangrenosum, showing ulceration with a characteristically undermined edge on the lower leg.

23.15 Skin and systemic diseases 5751 Thyroid disease and the skin Thyroid disease is discussed in detail in Chapter 13.3.1. However, there are several cutaneous manifestations of both hypothyroidism and hyperthyroidism. Skin features associated with hypothyroidism in- clude pale and cold extremities, absence of sweating, puffy oedema of hands and face, eczema craquele and pruritus, xanthomatosis (sec- ondary to hyperlipidaemia), coarse sparse hair, brittle/striated nails, purpura/ecchymoses, punctuate telangiectasia on arms and finger- tips, and delayed wound healing. Features associated with hyper- thyroidism include soft and dry skin, palmar erythema, flushing, increased sweating, fast nail growth, pruritus and urticaria, pretibial myxoedema, acropachy, and diffuse addisonian hyperpigmentation. Pruritus without a rash Pruritus associated with systemic disease has been dealt with else- where within this chapter, but individuals presenting with itch in the absence of skin disease, should be carefully assessed. It can some- times be difficult to distinguish secondary changes associated with excoriation from primary skin disease. However, detailed history (including drug history) and thorough systemic examination are crucial. Routine initial investigations might include renal function, full blood count with differential and haematinics, thyroid func- tion, and liver function, with consideration of other investigations dependent on the clinical findings, such as chest radiograph, HIV testing, and screening for malignancy. FURTHER READING Archer CB (2008). Dermatological aspects of internal medicine. In: Archer CB (ed) Ethnic dermatology—clinical problems and skin pigmentation, pp. 110–25. Informa Healthcare, London. Barham KL, et al. (2004). Vasculitis and neutrophilic vascular reac- tions. In: Burns T, et al. (eds) Rook’s textbook of dermatology, 7th edition, pp. 49.1–49.46. Blackwell Science, Oxford. Carroll R, et al. (2003). Incidence and prediction of non-melanomatous skin cancer post-renal transplantation: a prospective study in Queensland, Australia. Am J Kidney Dis, 41, 676–83. Durupt F, et al. (2008). Successful treatment of necrobiosis lipoidica with antimalarial agents. Arch Dermatol, 144, 118–9 Euvrard S, Kanitakis J, Claudy A (2003). Skin cancers after organ trans- plantation. N Engl J Med, 348, 1681–91. Finucane KA, Archer CB (2005). Dermatological aspects of medi- cine: recent advances in nephrology. Clin Exp Dermatol, 30, 98–102. Gawkrodger DJ (2004). Sarcoidosis. In: Burns T, et al. (eds) Rook’s text- book of dermatology, 7th edition, pp. 58.1–58.24. Blackwell Science, Oxford. Graham RM, Cox NH (2004). Systemic disease and the skin. In: Burns T, et al. (eds) Rook’s textbook of dermatology, 7th edition, pp. 59.1– 59.75. Blackwell Science, Oxford. Heinzerling L, et al. (2008). Insulin allergy: clinical manifestations and management strategies. Allergy, 63, 148–55. Johns CJ, Scott PP, Schonfled SA (1989). Sarcoidosis. Annu Rev Med, 40, 353–71. Jorizzo JL (1986). Behçet’s disease: an update based on the 1985 inter- national conference in London. Arch Dermatol, 122, 556–8. Kukreja T, Petersen J (2006). Thalidomide for the treatment of refrac- tory necrobiosis lipoidica. Arch Dermatol, 142, 20–2. Li N, et al. (1999). Identification of mycobacterial DNA in cutaneous lesions of sarcoidosis. J Cutan Pathol, 26, 271–8. Mailler-Savage EA, Adams BB (2008). Exogenous insulin-derived Acanthosis nigricans. Arch Dermatol, 144, 126–7. Morgan AJ, Schwartz RA (2008). Diabetic dermopathy: a subtle sign with grave implications. J Am Acad Dermatol, 58, 447–51. Radakovic S, et al. (2010). Dramatic response of chronic ulcerating necrobiosis lipoidica to ultraviolet A1 phototherapy. Photodermatol Photoimmunol Photomed, 26, 327–9. Sarkany RPE, et al. (2004). Metabolic and nutritional disorders. In: Burns T, et al. (eds) Rook’s textbook of dermatology, 7th edition, pp. 57.1–57.124. Blackwell Science, Oxford. Scadding JG, Mitchell DN (eds) (1985). Sarcoidosis, 2nd edition, pp. 1–12. Chapman & Hall, London. Shimanovich I, et al. (2008). Necrobiosis lipoidica in monozygotic twins. Arch Dermatol, 144, 119–20. Sterling JC (2004). Virus

infections. In: Burns T, et al. (eds) Rook’s text- book of dermatology, 7th edition, pp. 25.1–25.83. Blackwell Science, Oxford. Wells RS, Smith MA (1963). The natural history of granuloma annulare. Br J Dermatol, 75, 199–205. Young AW Jr, et al. (1973). Dermatologic evaluation of pruritus in patients on haemodialysis. N Y State J Med, 73, 2670–4.

Revision #1
Created 2026-01-22 16:42:57 UTC by Omar Ayman
Updated 2026-01-22 16:42:57 UTC by Omar Ayman