23.7 Cutaneous vasculitis, connective tissue disea

23.7 Cutaneous vasculitis, connective tissue diseases, and urticaria 5639 Volha Shpadaruk and Karen E. Harman

ESSENTIALS Vasculitis (angiitis) denotes necrotizing inflammation of the blood vessels; occlusive vasculopathy implies vascular occlusion without significant vascular inflammation (Box 23.7.1). A small-vessel cuta- neous vasculitis is the most common vasculitis affecting the skin, and may be the first sign of a systemic vasculitis, but 50% of patients have no systemic disease. The clinical findings must be integrated with the results of serological, pathological, and imaging studies to reach a diagnosis. Systemic lupus erythematosus is diagnosed if four or more of the American College of Rheumatology revised criteria for the clas- sification of the disease are present, either sequentially or simul- taneously. These include four mucocutaneous signs: malar rash, discoid rash, photosensitivity, and oral ulcers. Skin lesions are the first manifestation of systemic lupus erythematosus in 23–28% of patients; about 73% of patients report photosensitivity, and up to 91% develop cutaneous symptoms at some stage in the evolution of their disease. Dermatomyositis is an uncommon multisystem autoimmune disease in which inflammatory skin changes are associated with polymyositis of skeletal muscle. The clinical spectrum ranges from pure cutaneous disease, through coexisting patterns of cutaneous/ systemic disease, to isolated inflammatory polymyositis. Cutaneous involvement may precede the onset of myositis by several years, but some patients never have muscle involvement (amyopathic dermatomyositis). Scleroderma means thickened, fibrotic, bound-down skin. It might develop in association with a systemic connective

tissue disease (systemic sclerosis) or present as a localized cutaneous problem. Localized scleroderma, unlike systemic sclerosis, is a self-limiting condition confined to the skin and subcutaneous tissue; it does not transform into systemic sclerosis. Dermatologists tend to use the term ‘morphoea’ for localized disease, while paediatricians and rheumatologists refer to the same condition as ‘scleroderma’. Panniculitis is inflammation of the subcutaneous fat, sometimes associated with vasculitis. It presents with erythematous subcuta- neous nodules, most often on the lower leg. Historical perspective The systemic vasculitides are characterized by inflammation of blood vessels leading to tissue or end organ injury, depending on the size of the vessels affected. The initial descriptions of vasculitis were isolated case reports by William Heberden in the 1760s. Kussamul and Meier described a case of polyarteritis nodosa in 1866. In the twentieth century, the first description of granulomatosis with polyangiitis (Wegener’s granulomatosis), eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome), Takayasu arteritis and giant cell arteritis, and Kawasaki disease were published. Wegener’s granulomatosis, Churg–Strauss syndrome, and Henoch–Schönlein purpura were known by their eponyms until the present decade (see Box 23.7.2). The initial classification of vasculitis was proposed by Zeek in 1952, who recognized five types of vasculitis based on vessel size. The classification of vasculitis has subsequently evolved with the 23.7 Cutaneous vasculitis, connective tissue diseases, and urticaria Volha Shpadaruk and Karen E. Harman Box 23.7.2 New nomenclature adopted in the 2012 CHCC definitions • Wegener’s granulomatosis = granulomatosis with polyangiitis (GPA) • Churg–Strauss syndrome = eosinophilic granulomatosis with poly angiitis (EGPA) • Henoch–Schönlein purpura = IgA vasculitis CHCC, Chapel Hill Consensus Conference. Box 23.7.1 Definitions • Vasculitis (angiitis)—necrotizing inflammation of the blood vessels • Occlusive vasculopathy—vascular occlusion without significant vascular inflammation (i.e. occlusion without vasculitis)

section 23 Disorders of the skin 5640 recognition of new vasculitis syndromes, an improved under- standing of pathogenesis and the discovery of antineutrophil cyto- plasmic antibody (ANCA). While our understanding of vasculitis remains incomplete, classification systems are imperfect but key cri- teria include vessel size, clinical, and immunopathological findings. Important classifications historically include the 1990 American College of Rheumatology criteria (pre-ANCA) and the 1994 Chapel Hill Consensus Conference (CHCC) criteria. In 2011 another Chapel Hill Consensus Conference was convened to review the 1994 system. Key updates, published in 2012 (2012 CHCC) include a move away from eponyms to names reflecting aetiopathogenesis (Box 23.7.3), and the classification of ANCA-associated and im- mune complex-associated vasculitis as specific types of small-vessel vasculitis. Pathogenesis Vasculitis can be primary (idiopathic), or secondary, associated with diseases such as rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, infections, or malignancy. The exact pathological mechanisms causing vasculitis are unknown and are likely to vary in different types of vasculitis. In vasculitis associated with infection, direct invasion of vessels walls can occur, probably as a result of antigens on the surface of infectious agents binding to complementary endothelial ligands. In others, binding or trapping of immune complexes are likely to be a key factor in the pathogen- esis. In primary vasculitis, the pathogenesis is believed to be auto- immune and a good model for this comes from antiglomerular basement membrane (GBM) disease in which type IV collagen has been recognized as the antigen and target of the immune response. The additional role of genetic susceptibility is illustrated in this ex- ample by the association with HLA-DRB1*15:01. ANCA antibodies are detected in many patients with the ANCA-associated vasculit- ides and although ANCA have been shown to activate and

degranu- late neutrophils in vitro, it is unclear exactly what role it plays in these diseases. In addition to genetic predisposition, environmental fac- tors such as tobacco smoke, organic solvents, and infections might influence individual susceptibility to the development of vasculitis. An interesting observation to explain is the variability in dis- ease expression in terms of site, both size of blood vessels involved (e.g. small, medium, large), and organ (e.g. generalized or organ-specific). These differences might be due to physical factors, such as temperature, hydrostatic pressure and turbulence (e.g. turbulence may favour the deposition of immune complexes). In addition, blood ves- sels vary throughout the body, designed to meet the needs of their host organ. Endothelial antigen expression is likely to vary and this might explain the different patterns of disease according to the where the target antigen is expressed. Another factor to consider is the embry- ology of blood vessels: most vessels are derived from mesoderm with the exception of the aortic root and arch which are derived from the neural crest, and this might be part of the explanation for certain vas- culitides favouring the aortic arch, such as syphilitic aortitis, which along with neurosyphilis is a manifestation of tertiary syphilis. In many of the vasculitides, a common final pathway is the re- lease of proteolytic enzymes, and oxygen free radicals from activated neutrophils, and these damage the vessel walls and the surrounding tissues. Inflammation and necrosis of blood vessel walls leads to the extravasation of red blood cells, vascular obstruction, and tissue is- chaemia or infarction. The clinical features depend on the size of the affected vessels, the sites involved (frequently the earliest signs are in the skin), and the intensity of the inflammation (see Table 23.7.1). Assessment of patients with suspected vasculitis A description of individual vasculitides follows but when assessing a patient with suspected vasculitis, there are several general issues to consider. Firstly, is there involvement of small, medium, or large ves- sels? The clinical signs reflect the vessels involved (see Table 23.7.1) and will help narrow down the potential diagnoses. Is it localized or systemic? What is the cause and is it primary or secondary? Could it be a vasculitis mimic? The section dealing with cutaneous Box 23.7.3 Nomenclature of the vasculitides adopted by the 2012 International Chapel Hill Consensus Conference (CHCC 2012) Large-vessel vasculitis Takayasu arteritis Giant Cell Arteritis Medium-vessel vasculitis Polyarteritis nodosa Kawasaki disease Small-vessel vasculitis • ANCA-associated vasculitis Microscopic polyangiitis (MPA) Granulomatosis with polyangiitis (GPA) Eosinophilic granulomatosis with polyangiitis (EGPA) • Immune complex small-vessel vasculitis Antiglomerular basement membrane (GBM) disease Cryoglobulinaemic vasculitis IgA vasculitis (Henoch–Schönlein) Hypocomplementaemic urticarial vasculitis (anti-C1q vasculitis) Variable-vessel vasculitis Behçet’s disease Cogan’s syndrome Single-organ vasculitis Cutaneous leucocytoclastic angiitis Cutaneous arteritis Primary central nervous system vasculitis Isolated aortitis Others Vasculitis associated with systemic disease Lupus vasculitis Rheumatoid vasculitis Sarcoid vasculitis Others Vasculitis associated with a probable aetiology Hepatitis C virus-associated cryoglobulinaemic vasculitis Hepatitis B virus-associated vasculitis Syphilis-associated aortitis Drug-associated immune complex vasculitis (e.g. sulphonamides, peni- cillins, thiazide diuretics) Drug-associated ANCA-associated vasculitis (e.g. Propylthiouracil, hydralazine and allopurinol with induction of MPO-ANCA). Cancer-associated vasculitis Others

 Table 23.7.1 The cutaneous manifestations of vasculitis according to vessel size. Note that there is overlap and mixed signs may be seen due to involvement of vessels of variable size. Note that medium-sized vessels are sited deep in the skin so require a deep skin biopsy, including subcutaneous fat, in order to obtain a histological diagnosis. Vessel size Small Medium Large Clinical signs in the skin

Palpable purpura • Papules and plaques • Often in crops • Dependent sites, typically lower legs • May be necrotic & ulcerate • May be pustular See Fig. 23.7.1 Dermal and subcutaneous nodules May necrose & ulcerate See Fig. 23.7.2 Mainly affects internal organs & cutaneous involvement less common (no large vessels in the skin) Haemorrhagic vesicles & bullae See Fig. 23.7.1 Livedo reticularis Patchy or broken rather than a continuous network (livedo racemosa) See Fig. 23.7.3 May cause necrosis & ulceration of skin/mucosa in the territory of an affected large vessel e.g. scalp or tongue in GCA Urticarial papules & plaques • Last >24 hrs • Leave bruise-like marks Digital infarcts and gangrene Limb ischaemia Splinter haemorrhages Deep ulcers May be PG-like Nail-fold infarcts PG, pyoderma gangrenosum; GCA, giant cell arteritis. Fig. 23.7.1 Palpable purpura on the legs. Many lesions are bullous. These are signs of a small-vessel vasculitis, regardless of cause, which classically produces crops of palpable purpura on the lower legs. Fig. 23.7.2 Necrotic papules and ulcers on the leg in a patient with granulomatosis with polyangiitis (Wegener's granulomatosis). Note the appearances are quite different to the crops of palpable purpura seen on the lower legs as a typical sign of a small-vessel vasculitis (Fig. 23.7.1).

section 23 Disorders of the skin 5642 small-vessel vasculitis describes the general approach to a patient with suspected vasculitis and discusses differential diagnoses. Large-vessel vasculitis Giant cell arteritis (GCA) Giant cell arteritis, also known as temporal arteritis, affects the larger and medium-sized arteries, particularly those of the head and neck (Box 23.7.4). Patients, usually women aged over 50 years, can present with fever, headache, a tender temporal artery/scalp, jaw claudication, vision changes, including blindness, anaemia, and an elevated erythrocyte sedimentation rate. Cutaneous in- volvement is not common but might present as a tender scalp nodule that can ulcerate and might be misdiagnosed as a basal cell skin carcinoma (see Chapter 23.14). Scalp ulceration can be bilat- eral and occasionally, there might be ulceration or infarction of the tongue. Useful investigations include an erythrocyte sedimenta- tion rate (ESR), an ophthalmologic examination, and a temporal artery biopsy. If there is acute visual loss, therapy with systemic corticosteroids should be commenced while awaiting the results of investigations. Takayasu arteritis (TAK) Both giant cell arteritis and takayasu arteritis (TAK) are granu- lomatous vasculitides affecting the aorta and its major branches such that there is debate as to whether they are the same disease. TAK tends to affect younger patients, less than 50 (Box 23.7.5). The granulomatous arteritis of TAK is followed by fibrosis and stenosis. It might present with claudication or cold peripheries, limb ischaemia, unequal or absent pulses, bruits, and renovascular hypertension. Cutaneous manifestations are not common but in- clude inflamed and ulcerated nodules, or pyoderma gangrenosum- like ulcers. Useful diagnostic studies include arteriography, doppler ultrasonography, and MRI/MRA. (a) (b) Fig. 23.7.3 Patchy livedo (livedo racemosa) seen on the thigh (a) and knee (b). Physiological livedo reticularis is a continuous network and typically disappears in warm temperatures. In contrast, livedo racemosa is patchy and persistent. Box 23.7.4 Giant cell arteritis CHCC 2012 definition • An arteritis, often granulomatous, usually affecting the aorta and/or its major branches, with a predilection for the branches of the carotid and vertebral arteries. Often involves the temporal artery. Onset usu- ally in patients older than 50 and often associated with polymyalgia rheumatica. CHCC, Chapel Hill Consensus Conference. Box 23.7.5 Takayasu arteritis CHCC 2012 definition • An arteritis, often granulomatous, predominantly affecting the aorta and/or its major branches. Onset usually in patients younger than 50. CHCC, Chapel Hill Consensus Conference.

23.7 Cutaneous vasculitis, connective tissue diseases, and urticaria 5643 Medium-vessel vasculitis Polyarteritis nodosa (PAN) Polyarteritis nodosa is a life-threatening necrotizing vasculitis, which results in aneurysms that can be demonstrated by arteri- ography of renal or mesenteric arteries (Box 23.7.6). Historically, some cases have been associated with hepatitis B infection, but in the CHCC 2012 nomenclature, these cases should now be classified as hepatitis B virus-associated vasculitis. Polyarteritis nodosa is more common in men, with an average age of onset of approximately 50 years of age. It might present with non- specific constitutional symptoms, abdominal or testicular pain, periph- eral neuropathy, renal insufficiency with active sediment, and vascular hypertension. Cutaneous manifestations include livedo reticularis, cu- taneous nodules, ulcers, peripheral gangrene, and palpable purpura. There is a localized, cutaneous form of polyarteritis nodosa that behaves in a more benign fashion. Cutaneous polyarteritis nodosa Pathogenesis and pathology A benign cutaneous form of polyarteritis nodosa has been de- scribed, but the relationship of this condition to the systemic disease is uncertain, and the cause is unknown. A necrotizing vasculitis af- fects small and medium-sized muscular-walled arteries in the deep dermis and subcutis. Clinical features Painful cutaneous nodules, purpura, ulceration, and livedo reticularis (see ‘Thrombo-occlusive vasculopathies’) occur on the lower limbs (Fig. 23.7.4). The livedo is typically patchy or broken, rather than a continuous network as seen in physiological livedo (see Fig. 23.7.3). Cutaneous polyarteritis nodosa can be associated with fever, malaise, arthralgia, myalgia, and peripheral neuropathy, but major organs are not involved. Patients with hepatitis B might have features of chronic hepatitis. The disease is chronic and recurrent. Investigation Patients should be screened for systemic involvement, but labora- tory findings are generally unremarkable, except for leukocytosis and an elevated erythrocyte sedimentation rate. Deep incisional bi- opsies are necessary to demonstrate the primary vascular pathology. Treatment Treatment of patients who do not have hepatitis B include high-dose oral corticosteroids 1 mg/kg/day tapered down slowly (over a year). In patients with severe disease three daily IV pulses of methylprednisolone 500–1000 mg might be considered. Cyclophosphamide and other immunosuppressants and immunomodulators might be needed to achieve remission. Patients with hepatitis B-associated polyarteritis nodosa might benefit from a combination of antivirals and immuno- suppression. Pain control is important in such patients (some patients require opiates). Compression bandaging can promote healing, but might not be tolerated because of pain. Kawasaki disease Kawasaki disease (mucocutaneous lymph node syndrome) is a multisystem vasculitis of infants and small children (Box 23.7.7). It is most common in Japan with an increased incidence in later winter or spring. The disease follows an acute course over 4–6 weeks, with high fever, oedema, and erythema of the palms and soles, and/or oedema of the hands and feet, an erythematous rash, bilateral conjunctival injec- tion, dry red fissured lips, a ‘strawberry’ tongue, and cervical lymph- adenopathy. Coronary aneurysms develop in about 20% of patients, and ischaemic heart disease causes myocardial infarction and sudden death. Useful investigations include an ESR, coronary angiogram, or echocardiogram. Intravenous γ-globulin plus aspirin controls fever and reduces the formation of aneurysms. Box 23.7.6 Polyarteritis nodosa CHCC 2012 definition • A necrotizing arteritis of medium-sized or small arteries without glom- erulonephritis or vasculitis in arterioles, capillaries, or venules; and not associated with ANCA. CHCC, Chapel Hill Consensus Conference. Fig. 23.7.4 Painful ulcers on a background of livedo on the lower legs. The ulceration was preceded by palpable purpura and nodules. A biopsy showed a medium-vessel vasculitis and there was no evidence of systemic involvement. The findings were consistent with the benign cutaneous form of polyarteritis nodosa. Box 23.7.7 Kawasaki disease CHCC 2012 definition • An arteritis associated with mucocutaneous lymph node syndrome and predominantly

affecting medium-sized and small arteries. Coronary arteries are often involved. Aorta and large arteries may be involved. Usually occurs in infants and young children. CHCC, Chapel Hill Consensus Conference.

section 23 Disorders of the skin 5644 Small-vessel vasculitis ANCA-associated vasculitis (AAV) ANCA-associated vasculitis (Box 23.7.8) affects people of all ages, but is most common in adults in their 50s and 60s, and is the most common primary systemic vasculitis affecting adults. The three major subtypes have overlapping features, including the cutaneous features which are listed next. Although in the latest Chapel Hill Consensus Conference classification, AAV is included in small-vessel vasculitis, these disorders can also affect medium-sized ves- sels and the cutaneous clinical signs reflect this. Granulomatosis with polyangiitis
(GPA, Wegener's granulomatosis) Granulomatosis with polyangiitis presents wiith necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting pre- dominantly small- to medium-sized vessels (e.g. capillaries, venules, arterioles, arteries, and veins). Necrotizing glomerulo- nephritis is common. The condition can occur at any age, but increased incidence in young and middle-aged adults. Can cause sinusitis, pulmonary infiltrates, haemoptysis, haematuria, pauci-immune rapidly pro- gressing glomerulonephritis. Useful diagnostic studies include urin- alysis and microscopy, c-ANCA (90%), sinus/chest imaging, biopsy. Treatments include steroids and cyclophosphamide for induction of remission, methotrexate or azathioprine for maintenance; tri- methoprim/sulphamethoxazole might prevent upper airway relapse caused by infection. Microscopic polyangiitis (MPA) Microscopic polyangiitis is a necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e. ca- pillaries, venules, or arterioles). A necrotizing arteritis involving small- and medium-sized arteries may also be present. Necrotizing glomerulonephritis is very common. A pulmonary capillaritis without asthma often occurs. Granulomatous inflammation is absent. Compared with granulomatosis with polyangiitis, microscopic polyangiitis is not granulomatous and there is more renal and less pulmonary involvement. It can cause a pauci-immune rapidly progressing glomerulonephritis, sinusitis, pulmonary infiltrates, haemoptysis, and neuropathy. Useful diagnostic studies include urinalysis and microscopy, p-ANCA (70%), sinus/chest imaging, bi-opsy. Treatment approach is similar to that for granulomatosis with polyangiitis. Eosinophilic granulomatosis with polyangiitis (EGPA, Churg–Strauss syndrome) Eosinophilic granulomatosis with polyangiitis presents with eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predomin- antly affecting small- to medium-sized vessels, and associated with asthma and eosinophilia. ANCA is most frequent when glomerulo- nephritis is present. In addition to the lungs, the eosinophil-rich granulomatous in-flammation can affect peripheral nerves, kidneys, and skin. It can occur at any age, but is typically found in patients 30–40 years old. It can cause asthma, allergic rhinitis, pulmonary infiltrates, neur-opathy, and glomerulonephritis. Useful diagnostic studies include eosinophilia, ANCA (50%, perinuclear > cytoplasmic), sinus/chest imaging, biopsy. Chest radiograph might show shifting pulmonary infiltrates. The vasculitic phase does not develop until about three years after the onset of asthma in Churg–Strauss syndrome. Clinical features Cutaneous lesions have been described during the course of disease in around 70% of patients, but signs of a cutaneous vasculitis are present at disease onset in more than 40% of patients with micro- scopic polyangiitis and 8–10% of those with granulomatosis with polyangiitis (Wegener's granulomatosis). The cutaneous findings vary, and reflect involvement of small and medium-sized vessels (see Table 23.7.1) but the most common (and least specific) finding in all three conditions are: • Palpable purpuric rash on the

lower extremities (Fig. 23.7.1). • Progressive ulceration in granulomatosis with polyangiitis (Wegener's granulomatosis) may resemble pyoderma gangrenosum, and can affect unusual sites such as the face, neck, or perianal skin (pyoderma gangrenosum usually affects the lower legs). • Livedo reticularis. • Patients with granulomatosis with polyangiitis (Wegener's granulomatosis) or eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome) can develop lesions associated with a large-vessel vasculitis, such as cutaneous ulcers or subcutaneous nodules. • In both GPA and EGPA (Wegener's granulomatosis and Churg– Strauss syndrome), ulcerated papules (papulonecrotic lesions, see Fig. 23.7.2) resembling rheumatoid nodules are found on the limbs, particularly the elbows, but can occur on the face and scalp. These diseases are discussed in further detail in other organ- specific chapters (in particular Sections 15, 18, 19, and 21). Immune complex small-vessel vasculitis See Box 23.7.9. Box 23.7.8 ANCA-associated vasculitis CHCC 2012 definition • Necrotizing vasculitis, with few or no immune deposits, predomin- antly affecting small vessels (i.e. capillaries, venules, arterioles, and small arteries), associated with MPO-ANCA or PR3-ANCA. Not all pa- tients have ANCA. Add a prefix indicating ANCA reactivity (e.g. PR3- ANCA, MPO-ANCA, and ANCA negative). CHCC, Chapel Hill Consensus Conference. Box 23.7.9 Immune complex vasculitis CHCC definitions as revised in 2012 • Vasculitis with moderate to marked vessel wall deposits of immuno- globulin and/or complement components predominantly affecting small vessels (i.e. capillaries, venules, arterioles, and small arteries). Glomerulonephritis is frequent.

23.7 Cutaneous vasculitis, connective tissue diseases, and urticaria 5645 IgA vasculitis (Henoch–Schönlein purpura) Pathogenesis Henoch–Schönlein purpura is triggered by infection, often in the upper respiratory tract, and is associated with IgA immune com- plexes in the circulation and vessel walls (Box 23.7.10). It is the most common small-vessel systemic vasculitis in children, but it may also affect adults. Clinical features The cutaneous signs are similar to those of other cutaneous small- vessel vasculitides, but in children the urticarial component might be more prominent than in adults. A symmetrical macular erythema develops on the extensor surfaces of the limbs, the buttocks, and back. Lesions become raised, palpable, and purpuric, but regress over 10 to 14 days. In addition, children can have any combination of arth- ritis, gastrointestinal tract involvement, and nephritis. Infantile acute haemorrhagic oedema of the skin is a benign condition that is prob- ably a variant of Henoch–Schönlein purpura in which the oedema- tous component is particularly marked. If needed, useful diagnostic studies include skin biopsy or renal biopsy showing IgA deposition. Treatment In the absence of severe systemic disease, treatment is supportive. Corticosteroids or dapsone might be prescribed in severe disease, although it is not known if these drugs affect the duration of illness or the frequency of relapse. Rapidly progressive renal failure is rare, and the prognosis is excellent. Relapses are usually mild and do not require treatment. Cryoglobulinaemic vasculitis (and occlusive vasculopathy) Aetiology, pathogenesis, and pathology Vasculitis arising from presence of cryoglobulins (Box 23.7.11). Cryoglobulins are immunoglobulins that precipitate at low temper- atures and are classified according to their immunochemical com- position. More common in the middle-aged, women, and those with autoimmune or lymphoproliferative diseases. It is strongly associ- ated with hepatitis C virus infection. It can cause purpura, livedo reticularis, ulcers, neuropathy, arthralgias, and glomerulonephritis. • Type I cryoglobulins (monoclonal immunoglobulins IgG and IgM) are present in 25% of cases. Note that in this type, the cryo- globulin causes vascular occlusion rather than a vasculitis. • Type II mixed cryoglobulins (a mixture of monoclonal and poly- clonal immunoglobulins) are present in 25% of cases. • Type III mixed cryoglobulins (polyclonal immunoglobulins only) are present in 50% of cases. Most patients are women aged 30–50 years.

Type I cryoglobulinaemia is always associated with a malignant haematological disorder such as chronic lymphatic leukaemia, mul- tiple myeloma, or Waldenström's macroglobulinemia. The cryo- globulins obstruct the vessels rather than trigger an inflammatory vasculitis, and are associated with cold sensitivity (Fig. 23.7.5). A skin biopsy, best taken from affected but not ulcerated skin, re- veals an occlusive vascular disease (vasculopathy). The small cu- taneous blood vessels are plugged by homogenous eosinophilic material, and there is red blood cell extravasation with a perivascular mononuclear cell infiltrate, but no vasculitis. In most patients, hepatitis C virus (HCV) infection underlies type II mixed cryoglobulinaemia. This would now be termed HCV- associated cryoglobulinaemic vasculitis. Hepatitis C virus infection triggers B-cell clonal expansions with production of IgM, primarily in the liver. These expansions are associated with high serum levels of polyclonal rheumatoid factor and cryoglobulins, as well as mono- clonal gammopathy of undetermined significance and, rarely, non-Hodgkin's B-cell lymphoma. The pathogenesis of malignant Box 23.7.10 IgA vasculitis CHCC 2012 definition • Vasculitis, with IgA1-dominant immune deposits, affecting small ves- sels (predominantly capillaries, venules, or arterioles). Often involves skin and gut, and frequently causes arthritis. Glomerulonephritis indis- tinguishable from IgA nephropathy may occur. CHCC, Chapel Hill Consensus Conference. Box 23.7.11 Cryoglobulinaemic vasculitis 2012 CHCC definition • Vasculitis with cryoglobulin immune deposits affecting small vessels (predominantly capillaries, venules, or arterioles) and associated with serum cryoglobulins. Skin, glomeruli, and peripheral nerves are often involved. CHCC, Chapel Hill Consensus Conference. Fig. 23.7.5 Purpura on the lower leg and foot which has blistered in areas. Note that these are large patches rather than crops of palpable purpura as seen in a small-vessel vasculitis. A skin biopsy revealed an occlusive vasculopathy rather than a vasculitis. Investigations revealed a cryoprotein, which in this case was cryofibrinogenaemia but type I cryoglobulinaemia would give a similar picture.

 B-cell transformation is uncertain. HCV causes both cytotoxic and autoimmune hepatitis, and clonal B-cell expansion occus in blood and liver. HCV virions bind to IgG and form immune complexes that are precipitated in the vessel walls of many organs. The com- plexes then activate the complement cascade, producing a small- vessel vasculitis affecting venules, capillaries, and arterioles. Mixed cryoglobulinaemia can also be associated with connective tissue dis- eases such as rheumatoid arthritis or systemic lupus erythematosus, as well as other infections. Clinical features Patients with type I cryoglobulinaemia, an occlusive vasculopathy, complain of Raynaud's phenomenon, mottling of the skin, or blotchy cyanosis on exposure to cold. Acrocyanosis affects the helices of the ears as well as the fingers and toes (Fig. 23.7.6). Cold-induced le- sions might be urticarial and then become purpuric. Cold triggers the formation of large haemorrhagic bullae that break down to pro- duce ulcers. More than 90% of patients with type II mixed cryoglobulinaemia develop palpable purpura, and in most this is the first sign of the disease. Fifteen per cent (15%) of patients have chronic leg ulcers, usually above the malleoli. These are surrounded by purpura, but patients have no other evidence of stasis (Fig. 23.7.7). Patients may also have Raynaud's phenomenon (30%), cold urticaria (10%), arth- ralgia (70%), renal involvement (20–30%), and/or sensorimotor neuropathy (60%). Clinical investigation Useful diagnostic studies include cryoglobulins, rheumatoid factor, complement (C4), hepatitis C RNA, and a skin biopsy. Measuring complement C4 is a useful screening test because C4 is very low in mixed cryoglobulinaemia. Cryoglobulins are present in serum, but the blood specimen taken for cryoglobulins must be kept warm (37°C) and it can be easier to send the patient rather than the sample to the immunology laboratory. Rheumatoid factor can sometimes be detected. A skin

biopsy might show obstructive vasculopathy (Type I cryoglobulinaemia) or vasculitis (mixed cryoglobulinaemia). Treatment Underlying lymphoproliferative disorders or connective tissue diseases should be treated, and patients should keep warm. Compression bandaging might reduce venous stasis and improve leg ulceration. In hepatitis C virus infection, interferon-α reduces viral load and cryoglobulinaemia, but about 80% of responders relapse within 6 months. Few data are available on the response of neur- opathy, renal disease, or cutaneous ulceration to this treatment. The treatment for patients without hepatitis C virus infection, or those with progressive disease, can involve corticosteroids in combination with cytotoxic agents, although the new directly acting antiviral drugs might offer the best approach. Plasmapheresis has been used to treat rapidly progressive cryoglobulinaemic vasculitis. Hypocomplementaemic urticarial vasculitis Pathogenesis and pathology Urticarial vasculitis (Box 23.7.12) occurs in association with con- nective tissue diseases, serum sickness (approximately 10 days after the administration of drugs or vaccines), infection (including HCV), IgM or IgG gammopathy, and haematological malignan- cies. Skin biopsies show prominent dermal oedema with evidence Fig. 23.7.6 Acrocyanosis of the fingers in a young girl with an urticarial vasculitis, but no systemic disease. She also had chilblain-like lesions on the ears and nose. Although cold appeared to trigger cutaneous disease, no cryoglobulins were found. Fig. 23.7.7 Ulceration surrounded by palpable purpura in a patient with mixed cryoglobulinaemic vasculitis. Box 23.7.12 Hypocomplementaemic urticarial vasculitis CHCC 2012 definition • Vasculitis accompanied by urticaria and hypocomplementaemia affecting small vessels (i.e. capillaries, venules, or arterioles), and as- sociated with anti-C1q antibodies. Glomerulonephritis, arthritis, ob- structive pulmonary disease, and ocular inflammation are common. CHCC, Chapel Hill Consensus Conference.

 of a leukocytoclastic vasculitis, but changes of vasculitis might be quite subtle. Clinical features Urticaria is characterized by the presence of a recurring itchy rash consisting of smooth, pale papules and plaques with an erythema- tous halo (weals) that fade in about 24 h to leave normal skin. By contrast, the weals of urticarial vasculitis are tender or they burn, they last up to 72 h, and may resolve leaving bruising (Fig. 23.7.8). Urticarial vasculitis is associated with low complement levels in 18% of patients—these patients have hypocomplementaemic urticarial vasculitis and are included in the Chapel Hill Consensus Conference 2012 definition of vasculitis. This subtype is more likely to be associated with systemic disease, and patients have a higher incidence of arthritis, obstructive pulmonary disease, and gastro- intestinal symptoms than those with normal complement levels. Some patients with low complement levels have anti-C1q anti- bodies and overlapping features with systemic lupus erythematosus, including pleuritis, glomerulonephritis, eye symptoms, and posi- tive antinuclear antibodies. Treatment Antihistamines or nonsteroidal anti-inflammatory drugs (NSAIDs) can be effective. Prednisolone is helpful, but alternatives such as dap- sone, colchicine, or hydroxychloroquine should be considered to avoid the side effects of prolonged treatment with systemic corticosteroids. Single-organ vasculitis See Box 23.7.13. Small-vessel cutaneous vasculitis This is also known as leukocytoclastic angiitis/vasculitis, cutaneous small-vessel necrotizing vasculitis, allergic vasculitis, and hypersen- sitivity angiitis. Aetiology and pathology The aetiology of small-vessel cutaneous vasculitis is uncertain (idio- pathic) in at least 50% of patients, but has been ascribed to infections in 15–20% of patients, inflammatory diseases such as connective tissue diseases in 15–20% of patients, drugs in 10–15% of patients (usually 7–21 days after commencing the drug), and malignancies, especially lymphoproliferative disorders, in 5% of patients. Small-vessel cutaneous vasculitis involves dermal small vessels, predominantly

postcapillary venules. The histological findings include perivascular neutrophilic inflammation extending into vessel walls, with swelling and injury of endothelial cells; necrosis of vessel walls; fibrinoid deposition around vessels (fibrinoid ne- crosis); and extravasation of red blood cells. The presence of nu- clear dust is indicative of leukocytoclasis (fragmentation of the nuclei of neutrophils). Clinical features Palpable purpura, usually on the lower leg, is the hallmark of small-vessel cutaneous vasculitis (Fig. 23.7.9, Box 23.7.14) The purpuric lesions are palpable because the purpura is accompanied by inflam- mation and increased vascular permeability. This contrasts with the flat petechiae and purpura seen in noninflammatory condi- tions such as thrombocytopenic purpura. Radial diffusion of red blood cells that have leaked from small vessels in the upper dermis produces small oval or round purpuric papules. Thrombosis with Box 23.7.13 Single Organ Vasculitis CHCC 2012 definition • Vasculitis in arteries or veins of any size in a single organ that has no features that indicate that it is a limited expression of a systemic vas- culitis. The involved organ and vessel type should be included in the name (e.g. cutaneous small-vessel vasculitis (SVV), testicular arter- itis, central nervous system vasculitis). Vasculitis distribution may be unifocal or multifocal (diffuse) within an organ. Some patients originally diagnosed with single-organ vasculitis (SOV) will develop additional disease manifestations that warrant re-defining the case as one of the systemic vasculitides (e.g. cutaneous arteritis later becoming systemic polyarteritis nodosa, and so on). CHCC, Chapel Hill Consensus Conference. Fig. 23.7.8 Urticarial vasculitis: tender urticated papules and plaques that are associated with purpura and resolve with bruising. Fig. 23.7.9 Palpable purpura is the hallmark of small-vessel cutaneous vasculitis. Small oval or round purpuric papules are found in areas of stasis (below the knee), at pressure sites (elbows, sacrum, waist band), or at sites of cooling.

 infarction is unusual in a small-vessel cutaneous vasculitis, but ir- regularly outlined indurated areas of haemorrhagic infarct are produced when deeper dermal or subcutaneous vessels become thrombosed in other conditions. Patients present with a symmetrical purpuric rash in dependent areas such as the leg, at sites of trauma (Koebner phenomenon), pressure sites (elbows, sacrum, waist band), or sites of cooling. Oval or circular erythematous lesions rapidly become raised (palpable) and purpuric, sometimes coalescing into larger polycyclic lesions (Figs. 23.7.10). Some patients develop annular purpuric lesions with haemorrhagic or vesicular centres, or superficial ulceration. Intense inflammation produces haemorrhagic bullae or pustules. Lesions fade gradually over three or four weeks leaving macular pigmenta- tion (haemosiderin) or atrophic scars. Differential diagnosis Purpura does not blanch with light pressure, unlike erythema. Purpuric lesions can be divided into those that are associated with inflammatory pathology (vasculitis) and are palpable, and those that are noninflammatory and flat (i.e. macular). Scattered flat purpuric spots can be a nonspecific finding on the legs in association with inflammatory dermatoses such as psoriasis or stasis eczema. The frail sun-damaged skin on the forearms of older patients, or skin that has been thinned after prolonged ex- posure to corticosteroids, is prone to developing large flat bruises (ecchymoses) after minor trauma. Scurvy causes perifollicular purpura with corkscrew hairs in the centre. Disorders associ- ated with thrombocytopenia produce flat purpuric lesions and petechiae. Cholesterol emboli might produce asymmetrical acral petechiae and subcutaneous nodules, often in association with livedo reticularis (see ‘Thrombo-occlusive vasculopathies’). Livedo reticularis is also associated with vasculitis affecting deeper cutaneous vessels. Disseminated intravascular coagula- tion (see ‘Septic vasculitis’) produces extensive irregularly out- lined haemorrhagic areas. The vasculitic lesions in idiopathic small-vessel cutaneous vasculitis are clinically and histologically identical to the cu-

taneous lesions in small-vessel cutaneous vasculitis occurring as a component of a systemic disease. The clinician must rule out systemic disease and also search for other cutaneous signs of vasculitis, such as livedo reticularis or nodules. Patients with systemic vasculitis may give a history of prodromal symptoms such as rather nonspecific flu-like symptoms, myalgia, migra- tory arthralgia, or synovitis. Clinical investigation The history, physical examination, and investigations must de- termine the extent of any systemic disease and identify causative agents: drugs; infections including hepatitis B or C; or conditions associated with circulating immune complexes, such as con- nective tissue diseases, inflammatory bowel disease, lymphoma, multiple myeloma, leukaemia, and solid tumours (Box 23.7.15). If these laboratory studies are normal, further testing to rule out a systemic vasculitis is probably not warranted unless the history and physical examination are not consistent with limited cutaneous disease. A streptococcal sore throat is a common pre- cursor of vasculitis in children, and otitis media, dental caries, cystitis, and sinusitis occasionally play a role. In many countries tuberculosis or leprosy is the most common cause; bacterial endocarditis and meningococcal septicaemia are often missed. Other treatable infections occasionally causing vasculitis are syphilis and those caused by neisseria, rickettsiae, and myco- plasma. Although viral causes cannot usually be eliminated, any history of a recent flu-like illness or vaccination might be relevant. A skin biopsy to confirm a small-vessel cutaneous vasculitis should be taken from a palpable purpuric lesion about 12–24 hr old. A biopsy taken too late might not show the initial injury. However, the histology is unlikely to reveal the cause of the vascu- litis, exclude systemic disease, or distinguish one form of systemic vasculitis from another. In patients with evidence of medium vessel involvement (e.g. if there is patchy livedo reticularis or ulcerated nodules), an in- cisional biopsy down to fat is necessary to detect pathology in arterioles or small arteries, but if a large-vessel vasculitis is Box 23.7.14 Clinical features of small-vessel cutaneous vasculitis • Symmetric palpable purpura of the lower extremities and other de- pendent areas of the body. • Lesions typically develop in crops and may be associated with pruritus, pain, and burning. • Round, port wine-coloured papules, and plaques with inflammation may be seen. • Diascopy of purpuric lesions (application of direct pressure to the le- sion with a glass slide) demonstrates partial blanching; the blanchable component indicates underlying inflammation (erythema), whereas the nonblanchable component represents haemorrhage (purpura). • Other clinical presentations include urticarial lesions, ulcerative, or infarcted lesions, vesicles, pustules, nodules, livedo, and targetoid lesions. Ulcers or nodules may indicate deeper or medium vessel involvement. CHCC, Chapel Hill Consensus Conference. Fig. 23.7.10 Vasculitic papules have coalesced into plaques in this patient with chronic vasculitis. Stasis localizes disease and aggravates the clinical findings.

 suspected, a biopsy from involved tissue in muscle, nerve, or lung will be more informative than a skin biopsy. The investigation of the systemic vasculitides is discussed in more detail in Sections 19 and 21. Treatment Precipitating agents (drugs or infection) must be identified and removed, but it might still take several weeks for vasculitis to settle. Local factors that might exacerbate or localize vascu- litis (cooling, stasis, trauma) should be minimized by simple measures such as warmth, leg elevation, support stockings, and exercise. Dapsone (50–200 mg/day) is effective in controlling limited cu- taneous vasculitis. Colchicine (0.5 mg twice daily) and low-dose methotrexate (10–25 mg/week) have also been recommended. Most patients with small-vessel vasculitis limited to the skin do not re- quire systemic corticosteroids or more aggressive treatment with immunosuppressive agents. Prognosis Idiopathic small-vessel vasculitis confined to the skin

resolves within a few weeks or months. Most patients have a single episode, but about 10% have recurrent disease that may last months or years. Exercise-induced vasculitis fades in a few days. Increased understanding of the pathogenesis of vasculitis is likely to lead to the development of targeted immunotherapy with monoclonal antibodies to cell adhesion molecules or cyto- kines that will control the autoimmune response and reduce inflammation. Vasculitis associated with systemic disease Connective tissue diseases Patients with diseases such as systemic sclerosis, rheumatoid arth- ritis, or systemic lupus erythematosus can develop signs of small- vessel cutaneous vasculitis, including palpable purpuric lesions on the legs, palms, or digits, haemorrhagic bullae, papulonecrotic purpuric lesions, urticarial vasculitis, or punched-out necrotic ulcers (Box 23.7.16). Vasculitis can also involve larger vessels, particularly in rheumatoid arthritis (Chapter 19.5) and systemic lupus erythematosus, with livedo reticularis (see 'Thrombo- occlusive vasculopathies'), ulcers, nodules, digital gangrene, or pyo- derma gangrenosum-like lesions. Vasculitis associated with a probable aetiology Septic vasculitis Pathogenesis Organisms can damage blood vessels by direct invasion, by the release of endotoxins that provoke a thrombotic response (dis- seminated intravascular coagulation), or by inducing an immune- mediated vasculitis. Purpuric lesions are most often seen in infective endocarditis, meningococcaemia, gonococcaemia, Gram-negative septicaemia, and certain rickettsial infections. A septic vasculitis can follow any intravascular procedure. Clinical features The cutaneous signs in infective endocarditis include mucosal pe- techiae, Osler's nodes (tender erythematous spots on the pulps of the fingers and toes), and Janeway's lesions (nontender red or haemorrhagic macules or nodules on the palms and soles). In sub- acute disease, circulating immune complexes probably trigger a leukocytoclastic vasculitis in small vessels that is responsible for mucocutaneous lesions, but septic emboli may play a direct role in the pathogenesis of vasculitic lesions in acute disease. Unilateral emboli following a percutaneous arterial puncture may indicate a septic endarteritis. Disseminated intravascular coagulation (DIC) is a devastating disease characterized by extensive purpura, haematomas, haemorrhagic infarcts, and gangrene. Persistent cyanosis of the extremities is an early sign. DIC is not a vasculitis, but an occlusive vasculopathy in which fibrin thrombi occlude ca- pillaries, venules, and vessels in the deeper dermis and subcutis, leading to ischaemia and infarction. DIC is discussed in detail Chapter 22.7.5. The purpuric lesions of acute meningococcaemia are present on the limbs or trunk in 80–90% of patients within 12–36 h of dis- ease onset, but can be small and few in number (Chapter 8.6.5). These lesions are followed by disseminated intravascular coagu- lation, with large irregular indurated ecchymoses with central necrosis that may progress to extensive gangrene. Septic em- boli in Gram-negative septicaemia caused by Escherichia coli, Pseudomonas, or Klebsiella produce vasculitic lesions that pre- sent as erythematous weals and papules that become irregularly purpuric and necrotic. Box 23.7.15 Preliminary laboratory screening should include: Full blood count, Inflammatory markers (erythrocyte sedimentation rate, C-reactive protein), Urinalysis, renal function tests, Liver function tests, Hepatitis B and C serology, Complement levels (C3, C4), Immunoglobulins, Rheumatoid factor Antinuclear antibody ASO titre +/- throat swab if appropriate Cryoglobulins should be measured if C4 is low ANCA CHCC, Chapel Hill Consensus Conference. Box 23.7.16 Vasculitis associated with systemic disease CHCC 2012 definition • Vasculitis that is associated with and may be secondary to (caused by) a systemic disease. The name (diagnosis) should have a prefix term specifying the systemic disease (e.g. rheumatoid vasculitis, lupus vas- culitis, and so on). CHCC, Chapel Hill Consensus Conference.

 The immune complex-mediated febrile illnesses in pa- tients with chronic meningococcaemia or chronic disseminated gonococcaemia are associated with

arthralgia, arthritis, and cuta- neous vasculitis. Scattered purpuric papules and vesicopustules appear on the trunk and extremities in chronic meningococcaemia, but have a predilection for the palms, fingers, and soles in dissem- inated gonococcaemia. The histology is a leukocytoclastic vasculitis with thrombosis in small vessels. The maculopapular rash of Rocky Mountain spotted fever is ini- tially erythematous, but becomes petechial and purpuric within 24– 48 h. Rickettsia rickettsii invades the walls of small cutaneous vessels, inducing a focal lymphocytic vasculitis with extravasation of red blood cells, and occasional thrombosis. Infections are dealt with in detail in Section 8. Cutaneous vasculitis and malignancy Small-vessel cutaneous vasculitis, and urticarial vasculitis have been described in association with lymphoproliferative disorders such as Hodgkin's disease, mycosis fungoides, lymphosarcoma, adult T-cell leu- kaemia, multiple myeloma, and less often with solid tumours (e.g. cancer of the colon, kidney, prostate, head and neck, or breast). Vasculitis might present two to four years before the manifestation of the tumour. Thrombo-occlusive vasculopathies Livedo reticularis and livedo racemosa Clinical features Livedo reticularis is seen most often on the legs. The skin develops a mottled reddish-purple reticulated discoloration that reflects sluggish vascular flow in the superficial dermis (Fig. 23.7.11). Some venous stasis is common. A continuous livedo network is likely to be physiological, and disappears when the skin is warmed. Broken, discontinuous, or patchy and persistent livedo reticularis, that does not disappear with warming and sometimes in associ- ation with painful cutaneous ulceration and nodules (evidence of a vasculitis) (Figs 23.7.3 and 23.7.12), occurs with hyperviscosity states (polycythaemia rubra vera, antiphospholipid antibodies, cryoglobulinaemia), medium-vessel vasculitis (connective tissue diseases, polyarteritis nodosa, and granulomatosis with polyangiitis (Wegener's granulomatosis)), and emboli, including cholesterol em- boli. Patchy and persistent livedo is also termed livedo racemosa (Fig. 27.7.3), rather than reticularis. Differential diagnosis and investigation Erythema ab igne is a reticulated hyperpigmented staining that can develop on any skin surface after chronic exposure to heat from a radiator, open fire, or hot-water bottle. Deep biopsies from subcuta- neous nodules are required to demonstrate diagnostic pathology such as cholesterol emboli or a medium-vessel vasculitis. Livedoid vasculopathy This is also known as segmental hyalinizing vasculitis, livedo reticularis with summer/winter ulceration, and livedoid vasculitis. Pathogenesis and pathology This idiopathic disorder predominantly affects young to middle- aged women. The condition is primarily an occlusive vasculopathy rather than a necrotizing vasculitis. Hyaline thrombi occlude small vessels in the upper and mid dermis. Occlusion may be associated with endothelial swelling, extravasation of red blood cells, fibrinoid material in vessel walls, infarction of the superficial dermis, and scat- tered perivascular lymphocytes. Endothelial, platelet, or lymphocyte activation with the release of proinflammatory cytokines may play some part in the pathogenesis of hypercoagulation. Clinical features Focal purpuric lesions on the lower legs and dorsum of the feet break down to form small excruciatingly painful ulcers that are surrounded by a purpuric rim (Fig. 23.7.13). Ulcers heal slowly, leaving Fig. 23.7.11 Extensive livedo reticularis. Fig. 23.7.12 Painful cutaneous ulceration, necrotizing vasculitis, and livedo reticularis in a patient with antiphospholipid antibodies.

 atrophie blanche (porcelain-white stellate scars with a rim of telangi- ectasia) and net-like hyperpigmentation. The condition pursues a chronic course, sometimes with seasonal exacerbations. Investigation and treatment Livedoid vasculopathy can be a manifestation of an underlying coagulopathy, such as antiphospholipid syndrome or protein C defi- ciency, but in general, investigations reveal no evidence of abnormal- ities in fibrinolytic or coagulation systems. Pain must be controlled.

Antiplatelet therapy, antithrombotic regimens, fibrinolytic agents, and intravenous immunoglobulin have all been recommended, but there is no consensus over management, and treatment is difficult. Treatment for vasculitis with drugs such as systemic corticosteroids is generally ineffective. Hypertensive ulcer (Martorell's ulcer) Hypertensive ulcers were described in 1945. The pathogenesis might be linked to a thrombo-occlusive vasculopathy of cutaneous arteri- oles in long-standing hypertension, but the existence of this entity is controversial. A purpuric lesion appears on the anterolateral aspect of the shin between the mid and lower third of the leg. It becomes necrotic and forms a superficial ulcer with an erythematous or purpuric rim. Patients have no signs of venous or arterial insufficiency. The ulcers, which can be bilateral, are extremely painful. Management involves the control of hypertension, pain relief, and compression bandaging. Neutrophilic dermatoses Neutrophilic dermatoses This heterogeneous group is linked by the histopathological finding of a heavy dermal infiltrate of neutrophils with leukocytoclasis, but limited evidence of vasculitis. Sweet's syndrome (acute febrile
neutrophilic dermatosis) Sweet's syndrome was described in 1964. The condition usually af- fects women in their sixth decade. Pathogenesis and pathology The cause is unknown and 50–70% of cases are idiopathic, but in up to 50% of cases Sweet's syndrome may be associated with malig- nancy (haematological or solid tumours) or immunological disease (rheumatoid arthritis, dermatomyositis, relapsing polychondritis, inflammatory bowel disease). Less frequently, a variety of infections or certain drugs such as granulocyte colony stimulating factor ap- pear to have precipitated the disease. A skin biopsy shows a dense neutrophilic infiltrate in the upper dermis, with leukocytoclasis and nuclear dust. The dermis is oedematous. Vessels show endothelial swelling without a true vasculitis. Clinical features The syndrome is characterized by the sudden onset of fever, neutrophilia, and tender erythematous nodules and plaques, most frequently on the face and upper trunk (Fig. 23.7.14). The plaques appear oedematous, but blisters are unusual; occasionally they may be pustular. Other features include conjunctivitis or episcleritis, oral ulcers, arthralgia, and arthritis. Investigations and treatment Infection should be excluded by blood culture. The erythrocyte sedi- mentation rate is elevated, and patients have a marked neutrophilia. Underlying malignancy should be excluded by the history, physical examination, and appropriate investigations. A skin biopsy is essential to confirm the diagnosis. Most patients respond rapidly to systemic corticosteroids (0.5–1.0 mg/kg) used in association with potent top- ical corticosteroids, but the disease might relapse as corticosteroids are reduced. A minority of patients have chronic relapsing disease. Bowel-associated dermatosis–arthritis syndrome Pathogenesis This syndrome is seen in 10–20% of patients who have had bowel bypass surgery to treat morbid obesity, or after extensive resection Fig. 23.7.13 Livedoid vasculopathy with small painful ulcers that eventually healed to leave porcelain-white stellate scars (atrophie blanche). This patient has no evidence of systemic disease or abnormalities in coagulation. A skin biopsy revealed an occlusive vasculopathy without vasculitis. Fig. 23.7.14 Sweet's syndrome: oedematous plaques in a woman with myeloid leukaemia.

 of the small bowel. It occurs less frequently in patients with an ab- normal segment of bowel in other diseases, such as diverticulitis or inflammatory bowel disease. The overgrowth of bacteria in a blind loop, with the deposition of immune complexes, is thought to trigger disease. The histopathological changes resemble those of Sweet's syndrome. Clinical features The syndrome is characterized by purpuric papules and small vesiculopustular lesions on the trunk and extremities. These might be associated with polyarthritis, malaise, and fever. Some patients have cryoglobulinaemia. Management should be directed at cor- recting the

underlying cause. Cutaneous lupus erythematosus Cutaneous lupus erythematosus (CLE) is an autoimmune disease, which has a broad range of cutaneous pathology. It is two to three times more common than systemic lupus erythematosus (SLE). Aetiology and pathogenesis The pathogenesis of cutaneous lupus erythematosus (CLE) is un- certain, but in genetically predisposed individuals ultraviolet (UV) light might play some part in triggering and perpetuating disease through apoptosis and the release of proinflammatory cytokines. UV exposure can also lead to increased synthesis and expression of the Ro/SS-A antigen on keratinocytes. It has been hypothesized that autoantigens on the surface of apoptotic cells might stimulate the immune system, and antibodies to Ro are very common in sub- acute cutaneous lupus erythematosus (SCLE) and may be detected in other types of cutaneous lupus erythematosus. Drugs that cause photosensitive SCLE skin lesions also trigger the production of Ro (SS-A) autoantibodies. However, the role of these autoantibodies in the pathogenesis is not proven. Certain genes (e.g. HLA, TNFα gene promoter) increase susceptibility to subacute cutaneous lupus erythematosus. Pathology Skin biopsies show a lichenoid (interface) dermatitis with apoptotic basal keratinocytes, a T-cell inflammatory infiltrate at the dermo– epidermal junction, periadnexal inflammation, and perivascular in- flammation without vasculitis. Inflammation and basal cell damage are most marked in chronic cutaneous lesions. The prevalence of cutaneous lupus ranges from 14.6 to 68 per 100 000 people. All races are affected. Most forms of cutaneous lupus erythematosus affect women more than men. Classification Cutaneous lupus erythematosus is classified into acute, subacute, and chronic subtypes (Box 23.7.17), but patients often have more than one type of lesion. The terms discoid lupus erythematosus (DLE) and subacute cutaneous lupus erythematosus (SCLE) are used in two ways: either to describe a subtype of lupus skin lesion, or to refer to subsets of patients who share certain clinical and laboratory features. At present, dermatologists use the only universally accepted criteria for the classification of systemic lupus erythematosus, which was proposed by the American College of Rheumatology (ACR). Box 23.7.17 Subtypes of cutaneous lupus erythematosus (LE) Acute cutaneous lupus erythematosus (ACLE) • Presents in third decade of life • Occurs in active systemic lupus erythematosus Localized form Oedematous malar erythema (‘butterfly rash’) Photosensitivity Nonscarring lesions, however depigmentation may occur Generalized form Occurs below and above the neck and described as ‘maculopapular rash of lupus’ May resemble a drug rash Subacute cutaneous lupus erythematosus (SCLE) • Affects young to middle-age females • May have systemic lupus erythematosus, but low risk of severe disease • Photosensitivity • Anti-Ro antibodies • Superficial scaly annular lesions (common) involve the V-area of the neck, the upper trunk, upper limbs, and hands (sparing the knuckles cf. dermatomyositis) • Papulosquamous lesions (less common) may resemble psoriasis or eczema • Face is affected less often than in other forms of cutaneous lupus erythematosus • Nonscarring, but postinflammatory hypopigmentation is common • Affected mothers may have infants with neonatal lupus erythematosus Chronic cutaneous lupus erythematosus—four types: Discoid lupus erythematosus (DLE) • Most common form of chronic cutaneous lupus erythematosus • Frequently occurs without evidence of systemic lupus erythematosus • Usually localized to the head and neck, but may be widespread • Erythematous telangiectatic plaques or hyperkeratotic plaques with adherent keratotic scale • Plaques on the face tend to spare the nasolabial fold • Acne-like plugged follicles involve the concha of the ears • Plaques may involve the vermillion border of the lips or eyelids • Lichen planus-like lesions develop on the buccal mucosa • Chronic plaques cause scarring and deformity • Perifollicular inflammation leads to irreversible hair loss (scarring alopecia) • Dyspigmentation (increased or decreased) is common in dark skins Lupus erythematosus profundus (LEP) • Subcutaneous nodules- painful and firm • Tends to involve the shoulders, upper

arms, face, and buttocks • Overlying skin may be affected by discoid lupus erythematosus • Fat loss is a disfiguring complication • Subcutaneous nodules may calcify and ulcerate Chilblain lupus • Less common form of chronic cutaneous lupus erythematosus • Resembling frostbite • Painful, violaceous plaques, and nodules in cold-exposed area • Ulceration or erosion occurs on acral surfaces (fingers, toes), nose, ears Lupus erythematosus tumidus • Occurring mainly in males • Extreme photosensitivity • Lesions on the face and trunk • Erythematous, oedematous, urticaria-like with sharp border and smooth surface

23.7 Cutaneous vasculitis, connective tissue diseases, and urticaria 5653 Acute cutaneous lupus erythematosus (ACLE) This condition occurs in third decade of life and it is frequently as- sociated with active systemic lupus erythematosus. There are two forms, localized and generalized. In the localized form, oedematous malar erythema develops in photosensitive patients with active systemic lupus erythematosus. The rash is commonly described as a ‘butterfly’ rash: erythema on the cheeks, over the nasal bridge, and sparing the nasolabial folds. The rash can be confused with acne rosacea and seborrhoeic dermatitis. The lesions are usually transient, resolving rapidly without scarring once the patient is protected from UV light. Subepidermal bullae are an uncommon manifestation associated with antibodies to basement membrane zone antigens, including type VII collagen. The rarer generalized form presents with a pruritic, widespread eruption of symmetrical macules and papules that are photosensi- tive and may look like a drug rash. It may resemble dermatomyo- sitis as both diseases involve the dorsum of the hand. However, dermatomyositis involves the distal and proximal interphalangeal and metacarpophalangeal joints, while they are spared in acute cutaneous lupus erythematosus (Fig. 23.7.16). Immunologically, antinuclear antibody (ANA), dsDNA, and anti-Sm antibodies are found in most cases. Subacute cutaneous lupus erythematosus (SCLE) Subacute cutaneous lupus erythematosus was first recognized in 1979 as a distinct subtype of lupus erythematosus with a low risk of severe systemic lupus erythematosus. This pattern of disease is associated with photosensitivity and anti-Ro (SS-A) antibodies. Subacute cutaneous lupus erythematosus may be induced by a variety of drugs, including hydrochlorothiazide, calcium-channel blockers, angiotensin-converting enzyme inhibitors, proton pump inhibitors, and terbinafine. The scaly, erythematous lesions develop in a photosensitive distri- bution (Figs. 23.7.15 and 23.7.16), and can be annular (Fig. 23.7.17) or, less frequently, papulosquamous (resembling psoriasis). Lesions do not scar but they might leave behind pigmentation change, usu- ally hypopigmentation. Women with subacute cutaneous lupus erythematosus might have infants affected by neonatal lupus erythematosus, because anti-Ro antibodies cross the placenta. These infants present with photosensitive cutaneous disease (usually subacute cutaneous lupus erythematosus) or congenital heart block, but rarely both. Infants can also develop transient haemolytic anaemia, thrombocytopenia, leukopenia, and elevated liver function tests. Skin signs resolve over four to six months, but heart block is permanent. Rarely, infants af- fected by neonatal lupus erythematosus develop a connective tissue disease later in life. Fig. 23.7.15 Subacute cutaneous lupus erythematosus: nonscarring scaly erythematous papules are distributed in a photosensitive distribution on the chest and arms. Fig. 23.7.16 Cutaneous lupus erythematosus involves the skin between the knuckles, by contrast with the scaly papules of dermatomyositis (Gottron’s papules), which occur over the knuckles. Fig. 23.7.17 Subacute cutaneous lupus erythematosus (SCLE) may adopt a striking annular configuration, when it can be confused with tinea corporis (ringworm), but typically the scale of SCLE is on the inner border of the rings, and the rash is in a photosensitive distribution.

section 23 Disorders of the skin 5654 Chronic cutaneous lupus erythematosus (CCLE) Discoid lupus erythematosus is the most common form of chronic cutaneous lupus erythematosus (Box 23.7.17). It occurs more often in females in their fourth and fifth decades of life. It has a more benign course compared with other chronic cutaneous lupus erythematosus subtypes. Most discoid lesions are localized to the head and neck, but it may be widespread and affects the extensor forearms and hands. (Figs. 23.7.18–23.7.23). Discoid lupus erythematosus le- sions appear as a well-demarcated, scaly, erythematous macule or papule, which gradually transforms into a coin-shaped (discoid) plaque with scale (which is painful to remove). Plaques tend to affect hair follicles and cause scarring alopecia. Sun exposure and trauma (Koebner phenomenon) tend to exacerbate the disease. Squamous cell carcinomas may rarely occur within chronic lesions of discoid lupus erythematosus. Lupus erythematosus profundus (LEP) is a lobular panniculitis that occurs in 1–3% of patients with cutaneous lupus erythematosus (Fig. 23.7.24). LEP tends to affect the upper arms, legs, face, and breasts. It has a chronic course, with relapses and remissions, and due to fat loss, leaves disfiguring, atrophic scars. Cold-induced chilblain lupus is characterized by purple plaques on the fingers or toes (Fig. 23.7.25) which may ulcerate (Fig. 23.7.26); chronic lesions develop a warty surface (Fig. 23.7.27). The histology is not specific, but this pattern of disease may be associated with sys- temic lupus erythematosus. Lupus erythematosus tumidus is an uncommon variant that does not scar, but is associated with photosensitivity. Smooth, erythema- tous, urticated nodules appear on sun-exposed skin, and may per- sist for weeks. The diagnosis is clinical, as most patients do not have lupus antibodies, and the histology may not be diagnostic.
Nonspecific cutaneous signs in systemic
lupus erythematosus Forty to seventy per cent (40–70%) of patients with systemic lupus erythematosus develop nonscarring alopecia. Causes include lupus hairs (hairs break off at the front of the scalp), telogen effluvium Fig. 23.7.18 Chronic erythematous telangiectatic plaques in a photosensitive distribution on the face of a woman who has systemic lupus erythematosus.
Fig. 23.7.19 Discoid lupus erythematosus. This man has well-defined, scaly plaques on the face. Note the pale areas of atrophic scarring. From R Graham-Brown, K Harman, G Johnston (2016) Lecture Notes: Dermatology, 11th Edition. Copyright © 2016, John Wiley and Sons. Fig. 23.7.20 Chronic discoid lupus erythematosus causes scarring and deformity, seen here on the bridge of the nose.

 (shedding after severe illness), and alopecia areata. In contrast, dis- coid lupus erythematosus can cause scarring alopecia (Box 23.7.17 and Fig. 23.7.21). Patients with systemic lupus erythematosus might have periungual erythema and discrete papular telangiectasia on the palms or finger tips. Some have Raynaud's phenomenon. About 10–20% of patients with systemic lupus erythematosus have some form of vasculitis. Linear telangiectasia is present on the posterior nail fold (a sign of a connective tissue disease also found in dermatomyositis, systemic sclerosis, and 5% of cases of rheumatoid arthritis). Thrombosed vessels might be carried forward into a ragged cuticle. Painless red-black lesions of the nail fold or finger pulp (Bywater's lesions) reflect micro-infarcts of superficial dermal vessels, and are most common in rheumatoid arthritis, but can be seen in systemic lupus erythematosus (Fig. 23.7.28). Urticaria is common in systemic lupus erythematosus, but long- lasting tender urticarial lesions that fade to leave bruises are a sign of urticarial vasculitis, sometimes an indication of an underlying com- plement deficiency. A small-vessel cutaneous vasculitis (palpable purpura) might be associated with cryoglobulinaemia (see 'Small- vessel cutaneous vasculitis' earlier on in this chapter). Fixed livedo reticularis in a broken rather than a continuous physiological

pattern might be linked to the antiphospholipid syn- drome, a medium-vessel vasculitis, recurrent thromboses, and neurological complications. Atrophie blanche, a sign of vasculitis or Fig. 23.7.21 Discoid lupus erythematosus in the scalp causes a scarring alopecia that may be extensive and disfiguring. Fig. 23.7.22 The plugged lesions of discoid lupus erythematosus in the concha of the ears were misdiagnosed as acne, and in this patient with dark skin have caused hyperpigmentation. Fig. 23.7.23 Discoid plaques on the vermillion border of the lips are triggered by ultraviolet light. Fig. 23.7.24 Lupus panniculitis on the upper arm presented as a deep tender nodule. The overlying skin is affected by discoid lupus erythematosus. Chronic ulceration is a troublesome complication that may be precipitated by a biopsy.

section 23 Disorders of the skin 5656 obstructive vasculopathy, can be present on the plantar surface of the toes (Fig. 23.7.29) or fingers. Differential diagnosis Red faces are common, but the distribution and morphology of the rash will provide important clues to the underlying diagnosis. Patients with a malar (butterfly) rash that spares the sun-protected skin on the eyelids, behind the ears, and under the chin can be photosensitive, but drugs cause photosensitivity more often than lupus erythematosus. Pustules are not found in cutaneous lupus erythematosus; in- stead consider rosacea or steroid-induced acne (a complication in patients treating cutaneous lupus erythematosus with potent topical steroids). Seborrhoeic dermatitis produces a superficial scaly facial erythema involving the nasolabial folds (unlike lupus erythematosus), mid-forehead, and scalp (dandruff). Seborrhoeic dermatitis is not photosensitive, does not scar, and is not usually associated with hair loss (Chapter 23.6). The cutaneous signs in dermatomyositis (see ‘Cutaneous fea- tures of dermatomyositis’ next) are similar to those of lupus erythematosus; however, the intense itching that plagues patients with cutaneous dermatomyositis is not a feature of cutaneous lupus erythematosus. Both conditions are photosensitive, but the facial rash in dermatomyositis is more oedematous than in cutaneous lupus erythematosus, and tends to involve the nasolabial folds, un- like cutaneous lupus erythematosus. The rash of dermatomyositis targets the skin over the joints on the hands, whereas cutaneous lupus erythematosus tends to involve the skin between the joints (Fig. 23.7.16). In patients with subacute cutaneous lupus erythematosus, a drug- induced aetiology must be considered. The annular lesions might be mistaken for dermatophyte infection (ringworm), but the trailing edge of scale is on the inner edge of the ring and follows the erythema (Fig. 23.7.17), whereas in dermatophyte infection, scale on the outer Fig. 23.7.25 Purple plaques on the toes or fingers are characteristic of chilblain-like cutaneous lupus erythematosus. Fig. 23.7.26 Ulceration of the fingertips in a patient with chilblain lupus erythematosus. Fig. 23.7.27 Chronic hyperkeratotic chilblain lesions may fissure. Fig. 23.7.28 Vascular involvement in systemic lupus erythematosus may present with infarcts of the nail fold (Bywater’s lesions). This patient also has extensive atrophie blanche (hypopigmented atrophic skin with telangiectasia) on the dorsa of the fingers, indicative of vascular damage.

23.7 Cutaneous vasculitis, connective tissue diseases, and urticaria 5657 edge of the expanding ring is followed by erythema. Subacute cu- taneous lupus erythematosus must also be differentiated from ery- thema multiforme (Chapter 23.16) and psoriasis (Chapter 23.5). Psoriasis might coexist with cutaneous lupus erythematosus and can be exacerbated by the antimalarials used to treat cutaneous lupus erythematosus; check for psoriatic nail pitting or onycholysis. Hypertrophic discoid lupus erythematosus may simulate a squa- mous cell skin cancer. Clinical investigation Systemic disease should be excluded by the history, physical examination, and laboratory studies including examination of the urine, a full blood count, routine biochemistry, and

immun- ology (antinuclear antibodies, antibodies to extractable nuclear antigens, antihistone antibodies in suspected drug-induced lupus erythematosus, and complement levels). The diagnosis should be confirmed by the histological examination of a skin biopsy. Immunofluorescence testing is not required unless the lesions are bullous. In annular subacute cutaneous lupus erythematosus, dermatophyte infection should be excluded by mycological culture of a skin scrape. Treatment Treatment aims to minimize scarring and pigment change by controlling cutaneous disease. Patients should be advised to stop smoking (smokers have disease that is more severe and which is less responsive to antimalarials, possibly due to altered drug metabolism). Patient education on heat, sun, and drug avoid- ance is important. Also patients should be advised to avoid manipulation of the lesions as it may trigger new lesions (Koebner phenomenon). Photoprotection is essential (Box 23.7.18). Some patients are sen- sitive to both UVA (penetrates glass) and UVB, while others are sen- sitive to UVA alone or UVB alone. Occasionally, visible light triggers disease. Adequate sun protection will reduce the need for topical corticosteroids or systemic treatment. Physical sunscreens with ti- tanium dioxide or zinc oxide provide good broad-spectrum pro- tection. Sunblocking films can be applied to glass to prevent UVA penetration. In such patients vitamin D levels should be monitored and addressed as necessary. Very potent topical corticosteroids or calcineurin inhibitors are required to control inflammation and prevent scarring. Initially, a very potent topical corticosteroid (such as clobetasol propionate 0.05% ointment) should be thinly applied twice daily to all lesions, including those on the face. Clobetasol propionate scalp application can be used for discoid lesions in the scalp. It might take several weeks of treatment before the inflammation settles, particularly in thick discoid lesions. Atrophy is unlikely if treatment is supervised, but the strength of corticosteroid should be reduced gradually to less potent preparations as soon as the inflammation is controlled and the lesions have flattened. Calcineurin inhibitors have emerged in recent years and are an alternative to topical corticosteroids, especially for use on the face. Tacrolimus 0.1% ointment is usually effective and prevents develop- ment of telangiectasia (a side effect of topical steroids). Patients should be shown how to apply the treatment (steroid phobia causes undertreatment), and be advised that treatment aims to control inflammation and further damage, but will not alter scars or pigmentation. Patients with disfiguring scars or pigment change need advice on the use of cosmetic camouflage creams. Patients with widespread cutaneous lupus erythematosus or lo- calized disease that does not respond to topical treatment need systemic treatment with an antimalarial in addition to topical treat- ment. Hydroxychloroquine 200 mg twice daily (<6.5 mg/kg per day) is effective after about 8–12 weeks in most patients, and is well- tolerated, but is less effective in smokers. Ocular toxicity has been reported with the related drug chloroquine, but hydroxychloroquine may be safer, provided the maximum dose is not exceeded. Visual acuity should be checked, and patients should see an optician an- nually. Mepacrine (quinacrine) can be used in combination with hydroxychloroquine. Other options include dapsone, thalidomide, and gold. Systemic corticosteroids can be used (e.g. prednisolone 0.5–1 mg/ kg/day) and tapered over 2–4 weeks. Immunosuppressants such as methotrexate can be used, with recommended dose 7.5–25 mg or- ally or subcutaneously once a week. Immunomodulators, such as dapsone (25–150 mg/day), have been shown to be effective in some cases of lupus panniculitis, subacute cutaneous lupus erythematosus, and discoid lupus
Fig. 23.7.29 This woman with systemic lupus erythematosus had no signs of active disease apart from atrophie blanche on the plantar surface of her toes. Atrophie blanche indicates either obstructive vasculopathy or vasculitis. The skin may ulcerate after minor trauma or in cold weather. It is important to examine the toes of any patient with a connective tissue disease.
Box 23.7.18 Strategies for photoprotection • Limit sun exposure,

particularly between 11.00 a.m. and 2.00 p.m. • Wear clothing with a tight weave • Wear wide-brimmed hats (a brim of 7 cm) • Use high-factor broad-spectrum sunscreens containing the physical blocker titanium dioxide or zinc oxide to block the entire UV and vis- ible light spectrum. • Apply sunscreen liberally in the morning to all exposed sites • Reapply sunscreen four hourly during the hours of sunlight • Consider vitamin D supplements in patients who need to photoprotect

section 23 Disorders of the skin 5658 erythematosus. Dapsone can cause agranulocytosis, haemolysis, methaemoglobineamia, or hypersensitivity reactions. Patients who have glucose-6-phosphate dehydrogenase (G6PD) deficiency should not take this drug. Rituximab, a chimeric monoclonal antibody that targets CD20, can be effective in cases of refractory subacute cutaneous lupus erythematosus and systemic lupus erythematosus with cutaneous lesions. Prognosis Systemic lupus erythematosus is most frequent in patients with acute cutaneous lupus erythematosus or lupus erythematosus- nonspecific skin lesions. One-half of patients with subacute cuta- neous lupus erythematosus fulfil the criteria for systemic lupus erythematosus, but only 10–15% of patients presenting with sub- acute cutaneous lupus erythematosus develop severe manifestations of systemic lupus erythematosus. Drug-induced subacute cutaneous lupus erythematosus does not always reverse on withdrawal of the triggering drug. Discoid lupus erythematosus eventually remits in 50% of those with localized disease (confined to the head and neck). Most pa- tients with localized chronic cutaneous disease, including lupus panniculitis and lupus erythematosus tumidus, do not develop sig- nificant systemic disease. Discoid lupus erythematosus occurs with systemic lupus erythematosus in 5–10% of patients, but those with widespread discoid lupus erythematosus are most at risk. The course is benign and renal disease, if it occurs, is usually mild. Dermatomyositis Dermatomyositis is a multisystem autoimmune disorder affecting skin, muscle, and blood vessels. It has characteristic cutaneous changes and can be associated with muscle weakness and inflam- mation. In adults, the disease is often associated with an underlying malignancy (carcinoma or lymphoma). Aetiology, genetics, pathogenesis, and pathology The cause of the disease is unknown. However, T lymphocytes, pre- dominantly of the CD4 + phenotype, appear to play a pathogenic role in mediating microvascular injury and the apoptosis of basal kera- tinocytes. Cytokines and chemokines released by activated T cells and keratinocytes can induce and perpetuate inflammation. UV-induced apoptosis might also play a part in the pathogenesis of skin lesions. A range of factors might be important in the aetiology of the disease: genetics (HLA-B* in children and HLA-DR3 and B14 in adults); infections (toxoplasmosis, parvovirus B19, coxsackie B virus, staphylococcal osteomyelitis and arthritis); malignancy (lung, breast, female genital tract, gastrointestinal tract, kidney or testes and lymphoma); autoantibodies (Jo-1, PL-12, PM-1). The cutaneous histological features include an interface derma- titis (vacuolar degeneration of basal keratinocytes and apoptosis), mild perivascular inflammation, oedema, and deposition of dermal mucin. The histological features are usually similar to those of cu- taneous lupus erythematosus, but the acute vesiculobullous variant might resemble graft-versus-host disease. Dermatomyositis affects adults and children of all races. Females are affected more often than males. Clinical features Skin and muscle involvement usually present within a short time of each other, but the extent of skin involvement does not correlate with severity of muscle disease. Skin and muscle problems present concurrently in 60% of patients, whereas in 10% muscle involve- ment precedes inflammatory cutaneous disease, and in 30% the skin involvement presents weeks or a few months before the onset of myositis (Box 23.7.19). The term amyopathic dermatomyo- sitis (dermatomyositis sine myositis) describes a subset of patients,

usually female, in whom muscle involvement does not develop until up to 20 years after the onset of cutaneous dermatomyositis. These patients are still at risk of interstitial lung disease or internal malignancy. Cutaneous dermatomyositis, unlike cutaneous lupus erythema tosus, can cause pruritus, burning, and pain. Ultraviolet light exacerbates or triggers the rash in up to 50% of patients, but pa- tients might not realize that the rash is photosensitive. A symmet- rical violaceous or heliotrope (violet-red) erythema of the eyelids or periorbital skin is associated with fine scale and periorbital oedema or facial swelling (Figs. 23.7.30 and 23.7.31). Intense oe- dema can lead to blisters. Erythema also affects the cheeks, the V-area of the upper chest and neck, the posterior neck, upper back, and shoulders (shawl sign), the extensor aspects of the shoulders, Box 23.7.19 Clinical features of dermatomyositis Dermatomyositis is an idiopathic inflammatory myopathy associated with a characteristic skin rash. Key features are a proximal myopathy and cutaneous findings which typically include erythema on sun-exposed sites, a heliotrope rash, and oedema on the eyelids, Gottron's papules (over the joints), periungual erythema with ragged cuticles and dilated nailfold capillaries. Fig. 23.7.30 Periorbital oedema and facial swelling was misdiagnosed as angioedema in this woman with dermatomyositis.

 arms, forearms, and fingers, and bony prominences of the el- bows, knees, knuckles, and greater trochanter of the hip (holster sign). Scalp involvement can be associated with diffuse alopecia (Fig. 23.7.32). The hands should be examined using magnification (an ophthal- moscope or dermatoscope) to assess the nail fold. Signs in the hands or nails can be diagnostic, and are listed in Box 23.7.20 (Figs. 23.7.33 to 23.7.36). Chronic inflammation results in poikiloderma (hypo- and hyperpigmentation, atrophy, and telangiectasia). Vasculopathy, with necrosis and ulceration, and cutaneous calcinosis (Fig. 23.7.37) are less common in adults than children. Other clinical features include interstitial lung disease, which can be fatal, Raynaud's phenomenon, and constitutional symptoms such as fever, fatigue, and weight loss. In severe cases, the myopathy can affect the oesophageal and respiratory musculature. A subset of patients might present with 'mechanic's hands' (Box 23.7.20 and Fig. 23.7.36), skin changes on the digits that simulate Fig. 23.7.31 The characteristic heliotrope (violet-red) erythema of the eyelids is revealed more clearly when the patient closes her eyes. From Harris A et al. (1995). Dermatomyositis presenting in pregnancy. Br J Dermatol, 133, 783–5, with permission. Copyright © 2006, John Wiley and Sons. Fig. 23.7.32 Scalp erythema with hair loss may be difficult to manage in dermatomyositis, and simulates the scarring alopecia in chronic cutaneous lupus erythematosus. Box 23.7.20 Dermatomyositis: signs in the hands • Periungual erythema • Tortuous nailfold capillaries and capillary dropout (avascular areas) • Thickened irregular cuticles with capillary haemorrhage • Gottron's papules (flat-topped violaceous scaly papules over the dorsal interphalangeal joints) are present in about one-third of patients, and are pathognomonic of dermatomyositis. Gottron's papules evolve into hypopigmented atrophic areas with irregular telangiectasia. • Linear streaks of erythema over the extensor tendons of the fingers. • Mechanic's hands: hyperkeratosis, scaling, and fissuring on the tips and lateral aspects of the digits simulates a contact dermatitis Fig. 23.7.33 Periungual erythema, tortuous nailfold capillaries, capillary dropout (avascular areas), and/or thickened irregular cuticles with capillary haemorrhage are more common in dermatomyositis than in lupus erythematosus. Fig. 23.7.34 Flat-topped violaceous scaly papules over the dorsal interphalangeal joints (Gottron's papules) are pathognomonic of dermatomyositis. Chronic papules develop depressed porcelain-white centres, with prominent telangiectasia (see Fig. 23.7.35).

section 23 Disorders of the skin 5660 those of a contact dermatitis seen in a manual worker. These changes can be a manifestation of the antisynthetase syndrome, a subset of dermatomyositis characterized by these skin changes plus Raynaud's phenomenon, interstitial lung disease, arthritis, and fevers. It is associated with antibodies to aminoacyl-tRNA synthetases, most commonly anti-Jo1. Dermatomyositis is associated with internal malignancy in 20–30% of adult patients, most commonly ovary, lung, gastrointestinal tract, breast, and lymphomas. The increased risk can persist for five years after diagnosis, but is greatest in the first year, and in women. Signs linked to malignancy include corticosteroid resistance, an intense erythematous flush on the shoulders, neck, face, and scalp (malig- nant suffusion) and cutaneous ulceration. Differential diagnosis Cutaneous lupus erythematosus can resemble dermatomyositis clinically and histologically, but intense pruritus is not a feature Fig. 23.7.35 Chronic changes in dermatomyositis. Note the Gottren's papules over the joints have been replaced with porcelain-white atrophic scars with telangiectasia. Fig. 23.7.36 Hyperkeratosis, scaling, and fissuring on the lateral aspects of the fingers (mechanic's hands) simulates contact dermatitis. Fig. 23.7.37 Cutaneous calcinosis, necrosis, and ulceration in a
12-year-old child with chronic dermatomyositis.

23.7 Cutaneous vasculitis, connective tissue diseases, and urticaria 5661 of lupus erythematosus. When cutaneous lupus erythematosus involves the hands, the rash tends to spare the joints, whereas Gottron's papules occur over the joints. Lesions tend to be oe- dematous in dermatomyositis, but hyperkeratotic in lupus erythematosus. Scalp erythema and scale might be confused with seborrhoeic dermatitis, but the purplish colour, periorbital oedema, and predi-lection of lesions for light-exposed skin suggest dermatomyositis. Alopecia is not a feature of dermatitis. Mechanic's hands might be misdiagnosed as contact dermatitis. Facial oedema might be mis- diagnosed as angioedema. Dermatomyositis can also simulate psor- iasis. Dermatomyositis or a dermatomyositis-like rash has been induced by several drugs. Clinical investigation Investigations are aimed at establishing a diagnosis and screening for underlying malignancy or internal organ involvement. A bi- opsy of involved skin is helpful and should reveal an interface dermatitis, but the changes are not specific and will not distinguish dermatomyositis from cutaneous lupus erythematosus. Muscle involvement should be investigated with serum muscle enzymes, electromyography, and muscle biopsy or muscle MRI. Patients with pulmonary symptoms should have chest radiography and pulmonary function tests, and high-resolution computed tomog-raphy (CT) is the investigation of choice for associated interstitial lung disease. Autoantibodies are found in approximately 80% of patients with dermatomyositis. About a third have antinuclear antibodies. There are several myositis-specific antibodies associated with dermato- myositis of which the commonest are anti-Jo1 (15–20%), anti-Mi2 (<10%), anti-SRP (5–10%), anti-p155 (15–20%), and anti-MDA5 (50–75% Asian patients). Other autoantibodies which might be detected include anti-Ro/SS-A, anti-La/SS-B, and anti-PM/Scl; these can indicate the existence of an overlapping connective tissue disease. A thorough history and physical examination are important in screening for underlying malignancy or disease-associated organ involvement. Investigations other than routine blood tests, urin- alysis, and faecal occult bloods should be guided by clinical find- ings but might include chest radiography, CT/MRI of the chest, abdomen, and pelvis and endoscopy. Women should be offered mammography and bimanual examination of the pelvis, with a cervical smear, CA125 blood levels, and transvaginal ultrasonog- raphy. Reinvestigation for internal malignancy should be considered periodically. Criteria for diagnosis The diagnosis of cutaneous dermatomyositis is based on the pres- ence of the typical cutaneous signs, with or

without muscle in- volvement, combined with the cutaneous histology of an interface dermatitis. Treatment Treatment options for dermatomyositis are summarized in Box 23.7.21. Pruritus, skin pain, and burning can be difficult to manage, but may be helped by sedating antihistamines such as hydroxyzine, cooling baths, aqueous cream with 1% menthol, and moisturizers or soap substitutes to prevent dry skin (common in older people). Cutaneous dermatomyositis is less responsive to treatment than cutaneous lupus erythematosus, but the approach is similar. Optimal topical therapy will minimize the dose of systemic im- munosuppressive drugs. Protective clothing, wide-brimmed hats, and high-factor sun blocks are essential. Potent or highly potent top- ical corticosteroid ointments applied twice daily can control limited cutaneous disease, as may 0.1% tacrolimus ointment. Steroid lotions may relieve scalp irritation. Cosmetic camouflage can reduce dis- figurement, particularly in patients with long-standing disease and poikiloderma. Most patients require oral therapy, but randomized controlled trials are required to evaluate treatments. Hydroxychloroquine (200–400 mg/day) can be beneficial, but takes 8–12 weeks to have an effect, and up to six months for maximal benefit. Smoking might diminish its effectiveness so patients should be advised to stop smoking. Hydroxychloroquine is less effective in cutaneous dermatomyositis than in cutaneous lupus erythematosus. Ocular toxicity has been reported with the related drug chloroquine, but hydroxychloroquine might be safer provided the maximum dose is not exceeded. Visual acuity should be checked, and patients should see an optician annually. Oral prednisolone (0.5–1 mg/kg per day) in reducing doses over two to three months might control symptomatic cutaneous disease while hydroxychloroquine is taking effect. Bolus infusions of methylprednisolone (500 mg/day IV for three days) can be tried and often a good alternative to high dose of oral steroids. Dapsone may be helpful (50–300 mg/day). Immunosuppressives such as methotrexate (7.5–15 mg once a week), azathioprine (1.5–3 mg/kg/day), ciclosporin (100 mg/day), mycophenolate mofetil (2– 3 g/day in divided doses), and chlorambucil have been used with Box 23.7.21 Therapeutic ladder for treatment of cutaneous Dermatomyositis First line • Topical: corticosteroids and /or calcineurin inhibitors (pimecrolimus 1% cream, tacrolimus 0.03%, or 0.1% ointment); sunscreen • Antimalarials—Hydroxychloroquine usually given first and may be combined with others • Strict photo protection (see Box 23.7.18) • Antipruritics—antihistamines (hydroxyzine), tricyclic antidepressants (doxepin, amitriptyline, nortriptyline) Second line • Methotrexate • Mycophenolate mofetil • Azathioprine • Dapsone • Systemic corticosteroids Third line • Intravenous immunoglobulin • Tumour necrosis factor (TNF)-α inhibitors • Rituximab • Cyclophosphamide • Ciclosporin A • Other systemic agents: thalidomide, rapamycin • Other therapies: stem-cell transplant, plasmapheresis, total body irradiation

 varying success in refractory skin disease. Several studies indicated a successful role of intravenous immunoglobulin, 1 g/kg for two days per month for 4–6 months. TNFα might play a part in the patho- genesis of dermatomyositis and TNFα inhibitors, such as infliximab, have been tried, as has the anti CD20 biologic therapy rituximab, with some success. In severe cases plasma exchange and extracor- poreal chemotherapy might be useful. Prognosis The prognosis is variable and unpredictable. Some patients have acute and fulminant disease, whereas in others it runs a chronic course punctuated by remissions and relapses. Skin and muscle disease tend to respond in parallel with treatment, but as immunosuppressants are gradually withdrawn, cutaneous disease may relapse without recurrence of muscle weakness. Interstitial lung disease and underlying, internal malignancy can be fatal. Scleroderma The sclerodermatous disorders are characterized by tight, stiff, fi- brotic skin which feels hard (sclero). It may be localized or general- ized and may be purely cutaneous or part of a multisystem disease.

The different subtypes are outlined in Fig. 23.7.38. Systemic sclerosis Systemic sclerosis is reviewed in detail in Chapter 19.11.3, but the cutaneous features are discussed next. Aetiology, genetics, pathogenesis, and pathology Systemic sclerosis is a connective tissue disease that is character- ized by collagen accumulation (fibrosis) associated with vascular injury and autoantibodies. The small arteries and microvasular beds of target organs appear to be damaged before the onset of fi- brosis. Mesenchymal cells (fibroblasts, smooth muscle cells, and endothelial cells), activated by unknown stimuli, produce in- creased amounts of collagen, proteoglycan, and fibronectin, while lymphocyte activation produces autoantibodies and cytokines. The generation of autoantibodies is influenced by hereditary factors, including the presence of certain major histocompatibility com- plex genes. It has been suggested that autoantibodies to basement membrane antigens might be involved in vascular injury, and that chronic activation of B cells, with release of cytokines, might play some part in the stimulation of fibroblasts and the development of skin fibrosis, but it is still not clear if autoantibodies have a direct role in the pathogenesis. Skin biopsies show thickened dermis, with broad collagen bun- dles extending into subcutaneous fat. The walls of small vessels are thickened, with intimal fibrosis and thrombosis. Epidemiology The distribution of clinical subtypes and antibody prevalence varies among populations and geographic regions. The prevalence of sys- temic sclerosis is reported to be between 13 and 105–140 per mil- lion, and it has an annual incidence of between 2.6 and 20–28 per million. Genetic, ethnic, and environmental factors may explain these variations. Systemic sclerosis is more common in women, and black women are most at risk. The average age of onset is between 40 and 50 years, with limited cutaneous systemic sclerosis occurring in older women more than often diffuse cutaneous disease. Raynaud’s phenomenon occurs in 3–15% of the population. Clinical features Systemic sclerosis is divided into two major subtypes, depending primarily on the extent of cutaneous involvement (Fig. 23.7.38). The clinical features are given in Box 23.7. 22. Limited cutaneous systemic sclerosis This is also known as CREST; C: calcinosis cutis, R: Raynaud’s phenomenon, E:oesophageal dysmotility: S: sclerodactyly, T: telangiectasia. Raynaud’s phenomenon is the first sign of disease, and can pre- cede other features by 10–15 years. Symmetrical thickening and tightening of the skin distal to the metacarpophalangeal joints (sclerodactyly) restricts opposition of the palms when the wrists are extended. This prayer sign indicates joint or skin pathology, or short- ening of the finger flexor muscles. Well-defined telangiectatic mac- ules (mats) appear on the hands, tongue, lips, and face (Fig. 23.7.39). Raynaud’s phenomenon is associated with linear periungual nailfold telangiectasia (usually without capillary dropout) (Figs. 23.7.40 and 23.7.41), atrophy of the finger pulps with breaking of the finger nails, resorption of bone in the terminal phalanges, and painful ischaemic ulceration that heals leaving pitted scarring of the finger tips (Fig. 23.7.42). Nodules of cutaneous calcinosis can become inflamed and ulcerate, discharging chalky material (Fig. 23.7.43). Cellulitis might complicate ulceration. Systemic problems, such as oesophageal dysmotility causing dys- phagia, interstitial lung disease with pulmonary hypertension, or biliary cirrhosis, might not develop for decades, if at all. Diffuse cutaneous systemic sclerosis The disease starts abruptly with the sudden onset of non- pitting oedema of the hands, feet, and face, often associated Limited Cutaneous Diffuse Cutaneous Plaque Localized Scleroderma (Morphoea) Systemic Sclerosis Linear Eosinophilic Fasciitis Fig. 23.7.38 Scleroderma subsets.

 with constitutional symptoms and a rheumatoid-like arthritis. Raynaud’s phenomenon usually develops within one year of the skin changes. Patients might complain of pruritus. The nailfold capillaries are distorted

and irregular; fingers and toes become dusky and cyanotic. Sclerodactyly and flexion contractures produce a claw-like deformity with painful ulcer- ations of the finger tips and knuckles (rat-bite necroses). Sclerosis spreads to the proximal extremities, chest, face, scalp, and trunk over 3–12 months, or might be present at disease onset. Facial sclerosis gives the face a mask-like stiffness with a reduced mouth aperture (Fig. 23.7.44), radial furrowing around the lips, and a pinched nose. The skin of the neck is ridged and tightened when the head is extended. This neck sign is positive in more than 90% of patients. Pigment change is common, with either generalized hyperpigmentation or focal hypo- or hyperpigmentation in areas of sclerosis. Signs of systemic involvement include hypertension and abnor- malities in gastrointestinal, pulmonary, renal, or cardiac function (Chapter 19.11.3). Box 23.7.22 Clinical features of systemic sclerosis Limited cutaneous systemic sclerosis • Raynaud's phenomenon for years or decades • Dilated nailfold capillary loops, usually without capillary destruction • Skin sclerosis limited to the hands, face, neck, feet, and forearms, or absent • May have cutaneous calcinosis, telangiectasia, or oesophageal hypomotility • Late incidence of pulmonary hypertension, with or without interstitial lung disease • Anticentromere antibodies in 70–80% • Also known as CREST Diffuse cutaneous systemic sclerosis • Onset of Raynaud's phenomenon within one year of onset of skin changes • Nailfold capillary dilatation and capillary destruction (also seen in dermatomyositis and overlap syndromes) • Skin sclerosis (tightness, thickening, nonpitting induration) affecting the arms, chest, abdomen, back, or thighs, in addition to acral sclerosis (face, feet, hands) • Sclerodactyly (fingers and/or toes), digital pitting scars, or loss of substance of the digital finger pads (pulp loss) • Tendon friction rubs • Early interstitial lung disease (bibasilar pulmonary fibrosis), oli- guric renal failure, diffuse gastrointestinal disease, and myocardial involvement • Anti-DNA topoisomerase I (anti-Scl-70) antibodies in 30% • Absence of anticentromere antibodies Fig. 23.7.39 Well-defined telangiectatic macules (mats) on the face of a man with long-standing limited cutaneous systemic sclerosis. This patient also has cutaneous calcinosis, Raynaud's phenomenon, oesophageal hypomotility, and anticentromere antibodies. Fig. 23.7.40 Linear periungual nailfold telangiectasia in a young female patient with limited cutaneous systemic sclerosis and Raynaud's phenomenon. Fig. 23.7.41 Linear periungual telangiectasia in the nail fold of the patient illustrated in Fig. 23.7.40, viewed through a dermatoscope.

 Differential diagnosis Raynaud's phenomenon with normal nailfold capillaries and no autoantibodies might be idiopathic or linked to β-blocker therapy, hyperviscosity syndromes, emboli, or atherosclerosis. Systemic scler- osis must be distinguished from localized forms of scleroderma (see 'Localized scleroderma'), but these patients do not have Raynaud's phenomenon, and the nailfold capillaries are normal. Some features of systemic sclerosis, including Raynaud's phenomenon, might be present in patients with rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis/polymyositis, and Sjögren's syndrome. Environmental agents and some drugs can induce a scleroderma- like disease (Box 23.7.23). Cutaneous thickening and induration is seen in conditions such as lipodermatosclerosis (the lower leg in venous stasis), sclerodema adultorum (triggered by infection— firm nonpitting oedema of the face, neck, trunk; increased dermal acid mucopolysaccharides), scleromyxoedema (increased dermal acid mucopolysaccharides), chronic graft-versus-host disease, and porphyria cutanea tarda (sun-exposed skin, blistering, skin fragility). Clinical investigation Evaluation should include the assessment of systemic involve- ment (lung, heart, kidney, gastrointestinal tract), functional im- pairment and impact on quality of life. Skin thickening is assessed by palpating and pinching the skin. Generally, a skin biopsy is not required. Autoantibodies specific for different subtypes of

systemic scler- osis, or for overlap syndromes with other connective tissue dis- eases, are present in 95% of patients, usually at the onset of disease (Table 23.7.2). These persist throughout the course of the disease. Less than 1% of patients have more than one systemic sclerosis- specific antibody. Criteria for diagnosis Raynaud's phenomenon is defined as episodic bilateral di- or triphasic vascular reactions (pallor, cyanosis, and erythema) of the fingers, toes, ears, or nose that are provoked by cold or emo- tion. The diagnostic criteria for systemic sclerosis are discussed in Chapter 19.11.3. Treatment Moisturizers and sedating antihistamines might reduce prur- itus. Patients should avoid nicotine and keep peripheries warm Fig. 23.7.42 Raynaud's phenomenon, atrophy of finger pulps with breaking of fingernails, calcinosis, and painful ulceration heals leaving pitted scarring of the finger tips in limited cutaneous systemic sclerosis. Fig. 23.7.43 Nodules of cutaneous calcinosis may become inflamed and ulcerate, discharging chalky material. Telangiectatic mats are visible on the palm and finger pulps. Fig. 23.7.44 Reduced mouth aperture in a patient with diffuse cutaneous systemic sclerosis. Box 23.7.23 Agents that cause a scleroderma-like disease • Chemicals (polyvinyl chloride, solvents, pesticides) • Drugs (bleomycin, pentazocine, ethosuximide, penicillamine) • Paraffin • Contaminated rapeseed oil (toxic oil syndrome) • L-tryptophan • Gadolinium based MRI contrast media (nephrogenic systemic fibrosis)

 (Box 23.7.24). Fingertip ulceration in Raynaud's phenomenon might be complicated by secondary infection. Moisturizers (ointments) relieve dryness and cracking of the fingers. Topical antibiotics or antibiotic–steroid combinations can be helpful in superficial ulcers. Hydrocolloid dressings can relieve pain and promote healing. Systemic treatments to improve peripheral circulation, prevent the synthesis and release of harmful cytokines, and inhibit or reduce fibrosis are discussed in Chapter 19.11.3, but placebo-controlled trials are needed to evaluate these treatments. Prognosis Patients with systemic sclerosis have a fourfold risk of death com- pared with the general population, but the risk of death varies be- tween subgroups. Renal, pulmonary, and cardiac involvement are independent adverse predictors, but as the severity of the cardiovas- cular, pulmonary, and renal disease correlates with the extent of cu- taneous involvement, the extent of skin sclerosis is a useful marker of severity and prognosis. Ten-year survival in patients with limited cutaneous systemic sclerosis is 65–88%, whereas that in patients with diffuse cutaneous disease ranges from 61 to 75%. An erythrocyte sedimentation rate greater than 15–25 mm/h, or a haemoglobin level lower than 12.5–11 g/dl, is associated with a 2.5–3-fold increase in mortality. Specific autoantibodies provide additional prognostic information (Table 23.7.2). Localized scleroderma Localized scleroderma (morphoea) refers to a group of conditions in which increased collagen deposition causes localized skin thickening (Fig. 23.7.45). Some patients have more than one type of lesion. Aetiology, genetics, pathogenesis, and pathology The pathogenesis of localized scleroderma is unknown, but auto- antibodies might play a role. The activation of T lymphocytes and cytokine release can stimulate dermal fibroblast proliferation and collagen production. Endothelial cells also appear to be activated. Infection with agents such as Borrelia burgdorferi has been impli- cated in the pathogenesis of some cases of morphoea, but these find- ings have not been substantiated. The histological features are similar to those in the involved skin in systemic sclerosis. The histological features of eosinophilic fasci- itis, a deep variant, include marked inflammation including eosino- phils, and fibrous thickening of the deep fascia and subcutis. Epidemiology The prevalence of localized scleroderma has been estimated to be 27 cases per million. Females are affected more often than males. Linear scleroderma is more common in children, whereas plaque- type morphoea (the most common form of localized scleroderma) is more common in adults. Clinical features

Plaque morphoea Patients have one or more lesions, usually on the trunk. These start as erythematous patches that progress to indurated smooth shiny white or yellow plaques with violet borders (the lilac ring) (Fig. 23.7.45). This form of morphoea is self-limiting. Inactive Table 23.7.2 Autoantibodies in systemic sclerosis Antibody Type of sclerosis Clinical associations Anticentromere antibodies Limited cutaneous sclerosis High risk: calcinosis, ischaemic digital loss, pulmonary hypertension Low risk: pulmonary fibrosis Low mortality Anti-Scl-70 (topoisomerase) antibodies Diffuse cutaneous sclerosis Pulmonary fibrosis High mortality from ventricular failure secondary to pulmonary disease Anti-Th/To antibodies Mild skin involvement Severe pulmonary fibrosis Poor prognosis Anti-RNA polymerase family antibodies Diffuse cutaneous sclerosis Systemic sclerosis-related renal crisis High mortality Antifibrillarin antibodies/anti-U3 RNP antibodies Diffuse cutaneous sclerosis Some populations: myositis, pulmonary hypertension, renal disease Box 23.7.24 Improving peripheral circulation and treating Raynaud's phenomenon • Avoid nicotine and β-blockers • Thermal underwear to raise core temperature • Thermal gloves and/or socks • Thick-soled padded footwear • Warm hands for 5 min every 4 h in warm water • Warm hands in warm water before going outdoors • Heat pads (purchased in outdoor activity shops) • Hand or foot warmers (battery powered) • Glyceryl trinitrate (nitroglycerin) patches • Oral calcium antagonists (e.g. nifedipine) • Angiotensin receptor inhibitors (e.g. losartan), or phosphodiesterase inhibitors (e.g. sildenafil) • Iloprost is used in critical ischaemia Fig. 23.7.45 Plaque morphoea is the most common form of localized scleroderma. Note the hyperpigmented bands beneath the breasts and on the lower abdomen. On palpation, these areas felt firm and thickened, typical of morphoea.

section 23 Disorders of the skin 5666 lesions hyperpigment (Fig. 23.7.46). Generalized morphoea is a rare variant, usually seen in adults, in which much of the skin becomes sclerotic. Internal organs are not involved, but involvement of the chest wall causes disabling restrictive lung defects. Linear scleroderma A unilateral sclerotic band extends along a limb. Deep atrophy might affect underlying subcutaneous tissues, including muscle and bone, so that the limb becomes shortened and wasted. The face is affected in the rare en coup de sabre linear variant in children (Fig. 23.7.47). Disfiguring hemifacial atrophy might be the end result if deeper tis- sues are affected. These children can also develop neurological com- plications (seizures, headache, and hemiparesis), eye problems, and misalignment of the jaws. Eosinophilic fasciitis (Shulman's syndrome) This scleroderma-like disorder involves the deep fascia, and might be triggered by vigorous exercise. Patients develop symmetrical in- duration of the skin and subcutaneous tissues, usually of the distal limbs. The reddish-brown subcutaneous plaques are initially oe- dematous, but become indurated and brawny. Peripheral eosino- philia is common. Differential diagnosis Early plaque morphoea can simulate both granuloma annulare and erythema chronicum migrans (see 'Annular erythemas', next). Extragenital lichen sclerosus resembles plaque morphoea, but in li- chen sclerosus the surface is slightly hyperkeratotic with follicular plugs. Patients might also have genital lichen sclerosus. Some pa- tients have both lichen sclerosus and morphoea. Eosinophilic fasciitis must be differentiated from conditions such as cellulitis, deep venous thrombosis, postirradiation injury, toxic oil syndromes, and l-tryptophan-induced eosinophilia–myalgia syndrome. Clinical investigation A deep elliptical skin biopsy that extends from normal into abnormal skin can be helpful in diagnosing plaque morphoea, but sometimes the changes are subtle. A full-thickness biopsy that includes fascia and muscle is required in deep variants such as eosinophilic fasciitis. Patients might have autoantibodies, including antinuclear anti- bodies, anti-Scl-70, anticentromere antibody, anti-double-stranded DNA, anticardiolipin antibody, and rheumatoid factor, but their sig- nificance is unclear. Bone and joints should be evaluated in patients with linear sclero- derma, and limb length

discrepancy should be excluded. In linear scleroderma affecting the face, a periodic eye examination should be performed, and MRI considered to detect central nervous system involvement. Treatment Treatments have not been evaluated in controlled trials. Plaque morphoea remits spontaneously, and no treatment is required, but a potent topical corticosteroid ointment can be used until the inflammatory ring has settled. Psoralen UVA bath and oral phototherapy (PUVA) and low-dose UVA1 (340–400 nm) have been reported to be effective in widespread morphoea and linear scleroderma. Linear scleroderma is difficult to manage, and a multidisciplinary approach is essential. Complications such as joint contrac- tures or malocclusion should be addressed. Monthly intralesional triamcinolone might halt the progression of disease affecting the scalp and forehead. Intravenous methylprednisolone, oral prednis- olone, and/or methotrexate have been recommended for progressive linear disease. Once the disease is inactive, reconstructive surgery can reduce deformity. Eosinophilic fasciitis eventually remits spontaneously in many patients, but oral corticosteroids, methotrexate, and azathioprine have been prescribed. Fig. 23.7.46 The sclerotic plaque on the hip of this child is pigmenting as it softens. Fig. 23.7.47 En coup de sabre morphoea, now inactive, has left a linear groove on the forehead of this young woman.

 Prognosis Plaque morphoea is a self-limiting disease that usually slowly re- solves over three to five years. Eosinophilic fasciitis also remits spon- taneously in about one-third of patients. Rheumatoid arthritis Rheumatoid arthritis (RA) is a chronic inflammatory arthritis in which extra-articular manifestations are common. It is discussed in detail in Chapter 19.5, but the cutaneous manifestations are outlined next. Cutaneous features The common cutaneous features of rheumatoid arthritis are listed in Box 23.7.25; these signs are most obvious in the hands. Rheumatoid nodules (RN) are found in 20–30% of patients. They are firm, subcutaneous, painless papules or nodules located at the periarticular regions mainly on the extensor surfaces of the fingers and elbows. Nodules are linked to both seropositivity for rheuma- toid factor, and severe systemic manifestations. Rarely, nodules may ulcerate or become infected. The nodules are composed of fibrin- like material surrounded by palisading histiocytes with an outer zone of chronic inflammatory cells. Similar nodules may be found in 5–7% of patients with systemic lupus erythematosus. Rheumatoid vasculitis is most common in seropositive pa- tients with long-standing nodular disease and is regarded as a late complication of rheumatoid arthritis. Vasculitis can involve small or medium-sized vessels and the clinical signs vary accordingly. Medium vessel involvement presents with broken livedo, nodules, and painful punched-out ulcers, often along the lateral malleoli or pretibial region. Twenty per cent (20%) of patients with severe vasculitis have digital gangrene. It can involve internal organs and therefore can be potentially life-threatening. Small-vessel cutaneous vasculitis manifests as palpable purpura, which might become nec- rotic and ulcerate, or urticarial vasculitis. Vasculitic lesions are common on the fingers, even in patients without systemic vasculitis. They include splinter haemorrhages, linear telangiectasia in the nail fold, and petechiae and brownish purpuric lesions of the nail fold or finger pulp (Bywater’s lesions) that might infarct and heal leaving small scars. Ten per cent (10%) of patients with rheumatoid arthritis have leg ulcers, but the pathogenesis is multifactorial (Fig. 23.7.48). Trauma, skin fragility, and immobility with venous stasis cause leg ulcers more often than vasculitis. Painful rapidly enlarging ulcers with undermined bluish-red borders can be caused by pyoderma gangrenosum (Fig. 23.7.49) (Chapter 23.15). Patients with Felty’s syndrome (rheumatoid arthritis, leukopenia, and splenomegaly) might develop chronic leg ulcers that are refractory to treatment. Interstitial

granulomatous dermatitis with arthritis is an un- common condition of unknown cause that can be associated with severe rheumatoid arthritis and other systemic autoimmune dis- eases. Tender linear indurated bands arise symmetrically on the axilla, trunk, and inner portions of the thighs. Rheumatoid neutro- philic dermatitis, another condition of unknown cause, is associated with severe rheumatoid arthritis, and is characterized by papules, plaques, nodules, and urticarial weals. Blistering diseases, including mucous membrane pemphigoid, pemphigus, epidermolysis bullosa acquisita, and subcorneal pustular dermatoses, have been reported in association with rheumatoid arthritis. Panniculitis Introduction Panniculitis is a group of diseases characterized by the inflamma- tion of subcutaneous fat. There are many causes, as detailed in Box 23.7.26, and the most common types are described next. Aetiology, genetics, pathogenesis, and pathology The panniculitides are classified histologically according to whether they predominantly affect the fibrous septa, that separate lobules of fat, or affect the fat lobules themselves, and whether there is an asso- ciated vasculitis. Panniculitis might commence in subcutaneous fat, Box 23.7.25 Cutaneous features of rheumatoid arthritis (RA) Rheumatoid arthritis specific skin changes: • Rheumatoid nodules or nodulosis • Rheumatoid neutrophilic dermatosis • Rheumatoid vasculitis (signs of small or medium vessel involvement) Rheumatoid arthritis: • Related nonspecific skin manifestations • Pale, shiny, and atrophic skin in long-standing disease • Skin fragility and easy bruising • Palmar erythema • Erythema nodosum • Livid (Raynaud-like) fingertips • Onycholysis • Periungual erythema and dilated nailfold capillaries • Pyoderma gangrenosum • Urticaria • Leg ulcers (often multifactorial: vasculitis, stasis, pyoderma gangrenosum, Felty’s syndrome) • Pressure ulcers Fig. 23.7.48 Leg ulcers are common in rheumatoid arthritis, and difficult to manage. Biopsy may not be diagnostic. Stasis, trauma, and vasculitis have contributed to ulceration in this man with long-standing rheumatoid arthritis.

section 23 Disorders of the skin 5668 or be caused by dermal inflammation extending into subcutaneous fat. The common subtypes of panniculitis are listed in Box 23.7.26. Some of the panniculitides likely to be encountered by the general physician are considered next, but many are covered elsewhere in organ-specific chapters. Septal panniculitis Erythema nodosum Aetiology The pathogenesis is unknown, but erythema nodosum may be a hypersensitivity response to an infection or an underlying inflammatory disease. Inflammation might be triggered by immune complexes deposited in the venules of the septa in sub- cutaneous fat. A type IV delayed hypersensitivity reaction might be involved. Erythema nodosum is frequently linked to streptococcal infec- tions in children. The most common associations in adults include infections (bacterial, including TB, viral, fungal), drugs, sarcoidosis (erythema nodosum and bilateral hilar adenopathy), lymphoma, and inflammatory bowel disease, as well as miscellaneous condi- tions ranging from Sweet’s syndrome to pregnancy. In about one- third of cases no precipitating factor is identified. Erythema nodosum is a septal panniculitis. The septa are in- flamed and thickened, neutrophils are present in early lesions, Fig. 23.7.49 Pyoderma gangrenosum presents as painful, rapidly enlarging ulcers with undermined bluish-red borders. In the early stages, this may respond to topical treatment with a very potent corticosteroid or tacrolimus. Box 23.7.26 Subtypes of panniculitis Septal panniculitis With large-vessel vasculitis: • Superficial thrombophlebitis (see Chapter 23.12) • Cutaneous polyarteritis nodosa Without vasculitis: • Erythema nodosum • Rheumatoid nodule • Necrobiosis lipoidica (see Chapter 23.15) • Scleroderma and eosinophilic fasciitis Lobular panniculitis With large-vessel vasculitis: • Nodular vasculitis Without vasculitis: • α1-Antitrypsin deficiency • Cold panniculitis • Sclerosing panniculitis (lipodermatosclerosis) (Fig. 23.7.50) • Calciphylaxis • Lupus panniculitis (lupus profundus) • Pancreatic panniculitis • Infective

panniculitis (infection of subcutaneous fat in immunosup- pressed patients) • Traumatic or factitial panniculitis • Cytophagic histiocytic panniculitis and subcutaneous T-cell lymphoma • (Weber–Christian disease is no longer considered to be a distinct entity) Fig. 23.7.50 Sclerosing panniculitis (lipodermatosclerosis) is a lobular panniculitis found in association with venous stasis.

 a perivascular lymphocytic infiltrate is present in the overlying dermis, and variable numbers of giant cells and histiocytes form granulomas. Vasculitis is not a feature of typical erythema nodosum, but the erythema nodosum-like lesions that develop in Behçet's and Crohn's disease have a vasculitic histology. Epidemiology Erythema nodosum is the most common type of panniculitis. Most cases appear between the second and fourth decades, with a peak incidence between the ages of 20 and 30 years. It occurs more fre- quently in women. Both the incidence and prevalence of associated aetiological fac- tors vary geographically. Most cases occur in the first half of the year, possibly linked to an increase in streptococcal infections; one of the most common causes in the United Kingdom is a strepto- coccal sore throat. Sarcoidosis and tuberculosis are common causes where the incidence of these diseases is high. Ulcerative colitis and Crohn's disease are common associations seen in secondary care in the United Kingdom. Worldwide, erythema nodosum is com- monly caused by lepromatous leprosy. This is a widespread and often very persistent reaction to local antigen, and is not typical of erythema nodosum in general. It can become pustular and necrotic. Other associations of erythema nodosum include blastomycosis, coccidioidomycosis, Trichophyton verrucosum, lymphogranuloma venereum, cat-scratch disease, ornithosis, leukaemia, Epstein– Barr virus, Hodgkin's disease, tularaemia, histoplasmosis, yersinia, pregnancy, and drugs such as the contraceptive pill and sulphonamides. Clinical features Tender, erythematous, warm nodules measuring 1–5 cm or more in diameter are distributed symmetrically on the shins, ankles, and knees (Fig. 23.7.51). Less often, nodules appear on the arms or trunk. The nodules fade over two to six weeks (more quickly in children), taking on the appearance of a deep bruise. They do not ulcerate, and resolve without loss of fat or scarring. Erythema nodosum can be associated with fever, malaise, arthralgia, and headache, or problems such as abdominal pain, vomiting, or diar- rhoea. A chronic migratory variant (subacute nodular migra- tory panniculitis; erythema nodosum migrans) is less common (Fig. 23.7.52). Differential diagnosis Lesions are subcutaneous and erythematous rather than purpuric. The symmetrical distribution suggests an endogenous reaction rather than an exogenous cause such as trauma, cellulitis, or in- sect bite. Erythema nodosum can be differentiated clinically from nodular vasculitis (erythema induratum of Bazin; see 'Nodular vas- culitis' next) by the distribution of the lesions (shins rather than calves) and the absence of ulceration, atrophy, or scarring. The cord-like lesions of superficial thrombophlebitis are usually on the sides of the leg. Investigation Underlying causes must be excluded by history taking and exam- ination. Investigations should be guided by the local prevalence of aetiological factors such as bacterial, viral, fungal, or protozoal infections. Preliminary investigations might include a full blood count, erythrocyte sedimentation rate, urinalysis, and chest radiog- raphy. A skin biopsy is seldom required. Treatment Underlying causes should be identified and treated. Pain relief with NSAIDs is generally all that is required for erythema nodosum. Elevation or bed rest can be helpful in acutely painful disease, and patients might benefit from support stockings to control swelling. Potassium iodide has been recommended in persistent disease. Fig. 23.7.51 Erythema nodosum presenting with tender erythematous nodules on the shins in a patient with sarcoidosis. Fig. 23.7.52 The chronic migratory form of erythema nodosum presented as a tender expanding indurated lesion on the leg that persisted for several months. Panniculitis was demonstrated on biopsy. No trigger was

identified.

section 23 Disorders of the skin 5670 Rarely, oral corticosteroids are needed, but infection must be excluded first. The prognosis will depend on that of the underlying disease. Idiopathic erythema nodosum is a self-limiting condition with an excellent prognosis. Relapses are uncommon. Lobular panniculitis Nodular vasculitis (erythema induratum of Bazin) Aetiology Nodular vasculitis is the most common form of lobular panniculitis with vasculitis. It is considered to be a reactive disorder. Bazin de- scribed this form of vasculitis in 1861, and a link with tuberculosis was recognized in the early 1900s. Mycobacterium tuberculosis
DNA has been demonstrated in cutaneous biopsy specimens; how- ever, in many patients no underlying factor is identified. Stasis and cooling play some part in the localization of disease. The path- ology is a lobular panniculitis with fat necrosis and vasculitis, pri- marily affecting the venules and veins of the fibrous septa. This disease affects obese middle-aged women. Clinical features Tender indurated erythematous nodules and plaques develop slowly on the calves of fat legs, where the skin is cyanotic and cold. The subcutaneous nodules might ulcerate and heal slowly, leaving atrophic scars. Recurrences are frequent. Patients tend to have evidence of venous insufficiency of the lower legs, but are otherwise healthy. Nodular vasculitis runs a protracted course over many years. Tuberculosis should be excluded by chest radiography and a Mantoux test. A deep incisional biopsy is required to demonstrate the pathology. The indolent presentation, distribution of lesions, ulceration, and scarring differentiate nodular vasculitis from ery- thema nodosum. Treatment Tuberculosis must be treated. Venous stasis should be controlled by weight loss, compression bandages, elevation, and exercise. NSAIDs might relieve pain. α1-Antitrypsin deficiency Lung and liver disease associated with deficiency in α1-antitrypsin are discussed elsewhere (Chapter 12.13). Pathogenesis, genetics, and pathology α1-Antitrypsin (AAT) is a circulating inhibitor of serine protease. Subnormal levels of AAT can result in panniculitis, as well as pul- monary or liver disease. The genetic variants are classified into four primary categories (Z,S,M,F). The 90 or more allelic variants of the AAT gene can be divided into three major categories of muta- tion, which result in enzyme deficiency, null mutations, or altered enzyme function. Enzyme function can be significantly impaired, despite normal serum levels of AAT, but most cases associated with panniculitis have the ZZ genotype, with AAT levels below normal. The most common histological findings are an acute lobular panniculitis accompanied by neutrophils, fat necrosis, and foamy macrophages. α1-Antitrypsin allele studies have estimated a frequency of 116 million carriers globally, and 3.4 million individuals with the known deficiency allele combinations. Approximately 70 000 to 100 000 individuals in the United States of America and Europe have α1-antitrypsin deficiency. The sexes are affected equally. Adults are affected by panniculitis more often than children. Clinical features Recurrent erythematous plaques and nodules develop on the hips, thighs, and buttocks. Nodules may suppurate, with the release of oily material (Fig. 23.7.53). Panniculitis is characteristically induced or exacerbated by trauma. α1-Antitrypsin deficiency is also associated with emphysema, hepatitis, cirrhosis, vasculitis, and angioedema. The proximal distribution combined with nodules that ulcerate and suppurate, helps distinguish this from other panniculitides. Investigation and treatment A deep biopsy of a fresh nodule will reveal a suppurative panniculitis. The serum level of α1-antitrypsin and its phenotype are only useful if the clinical and histological findings are compatible with panniculitis associated with α1-antitrypsin deficiency. This panniculitis might respond to drugs that inhibit neutro- phil function, such as dapsone or colchicine. Tetracycline anti- biotics can have a direct effect on serine proteases released from neutrophils, and can be helpful in some patients. NSAIDs and Fig. 23.7.53

This patient presented with recurrent painful, erythematous nodules, and plaques. The involvement of the torso and proximal limbs, and the tendency to break down and leak fluid, was in keeping with a diagnosis of α-1-antitrypsin deficiency. The diagnosis was confirmed by demonstrating low serum levels and a ZZ genotype. This image shows a plaque on the upper arm from which fluid is beginning to leak.

23.7 Cutaneous vasculitis, connective tissue diseases, and urticaria 5671 hydroxychloroquine have also been recommended. Severe, unre- sponsive disease can be treated with pooled human α-1-antitrypsin (there is no recombinant form available yet). Cold panniculitis This form of panniculitis is seen most often in the winter in plump young female horse riders wearing tight clothing that provides insufficient insulation and restricts the blood supply to the subcutaneous fat. The rider develops chilblains affecting the thighs (Chiltern chaps) (Fig. 23.7.54) and buttocks (Berkshire buttocks). The ill-defined mottled bluish-red plaques resolve without scarring. Riders should be advised to wear loose-fitting warm clothing. Weber–Christian disease More than 70 years ago Weber used this term to describe a nodular relapsing panniculitis with fever and lipoatrophy (Fig. 23.7.55). Many cases considered to be examples of Weber–Christian disease have subsequently been given more specific clinicopathological diagnoses, and most authors no longer consider it to be a distinct entity. Annular erythemas This group of disorders, also known as gyrate or figurate erythemas, is characterized by lesions that begin as red papules or macules and spread centrifugally to produce rings or arcuate shapes. Erythema annulare centrifugum Erythema annulare centrifugum is thought to be a hypersensitivity reaction, and has been linked to a variety of aetiological factors ran- ging from infection to drugs and malignancy, but in most cases the cause is unknown. Lymphocytes cluster tightly around the small blood vessels in the superficial and mid dermis. Epidermal changes (spongiosis, parakeratosis) might be present in superficial lesions. It is more common in adults than children. Clinical Patients have one or more lesions, most often on the trunk or prox- imal limbs (Fig. 23.7.56). The lesions start as erythematous papules or macules, and slowly expand by 2–3 mm/day into well-defined annular or arcuate shapes (maximum 10 cm diameter) with central clearing, and then fade over days to weeks to leave normal skin. The trailing inner edge of the erythematous ring can be finely scaly in Fig. 23.7.54 Cold panniculitis causes mottled bluish-red chilblains on the thigh of a young female horse rider, so-called ‘Chiltern chaps’. Fig. 23.7.55 Multiple areas of lipoatrophy on the arm. Lipoatrophy, appearing as indented areas, may be a consequence of some forms of panniculitis.

section 23 Disorders of the skin 5672 superficial lesions. Sometimes lesions are oedematous and vesicular; they can be itchy. Most cases pursue a chronic course over several years, but eventu- ally regress spontaneously. Differential diagnosis The scale of tinea corporis (ringworm) is more pronounced, and typically is on the outer margin of the ring. Sometimes psoriasis can be annular but there would usually be other features including more typical plaques. Cutaneous lupus and sarcoidosis can also be annular occasionally, but would have distinct histological fea- tures. Granuloma annulare tends be less erythematous, the ring is composed of coalescing papules that give the lesion a beaded edge if the skin is stretched, lesions are smooth not scaly, and the evolution is less rapid than erythema annulare centrifugum. The cutaneous lesions of subacute cutaneous lupus erythematosus are widespread and are linked to photosensitivity. Neonatal cutaneous lupus should be considered in infants. Smooth annular lesions can also be a manifestation of urticaria, but these fade over 24 h. Erythema annulare centrifugum should also be differentiated from the other annular erythemas: erythema migrans and gyrate ery- thema

(see next). Investigation and treatment Fungal infection should be excluded by taking a skin scrape for mycological culture. Topical corticosteroids can relieve irritation, but have no effect on the course of the disease. Erythema gyratum repens Waves of rapidly expanding (1 cm/day) erythematous concentric bands give the skin the appearance of wood grain. This is a rare manifestation of internal malignancy. Erythema migrans Pathogenesis Erythema migrans is the first sign of Lyme borreliosis, an infection caused by spirochaetes of the group Borrelia burgdorferi sensu lato, which is transmitted by the bite of Ixodes scapularis and related ticks (see Chapter 8.6.33). B. burgdorferi sensu stricto transmits the dis- ease in the United States of America, whereas Borrelia garinii and Borrelia afzelii cause most of the illness in Europe. The skin is in- filtrated by T lymphocytes, with a predominance of CD4+ helper/ inducer cells, as well as numerous plasma cells and CD68+ macro- phages. Epidermal Langerhans' cells are invaded by B. burgdorferi in early Lyme borreliosis. Epidemiology Lyme borreliosis occurs with similar frequency in men and women, and affects people of all ages. The disease is found in forested areas throughout most of Europe, but particularly in Germany (Black Forest), Austria, Slovenia, and Sweden. It has been reported in Russia, Mexico, Asia, Australia, and South Africa. Lyme disease also occurs in the coastal areas of the north-east United States of America, the upper Midwest, and the West Coast. Birds, mice, deer, voles, and lizards are the major reservoirs of borrelia. Clinical features The disease is divided into three stages: early localized disease, early disseminated disease, and persisting late disease. Erythema migrans occurs around 7–10 days after the tick bite in patients with early localized disease. A small erythematous macule or papule appears at the site of the bite, usually the knee, groin, or ax- illa. As spirochaetes spread through the skin, the erythema extends over days to weeks to produce either an annular lesion with central clearing, or a roundish erythematous patch (Fig. 23.7.57). Lesions Fig. 23.7.57 Erythema migrans occurs around 7–10 days after the tick bite, and continues for days to weeks. Doxycycline is the treatment of choice for early localized disease. Fig. 23.7.56 Erythema annulare centrifugum is the most common of the annular erythemas. Scale is visible on the inner edge of the erythematous ring.

 range in size from 10 cm to more than 50 cm diameter. A papule with a punctum might be visible in the centre of the primary le- sion. Erythema migrans is not scaly and the signs can be subtle, but are more obvious if the skin is warmed. The lesion might be slightly pruritic. Flu-like symptoms are common in the early localized stage. The haematogenous spread of spirochaetes might induce additional lesions. The rash clears spontaneously, usually in three days to eight weeks, but persistence for more than one year has been recorded. Late cutaneous manifestations are seen more frequently in Europe than in the United States of America. Acrodermatitis chronica atrophicans is a chronic progressive skin condition characterized by bluish-red discoloration of the skin on acral surfaces (dorsa of hands and feet, lower leg). Initially the skin is swollen, but this is followed by atrophy, when the skin appears thin and wrinkled. These changes might be associated with arthritis or polyneuropathy. Lymphadenosis benigna cutis is another chronic manifestation of borrelia infection, in which painless erythematous nodules develop on the ear lobe, nipple, or scrotum. Systemic manifestations (cardiac, rheumatological, ophthalmo- logical, neurological) are discussed elsewhere (see Chapters 16.7.1, 24.16). Treatment If the tick is attached for less than 48 h, infection is less likely. A single 200 mg dose of doxycycline prevents Lyme borreliosis when given within 72 h of a tick bite. A 14–21-day course of doxycycline is re- commended for early localized or disseminated infection. The prognosis is excellent in patients with erythema migrans treated for Lyme borreliosis; persistent infection and relapses are rare. The natural course of disease in

European borreliosis is not as well defined as in the United States of America. Urticaria and angioedema Introduction Urticaria (‘hives’ or ‘nettle rash’) is characterized by a red (ery- thematous), raised, itchy (pruritic) eruption of papules and plaques resulting from vasodilatation, increased blood flow and vascular permeability in the superficial (papillary) dermis. Chronic urticaria/ angioedema presents with weals, angioedema, or both occurring most days and lasting more than six weeks. Acute urticaria is characterized by an episode of spontaneous weals lasting for less than six weeks. Angioedema consists of transient swellings of the deep (reticular) dermis, subcutaneous and submucosal tissues, and may coexist with urticaria. The swelling is usually painful rather than itchy. Anaphylactic/anaphylactoid episodes involve multiple organ sys- tems and can also be associated with urticaria and angioedema. The latter are discussed in detail in Chapters 4.3 and 17.3. Chronic urticaria or angioedema is defined as disease on most days for longer than six weeks. Aetiology and pathology The principal underlying disease mechanism is mast cell acti- vation, which results in mast cell degranulation, releasing hista- mine, cytokines, chemokines, and other inflammatory mediators such as prostaglandins and leukotrienes. Together the effects in- clude vasodilatation and increased vascular permeability. The mast cell component of urticaria (weals and pruritus) responds well to antihistamines. However, antihistamines are less effective in con- trolling the angioedema, probably due to their inability to affect nonhistamine-related tissue oedema which might be involved in the pathogenesis of angioedema. Histologically, the appearance is variable, but there can be evi- dence of dermal oedema and an infiltrate, possibly including CD4

- T cells, monocytes, neutrophils, basophils, and eosinophils. In the setting of urticarial vasculitis, there are likely to be other histological features such as leukocytoclastic vasculitis, as described earlier in the chapter. Although IgE-mediated allergy is a frequently considered explan- ation for urticaria, it comprises only one mechanism through which mast cell degranulation can occur. Such degranulation can be in- duced through several mechanisms, and this has led to a reclassifica- tion of urticaria and angioedema based on aetiology (Table 23.7.3). It has relatively recently been recognized that up to 40–60% of adults with chronic urticaria have IgG antibodies specific to the α-subunit of the high-affinity IgE receptor on mast cells, or IgG antibodies specific to IgE, suggesting an autoimmune mechanism in these patients. Indeed, 27% have antithyroglobulin and/or antimicrosomal antibodies. Hereditary C1 esterase inhibitor deficiency is an autosomal dom- inant disorder, but with a spontaneous mutation rate of 25% and a prevalence of 1 in 50 000. In type I disease, there is a relative defi- ciency of C1 esterase inhibitor, and in type II disease there are func- tional defects rather than loss of inhibitor levels. There is a very rare third type with normal levels and function of C1 esterase inhibitor. Acquired C1 inhibitor deficiency can be associated with systemic disease, including lymphoproliferative and autoimmune diseases. In the presence of C1 esterase inhibitor deficiency, the classical com- plement pathway can be excessively or inappropriately activated. The incidence of angiotensin-converting enzyme (ACE) inhibitor-associated angioedema is 0.1–0.2%, and might result from the re- duced metabolism and increased availability of bradykinin. It can occur after many years of uneventful drug use. Similarly, angioedema can also be associated with angiotensin receptor blockers (ARB). Patients often present with swelling of the tongue, lips, pharynx, larynx, and viscera without urticaria. The episodes of angioedema can recur months after the withdrawal of the drug. Clinical features Urticaria is characterized by transient red raised itchy weals,

varying from a few millimetres to large areas covering many centimetres. The lesions typically last less than 24 h, with no residual changes; however, the presence of more prolonged lesions, particularly when painful or associated with residual bruising, should raise the possi- bility of an underlying vasculitic aetiology (i.e. urticarial vasculitis). Angioedema consists of transient deeper swellings of subcuta- neous or submucosal tissue, which are typically slightly more prolonged than urticarial lesions and can persist for several days. Angiotensin-converting enzyme inhibitor-associated angioedema might start many years after starting the drug, and can take months to settle after stopping. Persisting disease after termination of ACE inhibitor therapy should prompt the possibility of ACE inhibitor- exacerbated idiopathic angioedema.

section 23 Disorders of the skin 5674 As the typical lesions are frequently not present at examination, a detailed history is the cornerstone of diagnosis and should include the nature of the lesions, their frequency, timing, and any putative triggers, as well as other symptoms, drug history, and family his- tory. Although delayed reactions are well described (e.g. wheat and carbohydrate antigens associated with meat), potential allergic food triggers are most frequently relevant in the 60 min before the onset of the episode. The clinical features of allergic disease are discussed in Chapter 4.3. It can be helpful to test for dermographism by gentle rubbing of the skin and examining for an urticarial response within a few minutes. A diagnosis of C1 esterase inhibitor deficiency is suggested by a history of recurrent episodes of angioedema and abdominal pain. The swellings are not typically pruritic. Although urticaria is not as- sociated, there can be prodromal erythema in up to 25%. Classically, the oedema develops over 12–36 h and takes 2–5 days to subside. Episodes can arise spontaneously or following minor trauma, such as dental work. Other triggers include oestrogens, angiotensin- converting enzyme inhibitors, or infection. Clinical investigation and treatment Table 23.7.3 shows a possible investigation strategy based on the known aetiologies. The approach to the investigation of allergic dis- ease is discussed in Chapter 4.3. In practice, it is not uncommon for all investigations to be normal in spontaneous chronic urti- caria/angioedema, which are then, rather unsatisfactorily, currently grouped as idiopathic. C4 is a useful screening test for untreated C1 esterase inhibitor deficiency, and if low, then C1 esterase inhibitor levels and/or function can be measured. Management of chronic spontaneous urticaria Start with a regular long-acting nonsedating H1 antihistamines, unless the episode frequency is low, in which case the antihistamine can be taken as required. It might be necessary to increase the dose Table 23.7.3 Classification and investigation of urticaria/angioedema Aetiology Mechanism Investigations Spontaneous Cause unknown Can be triggered by stress, infection, drugs (e.g. NSAIDs) Typically negative FBC: eosinophil count can be raised in parasitic infection and in drug-induced urticaria Urinalysis: haematuria and proteinuria,- to screen for infection and renal tract involvement in vasculitis Acute phase response: elevated ESR or CRP, indicates infection, vasculitis or paraproteinaemia (high ESR and normal CRP) Thyroid function and autoantibodies Skin biopsy: if unusual clinical features or suspected vasculitis Autoimmune IgG auto-antibody to mast cell IgE receptor or to IgE bound to mast cells Associated with autoimmune thyroiditis Thyroid antibodies, thyroid function, ANA Specialist centres may undertake a basophil histamine release test and an autologous serum skin test Inducible Physical induction of mast cell degranulation Aquagenic: contact with hot or cold water Cholinergic: exercise, heat, or emotion Cold-induced: cold wind, cold water Delayed pressure: sitting, lying, tight clothing Dermographism: minor trauma Solar: sunshine Heat induced: hot shower/bath Challenge testing with appropriate stimuli, e.g. dermographism, ice cube, exercise, pressure Cryoglobulins (cold

urticaria) Allergic contact urticarial (IgE-mediated) IgE specific to food, airborne allergens, drugs (e.g. penicillin, latex, pollens, grass) Skin prick testing or specific IgE to allergen Drug-induced Increased availability of bradykinin (ACE inhibitors, ARBs), NSAIDS, opiates Response to avoidance C1 esterase inhibitor deficiency Genetic: enhanced kinin producation, activation of complement, fibrinolysis, and coagulation system Acquired: binding of C1 by paraprotein C4 and C1 esterase inhibitor level/function, autoimmune screen, lymphoproliferative screen Vasculitis Vessel wall inflammation Deposition of immunoglobulin and complement Triggered by infection, e.g. hepatitis B/C or streptococcus, drugs (penicillin, allopurinol, quinolones, carbamazepine), autoimmune disease, malignancy, paraproteinaemia. FBC, liver, and renal function tests, ESR, urinalysis, ASOT, hepatitis
B/C, Ig electrophoresis, autoimmune screen, ANCA, C3, and C4,
skin biopsy Lymphoproliferative Paraproteinaemia Paraprotein in blood and urine Food constituent (non-IgE),
e.g. salicylates (rare) Unknown Response to exclusion Infection Complement activation due to immune complex formation Parasites, viral exanthems, EBV, hepatitis B and C Relevant serology, stool microscopy ACE, angiotensin-converting enzyme; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; ARB angiotensin receptor blocker; ASOT, antistreptolysin O titre; CRP, C-reactive protein; EBV, Epstein–Barr virus; ESR, erythrocyte sedimentation rate; FBC, full blood count; NSAID, nonsteroidal anti-inflammatory drug.

23.7 Cutaneous vasculitis, connective tissue diseases, and urticaria 5675 (up to four times recommended dose) or add a second antihista- mine to gain satisfactory control, as long as the benefits outweigh the risks. If these measures fail it might be necessary to consider using other approaches, such as the use of a leukotriene-receptor antag- onist. Tranexamic acid can be a helpful adjunct to the therapy of angioedema. Other agents such as ciclosporin, omalizumab, mycophenolate mofetil, methotrexate, and tacrolimus can be used for very severe disease. It is advisable to avoid ACE inhibitors. The carrying of adrenaline autoinjectors should be considered if there is a history of angioedema affecting the upper airway, or if there are other anaphylactoid features, subject to the ab- sence of contraindications. Clearly, if there is an allergic cause for the urticaria/angioedema, or if there is a defined trigger, then the patient should be counselled on avoidance. It is also wise to avoid potential exacerbating factors such as aspirin and NSAIDs. Acute treatment for a severe episode associated with hereditary C1 esterase inhibitor deficiency can be with C1 inhibitor concen- trate or fresh frozen plasma. Prophylactic treatment of hereditary angioedema is often by attenuated androgens and/or tranexamic acid; there are several new developments, including genetically en- gineered C1 esterase inhibitor, kallikrein inhibitor, and bradykinin B2 receptor antagonist. Prognosis Up to 20% of patients with chronic urticaria attending hospital departments will be symptomatic 10 years after first presentation. More prolonged duration associates with more severe disease, the presence of angioedema, and positive antithyroid antibodies. FURTHER READING Cutaneous vasculitis Calabrese LH (2014). Vasculitis: determinants of disease patterns. Nat Rev Rheumatol, 10, 454–62. Cardy CM, Carruthers D (2010). Large vessel vasculitides. Medicine, 38, 97–100. Forbess L, Bannykh S (2015). Polyarteritis nodosa. Rheum Dis Clin North Am, 41, 33. Goeser R, Laniosz V, Wetter A (2014). A practical approach to the diagnosis, evaluation, and management of cutaneous small-vessel vasculitis. Am J Clin Dermatol, 15, 299. Hewins P, Jayne D (2010). Medium vessel vasculitis. Medicine, 38, 93–6. Houchens N, Parekh V (2014). An approach to the evaluation and management of vasculitis. Hospital Medicine Clinics, 3, e362–e77. Kallenberg CGM (2014). Key advances in the

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