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19.11.8 Polyarteritis nodosa 4569 Groh M, et al. (2015). Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management. Eur J Intern Med, 26, 545–53. Guillevin L, et al. (2011). The Five-Factor Score revisited: assess- ment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. Medicine (Baltimore), 90, 19–27. Guillevin L, et al. (2014). Rituximab versus azathioprine for mainten- ance in ANCA-associated vasculitis. N Engl J Med, 371, 1771–80. Hagen EC, et al. (1996). Development and standardization of solid phase assays for the detection of anti-neutrophil cytoplasmic anti- bodies (ANCA): a report on the second phase of an international co- operative study on the standardization of ANCA assays. J Immunol Methods, 196, 1–15. Hellmich B, et al. (2007). EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis: focus on anti-neutrophil cytoplasm antibody-associated vasculitis. Ann Rheum Dis, 66, 605–17. Hiemstra TF, et al. (2010). Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody- associated vasculitis: a randomized controlled trial. JAMA, 304, 2381–8. Jayne D, Rasmussen N (2015). Twenty-five years of European Union collaboration in ANCA-associated vasculitis research. Nephrol Dial Transplant, 30, i1–i7. Jayne D, et al. (2003). A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoanti- bodies. N Engl J Med, 349, 36–44. Jayne DR, et al. (2007). Randomized trial of plasma exchange or high- dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol, 18, 2180–8. Jennette J, et al. (2012). 2012 Revised International Chapel Hill con- sensus conference nomenclature of vasculitides. Arthritis Rheum, 65, 1–11. Jones RB, et al. (2010). Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med, 363, 211–20. Kallenberg CG, Heeringa P. (2013). Complement is crucial in the pathogenesis of ANCA-associated vasculitis. Kidney Int, 83, 16–18. Lyons PA, et al. (2012). Genetically distinct subsets within ANCA- associated vasculitis. N Engl J Med, 367, 214–23. Masi AT, et al. (1990). The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum, 33, 1094–100. Merkel PA, et al. (2009). Comparison of disease activity measures for anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vas-

culitis. Ann Rheum Dis, 68, 103–6. Mukhtyar C, et al. (2008). EULAR Recommendations for the manage- ment of primary small and medium vessel vasculitis. Ann Rheum Dis, 68, 310–7. Ntatsaki E, et al. (2014). BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis. Rheumatology (Oxford), 53, 2306–9. Pagnoux C, et al. (2008). Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. N Engl J Med, 359, 2790–803. Rasmussen N, et al. (1995). European therapeutic trials in ANCA- associated systemic vasculitis: disease scoring, consensus regimens and proposed clinical trials. Clin Exp Immunol, 101, 29–34. Stegeman CA, et al. (1994). Association of chronic nasal carriage of Staphylococcus aureus and higher relapse rates in Wegener granulomatosis. Ann Intern Med, 120, 12–17. Stone JH, et al. (2010). Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med, 363, 221–32. Watts R, et al. (2007). Development and validation of a consensus methodology for the classification of the ANCA-associated vascu- litides and polyarteritis nodosa for epidemiological studies. Ann Rheum Dis, 66, 222–7. Xiao H, et al. (2014). C5a receptor (CD88) blockade protects against MPO-ANCA GN. J Am Soc Nephrol, 25, 225–31. 19.11.8 Polyarteritis nodosa Loïc Guillevin ESSENTIALS Polyarteritis nodosa is a necrotizing angiitis, often associated with hepatitis B infection, that predominantly affects medium- sized arteries. Patients usually have systemic features; specific manifestations include peripheral neuropathy, mononeuritis multiplex, skin lesions (subcutaneous nodules, purpura), hyper- tension, renal insufficiency, gastrointestinal haemorrhage/perfor- ation, and orchitis. Elevated markers of inflammation are found in most patients, but serum antineutrophil cytoplasmic anti- bodies are not present. Standard treatment of hepatitis B negative cases is with corticosteroids (typically initiated with intravenous methylprednisolone) and cyclophosphamide; hepatitis B posi- tive cases are treated with an antiviral agent, corticosteroid and plasma exchange, with corticosteroid discontinued as soon as disease comes under control. Severe gastrointestinal involvement is the primary cause of early death; later deaths may result from treatment side effects. Introduction Polyarteritis nodosa (PAN) is a necrotizing angiitis that predom- inantly affects medium-sized arteries. It is rarely seen in developed countries, since hepatitis B virus (HBV) infection, considered one of its major causes, has been treated or prevented by hygiene measures, specific prophylaxis against infectious diseases, or vaccination. Classification criteria and diagnosis The Chapel Hill Nomenclature defines polyarteritis nodosa as a necrotizing arteritis of medium- or small-sized arteries, very rarely with vasculitis in arterioles, capillaries or venules, without glom- erulonephritis or antineutrophil cytoplasm antibodies (ANCA). Diagnosis is based on clinical manifestations, pathology, other complementary investigations such as angiography, and ANCA- negativity (Table 19.11.8.1).

section 19 Rheumatological disorders 4570 Epidemiology Polyarteritis nodosa affects all racial groups. The annual inci- dence of polyarteritis nodosa-type systemic vasculitis in the gen- eral population ranges from 4.6/1 000 000 inhabitants in England, to 9.0/1 000 000 inhabitants in Olmsted County, Minnesota, and 77/1 000 000 inhabitants in hepatitis B virus-hyperendemic Alaskan Eskimos. In a German study, the polyarteritis nodosa incidence was extremely low (0.3–0.4/1 000 000). Comparison of incidences in Lugo, Spain, and Norwich, United Kingdom found, respectively, 6.2 and 9.7/1 000 000 inhabitants. In France, its prevalence was 34/1 000 000 inhabitants in a northern suburb of Paris. Aetiology and precipitating factors A close polyarteritis nodosa–hepatitis B virus-infection re- lationship is well recognized. In France, hepatitis B virus infection transmitted by contaminated blood transfusions dis- appeared decades ago. Meanwhile, intravenous drug abuse has rapidly become a major cause of hepatitis B virus-related polyarteritis nodosa, as is sexual hepatitis B virus transmission to nonvaccinated individuals at risk. The

development of antihepatitis B virus vaccines and their administration to people at risk also explains the dramatic decrease in the number of new cases since 1989. Moreover, polyarteritis nodosa frequency, due to hepatitis B virus infection or not, has also decreased in par- allel, declining from around 40% during 1972–6 to 17% during 1997–2002. We hypothesize that all polyarteritis nodosa results from infection, even though a pathogen has not been isolated from all patients. Infections with hepatitis C, parvovirus B19, or human immuno- deficiency virus have explained a few polyarteritis nodosa cases. Polyarteritis nodosa has also been described in the context of can- cers or haematological diseases, mainly malignant conditions such as hairy-cell leukaemia. Histology The histological lesion defining polyarteritis nodosa is a focal seg- mental necrotizing vasculitis affecting medium-sized arteries, rarely arterioles, and only extremely rarely capillaries and venules. The acute phase of arterial wall inflammation is characterized by fibrinoid necrosis of the media and dense pleomorphic cellular infiltrates, predominantly comprised of neutrophils and variable numbers of lymphocytes and eosinophils, leading to destruction of the normal vessel-wall architecture. Arterial aneurysms and thromboses can form at lesion sites. Fibrotic endarteritis character- izes arterial healing that may lead to aneurysm regression or vessel occlusion. Biopsies can be diagnostic. Muscle biopsy is indicated for patients complaining of myalgias or with general symptoms, and nerve bi- opsy of a sensory branch of the sciatic or peroneal nerve for patients suffering from distal sensory or sensorimotor mononeuropathy multiplex. Clinical features Although polyarteritis nodosa can develop at all ages, most patients are between 40 and 60 years old, with no sex predominance. Patients usually have systemic features, with two-thirds having weight loss and fever, and half suffer from myalgias and arthralgias. Some pa- tients are bedridden due to the peripheral neuropathy, intense pain, and severe amyotrophy. Neurological manifestations Peripheral neuropathy, the most frequent polyarteritis nodosa manifestation, affects 50–75% of the patients and is the earliest symptom for 23–33% of them. Its onset is usually acute. Sensory signs cause hypo- or hyperesthesia, dysesthesia and/or frank pain, which represent the most prominent and earliest features. Motor deficits usually appear later, but also occur with sudden onset. The first manifestations often affect the lower limbs, mainly in a distal and asymmetrical distribution. The following nerves are preferentially involved: superficial peroneal, sural, radial, cu- bital and/or median. In late stage polyarteritis nodosa, so many nerves can be involved that mononeuritis multiplex can be mis- taken for a symmetrical process. Electromyography-documented axonal neuropathy may be more extensive than expected based on clinical manifestations. Mononeuropathy (simplex) is seen less frequently. With treatment, mononeuropathy multiplex regresses slowly and patients may recover without sequelae, although 12–24 months are often necessary to obtain and evaluate maximum recovery. However, the degree of recovery varies and is unpredictable. Paresthesias usually persist longest, and sometimes indefinitely. Central nervous system involvement affects c.5% of polyarteritis nodosa patients, usually manifesting as encephalopathy, with Table 19.11.8.1 Proposed diagnostic criteria for polyarteritis nodosaa Criteria Odds ratio 95% CI R^2 Positive for PAN HBV infection 16.85 6.30–45.08 0.320 Myalgias 1.93 1.06–3.53 0.517 Mononeuropathy or polyneuropathy 3.36 1.93–5.86 0.619 Angiographic abnormalities 20.40 7.30–56.99 0.640 Testicular pain or tenderness 5.27 1.98–28.26 0.661 Negative (exclusion) for PAN ANCA-positivity 0.11 0.05–0.23 0.668 Glomerulonephritis 0.07 0.02–0.29 0.674 Recent asthma onset 0.01 0.01–0.06 0.433 ANCA, Antineutrophil cytoplasm antibody; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; HBV, hepatitis B virus; MPA, microscopic polyangiitis; PAN, polyarteritis nodosa. a Based on the analysis of 582 systemic vasculitis patients with all data available in

the French Vasculitis Study Group’s database: 194 PAN (among whom 117 had HBV-related PAN) and 388 other systemic vasculitides (144 GPA; 115 EGPA; 101 MPA; 28 cryoglobulinemia). Henegar et al. (2008). Arthritis Rheum 58(5): 1528–38.

19.11.8 Polyarteritis nodosa 4571 impaired cognitive function, focal or multifocal disturbances of the brain and spinal cord, and seizures, strokes and/or subarachnoid haemorrhages, resulting from either cerebral artery vasculitis or a consequence of malignant hypertension. Cerebrospinal fluid ana- lysis is usually normal. Cranial nerve palsies, occurring in c.1% of polyarteritis nodosa patients, mostly affect oculomotor (III), trochlear (IV), abducens (VI), facial (VII) and/or acoustic (VIII) nerves. Ocular involvement The eye can be affected in polyarteritis nodosa, sometimes severely (e.g. with uni- or bilateral choroiditis, iritis, iridocyclitis, retinal de- tachment and/or retinal vasculitis). Skin manifestations Cutaneous lesions are present in about half of patients, with cuta- neous or subcutaneous nodules being the hallmarks of polyarteritis nodosa. They occur along the trajectories of superficial arteries and often disappear spontaneously within a few days. The most common cutaneous finding is palpable purpura, often necrotic, corresponding to subcutaneous small-vessel vasculitis as- sociated with medium-sized–vessel involvement (Fig. 19.11.8.1). Ulcerations and livedo are less common. Livedo reticularis in polyarteritis nodosa is typically localized to the lower limbs, backs of the arms and, sometimes, the trunk. A biopsy of infiltrated and/ or central lesion zones may show vasculitis. Painful ulcerations may develop, frequently associated with indurated plaques resulting from the coalescence of nodules. Embolization of peripheral thrombi may cause infarction of toes and/or fingers or some cutaneous areas, when cholesterol emboli are a possible differential diagnosis. Renal manifestations Renal artery involvement can cause mild-to-severe and malignant hypertension and/or vascular ischaemic nephropathy with renal insufficiency, known to be a poor-prognosis factor. Angiography may reveal renal parenchymal infarcts and characteristic multiple stenoses and microaneurysms of branches of celiac, mesenteric and renal arteries (Fig. 19.11.8.2). The lesions may disappear with ef- fective vasculitis therapy. Renal function outcome remains unpredictable. Usually mild hypertension, a consequence of vascular nephropathy, occurs in a mean of 40% of polyarteritis nodosa patients. Cardiac manifestations Congestive heart failure is specifically due to vasculitis of the coronary arteries or their branches, with myocardial arteriolar infarcts in some patients. Specific cardiomyopathy can develop as early as three to four months after the onset of polyarteritis nodosa. Coronary aneurysms have been found, but their pres- ence suggests Kawasaki disease rather than polyarteritis nodosa. Valve involvement and pericarditis are rare in polyarteritis nodosa. Arteritis of the sinus node or neighbouring nerve fibres can cause arrhythmias and conduction disorders, mainly supraventricular. Gastrointestinal manifestations Involvement of the gastrointestinal tract is one of the most se- vere manifestations of polyarteritis nodosa, reportedly affecting one-third of patients, especially those with hepatitis B virus- related disease (50%). Gastrointestinal involvement can be the first manifestation of vasculitis, most frequently with abdominal pain. Gastrointestinal haemorrhage and small intestinal perfor- ation are the most feared manifestations. When present, ischaemic vasculitis mainly affects the small bowel, more rarely the colon or stomach. Gallbladder or appendix vasculitis is rare but can be the first sign of polyarteritis nodosa, sometimes isolated. Likewise, acute necrotizing or (less commonly) chronic pancreatitis, some- times with pseudocysts, has been diagnosed in approximately 2– 3% of patients with polyarteritis nodosa, the prognosis of which is extremely dismal because of the regular association with severe small intestine ischaemia and/or perforations. Liver and/or spleen infarct(s) can occur. Angiography is the most informative investigation, able to de- tect infarcts,

haematomas, or more suggestive arterial stenoses and microaneurysms in most patients with gastrointestinal symptoms. Microaneurysms tend to be 1–5 mm or more in diameter, and are mainly found in renal, celiac, mesenteric, (less frequently) hepatic or (more rarely) splenic arteries. Orchitis While rare, unilateral orchitis is one of the most characteristic mani- festations of polyarteritis nodosa. Caused by testicular artery is- chaemia, it is rarely the first disease manifestation. Pulmonary manifestations The lungs are spared in polyarteritis nodosa. Although vasculitis of bronchial arteries has been reported in autopsy studies, this had been clinically asymptomatic. Fig. 19.11.8.1 Typical cutaneous lesions and livedo reticularis on a patient with cutaneous polyarteritis nodosa. Reproduced from Watts RA et al. (eds) (2013). Oxford Textbook of Rheumatology,
4th edn, by permission of Oxford University Press.

section 19 Rheumatological disorders 4572 Localized forms of polyarteritis nodosa Localized disease is rare, except for the limited cutaneous forms that represent less than 10% of all polyarteritis nodosa cases. Isolated involvement of one skeletal muscle or muscle group and isolated neuropathy (mononeuritis multiplex or simplex), without sys- temic symptoms, have been described; likewise exceptional cases involving only one organ—appendix, gallbladder or uterus (in order of decreasing frequency). Laboratory tests Elevated markers of inflammation are found in most patients. Leukocytosis or (sometimes) eosinophilia over 1500/mm3, and normochromic anaemia, are common laboratory findings. Hepatitis B surface antigen (HBsAg) should be sought system- atically. Antineutrophil cytoplasm antibodies are not present in polyarteritis nodosa. Outcome and prognosis Systemic polyarteritis nodosa is an acute disease that can be severe and even fatal if not treated adequately. During the 5 years after diagnosis c.25% of patients relapse, but only c.10% of hepatitis B virus-positive patients whose viral infection has been treated. The clinical pattern of relapse can differ from the initial presentation, with previously unaffected organs being involved. Although relapse severity cannot be predicted, the most frequent clinical features at relapse are rash and arthralgias, and these are generally less severe than during the initial first flare. Deaths A quarter of the patients die during follow-up, some during the first months post-diagnosis from treatment-refractory multivisceral involvement. Severe gastrointestinal involvement, with perforations or haemorrhage, is the primary cause of early death within the first year, and infections and heart disease are the next most common. Later deaths may result from treatment side effects. Hepatitis B virus infection has not been identified as a factor of severity. Evaluation of prognosis In 1996 a Five-Factor score was developed to evaluate prognosis at the time of diagnosis of systemic necrotizing vasculitides, including polyarteritis nodosa. A recent iteration described the following four factors as significantly associated with higher 5-year mortality: age above 65 years, cardiac symptoms, gastrointestinal involvement and renal insufficiency (stabilized peak creatinine ≥150 µmol/litre (1.7 mg/dl)), with each item’s presence accorded 1 point. Ear, nose, and throat symptoms, absent in polyarteritis nodosa, were associ- ated with a better prognosis and scored minus 1 point. For systemic necrotizing vasculitis patients, respective 5-year mortality rates for aggregate scores 0, 1 or ≥2 were 9%, 21% or 40%. This knowledge guides physicians’ therapeutic choices, with more aggressive and higher risk treatments being reserved for those with worse predicted outcome. Treatment Corticosteroids All patients receive corticosteroids. For hepatitis B virus-related polyarteritis nodosa, these should be administered for a few days only, as opposed to approximately 12 months for other forms of polyarteritis nodosa. High doses may be useful initially. Methylprednisolone pulses (usually 7.5–15 mg/kg IV over 60 min, repeated at 24 h intervals for 1–3 days) are widely infused to ini-

tiate treatment, especially when life-threatening organ involvement is present or during the extension phase of mononeuropathy multi- plex. This regimen acts rapidly and is relatively safe. Oral cortico- steroid (prednisone or its equivalent of methylprednisolone) is given at a starting dose of 1 mg/kg/day. As the patient's clinical status im- proves and the biological markers of inflammation (C-reactive (a) (b) Fig. 19.11.8.2 Renal angiogram in two patients with polyarteritis nodosa demonstrating (a) numerous microaneurysms and (b) renal artery thrombus causing significant occlusion of the renal artery and additional evidence of tapering of the intrarenal vasculature. Reproduced from Turner NN et al. (eds) (2015). Oxford Textbook of Clinical Nephrology, 4th edn, by permission of Oxford University Press.

19.11.9 Small vessel vasculitis 4573 protein, erythrocyte sedimentation rate) return to normal, usually within three weeks, tapering of prednisone dose can begin. Cyclophosphamide Pulse cyclophosphamide is currently preferred to oral cyclophospha- mide. Six pulses administered within three months usually obtain disease control, but treatment should be adjusted to the patient's condition: renal function, haematological data, and the disease's re- sponse to previous therapies. Lower dose IV cyclophosphamide for patients above 65 years was as effective as higher dose and was asso- ciated with fewer side effects. Because daily oral cyclophosphamide intake (2 mg/kg/day for three months) caused major adverse events, including haemorrhagic cystitis, bladder polyposis, bone-marrow suppression, ovarian failure and cancer (mainly bladder cancer and haematological malignancies), it is prescribed less frequently. Other cytotoxic agents Azathioprine, methotrexate and several other cytotoxic agents are reserved for patients with contraindications to cyclophospha- mide or as maintenance therapy for a recommended duration of 12–18 months. Plasma exchanges To date, there is no evidence to support the use of plasma exchange in polyarteritis nodosa without hepatitis B virus infection. Therapeutic specificities of hepatitis B virus-related polyarteritis nodosa For hepatitis B virus-related polyarteritis nodosa, conventional corticosteroid and cyclophosphamide induction therapy al- lows virus replication, favouring subsequent liver cirrhosis. Thus, at treatment onset, the preferred strategy is to combine plasma exchange and an antiviral agent specific for HBV infection with corticosteroid to rapidly control the most severe life-threatening polyarteritis nodosa manifestations, which are common during the first weeks of the disease. Corticosteroids are then abruptly discontinued to enhance immunological clearance of hepatitis B virus-infected hepatocytes and favour seroconversion from HBeAg-positivity to anti-HBeAb–positivity. Excellent overall therapeutic results have been obtained with this combination of antiviral agent, corticosteroid, and plasma exchange, with up to 90% recovery and 60% seroconversion to anti-HBe. FURTHER READING Guillevin L, et al. (2005). Hepatitis B virus-associated polyarteritis nodosa: clinical characteristics, outcome, and impact of treatment in 115 patients. Medicine (Baltimore), 84, 313–22. Guillevin L, et al. (2011). The five-factor score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. Medicine, 90, 19–27. Henegar C, et al. (2008). A paradigm of diagnostic criteria for polyarteritis nodosa: analysis of a series of 949 patients with vascu- litides. Arthritis Rheum, 58, 1528–38. Pagnoux C, et al. (2010). Clinical features and outcomes in 348 patients with polyarteritis nodosa: a systematic retrospective study of pa- tients diagnosed between 1963 and 2005 and entered into the French Vasculitis Study Group Database. Arthritis Rheum, 62, 616–26. 19.11.9 Small vessel vasculitis Richard A. Watts ESSENTIALS Small vessel vasculitis is vasculitis affecting predominately small intraparenchymal arteries, arterioles, capillaries, and venules. There are two main types: antineutrophil cytoplasmic antibody associated (see Chapter 19.11.7) and immune complex mediated. IgA vasculitis (Henoch-Schönlein

purpura)—vasculitis of unknown cause with IgA1-dominant immune deposits. It predominantly af- fects children and typically involves skin (usually palpable purpura of the lower limbs), gut (abdominal pain), joints (usually oligoarticular), and kidneys (glomerulonephritis indistinguishable from IgA neph- ropathy). Most cases do not require specific therapy. Cryoglobulinaemic vasculitis—vasculitis with cryoglobulin im- mune deposits affecting small vessels. Cryoglobulin production can be stimulated by processes including infection (notably hepa- titis C), autoimmunity, and malignancy. Clinical presentation is with purpura (typically on the calves), peripheral neuropathy, nephritis, arthralgias, and systemic symptoms. Treatment involves resolution of the underlying cause. Hypocomplementaemic urticarial vasculitis—vasculitis accom- panied by urticaria and hypocomplementemia affecting small ves- sels and is associated with anti-C1q antibodies. Cutaneous vasculitis—vasculitis confined to the skin, which may be triggered by infection, drugs, autoimmune disease, or malignancy. Variable vessel vasculitides—a range of conditions including re- lapsing polychondritis, MAGIC syndrome, and Cogan's syndrome. Introduction Small vessel vasculitis was defined by the Chapel Hill Consensus Conference (CHCC) on nomenclature of vasculitis 'as vasculitis af- fecting predominately small intraparenchymal arteries, arterioles, capillaries and venules, however, medium sized arteries and veins may also be affected'. There are two main groups of the vasculit- ides that affect small vessels: antineutrophil cytoplasmic antibody (ANCA)-associated and immune complex mediated. The former are covered in Chapter 19.11.7. IgA vasculitis (Henoch Schönlein purpura) IgA vasculitis (IgAV) was formerly known as Henoch Schönlein purpura. The revised nomenclature reflects the importance of IgA in pathogenesis. The Chapel Hill Consensus Conference defined IgA vasculitis as 'vasculitis with IgA1-dominant immune deposits, af- fecting small vessels (predominantly capillaries, venules, or arteri- oles)'. IgA vasculitis often involves the skin and gut, and frequently causes arthritis. Glomerulonephritis indistinguishable from IgA nephropathy may occur. The American College of Rheumatology produced classifica- tion critieria in 1990 but these have relatively poor sensitivity and

 specificity. Childhood classification criteria for IgA vasculitis have been developed (Table 19.11.9.1). Aetiology The aetiology of IgA vasculitis is unknown, but it frequently oc- curs after an infection several days to weeks before. The most fre- quently isolated organism is β-haemolytic streptococcus. Drugs such as a penicillin, ampicillin, erythromycin, and nonsteroidal anti-inflammatory drugs have been reported as precipitating agents. There is an association with HLA-DRB1*01 in Caucasians and there appears to be a familial association. Epidemiology IgA vasculitis predominately affects children with 75% of cases occurring below the age of 10 years and is the most common type of vasculitis in childhood. It is most common in children of Asian (Indian Subcontinent) origin. In the United Kingdom the incidence is 20.4/100 000 children and 1.3/100 000 adults aged above 16 years, with no major gender imbalance. Clinical features The classical features of IgA vasculitis are involvement of the skin, gastrointestinal tract, kidney, and joints. A rash is present in all cases, but may not be the presenting feature. The most common type of rash is nonthrombocytopaenic palpable purpura. This occurs in dependent and pressure bearing areas such as the legs and buttocks (Fig. 19.11.9.1) with a symmetrical distribution; it less frequently involves the arms. The rash evolves from red to purple and then be- comes rust coloured before fading. Skin ulceration is uncommon. The rash may be macular, papular or (less frequently) urticarial or vesicular. The major gastrointestinal symptoms are abdominal pain, which may be colicky in nature, nausea, and vomiting, with melaena or haematemesis. These features are due to bowel ischaemia and oe- dema.

Approximately 60–75% of cases will have abdominal pain. Joint pain typically affects the feet, ankle and knees, and less com- monly the arms, with an oligoarticular pattern; synovitis is not al- ways present. Development of permanent joint damage is rare. The joint manifestations may precede the development of palpable pur- pura by several days in up to 25% of cases. Renal involvement is potentially the most serious manifestation of IgA vasculitis, occurring in up to 80% of patients, most com- monly in older children and adults. Nonvisible haematuria is the most sensitive and earliest sign suggestive of nephropathy. Renal failure is noted in 30% of adults at presentation but is rare in chil- dren. Nephrotic syndrome is a rare presentation. The long-term renal outcome is difficult to predict: spontaneous recovery from severe kidney injury at presentation and progression in mild pres- entations are both well described. Other less common features include neurological involvement with headache, encephalopathy, mental state changes, and periph- eral neuropathies. Interstitial pulmonary disease is common but asymptomatic, with impairment of diffusion capacity during the ac- tive phase of disease. Clinical investigations Investigations reveal an acute phase response, with moderate leuko- cytosis and thrombocytosis. Serum IgA is elevated in a minority of patients. The presence of antineutrophil cytoplasmic antibody should suggest an alternative diagnosis, in particular granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis. Renal histology shows IgA dominant immune deposits in the walls of small vessels and glomeruli (Fig. 19.11.9.2). The initial lesion is a focal or diffuse proliferative glomerulonephritis; more advanced lesions show typically a mesangial proliferative and/or crescentic nephritis. Skin biopsy shows a leucytoclastic vasculitis with a neu- trophilic infiltration around the vessel walls and fibrinoid necrosis, together with IgA immunofluorescence in the walls of small vessels. This histology is not specific as leucocytoclasis may occur in hyper- sensitivity vasculitis. Differential diagnosis The differential diagnosis is from other forms of systemic vasculitis, in particular the antineutrophil cytoplasmic antibody-associated vasculides granulomatosis with polyangiitis and microscopic polyangiitis, and from other types of skin vasculitis. The diagnosis in children is made on the basis of history and physical findings. In adults a biopsy may be needed to confirm the diagnosis and determine prognosis, especially if there is renal in- volvement. There are no diagnostic criteria for IgA vasculitis, but classification criteria have been developed (Table 19.11.9.1). Treatment Most cases do not require specific therapy as the condition remits spontaneously on average within four weeks. Rest and adequate Table 19.11.9.1 Classification criteria for IgA vasculitis Palpable purpura or petechiae (mandatory criterion) with lower limb predominance in the presence of at least one of the following four features: • Diffuse abdominal pain • Any biopsy showing predominant IgA deposition • Arthritis or arthralgia (acute onset, any joint) • Renal involvement (any haematuria and/or proteinuria) These criteria were developed by European League against Rheumatism (EULAR) and Paediatric Rheumatology International Trials Organization (PRINTO) Fig. 19.11.9.1 Purpura occurring in IgA vasculitis. Reproduced from Watts RA et al. (eds) (2013). Oxford Textbook of Rheumatology, 4th edn, by permission of Oxford University Press.

 hydration are necessary; nonsteroidal anti-inflammatory drugs may help arthralgia but should not be used in those with renal impairment. Glucocorticoids and immunosuppressive drugs are commonly used in those with severe renal or gastrointestinal involvement, but this is controversial because there is no evidence that they improve long-term outcome, primarily because of the variability in outcome and difficulty in predicting a poor prog- nosis. A recent randomized controlled trial reported no evidence to support the use of glucocorticoids to prevent nephropathy in children. Prognosis/outcome In most patients IgA

vasculitis has a self limiting course: children usually have a single episode of disease, but relapses occur in 20% of adults. The long-term morbidity and mortality is determined by the severity of renal involvement: up to 11% of adults may develop end-stage renal disease. Cryoglobulinaemic vasculitis Cryoglobulins are immunoglulins that precipitate in vitro at temperatures below 37°C (Fig. 19.11.9.3). They are classified according to the clonality and type of the immunoglobulins: type I—monoclonal immunoglobulin, either IgM or IgG; type II—a mixture of monoclonal IgM and polyclonal IgG; type III—a mixture of polyclonal IgM and IgG. Types II and III are also known as mixed cryoglobulins as they have both IgG and IgM components. Many patients with cryoglobulinaemia remain asymptom- atic. Cryoglobulinaemic vasculitis was defined by the Chapel Hill Consensus Conference as 'vasculitis with cryoglobulin immune deposits affecting small vessels (predominantly capillaries, ven- ules, or arterioles) and associated with cryoglobulins in serum'. Aetiology Cryoglobulin production can be stimulated by several patho- logical process including infection, autoimmunity, and malig- nancy (Table 19.11.9.2). A strong association was first recognized in 1989 between hepatitis C virus (HCV) infection and predom- inately type II cryoglobulinaemia, and in some populations up to 90% of patients with mixed cryoglobulinaemia have circu- lating HCV-RNA. Cryoglobulinaemia has also been associated with hepatitis B virus and human immunodeficiency virus (HIV) infection. Fig. 19.11.9.2 Glomerulus from a patient with IgA vasculitis and proliferative glomerulonephritis with granular mesangial deposits of IgA (IgA immunofluorescence ×400). Reproduced with permission from Ball GV et al. (eds) (2014). Oxford Textbook of Vasculitis, 3rd edn, by permission of Oxford University Press. Fig. 19.11.9.3 Cryoglobulin precipitation in a cryocrit tube. Reproduced with permission from Ball GV et al. (eds) (2014). Oxford Textbook of Vasculitis, 3rd edn, by permission of Oxford University Press.
Table 19.11.9.2 Major causes of mixed cryoglobulinaemia Autoimmune diseases Sjogren's syndrome Systemic lupus erythematosus Rheumatoid arthritis Systemic sclerosis Antineutrophil cytoplasmic antibody-vasculitis Infections Hepatitis C Hepatitis B HIV—1 HTLV-1 Hepatitis A Malignancy B-cell lymphoma Hodgkin's lymphoma Multiple myeloma

 Epidemiology The incidence and prevalence of cryoglobulinaemia is unknown. Mixed cryoglobulinaemia is the most common type, with the proportion of type II to type III varying between studies. The prevalence of hepatitis C virus infection in patients with mixed cryoglobulinaemia is 30—(nearly) 100%, with the highest preva- lence in patients from the Mediterranean. Between 12–56% of hepatitis C virus-infected patients have cryoglobulinaemia, with the highest rates in Mediterranean patients. Cryoglobulinaemic vas- culitis is therefore more common in areas endemic for hepatitis C virus. It has a predilection for women (3:1). Monoclonal (type I) cryoglobulinaemic vasculitis is a rare dis- order, occurring infrequently in patients with lymphoprolifera tive disorders including multiple myeloma and Waldenström's macoglobulinaemia. Pathology Tissue injury may arise from cryoglobulin precipitation in the microcirculation leading to vascular occlusion, or by immune complex-mediated inflammation. Vascular occlusion is more common in type 1 cryoglobulinaemia, where there may be high concentrations of cryoglobulin with hyperviscosity syndrome and cold-induced acral necrosis. Immune complex-mediated vasculitis is more common in mixed cryoglobulinaemias, particularly type II. Clinical features The classical triad of purpura, arthralgia, and weakness was first de- scribed by Meltzer and colleagues in 1966, but only occurs in 40% of patients. The clinical features of patients with cryoglobulinaemic vasculitis are given in Table 19.11.9.3. The most obvious feature of cryoglobulinaemic vascu- litis is purpura due to the precipitation of immune complexes in the small vessels of the dermis and subcutaneous tissue (Fig. 19.11.9.4). The lesions

are most typical on the calves, al- though thighs and trunk may be involved. The purpura may be intermittent early in the disease course, with lesions disappearing over 12 weeks. Persistence of vasculitic lesions may lead to the de- velopment of ulcers, characteristically over the malleoli, and this is an indication for more intensive therapy. Ulceration and skin necrosis is much less common in hepatitis C virus positive pa- tients. Raynaud's phenomenon is seen more commonly in hepa- titis C virus negative patients. Peripheral neuropathy has been reported in up to 69% of cases, most commonly sensory (76%), with a mixed sensorimotor neur- opathy and mononeuritis multiplex being much less common. Symptomatically this presents with parasthesiae, painful dysaes- thesia, and myalgia in the legs. Renal involvement with a nephritic syndrome is found in 20% at diagnosis: this may be acute or follow a more chronic slowly progressive process. Biopsy reveals a membranoproli ferative glomerulonephritis characterized by immune complex deposition. Arthralgias affecting the hands, wrists and knees occur in about 10% of cases: these are intermittent and migratory, and not associ- ated with evidence of synovial inflammation. Systemic symptoms such as fever, weight loss, and myalgia are common. Table 19.11.9.3 Clinical and biological features of cryoglobulinaemia vasculitis Hepatitis
C virus –ve monoclonal Hepatitis
C virus –ve mixed Hepatitis
C virus +ve mixed Number of patients 64 242 165 Age (y) 65 63 60 Female (%) 56 69 54 Clinical features Skin (%) 86 83 76 Purpura (%) 69 75 71 Raynaud's phenomenon (%) 30 26 - Necrosis (%) 28 16 1 Ulcers (%) 27 14 4 Livedo (%) 13 2 4 Joints (%) 28 40 53 Peripheral neuropathy (%) 44 52 74 Central nervous system (%) 0 2 9 Renal (%) 30 35 34 Gastrointestinal 0 5 7 Biological features Cryoglobulin (g/l) 1.55 0.94 1.04 C4 (g/l) 0.09 0.07 0.09 Normal cryoglobulin level <0.05 g/l. Normal C4 complement fraction level is
0.14–0.40 g/l. Table from Terrier B and Cacoub P (2013). Cryoglobulinemia vasculitis: an update. Current Opinion in Rheumatology, 25(1): 10–18, with permission. Fig. 19.11.9.4 Lower limb purpuric lesions in a patient with type II hepatitis C virus-related cryoglobulinaemia. Reproduced with permission from Ball GV et al. (eds) (2014). Oxford Textbook of Vasculitis, 3rd edn, by permission of Oxford University Press.

19.11.9 Small vessel vasculitis 4577 Differential diagnosis The differential diagnosis includes other types of small vessel vas- culitis such as IgA vasculitis and microscopic polyangiitis. The presence of rheumatoid factor leads to consideration of vasculitis associated with rheumatoid arthritis, but other typical features of rheumatoid arthritis such as synovitis will be absent. The presence of antinuclear antibody (ANA) suggests that there may be an asso- ciated autoimmune disease such as systemic lupus erythematosus or Sjogren's syndrome. Clinical investigations Diagnosis is based on clinical presentation and the presence of circulating cryoglobulins. Sample collection and handling is cru- cial when testing for these. The blood should be collected in pre- warmed syringes, transported, clotted, and centrifuged at 37–40°C. The serum is thereafter stored at 4°C for seven days. Type I cryo- globulins precipitate within hours, whereas mixed cryoglobulins can take days to precipitate. High titres of rheumatoid factor are present in 70% of patients. Antineutrophil cytoplasmic antibodies, antinuclear antibodies, and anticardiolipin antibodies are usually absent. Complement levels (C4) are low in 90% of cases, as may be total haemolytic comple- ment levels. Viral serology, especially hepatitis C virus, should be performed looking for evidence of a precipitating infection. In type 1 cryoglobulinaemia an underlying B-cell lyphoproliferative disorder should be sought—Waldenström's macroglobulinaemia, multiple myeloma, or a monoclonal gammopathy of unknown significance. Treatment Treatment of type I cryoglobulinaemic vasculitis

is that of the underlying lymphoproliferative disorder. The standard treatment of type II and III hepatitis C virus- related cryoglobulinaemic vasculitis has until recently been with pegylated interferon-α plus ribavirin and/or rituximab. About 30–40% of patients fail to respond or relapse with this combination. The addition of a protease inhibitor (NS3/4A in- hibitor) improves response rates, with 65–70% sustained viral response but with appreciable toxicity occurring in nearly 50%. Rituximab was shown in a randomized controlled trial to have better efficacy than conventional immunosuppressant therapy with corticosteroids, azathioprine, cyclophosphamide, or plasma- pheresis. Rituximab with pegylated IFN/ribavirin, compared with pegylated IFN/ribavirin alone, has a shorter time to clinical remission, better renal response rate, and higher rates of cryo- globulin clearance. However, developments in treatment of hepa- titis C virus are moving at pace, and the impact of new treatments and combinations of treatments on hepatitis C virus-related cryoglobulinaemic vasculitis will become apparent over the next few years. The treatment of nonhepatitis C virus associated type II and III cryoglobulinaemic vasculitis is that of the underlying disease, with the aim of improving the clinical features and suppressing produc- tion of the cryoglobulin producing B-cell clones. Prognosis/outcome hepatitis C virus positive patients with mixed cryoglobulinaemia vasculitis have 1-year survival of 96% and a 10 year survival of 63%. Deaths are mainly attributed to serious infections and end stage liver disease. A poor prognosis is associated with severe liver fibrosis, central nervous, renal, and cardiac involvement at baseline. In noninfectious mixed cryoglobulinaemia vasculitis patients the one- year survival is 91% and the 10-year survival 65%. Deaths were due to infection in 50% and vasculitis flare in 20%. Antiglomerular basement membrane disease Antiglomerular basement membrane disease was considered by the Chapel Hill Consensus Conference as an immune mediated small vessel vasculitis. The condition is covered in detail in Chapter 21.8.7. Hypocomplementaemic urticarial vasculitis Hypocomplementaemic urticarial vasculitis (HUV) was defined by the Chapel Hill Consensus Conference as ‘vasculitis accom- panied by urticaria and hypocomplementemia affecting small vessels (i.e. capillaries, venules, or arterioles), and associated with anti-C1q antibodies’. This association led the Conference to pro- pose the nomenclature anti-C1q vasculitis. Aetiology Up to 25% of patients have an associated autoimmune disease, most typically systemic lupus erythematosus. Epidemiology The epidemiology of hypocomplementaemic urticarial vasculitis is unknown. About 75% of cases are women. It is an uncommon cause of cutaneous vasculitis. Clinical features The urticarial lesions of hypocomplementaemic urticarial vasculitis differ from those seen in common urticaria, being of longer dur- ation (>24 hours) and painful rather than pruritic. Arthritis occurs in 80% of cases and is typically nondestructive. Other manifest- ations include ocular inflammation (uveitis, scleritis and episcleritis in 56%), angioedema (50%), and livedo reticularis (14%). Renal involvement is relatively uncommon (14%), but features may in- clude membranous and mesangial glomerulonephritis. A com- parison of patients with anti-C1q and those without, indicates that those with anti-C1q antibodies have more frequent systemic hypocomplementaemic urticarial vasculitis, angioedema, livedo reticularis, ocular involvement, musculoskeletal involvement, and kidney involvement, but less frequent pulmonary and gastrointes- tinal involvement. Differential diagnosis The differential diagnosis is from other types of systemic vasculitis, and systemic lupus erythematosus.

 Clinical investigations Laboratory findings include low complement levels of components of the classical pathway, namely C1q, C2, C3, and C4, together with an acute phase response. Antibodies against C1q are commonly present. These are also found in systemic lupus erythematosus and it has been suggested that hypocomplementaemic urticarial vasculitis represents a form of lupus. Antinuclear antibodies are present in 50% of patients;

cryoglobulins, rheumatoid factor, and antineutrophil cytoplasmic antibody may also be present. Skin biopsy shows a leucocytoclastic vasculitis with granular deposition C3, C1q, and immunoglobulins in the basement membrane zone. Treatment There are no randomized controlled trials on which to base therapy. Systemic glucocorticoids are effective in controlling the vasculitis. Hydroxychloroquine and colchicine may as effective as corticosteroids as first line therapy. Many patients respond well to dapsone. The urticarial lesions respond poorly to antihista- mines. Conventional immunosuppressive agents (azathioprine, mycophenolate mofetil and cyclophosphamide) may be effective in resistant cases. Prognosis/outcome Patients may have significant morbidity and mortality, most com- monly caused by chronic obstructive pulmonary disease and acute laryngeal oedema. Cutaneous vasculitis The term cutaneous small vessel vasculitis implies vasculitis con- fined to the skin and is synonymous with cutaneous leucytoclastic vasculitis, hypersensitivity vasculitis, or cutaneous necrotizing venulitis. Aetiology The aetiology is multifactorial: in more than 40% of cases no trig- gering factor is identified, 20% are secondary to infection, 10% to drugs, 15–20% to autoimmune disease, and 5% to malignancy. The most common infections are β-haemolytic streptococci and viral infection (upper respiratory tract hepatitis and HIV). The most common drugs include allopurinol, propylthiouracil, hydralazine, colony-stimulating factors, and antibiotics, but a very long list of drugs has been implicated, often anecdotally. Pathogenesis/pathology Cutaneous vasculitis is caused by immune complex deposition in the postcapillary venules, the complexes consisting of bound foreign antigens and antibodies that due to their size and solubility attach to the endothelium of small blood vessels. Deposition of immune complexes triggers an inflammatory cascade with complement acti- vation and endothelial damage. Clinical features The typical lesion is palpable purpura, which is present in up to 90% of cases. Lesions are red/purple in colour and are 2–5 mm in diameter. Differential diagnosis The differential diagnosis is from systemic vasculitis, in particular IgA vasculitis and other causes of purpuric lesions. Clinical investigations Investigation is directed at confirming the diagnosis and the confinement of the vasculitis to the skin, hence a full haemato- logical and biochemical profile is required, together with appro- priate autoantibody serology (ANCA, ANA, RF) and serology for infection. Skin biopsy shows leucocytoclasis, which is the result of neutro- phil disintegration and the release of nuclear dust, together with fi- brin deposition (Fig. 19.11.9.5). Treatment Treatment may not be required above and beyond removal of the triggering agent, or the underlying disease. Nonulcerating lesions may be treated with a mild topical steroid. Variable vessel vasculitides Relapsing polychondritis Relapsing polychondritis is a rare autoimmune condition that causes inflammation and destruction of cartilage. It affects men and women equally, with peak incidence at age 50 years. It pre- sents with nonspecific constitutional symptoms and specific features including auricular inflammation that spares the ear lobe (85% of cases, Fig. 19.11.9.6), and nasal chondritis (50%), which can lead to saddle nose deformity. Stridor suggests tra- cheal involvement, which is the most serious complication. Arthralgia of large and small joints and of the axial skeleton is common. Inflammatory markers are raised; immunological tests are typically negative; 18FDG-PET can determine the ex- tent of inflammatory lesions and response to treatment. Mild cases are treated with nonsteroidal anti-inflammatory drugs. Laryngotracheal involvement requires high dose steroids; other Fig. 19.11.9.5 Skin biopsy showing a small blood vessel with fibrinoid necrosis, endothelial swelling and red cell extravasation consistent with leucocytoclastic vasculitis (haematoxylin and eosin ×400). Reproduced with permission from Ball GV et al. (eds) (2014). Oxford Textbook of Vasculitis, 3rd edn, by permission of Oxford University Press.

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