19.11.7 ANCA- associated vasculitis 4556 David Jay

19.11.7 ANCA- associated vasculitis 4556 David Jayne

section 19 Rheumatological disorders 4556 FURTHER READING Alibaz-Oner F, Direskeneli H (2015). Update on Takayasu's arteritis. Presse Med, 44, e259–65. Dasgupta B, et al.; BSR and BHPR Standards, Guidelines and Audit Working Group (2010). BSR and BHPR guidelines for the management of giant cell arteritis. Rheumatology (Oxford), 49, 1594–7. Hayreh SS, Zimmerman B, Kardon RH (2002). Visual improve- ment with corticosteroid therapy in giant cell arteritis: report of a large study and review of literature. Acta Ophthalmol Scand, 80, 355–67. Keser G, Direskeneli H, Aksu K (2014). Management of Takayasu arteritis: a systematic review. Rheumatology (Oxford), 53,
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grouping of three syndromes of acute and chronic inflam- mation characterized by their clinical and histological pheno- types. They comprise (1) granulomatosis with polyangiitis (formerly known as Wegener’s granulomatosis), (2) microscopic polyangiitis, and (3) eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss syndrome). Pathology—the defining histological lesion is a microscopic vas- culitis affecting arterioles, capillaries, or venules associated with few or no deposits of immunoglobulin or complement. Granulomata, involving or close by blood vessels, are commonly present in granulomatosis with polyangiitis. Clinical features—disease involves multiple organ systems with considerable heterogeneity in extent and severity of organ involve- ment between patients, and overlapping clinical and histological features between syndromes. Most patients are unwell at the time of diagnosis with constitutional symptoms of fatigue and mal- aise, fevers, night sweats, weight loss, headache, and polymyalgia. The commonest specific manifestations are in the upper respira- tory tracts (destructive lesions), trachea-bronchi, lungs (infiltrates, pulmonary haemorrhage), kidneys (focal, necrotizing, crescentic glomerulonephritis), skin (purpura), and nervous system (peripheral neuropathy, mononeuritis multiplex). Management—the goals of therapy are to achieve a remission in disease activity, prevent relapse, and minimize drug toxicity and the risk of comorbid conditions. An induction phase of 3–6 months with (typically) a combination of high-dose glucocorticoids and ei- ther cyclophosphamide or rituximab, is followed by a longer remis- sion maintenance phase with (typically) lower dose glucocorticoid and one of azathioprine, methotrexate, mycophenolate mofetil, or rituximab. Prognosis—advanced renal failure, increasing age, a high disease activity at diagnosis and the MPO-ANCA subtype are adverse pre- dictors. Infection, in part attributable to treatment, and alveolar haemorrhage are the most common causes of early death while in- creased risks of malignancy and cardiovascular disease contribute to later mortality. Introduction The antineutrophil cytoplasmic antibody (ANCA)-associated vas- culitides (AAV) are a grouping of three syndromes of acute and chronic inflammation characterized by their clinical and histo- logical phenotypes (Fig. 19.11.7.1). They comprise granulomatosis with polyangiitis (GPA, formerly Wegener’s granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome). They involve multiple organ systems with considerable heterogen- eity in extent and severity of organ involvement between patients,
Table 19.11.6.8 Diagnostic criteria for IgG4-related disease 1. Diffuse/ localized swelling or mass in one or more organs 2. Elevated serum IgG4 concentrations (greater than 135 mg/dl) 3. Histopathological features: (a) Marked lympho-plasmacytic infiltration with fibrosis (b) Infiltration of IgG4+ plasma cells >10/HPF ratio of IgG4/IgG ratio >40% Diagnosis is definitive if all criteria are met, probable if only criteria 1 and 3 are present and possible if only criteria 1 and 2 are fulfilled. Adapted from Umehara et al. (2012) Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. Modern Rheumatology, 22(1): 21–30, reprinted by permission of Taylor & Francis Ltd (http://www.tandfonline.com).

 and overlapping clinical and histological features between syn- dromes. The defining histological lesion is a microscopic vascu- litis affecting arterioles, capillaries, or venules associated with few or no deposits of immunoglobulin or complement. However, involvement of larger vessels, including the aorta, can occur, im- mune complex deposition can be more prominent, and ANCA can be absent from the circulation. Granulomata, involving or close by blood vessels, are commonly present in granulomatosis with polyangiitis, but can also be seen in microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis. The autoimmune basis for ANCA-associated vasculitis was presumed due to the ab- sence of a

causative agent and confirmed by the subsequent associ- ations with ANCA and HLA Class II. History Friedrich Wegener described a series of three autopsy cases in Germany in 1936 with a triad of necrotizing granulomatosis with vasculitis of the upper and lower respiratory tract, and glomer- ulonephritis. By 1954 Goodman and Churg, in New York, as- sembled a review of 22 cases and confirmed the term ‘Wegener’s granulomatosis’. At the same time, Churg and Strauss recognized a variant vasculitic syndrome with predominant eosinophilic in- filtration in diseased tissues, asthma, and peripheral eosinophilia, both microscopic and medium-sized vessel vasculitis and granu- lomata, which became termed Churg-Strauss syndrome. In 1948 Davson, Ball, and Platt described a microscopic form of polyarteritis often associated with a necrotizing glomerulonephritis but without granulomata, a finding supported by Goodman and Churg in 1954. Through the next 40 years, there was varying uptake of the term microscopic polyangiitis, such patients were often not differenti- ated from polyarteritis nodosa, and those with renal involvement were also termed ‘idiopathic’ rapidly progressive, or crescentic, glomerulonephritis. In 1990 the American College of Rheumatology developed clas- sification criteria for vasculitic syndromes. This system did not include a subgroup for microscopic polyangiitis and did not in- clude ANCA. These criteria for granulomatosis with polyangiitis (Wegener’s) and eosinophilic granulomatosis with polyangiitis (Churg-Strauss) have been used in subsequent clinical trials. The first Chapel Hill Consensus Conference in 1993 produced disease definitions based on clinical and histological criteria for all the primary vasculitis syndromes, including microscopic polyangiitis, and has served as an important foundation for vas- culitis research. An update in 2012 subdivided small vessel vascu- litides into ‘ANCA associated’ and ‘immune complex’ groupings, and replaced certain eponyms, such as Wegener’s, with descriptive terms (Fig. 19.11.7.2). Eosinophilia 15% renal 40% ANCA EGPA 90% renal Mainly MPO-ANCA Asia Median age 65 yr MPA Respiratory tract Granulomata 70% renal Mainly PR3-ANCA Median age 55yr GPA Fig. 19.11.7.1 The three subtypes of ANCA-associated vasculitis
(GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; PR3, proteinase 3; MPO, myeloperoxidase). Medium vessel vasculitis Polyarteritis nodosa Kawasaki disease Large vessel vasculitis Takayasu arteritis Giant cell arteritis ANCA-associated vasculitis Microscopic polyangiitis Granulomatosis with polyangiitis Eosinophilic granulomatosis with polyangiitis Immune complex SVV Anti-GBM disease Cryoglobulinemic vasculitis IgA vasculitis (Henoch-Schönlein) Hypocomplementemic urticarial vasculitis (Anti-C1q vasculitis) Small vessel vasculitis Fig. 19.11.7.2 The 2012 Chapel Hill Consensus Classification of primary systemic vasculitis. Adapted from Jennette JC et al. (2013). 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis & Rheumatism, 65: 1–11, © 2013, American College of Rheumatology.

 ANCA An association of autoantibodies to cytoplasmic components of neutrophils with granulomatosis with polyangiitis (then Wegener’s) described in 1985 became a turning point in vasculitis research and led to major advances in the understanding of disease patho- genesis, diagnosis, and treatment. ANCA were recognized by the staining pattern of IgG immunoglobulins within patient sera when overlayed on normal, fixed neutrophils. Two patterns were recog- nized: binding to the primary azurophilic granules, ‘cytoplasmic’ or C-ANCA, or binding around the cell nucleus, ‘peri-nuclear’ or P-ANCA. Within five years the target autoantigen for C-ANCA was iden- tified as the 29kd serine protease proteinase 3 (PR3), and for P-ANCA, the primary granule enzyme, myeloperoxidase (MPO) (Fig. 19.11.7.3). The P-ANCA binding was a fixation artefact and with other techniques, autoantibodies to myeloperoxidase pro- duced a

C-ANCA pattern. Solid phase autoantigen specific as- says were developed and the terms PR3-ANCA and MPO-ANCA adopted. Other neutrophil cytoplasm autoantibodies were detected, for example, to lactoferrin, cathepsin G and bacterial permeability increasing protein (BPI), but only PR3-ANCA and MPO-ANCA retained a high specificity for vasculitis and were demonstrated to have clinical utility in routine practice. PR3-ANCA is the predominant autoantigenic specificity found in granulomatosis with polyangiitis and MPO-ANCA in microscopic polyangiitis. The frequency of ANCA positivity is lower in early or limited presentations in granulomatosis with polyangiitis or after the onset of immunosuppressive treat- ment. Fewer eosinophilic granulomatosis with polyangiitis patients are ANCA-positive and MPO-ANCA is the predominant serotype (Table 19.11.7.1). Dual positivity for PR3-ANCA and MPO-ANCA is rare and usually a testing artefact, but is seen in drug-induced causes of ANCA-associated vasculitis. It is cur- rently recommended that both the indirect immunofluores- cence and solid phase assays are used in routine ANCA testing laboratories. Epidemiology Incidence and prevalence The incidence of ANCA vasculitis in Europe and Japan is between 13 and 20/million with varying distribution of the three syndromes (Table 19.11.7.2). Granulomatosis with polyangiitis being more common in Europe and microscopic polyangiitis more common in Japan. Earlier incidence estimates were lower due to problems with ascertainment. Prevalence rates in Northern Europe are 100–250/ million, with the number rising as patient survival has improved and there is near complete case identification. Geography and ethnicity The incidence of granulomatosis with polyangiitis and eosino- philic granulomatosis with polyangiitis is highest the further Fig. 19.11.7.3 The patterns of antineutrophil cytoplasm autoantibodies (ANCA) seen on indirect immunofluorescence. (a) Cytoplasmic ANCA (C-ANCA). (b) Peri-nuclear-ANCA (P-ANCA). Table 19.11.7.1 The frequencies of ANCA serotypes in the different ANCA-associated vasculitis subgroups at the time of diagnosis PR3-ANCA MPO-ANCA Either PR3-ANCA or MPO-ANCA GPA 66% 24% 90% MPA 27% 58% 85% EGPA 5% 35% 40% GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis. PR3, proteinase 3; MPO, myeloperoxidase. Table 19.11.7.2 The incidence and prevalence of ANCA-associated vasculitis syndromes Incidence Europe
(/million/year) Incidence Japan
(/million/year) Prevalence Europe
(/million) GPA 8–11 2 140–160 MPA 3–10 18 60–90 EGPA 1–2 <1 11–14 Total 13–20 20 150–250 GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis.

 from the equator whether in the Northern or Southern hemi- sphere. This has been attributed to lower ultraviolet light ex- posure or different microbial colonization in cooler, temperate climates. Ethnic differences in the proportion of patients with PR3 as opposed to MPO-ANCA exist, with approximately equal rates in Western Europe, but a strong predominance, 95%, of MPO- ANCA in China and Japan. Age and sex The peak age of onset for granulomatosis with polyangiitis is 40– 60 years, with a female preponderance in younger age groups. Microscopic polyangiitis occurs approximately 10 years later, with the frequency increasing over 70 years of age. EGPA has a peak age of onset of 30–50 years, but the characteristically long prodrome complicates defining the time of disease onset. ANCA vasculitis is a rare vasculitis in children and very rare in young children. Granulomatosis with polyangiitis is the most common form in childhood and is typically seen in adolescents when it behaves in a similar manner to adults. Aetiology Genetics Familial, ANCA-associated vasculitis is very rare, with some sibling pairs reported, and no monogenic causes have been found. A large genome wide association survey has

demonstrated that patients with PR3-ANCA and MPO-ANCA are genetically distinct, and that genetic associations are stronger with the autoantibody sero- type than clinical syndrome of granulomatosis with polyangiitis or microscopic polyangiitis. PR3 and MPO-ANCA were associated with loci in the HLA-DQ and HLA-DR regions of major histo- compatibility complex (MHC) Class II, respectively. PR3-ANCA positive patients were additionally associated with polymorphisms near the gene encoding for PR3 and with α-1 antitrypsin, the major protease inhibitor of PR3. Associations reported from candidate gene studies include PTPN22, CTLA4, and complement C3 await further confirmation. Secondary causes The causal association of ANCA vasculitis with other agents or diseases identifies secondary vasculitis and is of importance both in correct classification and management, as addressing the cause will contribute to control of disease (Table 19.11.7.3). Environmental exposure to silica, typically in coal miners, is as- sociated with MPO-ANCA vasculitis and the strength of associ- ation depends on the severity of silica induced interstitial lung disease. There is no strong evidence to support a causal asso- ciation with other environmental exposures or occupations, or smoking. Propylthiouracil is the most common drug-induced cause of ANCA vasculitis: other drugs implicated in aetiology include penicillamine, hydralazine, and minocycline. Nasal co- caine can cause a destructive nonvasculitic granulomatous dis- ease of the upper respiratory tract difficult to distinguish from localized granulomatosis with polyangiitis. This association is further complicated by the occurrence of systemic micro- scopic polyangiitis with the cocaine/levamisole combination. Drug-induced causes of vasculitis are usually associated with MPO-ANCA, but other neutrophil antigens such as cathepsin G, elastase or lactoferrin may be targeted, or may occur with nonneutrophil autoantibodies. ANCA vasculitis can occur in the setting of chronic bacterial infection, such as bronchiectasis, cystic fibrosis, infective endocar- ditis, and bacterial abscesses, when MPO-ANCA is the predom- inant ANCA subtype. Tuberculosis, both latent and clinically overt infection, can be associated with an ANCA-associated vasculitis diagnosis. Nasal infection with Staphylococcus aureus has been associated with relapse in granulomatosis with polyangiitis and may play an aetiologic role supported by the respiratory epithe- lium being the first site of injury in this syndrome. Urinary infec- tion with E. coli has been shown to induce another antineutrophil antibody, to leucocyte associated membrane protease (LAMP2), through molecular mimicry, and transient antiLAMP2 antibodies occur in patients with renal vasculitis, but the link in humans to urinary infection is undetermined. Although vasculitis can be caused by chronic viral infections, including HIV, hepatitis B and C and Varicella Zoster, an aetio- logical link of these viruses to ANCA-associated vasculitis is not clear. In older patients, an epithelial malignancy may be found at the time of an ANCA-associated vasculitis diagnosis. MPO-ANCA is present in 20% of patients with systemic lupus erythematosus (SLE) and nephritis, but the significance of this is uncertain although cases of a necrotizing, pauci-immune glomer- ulonephritis have been reported in SLE suggesting a genuine dual pathology. One-third of patients with antiglomerular basement membrane (GBM) disease are ANCA positive, again usually MPO- ANCA, and these patients display features of extrarenal vasculitis and pursue a relapsing disease course, typical of ANCA-associated Table 19.11.7.3 Secondary causes of ANCA-associated glomerulonephritis Exposure Autoantibody association Environmental Silica MPO-ANCA Risk proportionate to exposure Drugs Propylthiouracil MPO-ANCA > PR3-ANCA Other autoantibodies frequent Penicillamine Hydralazine Minocycline Cocaine, especially in combination with levamisole Infection Chronic bacterial MPO-ANCA > PR3-ANCA Bronchiectasis, cystic fibrosis, infective endocarditis Tuberculosis PR3-ANCA or MPO-ANCA Malignancy Other inflammatory disorder Systemic lupus erythematosus MPO-ANCA > PR3-ANCA Anti-GBM disease PR3, proteinase 3; MPO, myeloperoxidase; GBM, glomerular basement membrane.

section 19 Rheumatological disorders 4560 vasculitis. As both ANCA and anti-GBM antibodies are present at the time of diagnosis the causal inter-relation between these two dis- orders is not known. Pathology Neutrophils, macrophages, and ANCA ANCA-associated vasculitis is a neutrophil predominant vascu- litis of microscopic vessels. Neutrophils can be seen marginating on the surface of the vessel wall and in the wall itself where they cause endothelial cytotoxicity through release of free radicals, pro- teases, and other products. There is subsequent thrombotic occlu- sion of the lumen, extravasation of blood through ruptured vessel walls and distal infarction. This process has been shown to be ANCA dependent in in vitro systems and animal models, and ANCA are thought to contribute to the pathogenesis in humans. A murine model of MPO-ANCA vasculitis has been developed that is de- pendent on MPO-ANCA, but development of PR3 ANCA models has been hampered by the lack of a murine homologue. There is no robust model of ANCA-associated granuloma formation. ANCA antigens, stored in the primary cytoplasmic granules, translocate to the neutrophil cell surface following priming, for ex- ample, with tumour necrosis factor, complement factor 5a (C5a) or interleukin-1. They are then available for binding by ANCA, and surface antibody is then cross-linked by neutrophil Fc receptors that trigger an intracellular cascade leading to neutrophil degranulation and superoxide release. ANCA antigens are also present in macro- phages and macrophages are present at sites of injury but their role in the inflammatory process is less well understood. Dendritic cells in the tissue, especially in the respiratory tract may play an initiating or continuing role though stimulation by microbial ligands of Toll like receptors. Granulomata, B and T cells In granulomatosis with polyangiitis, dense peri- vascular areas of in- flammation have the appearance of poorly formed granulomata with multinucleate giant cells, macrophages, and lymphocytes. Activated B cells and ANCA secreting plasma cells can be seen in the inflamma- tory infiltrate along with activated CD4 and CD8 lymphocytes sug- gesting a tertiary lymphoid organ function. The mechanisms leading to granulomata are poorly understood, but Th1, Th17, and NK T cell activation with sustained antigen presentation through dendritic cells are implicated. Lymphocytes are less common at sites of small vessel vasculitis, such as glomerulonephritis, although interstitial T cell in- filtration occurs and has been associated with an adverse prognosis. Complement Scanty deposits of IgG and complement can be seen or may be com- pletely absent. Special stains for C3 split products, C3d, and for the C5b-9 terminal attack complex have highlighted that alternative complement pathway activation and complement mediated cell lysis is occurring. A positive feedback loop has been described by which neutrophil products, properdin and factor B, accelerate the C3 convertase leading to cleavage of C5 and an increase in the neu- trophil chemoattractant and primer C5a. Inhibition of C5a in a C5 receptor humanized murine model has abrogated the evolution of ANCA vasculitis (Fig. 19.11.7.4). Genetics Background Dysregulation of the immune system T cells B cells Interaction Neutrophil Proinflammatory cytokine Complement system Alternative pathway C5a C5b c.C9 (Membrane attack complex) PR3/MPO Priming ANCA, anti LAMP-2Ab? anti Moesin Ab? Cytotoxicity Activation NETs Perforin T effector cells Inflammation of small vessel ROS Vascular endothelium • HLA-DP, SERPINA1, PRTN3 (for GPA) • HLA-DQ (for MPA) • Others ... PTPN22?, CTLA4? Environments • Air pollutants... Silica • Infection ... S.aureus, E-coli • Drug ..... Propylthiouracil, Cocaine Fig. 19.11.7.4 A schematic representation of the pathogenesis of ANCA-associated vasculitis. Reprinted from Furuta S and Jayne DRW (2013). Antineutrophil cytoplasm antibody-associated vasculitis: recent developments. Kidney International, 84(2): 244–249, copyright 2013, with permission from Elsevier.

19.11.7 ANCA-associated vasculitis 4561 Clinical features There is considerable heterogeneity between patients in the ex- tent and severity of their clinical presentation. Certain pat- terns of disease can be described (Table 19.11.7.4) but many patients have unusual or incomplete presentations that com- plicate and delay diagnosis. While clinical features, such as purpuric rash or collapse of the nasal septum, lead to rapid suspicion of a vasculitis, others mimic more common dis- eases, for example, chest infections or inflammatory arthritis, leading to delayed diagnoses and treatment. The pattern of organ distribution differs between syndromes and ethnicities (Table 19.11.7.5). Prodromal phase GPA and MPA patients exhibit symptoms for, on average, six months before the diagnosis is made. They consist of intermit- tent features of systemic disturbance and focal inflammatory features, such as, a flitting arthritis, episcleritis, or purpuric rash. In granulomatosis with polyangiitis ear, nose, and throat symptoms predominate. The prodromal phase can be much longer in eosinophilic granulomatosis with polyangiitis, where Table 19.11.7.4 Common clinical presentations of ANCA-associated vasculitis Clinical pattern Clinical features Specific features Serology Histology Diagnosis ‘Classical’
GPA/Wegener’s Destructive ENT lesions. With or without pulmonary disease with or without nephritis Nasal congestion, epistaxis, crusting, conductive deafness, hoarseness, stridor Pulmonary nodules or cavities Usually PR3-ANCA, may be negative in ENT localized presentations Low yield of confirmatory histology on ENT biopsies, higher yield on guided lung biopsies but usually not justified GPA Renal Nephritis Haematuria with proteinuria with or without elevated serum creatinine PR3-ANCA or MPO- ANCA, fewer than 10% are ANCA negative High yield from renal biopsy of a pauci-immune, necrotizing, crescentic glomerulonephritis GPA, if destructive respiratory tract features are present, otherwise MPA Pulmonary renal syndrome Diffuse alveolar haemorrhage with nephritis Haemoptysis, dyspnoea, pulmonary infiltrates with nephritis PR3-ANCA or MPO- ANCA, fewer than 10% are ANCA negative High yield from renal biopsy of a pauci-immune, necrotizing, crescentic glomerulonephritis GPA, if destructive respiratory tract features are present, otherwise MPA Systemic
vasculitis At least one of: skin, joint, eye, nerve, lung, kidney, or other organ vasculitis without prominent ENT disease Purpura, arthritis, scleritis, neuropathy, pulmonary infiltrates, nephritis PR3-ANCA or MPO- ANCA or ANCA negative Skin histology is non- specific, renal biopsy best if nephritis present. Nerve biopsy if serology negative and predominant organ involved Usually MPA but can evolve into GPA ‘Classical’ EGPA/ Churg-Strauss Maturity onset asthma, nondestructive ENT disease and vasculitic features (nerve, heart and gut involvement more common than GPA/MPA) Wheeze, rhinitis, nasal polyps, sinusitis, conductive deafness; with neuropathy, abdominal pain, myocarditis Eosinophilia and eosinophils >10% of white cell count.

> 60% ANCA negative, if positive, usually MPO- ANCA, and associated with nephritis and neuropathy Eosinophil predominant infiltrate. Biopsy not required for classical presentations but useful for gut involvement and nephritis EGPA Note; all presentations are associated with a prodrome of constitutional symptoms. (GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; PR3, proteinase 3; MPO, myeloperoxidase). Table 19.11.7.5 The frequency of organ involvements in 735 patients recruited into European Vasculitis Society trials Organ involvement (%) All patients (n = 735) MPA (n = 332) GPA (n = 403) P value

> Systemic 91 85 95 <0.001 Cutaneous 23 18 27 0.007 Mucous membranes/eye 28 15 39 <0.001 Ear, nose, and throat 54 20 81 <0.001 Chest 54 42 63 <0.001 Cardiovascular 6 5 7 0.40 Abdominal 5 6 4 0.30 Renal 88 98 81 <0.001 Neurological 20 15 23 0.010

section 19 Rheumatological disorders 4562 an ‘allergic’ phase of rhinitis and asthma can precede the appear- ance of vasculitis by many years. Systemic Most ANCA-associated vasculitis patients are profoundly un- well at the time of diagnosis with constitutional symptoms of fa- tigue and malaise, fevers, night sweats, weight loss, headache, and polymyalgia. In occasional elderly patients, there are no focal fea- tures of vasculitis and this presentation can be labelled as a ‘failure to thrive’ with diagnosis relying on serological testing. Respiratory tract Destructive lesions of the ear, nose or throat (ENT) region with granulomata and vasculitis are the hallmark of granulomatosis with polyangiitis and can be the only organ specific manifestation (local- ized granulomatosis with polyangiitis) or be in combination with pul- monary and renal disease, the classical triad described by Wegener. The nasal mucosa is congested and ulcerated with large bloody crusts developing on its surface, which detach through the nose or back of the throat. Epistaxis and nasal congestion is common and there may be pain across the nasal bridge and progressive collapse of the nasal car- tilage. Similar inflammation occurs within the nasal sinuses leading to opacification, infection, and chronic facial pain and headache. Mucosal inflammation can be visualized on magnetic resonance (MR) imaging and bone destruction on plain X-ray or computed tomography (CT). Involvement of the Eustachian tubes cause secretory otitis media, conductive deafness, middle-ear infection, and tympanic rupture. Laryngeal disease results in hoarseness and subglottic stenosis. This lesion being more frequent in younger, female, granulomatosis with polyangiitis patients, and often appearing some months after the diag- nosis. Ear, nose, and throat involvement is uncommon in microscopic polyangiitis when it is nondestructive and clears rapidly with therapy. Symptoms of pulmonary involvement include cough, haemop- tysis, and shortness of breath. Alveolar capillaritis appears as patchy or diffuse radiologic infiltrates, and may be asymptomatic or asso- ciated with hypoxia and respiratory failure. In granulomatosis with polyangiitis, multifocal infiltrates with cavities of varying size can be seen. Thickening of the bronchial walls similar to bronchiectasis oc- curs and localized tracheal or bronchial stenoses in granulomatosis with polyangiitis can cause distal pulmonary collapse or infection. Interstitial lung disease, pulmonary fibrosis, can be seen in a mi- nority of patients at diagnosis and may slowly progress to respiratory failure despite stability of other vasculitic manifestations. Chest CT scanning is required to define and monitor pulmonary pathology, supported by pulmonary function testing (Fig. 19.11.7.5). Bronchoscopic evaluation of tracheo- bronchial disease allows as- sessment of vasculitic activity based on hyperemia, ulceration, and contact bleeding, as well as later cictricial scaring. Bronchoalveolar lavage can help define alveolar haemorrhage as serial aspirates be- come progressively more blood stained. Histological yield from bronchoscopic biopsies is moderate although small vessel vasculitis can be identified. Exclusion of infections, such as tuberculosis, is ne- cessary for atypical pulmonary presentations. Renal The characteristic feature of renal disease in all three ANCA vascu- litis syndromes is a focal, necrotizing, crescentic glomerulonephritis. Haematuria with proteinuria is almost always present, and it can be visible and is associated with red cell casts. Renal function deteriorates over weeks and months and ANCA vasculitis is the most common cause of the presentation of rapidly

progressive glomerulonephritis. Renal biopsy is indicated in a patient with urinary abnormalities and suspected vasculitis and has a high chance of demonstrating vascu- litis in the form of a glomerular capillaritis. As glomerular lesions progress the tuft is compressed by a crescent of epithelial and inflam- matory cells that lead to glomerular fibrosis or rupture. Interstitial inflammation comprises both a T cell tubulitis and severe peri-glom- erular inflammation. Arteritis of extraglomerular vessels occurs in 15%. Granulomata are uncommon, but seen in the interstitium in granulomatosis with polyangiitis if they occur. Fig. 19.11.7.5 Appearances of pulmonary involvement in ANCA- associated vasculitis. (a) Alveolar haemorrhage. (b) Usual interstitial pneumonitis. (c) Subglottic tracheal narrowing. (d) Cavitating nodules complicated by hydropneumothorax.

19.11.7 ANCA-associated vasculitis 4563 Renal function at diagnosis is the most important predictor of later renal failure, with 50% of those presenting with a glomerular filtra- tion rate below 50 ml/min developing end stage renal failure or not surviving by five years. A system of subclassification of glomerular histology in ANCA vasculitis, the ‘Berden’ classification, has been de- veloped based on the percentage of glomeruli affected by cellular or fibrotic crescents. The four categories, focal, crescentic, fibrotic and mixed correlate with risk of development of end stage renal disease (Fig. 19.11.7.6). Other adverse prognostic factors are MPO-ANCA positivity, interstitial inflammation, and extraglomerular arteritis. Fig. 19.11.7.5 Continued

> “ 50% globally sclerotic glomeruli Sclerotic class YES YES YES NO NO NO Focal class Crescentic class Mixed class 50% normal glomeruli 50% cellular crescents (a) Focal Mixed Sclerotic Crescentic Follow up in years to renal failure Renal survive 100 80 60 40 20 0 0 2 4 6 8 10 12 Focal censored Mixed censored Sclerotic censored Crescentic censored (b) Fig. 19.11.7.6 The Berden subclassification of glomerular histology in ANCA-associated glomerulonephritis (a) and association with risk of end stage renal disease (b). Reprinted from Berden AE et al. (2010). Histopathologic Classification of ANCA- Associated Glomerulonephritis. J Am Soc Nephrol, 21: 1628–1636. Copyright © 2010 by the American Society of Nephrology.

section 19 Rheumatological disorders 4564 Skin Purpura of varying sizes and ages, predominantly on the lower limbs, is the most frequent cutaneous manifestation of ANCA-as- sociated vasculitis. It is more polymorphic than in IgA vasculitis or cryoglobulinaemia, and can coalesce to frank ulceration. Ulceration can be the only manifestation, either single or multiple, and fea- tures of pyoderma gangrenosum may be seen. Other features of cutaneous disease are gum involvement, ‘strawberry’ gums, oral ul- ceration, splinter haemorrhage in the nail beds, and painful subcuta- neous swellings of panniculitis. Digital gangrene is a rare, dramatic presentation. Nervous system Peripheral neuropathy occurs in around 20% of ANCA-asso- ciated vasculitis patients and is more common in eosinophilic granulomatosis with polyangiitis. Multiple nerves are affected, ‘mononeuritis multiplex’, with a mixed motor, and sensory deficit. Nerve conduction studies reveal an axonal neuropathy. Involvement of the common peroneal nerve with foot drop is the most common feature. The onset of neuropathy is at the time of other vasculitis symptoms and may be painful in the affected limbs or painless. During the recovery phase, neuralgic pain can become

prominent and distressing to the patient who suspects deterior- ation. Recovery of sensation and power is slow but can lead to full recovery of function. Cranial nerves can also be affected and rare presentations include a small fibre painful neuropathy and ganglionopathy. Central nervous system involvement is rare in microscopic polyangiitis, while in granulomatosis with polyangiitis a pachy meningitis presenting with severe headache occurs and is readily demonstrated by gadolinium enhanced MR scan. Tumour-like granulomatous lesions occur rarely in the cerebral hemispheres and direct extension of nasal granulomatous disease to involve the pituitary gland or frontal hemispheres is seen. Transverse myelitis and peri-spinal haematomas have occurred rarely. Cerebrovascular events when they occur during the acute vasculitic phase are usually attributed to prior cerebrovascular disease and a pro-thrombotic state rather than a cerebral vasculitis. Eye ANCA vasculitis can affect any structure in the eye or orbit. Granulomatosis with polyangiitis can cause a painful, necrotizing scleritis with exposure of the uvea. Involvement of adjacent ocular structures such as the cornea, trabecular meshwork, and ciliary body leads to keratitis, corneal ulceration, uveitis, ocular hyper- tension, or glaucoma episcleritis, often bilateral, is seen in both granulomatosis with polyangiitis and microscopic polyangiitis and resolves quickly with treatment, it can be present as a diffuse pink colouring of the sclera and is a useful marker of systemic vas- culitis activity. Vasculitis of the optic chiasm or optic nerve causes sudden bilateral or unilateral blindness. Uveitis is less frequent but retinitis, choroiditis, retinal detachment, and necrosis occur. Central retinal artery occlusions and venous thrombosis may also be seen. Nasal disease in granulomatosis with polyangiitis often obstructs the naso-lacrimal duct with a risk of abscess forma- tion in the occluded duct and epiphora. Accumulation of orbital granulomatous inflammation behind the eye increases pressure in the orbit with proptosis and can be sight-threatening. Orbital muscles are affected through a cranial neuropathy, or granuloma- tous myositis. Gut Vasculitis can affect any gastro-intestinal structure but the small in- testine is the most frequent site of disease, with intestinal haemor- rhage or perforation as the presenting clinical features. Diagnosis of less severe involvement can be difficult with normal upper and lower intestinal endoscopy, but discontinuous bowel wall oedema on CT or ultrasound scanning can indicate inflammation. Pancreatitis, necrotizing cholecystitis and cholangitis are rare, granulomatous mass lesions can be mistaken for a pancreatic tumour. Heart Cardiac involvement in ANCA-associated vasculitis can present as chest pain due to pericarditis, heart failure and dysrythmias due to valvular heart disease or myocarditis, or be asymptomatic. The aortic valve can be affected by damage to the valve cusps or dilata- tion of the aortic valve ring leading to regurgitation. Disease of the thoracic aorta is probably underdiagnosed and can present late with aneurysm formation. Cardiac disease is more frequent in PR3 as compared to MPO-ANCA disease, but myocarditis is particularly frequent in eosinophilic granulomatosis with polyangiitis, in over 50%. Coronary arteritis, spasm, and aneurysm are rare manifest- ations. Investigations include troponin levels, echocardiography, and cardiac magnetic resonance imaging. Soft tissue peri-aortic masses of presumed inflammatory tissue have been observed. Laboratory features and imaging As an acute inflammatory disease, elevations of C-reactive pro- tein (CRP) and erythrocyte sedimentation rate (ESR) are almost always present at diagnosis, often at very high levels. Once therapy has been initiated the value of these markers is reduced and active disease can persist with normal levels or other factors, such as in- fection, can influence CRP and ESR. Haemoglobin may be reduced to the presence of chronic inflammation or chronic kidney dis- ease or be rapidly falling in the presence of alveolar haemorrhage. A neutrophilia is often present and has been shown to be an adverse prognostic factor, thrombocytosis is common in granulomatosis with polyangiitis, while thrombocytopaenia is rare and raises the possibility of a microangiopathic process rarely seen is severe vas- culitis. In

eosinophilic granulomatosis with polyangiitis, peripheral eosinophilia is characteristic of the disease. Thrombophilia studies are normal. Serum creatinine may be elevated in nephritis, while liver func- tion is very rarely disturbed. Urine analysis reveals nonvisible haematuria with proteinuria in the presence of nephritis, and the presence of red cell casts on urine microscopy indicates a severe glomerulonephritis. Typically, proteinuria is below 3 g/24 hours and features of nephrotic syndrome are not seen at diagnosis, but proteinuria can rise markedly during the recovery phase of severe nephritis. The possibility of an overlap nephritis with IgA nephrop- athy or antiglomerular basement membrane disease should also be considered.

19.11.7 ANCA-associated vasculitis 4565 Immunologic evaluation aims to confirm the presence of ANCA and exclude other immune causes of the presentation. There can be cross reactivity between some antinuclear antibody (ANA) as- says with ANCA, but specific antinuclear antigen assays, such as antidouble stranded DNA, Ro, La are negative. Rheumatoid factor may be positive at low titres and some ANCA vasculitis patients are mis-diagnosed in the prodromal phase as rheumatoid arth- ritis. Anticyclic citrullinated peptide (CCP) antibodies are nega- tive. Complement levels are normal and protein electrophoresis does not reveal a paraprotein or immunoglobulin light chain re- striction. Lupus anticoagulant and anticardiolipin antibodies are not detected, except in rare cases of overlap syndromes, more common in drug-induced vasculitis, when tissue infarction can be severe. Microbiologic evaluation aims to exclude secondary vasculitis caused by chronic viral infection, hepatitis B, C, or HIV, or chronic bacterial infection, as in infective endocarditis. In granulomatosis with polyangiitis, nasal colonization with Staphylococcus aureus has been associated with a higher relapse rate and should be looked for. In view of the need for immunosuppression evidence of previous infection with varicella zoster, Epstein–Barr virus, and cytomegalo- virus is useful information. Chest CT studies are abnormal in at least one-third of ANCA- associated vasculitis patients with a variety of abnormalities seen. Other imaging is directed by evidence of organ specific disease. In nephritis renal ultrasound is typically normal although ureteric disease can occur in eosinophilic granulomatosis with polyangiitis causing hydronephrosis. CT and MR examination of the nose, sinuses, and orbits defines the amount of bone destruction and soft tissue inflammation, especially useful in granulomatosis with polyangiitis with granulomatous disease. Evidence of aortic dis- ease in granulomatosis with polyangiitis should be seen on chest CT and requires further angiographic characterization. Medium artery involvement is rare in granulomatosis with polyangiitis and microscopic polyangiitis, although more frequent in eosinophilic granulomatosis with polyangiitis, similar to polyarteritis nodosa. Echocardiography and electrocardiogram (ECG) studies are indi- cated in all granulomatosis with polyangiitis and EGPA patients, al- though cardiac magnetic resonance imaging is more sensitive for detection of cardiac involvement. Diagnosis There are currently no consensus diagnostic criteria for ANCA- associated vasculitis, although the 1990 American College of Rheumatology classification criteria for Wegener’s (now granulomatosis with polyangiitis) have been adapted with the add- ition of ANCA serology for clinical trials, and those for Churg- Strauss (now eosinophilic granulomatosis with polyangiitis) remain in use. For the purpose of eligibility into clinical trials the European Vasculitis Society (EUVAS) have required a compatible clinical presentation supported by ANCA-positive serology or confirma- tory histology or both, and exclusion of other causes of the clinical presentation. Identification of causes of secondary forms of ANCA vasculitis and exclusion of mimics, including atheroembolic disease, myeloma, and the antiphospholipid syndrome, is important. For those with presumed vasculitis the European Medicines Evaluation Agency have devised an algorithm that categorizes patients as granulomatosis with polyangiitis, microscopic

polyangiitis, eosino- philic granulomatosis with polyangiitis, polyarteritis nodosa (PAN), or unclassified. Treatment Approaches to therapy The goals of therapy are to achieve a remission in disease ac- tivity, prevent relapse, and minimize drug toxicity, and the risk of comorbid conditions (Table 19.11.7.6). An induction phase of 3–6 months is followed by a longer remission maintenance phase. Prolonged follow-up is then required to manage the consequences of vasculitic damage, drug toxicity, and increased cardiovascular and malignancy risks. The initial approach to treatment of granulomatosis with polyangiitis and microscopic polyangiitis is similar with assessment of disease extent and severity and identification of patient factors that influence treatment choice. Attempts have been made to sub- group patients at diagnosis according to disease severity and to iden- tify factors predicting increased mortality risk (Table 19.11.7.7). However, avoiding diagnostic delay and the early institution of Table 19.11.7.6 Subgrouping of patients at diagnosis according to disease activity and extent Subgrouping by severity or extent Organ involvement Constitutional symptoms ANCA status Serum creatinine (μmol/litre) USA EUVAS Limited or nonsevere Localized One site, typically the upper respiratory tract in GPA No Positive or negative <120 Early systemic Any, except renal or imminent vital organ failure Yes Positive <120 Generalized or severe Generalized (or renal) Imminent vital organ failure or renal vasculitis Yes Positive <500 Severe Vital organ failure, typically renal Yes Positive

> 500 (renal presentations) Refractory Progressive disease despite conventional therapy Yes Positive or negative any GPA, granulomatosis with polyangiitis; EUVAS, European Vasculitis Society; USA, United States of America

section 19 Rheumatological disorders 4566 therapy are of primary importance in all subgroups. EGPA has been treated separately to granulomatosis with polyangiitis and micro- scopic polyangiitis in the few therapeutic trials that have been per- formed. Current guidelines reflect an international consensus into how ANCA-associated vasculitis should be managed. Induction therapy The combination of high-dose glucocorticoids with either cyclo- phosphamide or rituximab is the standard of care for new patients with ANCA-associated vasculitis. Cyclophosphamide is equally ef- fective as a daily oral or pulsed intravenous (IV) administration for the induction of remission. However, the IV protocols expose the patient to a lower cumulative cyclophosphamide dose, less frequent leucopaenia, and permit bladder protection. Cyclophosphamide is continued for 3–6 months, by which time remission will have been achieved in 80–90% of patients. Rituximab has similar efficacy to cyclophosphamide with two regimens used, either 375 mg/m2 /week for four weeks or 1000 mg repeated at two weeks. Daily oral pred- nisolone regimens commence at 1.0 mg/kg per day and reduce to 0–10 mg/day by six months. A few patients present with mild disease and no threatened loss of organ function, when methotrexate or mycophenolate mofetil can be considered as alternatives to cyclophosphamide or rituximab. Severe presentations These are characterized by loss of organ function, such as acute kidney injury, and the need to gain rapid control of vasculitis. IV methyl prednisolone is widely used at total doses of 1000–3000 mg, without a robust evidence base. Plasma exchange improves the chances of renal recovery in those presenting in renal failure (cre- atinine >500 μmol), but a role in other severe settings, including dif- fuse alveolar haemorrhage, awaits confirmation. Assessing response The activity of vasculitis is determined by a review of clinical fea- tures and circulating inflammatory markers, C-reactive

protein, and erythrocyte sedimentation rate. The Birmingham Vasculitis Activity Score (BVAS) lists 63 items of vasculitic disease in 10 system groups and serves as a useful checklist and catalogue of disease. An ‘on drug’ remission requires a BVAS of zero and is sup- ported by reduction or normalization of C-reactive protein and erythrocyte sedimentation rate. Certain disease features, such as nasal crusting and proteinuria, can be features of both disease ac- tivity and irreversible damage and adjudication of response can be difficult. ANCA levels fall with treatment but are not used as a target for therapy. Improvements in respiratory tract disease are accompanied by symptomatic and radiological improvement. Subglottic and endobronchial disease is rarely present at diagnosis but can appear when granulomatosis with polyangiitis is clinically inactive or at the time of relapse. It should be considered for persisting exertional dyspnoea, recurrent respiratory tract infections, or radiological opacities, and is best defined by CT scanning and bronchoscopy. Pulmonary function tests are useful in monitoring individual pa- tients but can be misleading when used for diagnosis. Changes in ear nose and throat and ophthalmic activity can be harder to assess and regular specialist review with nasendoscopy and direct laryngeal visualization is recommended. Vasculitic neuropathy recovers to variable degrees but some motor deficiency usually remains. A para- doxical deterioration in symptoms of dysaethesiae during the re- covery phase is common and responds to amitriptyline, gabapentin, or pregabelin. Eosinophilic granulomatosis with polyangiitis A similar approach to granulomatosis with polyangiitis and micro- scopic polyangiitis is adopted with cyclophosphamide and high- dose glucocorticoids disease for presentations threatening organ damage, such as cardiomyopathy or neuropathy. Nonsevere dis- ease can be treated with glucocorticoids alone, but an immuno- suppressive such as azathioprine or methotrexate is often used to minimize steroid exposure and reduce relapse risk. Observational data supports the use of rituximab when cyclophosphamide is contra-indicated or ineffective. The allergic components of EGPA—asthma, naso-sinus disease, and rash—are steroid respon- sive, but often recur as glucocorticoids are reduced and can be the most challenging manifestations to manage once the vasculitic fea- tures are controlled. Table 19.11.7.7 Disease state definitions in ANCA-associated vasculitis Activity state Definition Remission Absence of disease activity attributable to active vasculitis qualified by the need for ongoing stable relapse prevention therapy. ‘Active disease’ is not restricted to vasculitis only, but includes other inflammatory features, such as granulomatous inflammation
in granulomatosis with polyangiitis or tissue eosinophilia in eosinophilic granulomatosis with polyangiitis Response 50% reduction of disease activity score and absence of new manifestations Relapse Recurrence or new onset of disease attributable to active vasculitis Major relapse Recurrence or new onset of potentially organ- or life-threatening disease Minor relapse Recurrence or new onset of disease which is neither potentially organ threatening nor life threatening Refractory disease 1. Unchanged or increased disease activity in acute ANCA-associated vasculitis after at least four weeks treatment with standard induction therapy, or 2. Lack of response, defined as ≤50% reduction in the disease activity score, after at least 6 weeks of treatment, or 3. Chronic, persistent disease defined as the presence of at least one major or three minor items on the disease activity score list, after ≥12 weeks of treatment Low-activity disease state Persistence of minor symptoms (e.g. arthalgia, myalgia) that respond to a modest glucocorticoid increase and do not necessarily warrant an escalation of other therapies

 Induction treatment in children and older people The approach to therapy and responsiveness to medication is the same in the young and the old as in other age groups, but drug selec- tion and dosing may differ. In view of the fertility and malignancy

risks, rituximab is preferred to cyclophosphamide. Higher gluco- corticoid doses, up to 2 mg/kg per day, are used in children, due to increased rates of elimination. Elderly patients are more likely to present with renal impairment and have a high risk of infective com- plications. It is important to reduce cyclophosphamide dose, due to the increased susceptibility to cytopenias; lower dose glucocorticoid regimens have had similar efficacy with fewer adverse events. Remission maintenance therapy Disease relapse occurs in 75% of granulomatosis with polyangiitis and 30% of microscopic polyangiitis patients by five years. Both azathioprine and methotrexate are recommended to reduce relapse with a treatment duration of at least two years. The use of concomi- tant low dose prednisolone, 5–10 mg/day is more variable, although glucocorticoid withdrawal increases relapse risk. Despite these interventions, 25–30% will relapse by two years. Mycophenolate mofetil is an alternative especially if chronic kidney disease is pre- sent. Relapse risk is high after rituximab induction and repeat dose rituximab is an effective maintenance regimen, with doses of 500–1000 mg every six months. Rituximab is superior and probably safer to azathioprine and prednisolone and more reliably permits early glucocorticoid withdrawal. However, an increase in relapse risk is seen after completion of a repeat dose rituximab course. Circulating B cell counts and ANCA levels have been used to guide rituximab dosing but their value remains controversial. Relapse risk is influenced by diagnosis, ANCA serotype and serum binding level, and type of induction and maintenance treatment (Table 19.11.7.8). Review of these factors at two years is helpful in deciding the duration of maintenance therapy. Other factors to con- sider are the likely consequence of relapse if it occurs, the quality of disease activity monitoring, and tolerability of maintenance therapy. Management of relapse The symptoms and signs of relapse in an individual patient reflect those present prior to the original diagnosis. The diagnosis of relapse needs to be differentiated from infection or other potential causes, including malignancy. Infection may precede and precipitate relapse and this is a particular issue with bacterial infections in respiratory tract relapse in granulomatosis with polyangiitis. Mild relapses without threatened organ damage can be treated with prednisolone 20 mg/day but the risk of subsequent relapse is high and if inad- equately treated can develop into more severe relapse. Rituximab is more effective than cyclophosphamide for relapsing disease and is preferred to avoid a high cumulative exposure to cyclophospha- mide, glucocorticoid dosing is usually lower reflecting concern over previous exposure. Refractory disease Progression of vasculitis despite induction therapy, failure to at- tain disease remission, and disease relapse while receiving main- tenance therapy are defined as refractory disease. Before therapy is enhanced, causes for refractory disease—including infection, malig- nancy, and drugs—should be considered, as well as nonconcordance with the prescribed regimen. Drug intolerance, especially to gluco- corticoids or cyclophosphamide, and reductions in dosing due to intercurrent infection may also lead to primary treatment failure. This situation is associated with a high mortality due to deterior ating organ function and higher risks of treatment. Progressive or nonresponsive disease occurs in 5–10% and is treated with an in- crease in glucocorticoid, typically IV pulsed methylprednisolone 1000–3000 mg and switching from cyclophosphamide to rituximab. Rare failures of rituximab can be attributed to failure to achieve B cell depletion, or if there is underlying infection. Where the re- sponse to rituximab appears slow, pulse cyclophosphamide can be added until response is seen, but cyclophosphamide is not routinely required with rituximab. Alternative therapies that have been em- ployed include high-dose intravenous immunoglobulins, plasma exchange, alemtuzumab (anti-CD52), deoxyspergualin, and tumour necrosis factor blockade. Eosinophilic granulomatosis with polyangiitis can pursue a pri- mary progressive course requiring repeated courses of IV steroid; intravenous immunoglobulin and plasma exchange have also been used. However, a more common problem in EGPA is re- lapse

as glucocorticoids are reduced. Such patients are at risk of high glucocorticoid exposure and alternative strategies should be pursued to permit glucocorticoid reduction to conventional maintenance levels. A change in immunosuppressive may be effective in nonsevere disease. Rituximab, alemtuzumab, interferon-α and mepolizumab, an anti-interleukin (IL)-5 monoclonal antibody, have been used in this setting. Outcomes ANCA vasculitis has consequences on survival, organ damage, and development of comorbidities. Quality of life can remain de- pressed when clinical activity is absent and the late consequences of treatment contribute to irreversible organ damage (Fig. 19.11.7.7). Despite advances in therapy patients continue to have a mortality rate ratio of 2–3 compared to a control population, with advanced renal failure, increasing age, a high disease activity at diagnosis and the MPO-ANCA subtype being adverse predictors. Infection, in part attributable to treatment, and alveolar haemorrhage are the most common causes of early death while increased risks of malig- nancy and cardiovascular disease contribute to later mortality. Reduced cyclophosphamide exposure with current regimens has lowered bladder cancer and leukaemia risk but there remains Table 19.11.7.8 Factors influencing relapse risk of ANCA-associated vasculitis Clinical presentation Serology Treatment-related Diagnosis of GPA PR3-ANCA positive at diagnosis Steroid withdrawal Ear, nose, and throat involvement Persistent ANCA positivity after induction therapy Immunosuppressive withdrawal Serum creatinine <200 μmol/litre Rise in ANCA during remission Lower cyclophosphamide exposure ANCA, antineutrophil cytoplasmic antibody; GPA, granulomatosis with polyangiitis (Wegener's).

section 19 Rheumatological disorders 4568 an overall increase in risk ratio of 2.5–4 with nonmelanoma skin cancer being most apparent. Cardiovascular events have been as- sociated with higher disease activity at diagnosis and MPO-ANCA serotype, and patients in clinical remission have abnormal endo- thelial function, which might contribute to this risk. There is also an increased risk of thromboembolism, occurring in 5–15% in the first year and is highest when vasculitis is active. It has been linked to autoantibodies to plasminogen or tissue factor, but this requires confirmation. Nonhealing damage Ninety-five per cent (95%) of patients develop at least one item of irreversible damage as a result of vasculitis or its therapy. Damage of the upper respiratory tract is common in granulomatosis with polyangiitis, with deafness and chronic nasal and sinus symp- tomatology. Twenty per cent (20% of patients develop end-stage renal disease by five years with more having chronic kidney dis- ease of less severity. Renal survival is associated with serum cre- atinine at diagnosis and the percentage of normal glomeruli in the renal biopsy. However, even in those presenting with severe histo- logical findings and low numbers of normal glomeruli, treatment should be given as the chance of renal recovery is greater than for therapy-related death. A renal histology score has been developed with four categories associating with a progressively worse renal survival: focal, crescentic, mixed, and fibrotic. Treatment toxicity contributes to damage through glucocorticoid toxicity, including diabetes, bone disease, and cataracts; the infective and malignant complications of immunosuppression and acquired immunodefi- ciency a particular problem for ANCA-associated vasculitis patients receiving rituximab. Future directions The classification of vasculitis remains based on a phenotypic de- scription, but with the definition of genetic and serologic associ- ations it seems likely that the terms PR3 and MPO-ANCA vasculitis may replace granulomatosis with polyangiitis and microscopic polyangiitis. The discovery of polymorphisms linked with the autoantigen, a protease, and its major inhibitor, α-1 antitrypsin, has inspired new concepts of aetiology based on dysregulated neutro- phil maturation and autoantigen formation and control. The critical role of complement factor 5 in animal models of ANCA-associated vasculitis will, if replicated in the human disease, provide a new target for therapy, as agents blocking C5 are already in the clinic or clinical trials. A role of the microbiome (either of the

respiratory or urinary tract) in disease initiation is suspected from current evidence, but the mechanism is unclear and a role for antibiotics has only been demonstrated for those chronically infected with Staphylococcus aureus. The combination of agents used for induction and maintenance of remission has evolved from academic randomized controlled trials that have led to a high level of international consensus and the pub- lication of a series of management recommendations. Diagnostic delay and the availability of expert advice point to the importance of health service reform in the delivery of care to vasculitis pa- tients that will directly benefit treatment response, treatment safety, and longer-term outcomes. Newer targeted agents, in particular rituximab, have had a major impact on treatment regimens and have led to more pharmaceutical industry investment. Important needs for future drugs include achievement of more rapid and complete remission while sparing glucocorticoids, and reducing relapse risk while minimizing the need for long-term immunosuppression. The causes for vasculitis comorbidities, especially cardiovascular disease, are not understood, and the relative value of agents such as platelet inhibitors or cholesterol lowering drugs is not known. Certain aspects of quality of life improve with therapy, but de- pressed vitality and physical activity along with sleep disturbance are common long-term problems. Patient education and support, graded exercise programmes, and lifestyle modification deserve fur- ther exploration. FURTHER READING de Groot K, et al. (2005). Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum, 52, 2461–9. de Groot K, et al. (2009). Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody- associated vasculitis: a randomized trial. Ann Intern Med, 150, 670–80. Fahey JL, et al. (1954). Wegener’s granulomatosis. Am J Med, 17, 168–79. Flossmann O, et al. (2011). Long-term patient survival in ANCA- associated vasculitis. Ann Rheum Dis, 70, 488–94. Fujimoto S, et al. (2011). Comparison of the epidemiology of anti- neutrophil cytoplasmic antibody-associated vasculitis between Japan and the UK. Rheumatology (Oxford), 50, 1916–20. Outcomes Survival Relapse Malignancy Cardiovascular and thrmboembolic disease Quality of life Damage Renal ENT Lung etc Fig. 19.11.7.7 Multiple dimensions of long-term outcome in ANCA- associated vasculitis.

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