ANCA and complement

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21.10.2 The kidney in systemic vasculitis 4989 renal histology. It is a less common feature of the medium-vessel vasculitides (polyarteritis nodosa and Kawasaki’s disease) and is rare in large-vessel vasculitis. AAV is the most frequent cause of renal vasculitis and is the focus of this chapter, although other causes of renal vasculitis will also be discussed. Historical perspective The subgroups within primary systemic vasculitis were initially described as discrete clinicopathological syndromes: Henoch– Schönlein purpura in 1837, polyarteritis nodosa in 1866, Takayasu’s arteritis in 1910, MPA in 1923, Wegener’s granulomatosis in 1936, and Churg–Strauss angiitis in 1951. An international consensus on the definitions and terminology of vasculitis was achieved in Chapel Hill (North Carolina) in 1992, and updated in 2012, when several syndromes were renamed using descriptive rather than eponymous terms. There are no diagnostic criteria developed for clinical use, but criteria for clinical trials based on ANCA, histology, and clinical fea- tures have been effective. In the 1980s, the association of ANCA with Wegener’s granulomatosis and MPA was reported and the target autoantigens, proteinase 3 (PR3-ANCA) and myeloperoxidase (MPO-ANCA), identified. The availability of ANCA testing has been a major advance in the diagnosis and monitoring of vasculitis and has provided insights into pathogenesis and classification. Before 1960, systemic vasculitis with renal involvement was usually fatal. High-dose corticosteroids were partially effective in the short term, but it was the introduction of immunosuppres- sive therapy, and particularly cyclophosphamide, during the next decade that enabled sustained control of vasculitis to be achieved. An increasing awareness of the late toxicity of cyclophosphamide, particularly infertility and bladder and haematological malignan- cies, in the 1980s encouraged the development of strategies to min- imize cyclophosphamide exposure. Several additional agents have been introduced with the aim of improving control of fulminant or refractory disease, or reducing steroid or immunosuppressive exposure, and these include plasma exchange, intravenous im- munoglobulin, tumour necrosis factor-α (TNFα) blockade, and lymphocyte depletion. Rituximab, a B-cell-depleting monoclonal antibody, was licensed for the treatment of GPA and MPA in 2011, and apart from glucocorticoids remains the only licensed treat- ment for vasculitis. Aetiology, genetics, pathogenesis, and pathology Genetics Genome-wide association studies have revealed that polymorphisms of α1-antitrypsin, PR3, and HLA DP antigens are associated with PR3-ANCA positive disease, and of HLA DQ antigens with MPO- ANCA. Other polymorphisms, including cytotoxic T-lymphocyte- associated antigen 4 (CTLA4), tyrosine-protein phosphatase nonreceptor type 2, the third complement component, and the FcγRIII immunoglobulin receptor have been found in candidate gene studies. There is a modestly increased relative risk of family members having vasculitis, but familial cases are rare. Environment and drugs Occupational exposure to silica and other industrial dusts increases the risk of MPO-ANCA vasculitis, and an increased incidence of MPO-ANCA vasculitis was reported after the Kobe earthquake in 1995. Drug exposure

to hydralazine, penicillamine, minocycline, and the combination of cocaine and levamisole, has also been associated with MPA. Chronic nasal exposure to cocaine can produce necrosis and inflammation difficult to differentiate from localized GPA. Disease associations ANCA vasculitis occurs in the setting of chronic infections, including tuberculosis, infective endocarditis, and cystic fibrosis, and with cancer, in particular epithelial malignancies. Control of the precipitating path- ology usually results in resolution of the vasculitis. One-third of pa- tients with antiglomerular basement membrane (anti-GBM) disease have concurrent ANCA positivity and features of extrarenal vasculitis. MPO-ANCA occurring in 20% of lupus nephritis patients has been attributed to cross-reactive antidouble-stranded DNA antibodies, but a pauci-immune necrotizing glomerulonephritis can occur in sys- temic lupus erythematosus associated with ANCA. Co-occurrence of ANCA vasculitis with antiphospholipid antibodies is associated with extensive tissue necrosis and digital infarction. ANCA and complement The pathogenetic role of ANCA remains controversial because this pathology can occur without circulating ANCA, immune deposits are rarely present, and ANCA often persist without disease activity. Table 21.10.2.1 The classification of primary systemic vasculitis, updated in the 2012 Chapel Hill Consensus statement Predominant size of vessel involved Subgrouping ANCA-associated vasculitis Immune complex Small Granulomatosis with polyangiitis (GPA, formerly Wegener’s granulomatosis) IgA vasculitis (formerly Henoch–Schönlein purpura) Microscopic polyangiitis Cryoglobulinaemia Eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg–Strauss syndrome) Antiglomerular basement membrane disease Hypocomplementaemic urticarial vasculitis Medium Polyarteritis nodosa Kawasaki’s disease Large Giant cell arteritis Takayasu’s arteritis

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