CORRESPONDENCE

Presence of dual anti-MPO and anti-PR3 antibodies in Systemic Lupus Erythematosus/ANCA-Associated Vasculitis

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease associated with anti-nuclear antibodies (ANA), extractable nuclear antigens (ENA), and anti-double stranded DNA antibodies. Glomerulonephritis (GN) with immune complex deposition is found in 50% of cases.[1] Twenty per cent of patients with SLE have antineutrophil cytoplasmic antibodies (ANCA), which in certain patients is associated with ANCA-associated vasculitis (AAV).[2] The ANCA detected in such cases is reported in the literature as antimyeloperoxidase antibodies (MPO) rather than antiproteinase 3 (PR3) antibodies.[3] The prevalence of dual-positive AAV is up to 9% but these cases are not associated with SLE.[4] This is the first report of a case of SLE/AAV involving AAV (necrotising pauci-immune GN) with both anti-MPO and anti-PR3 antibodies.

A 70-year-old woman presented with thrombocytopenia (platelets 17×10^9/L), renal failure (creatinine 260 µmol/L) and deep vein thrombosis. She has a 10-year history of SLE characterised by panniculitis, photosensitivity, polyarthritis, oral ulceration, sicca symptoms, relapsing polychondritis, pulmonary hypertension, interstitial lung disease and pulmonary thromboembolism due to secondary antiphospholipid syndrome. Her laboratory investigations revealed a high titre (>2560) homogeneous ANA, anti-double-stranded-DNA antibodies and persistently elevated anticardiolipin and anti-beta-2 glycoprotein 1 antibodies. Her symptoms were non-responsive to methotrexate and leflunomide. A renal biopsy performed 1 year prior to presentation for a creatinine 110 µmol/L demonstrated hypertensive changes with no features of lupus nephritis.

Following the patients' admission, further investigations confirmed the presence of her homogeneous ANA and elevated antidouble-stranded DNA antibodies. Her ENA was negative. Her ANCA was uninterpretable due to the presence of her ANA but levels of both anti-MPO and PR3 antibodies were markedly elevated >100 U/mL (0–5). Her C reactive protein was 8 mg/L and her complement levels of C3 and C4 normal. Her full blood count revealed a mild normochromic microcytic anaemia (haemoglobin 101 g/L). Urine analysis revealed non-nephrotic range proteinuria, dysmorphic red cells and absence of casts. A renal biopsy captured 18 glomeruli: seven showed focal crescentic necrotising GN, seven were globally sclerosed and four demonstrated chronic ischaemic changes. Direct immunofluorescence (DIF) revealed no deposition of complement (C3, C1q), immunoglobulin (IgG, IgA, IgM), fibrinogen or light chains. Electron microscopy (EM) revealed a few small dense subepithelial, subendothelial and mesangial deposits in two glomeruli.

Radiology revealed large main pulmonary arteries consistent with pulmonary hypertension and changes suggestive of bronchiolitis obliterans. CT sinuses was normal.

A diagnosis of SLE/AAV overlap syndrome was made based on manifestations consistent with SLE (mucocutaneous, articular, haematological and pulmonary features with homogeneous ANA and antidouble stranded antibodies) and AAV (anti-MPO and anti-PR3 antibodies in association with pauci-immune GN).

Remission as per the European League Against Rheumatism (EULAR)/European Vasculitis Study Group (EUVAS) guidelines was induced with a regimen comprising pulse methylprednisolone for 3 days followed by tapered oral prednisone and intravenous cyclophosphamide for 6 months. Maintenance therapy was continued with mycophenolate mofetil. Her rash and synovitis resolved with improvement in her laboratory parameters (platelets 164×10^9/L, creatinine 134 µmol/L, absent dysmorphic red cells, undetectable anti-MPO and anti-PR3 antibodies). The patients' disease relapsed 15 months following completion of induction therapy manifesting as polyarthritis, thrombocytopenia (platelets 37×10^9/L), renal deterioration (creatinine 259 µmol/L, dysmorphic red cells) with elevation of both anti-MPO and anti-PR3 antibodies >100 U/mL. A renal biopsy was not performed as the patient was on anticoagulation and the clinical and laboratory evidence for a relapse of SLE/AAV was likely. Remission was attained with rituximab (two 1 g doses at day 0 and 14 in addition to tapering course of prednisone 1 mg/kg daily). Rituximab was continued as maintenance therapy 500 mg every 6 months for 2 years. The patients' renal function (creatinine 150 µmol/L) and platelets (193×10^9/L) recovered with abrogation of anti-MPO and anti-PR3 antibody levels (<1 U/mL).

The prevalence of overlapping antibodies in SLE and AAV is relatively common. Jarrot *et al* showed in a registry cohort study comprising consecutive renal biopsies in 101 patients with SLE and AAV that 30% of the 40 patients with SLE had a positive ANCA and 52% of the 61 patients with pauci-immune GN had a positive ANA. Only 2% of the cohort met the ACR and AAV criteria for a diagnosis of SLE/AAV overlap.[3] This study also compiled previous reports of SLE/AAV cases and found that none of the 34 cases tested for ANCA serology had anti-PR3 antibodies in contrast to 82% who had anti-MPO antibodies.[3] Patients showed a favourable response to therapy in the 75% of the 20/21 patients in the literature treated with cyclophosphamide and corticosteroids.[3] Mycophenolate therapy in lupus nephritis is insufficient to induce remission in the presence of AAV therefore emphasising the importance of performing a biopsy to establish the underlying renal histology. Our patient subsequently required rituximab therapy for relapsed disease.

Dual-positive AAV with crescentic GN has been described with drug induced vasculitis associated with propylthiouracil, levamisole, minocycline and hydralazine but these cases have not been associated with manifestations of SLE.[5]

The significance of glomerular immune complex deposits on EM is unclear as 26% patients with ANCA-associated GN, although the ANA status is unknown, have such deposits despite having pauci-immune GN on DIF.[6]

MPO and PR3 may be both pathogenic in AAV. Neutrophils generate neutrophil extracellular traps (NETs), a sticky mesh of proteins including MPO and PR3. Antigen presenting cells may take up MPO and PR3 from NETs resulting in recognition and activation of autoreactive T cells with induction of autoreactive B cells and production of anti-MPO and anti-PR3 antibodies and further NETosis.[7] Following the production of these autoantibodies, the antibody response may generalise to the rest of target autoantigens via the process of epitope spreading.[8] The presence of anti-PR3 antibodies confers an up to twofold higher relapse rate in AAV as compared with that of anti-MPO antibodies therefore requiring close disease monitoring.[9] Anti-PR3 antibodies may confer a greater risk of relapse due to homology between *Staphylococcus aureus*, known to be associated with AAV, and a peptide encoded by the reverse DNA strand to PR3 ('complementary' PR3, cPR3).[10] GPA patients are less able

to produce protective antibody responses to *S. aureus* than healthy individuals.[11]

Longitudinal studies are required to ascertain the prevalence of dual anti-MPO and anti-PR3 antibodies in SLE/AAV overlap and its prognostic relevance.

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