Mesangioproliferative glomerulonephritis, antiphospholipid antibodies, and Takayasu’s arteritis—is there a link?

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Introduction

Takayasu’s arteritis (TA) is a non-specific vasculitis of unknown aetiology primarily affecting the aorta and its principal branches [1,2]. Renal involvement is usually manifested by renovascular hypertension and/or ischaemic nephropathy [3]. Primary glomerular disease has only rarely been reported to occur in association with TA [4]. In these cases, the main histological picture described has been that of mesangioproliferative glomerulonephritis [4–6]. We herein describe a patient with TA of 15 years’ duration who presented with a pure nephrotic syndrome in whom renal biopsy demonstrated the above glomerulonephritis. Of note was the fact that the presence of antiphospholipid antibodies (APLA) was documented whereas antineutrophil cytoplasmic antibodies (ANCA) were negative. The unique occurrence of TA, proliferative glomerulonephritis, and APLA may imply a common underlying pathogenetic mechanism.

Case report

A 31-year-old Arab woman was admitted in December 1995 for the investigation of a nephrotic syndrome. Fifteen years previously (at the age of 16) she had undergone a lengthy and thorough evaluation for fever of unknown origin. Only after the development of asymmetric palpable pulses in her upper extremities (absence of left brachial and radial pulses) was aortography performed. This disclosed a dilated ascending aorta with irregular borders and a common origin of the innominate and left common carotid arteries. A 50% occlusion with poststenotic dilatation was evident at the origin of the left common carotid artery. The left subclavian artery was totally occluded in its middle third. Partial filling of the left brachial artery due to collateral circulation was present. The abdominal aorta showed interposed narrowed and dilated segments.

The remainder of the abdominal vascular tree appeared normal. She was consequently diagnosed as suffering from Takayasu’s disease (giant-cell arteritis). Steroid treatment was instituted leading to a rapid disappearance of her constitutional symptoms. Pulses in her left upper limb remained non-palpable. During the following 14 years she was infrequently seen on an outpatient basis, not being fully compliant regarding appointments and therapy. An echocardiogram performed a year prior to her present admission showed moderate aortic regurgitation.

On physical examination, temperature was 37.3°C, blood pressure 110/70 mmHg without peripheral oedema. The left brachial and radial pulses were absent. Apart from systolic and diastolic murmurs over the aortic valve, the rest of the examination was unremarkable. Laboratory data showed an ESR of 110/h (Westergren), serum haemoglobin 9.1 g/dl, WBC 12 000/µl, platelets 261 000/µl, urea 54 mg/dl, creatinine 0.6 mg/dl, albumin 3.0 g/dl, and cholesterol 244 mg/dl. On urinalysis there was 3+ protein with a bland urinary sediment. Quantitative proteinuria was 3.7 g/day. Complement levels (C3, C4) were within normal limits. A serological survey including ANF, ANCA, HBsAg, HCV, HIV, CMV, and EBV was negative. APLA (IgG anticardiolipin) was 45.0 (normal < 23 GPL units), IgM anticardiolipin and lupus anticoagulant were negative. A renal ultrasound showed both kidneys to be of normal size and echogenicity.

Percutaneous renal biopsy was performed. On light-microscopy, there were 17 glomeruli of which one was hyalinized. The remainder were of identical appearance consisting of a diffuse proliferative mesangial glomerulonephritis with leukocyte infiltration (exudative phase) (Figure 1). Immunofluorescence was positive for IgM along the glomerular basement membrane. On electron-microscopy, no humps or other electron-dense deposits and no fusion of foot processes were seen.
The patient was started on prednisone 1 mg/kg body-weight for 3 months, after which steroids were slowly tapered over the ensuing year. Proteinuria decreased only slightly to 2.7 g/day. Currently the patient is maintained on 7.5 mg/day of prednisone. Her renal function is intact (creatinine clearance of 90 ml/min) with persisting proteinuria of 2.1 g/day and a serum albumin of 3.1 g/dl.

Discussion

The commonest glomerular lesions observed in TA are non-specific ischaemic changes such as a collapsed (contracted) and/or hyalinized tuft [3]. Only isolated case reports have been published documenting primary glomerulopathy in association with TA. The histological picture described has included IgA nephropathy [7], membranoproliferative glomerulonephritis [8], crescentic glomerulonephritis [9], and mesangioproliferative glomerulonephritis [4–6]. In addition there are seven case reports of TA complicated by secondary (AA) amyloidosis [10–14], in two of whom there was also evidence of intercurrent tuberculosis [14]. As was seen in our patient, of the primary glomerular diseases, mesangioproliferative glomerulonephritis is the one most commonly encountered.

TA is a chronic inflammatory disease of large and medium-sized arteries. Although it shows a striking predilection for the aortic arch and its branches, emphasis has recently been placed on its systemic nature [12]. Thus multiorgan parenchymatous involvement has been described, highlighting the protean clinical manifestations of the disease. Among these, erythema nodosum, myocardiitis, pericarditis, interstitial lung disease, ulcerative colitis, rheumatoid arthritis and polymyositis have been reported [12]. It should therefore be hardly surprising that the kidney be involved in this systemic vasculitis. Rather the rarity of reported parenchymal renal involvement leads one to wonder whether this entity is not underdiagnosed.

Our patient initially presented with fever of unknown origin. In keeping with the literature, a prolonged period of time (1.5 years) elapsed before the diagnosis was finally established. Without doubt, however, the diagnosis of TA in our patient conforms to the criteria laid down by Ishikawa [15] or the modification proposed by Sharma et al. [16]. Glomerular damage in TA is most commonly manifested by microscopic dysmorphic haematuria and proteinuria, in general not of nephrotic range [4]. The presentation of a pure nephrotic syndrome, as in our case, is unusual (except in associated amyloidosis).

The precise factor(s) responsible for the arterial damage in TA are as yet unknown. Autoimmune activity is probably at play as evidenced by elevated ESR, hypergammaglobulinaemia, the existence of circulating antibodies against the aorta and other arteries [17,18], the presence of circulating immune complexes [19] and the favourable response to steroids. Two recent reports have noted the association of TA with the presence of serum ANCA, both pANCA and cANCA [7,20]. These antibodies have been ascribed a direct role in the pathogenesis of vasculitis rather than being a mere reflection of disease activity [21]. Of note, our patient was ANCA negative but APLA (IgG antcardiolipin) positive. A literature review has yielded only three other cases documenting the presence of APLA with TA. Lesoff and Glynn [22] reported a 13-year-old female with a diagnosis of SLE who presented at age 20 with absence of pulses in both upper extremities. Ferrante et al. [23] has commented on this case, postulating that it may have represented an APLA syndrome with thrombosis of the large arteries mimicking TA. A similar case reported by Asherson et al. [24] had a lupus-like illness complicated by occlusion of the axillary and subclavian arteries, in the presence of antcardiolipin antibodies and lupus anticoagulant.

Saxe and Altman [25] described one patient with SLE who had angiographically proven TA in association with IgM antcardiolipin antibody. Two additional cases of TA in whom lupus anticoagulant was positive and antcardiolipin antibodies were elevated have lately been described by Yokoi et al. [26]. Although infrequent, the finding of either ANCA or APLA in association with TA seems to suggest a contributory pathogenetic role of these antibodies in the vasculopathy of TA. The presently reported unique association of a proliferative glomerulonephritis in the above setting further implies a common underlying immune pathogenesis.

References

Fig. 1. Renal biopsy demonstrating a diffuse mesangioproliferative glomerulonephritis with leukocytic infiltration. All the glomeruli (17) were of identical appearance. (H&E × 180).

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