Autoimmune or infectious disease? That is the question

Sirs,

A 53-year-old man presented in our clinics with a 15-day history of purpura, arthritis and macroscopic haematuria. He was a non-smoker and teetotaler. He had a sister with vitiligo and a history of rheumatic fever with aortic and mitral valve replacement 2 years ago. Post-surgically, he was treated for staphylococcal sternotomy infection with antibiotics and surgical debridement, with no other complications since then.

On his presentation, he was afebrile, he had loud metallic closing heart sounds, palpable purpura in his legs, peripheral oedema, ankle arthritis and a haemorrhagic lesion on his vestibule.

He had normochromic-normocytic anaemia, impaired renal function (creatinine: 3.2 mg/dl, 3 months ago: 0.7 mg/dl), hypoalbuminaemia and increased ESR (60 mm/h) and CRP (11.4 mg/dl). Electrolytes and liver function tests were normal. Urine microscopy revealed glomerular red blood cells >100/high power field (hpf), white blood cells: 2-3/hpf, 2 mixed casts/hpf and 300mg/dl of protein. Chest-x-ray and fundoscopy were normal.

He was being treated by a private physician with ciprofloxacin for a referred serous fluid sternotomy leaking and prednisolone (15 mg/day) for his purpura.

He was admitted with a working diagnosis of ANCA-associated Vasculitis (AAV) or a chronic infection (*e.g.* infective endocarditis). At day 1, transthoracic heart-echo was normal. Blood cultures were obtained, serous fluid extracted from his cheloid sternotomy scar was sent for culture and the patient was treated empirically with antibiotics. At day 2, antinuclear antibodies and rheumatoid factor came back negative, C3 and C4 levels were normal, but p-ANCA were positive (1/40, cut-off<1/20; anti-myeloperoxidase, anti-proteinase3: negative). Transesophageal heart-echo was normal, 24-hours urine protein was 2.2 gr and the patient received 1 gr of methylprednisolone, with a working diagnosis of AAV. Later at day 2 and day 3: fluid and two out of six blood cultures came back positive for *Staphylococcus aureus*. At day 5, a bone scan revealed sternum osteomyelitis and a renal biopsy was performed. Its findings were consistent with IgA-dominant *Staphylococcus*-associated glomerulonephritis (IASAG) (Fig. 1). The patient was treated with daptomycin (IV) and rifampicin (po) for 6 weeks and subsequently with vibramycin (po) and clindamycin (po) for 6 weeks. Sternum wires were also removed. Following treatment, his renal function was improved (creatinine: 0.9 mg/dl) and his purpura and arthritis were resolved.

IASAG is a recently recognised entity representing an overlap between IgA-dominant infection-associated glomurelonephritis (which can be caused by other pathogens, such as *Streptococcus* and *Klebsiella* (1)) and *Staphylococcus aureus*-associated glomerulonephritis (SAAG) (which could be also IgA-negative or pauci-immune), mimicking AAV (1-4).

S. aureus source can be skin/soft tissue infections, endocarditis, intra-abdominal infections, septic arthritis and others (2) and a proposed pathogenetic mechanism is that *S. aureus* enterotoxin acts as superantigen driving the immune-complex formation (1, 2, 4).

IASAG is usually found in older males with comorbidities such as diabetes mellitus, endocarditis and hepatitis C. Intravenous drug usage and central venous catheters are other known risk factors 2, 4). IASAG presents with – usually significant – proteinuria and haematuria, while purpura and low C3/C4 levels are found in about 25% of the patients (1, 2, 4).

ANCA are present in about 20% of SAAG patients and can be detected in infection-associated glomerulonephritis with or without endocarditis (5). As for AAV (6), their role and formation in the context of infections are not fully explained. Mechanisms proposed, include molecular mimicry, complimentary peptides, TLR-mediated formation and cryptic antigen release (7).

Renal biopsies in IASAG are characterised by mesangial and endocapillary hypercellularity, subepithelial humps and IgA and C3 deposition. IgG and κ/λ light chains can also be seen (1, 2, 4), while crescents

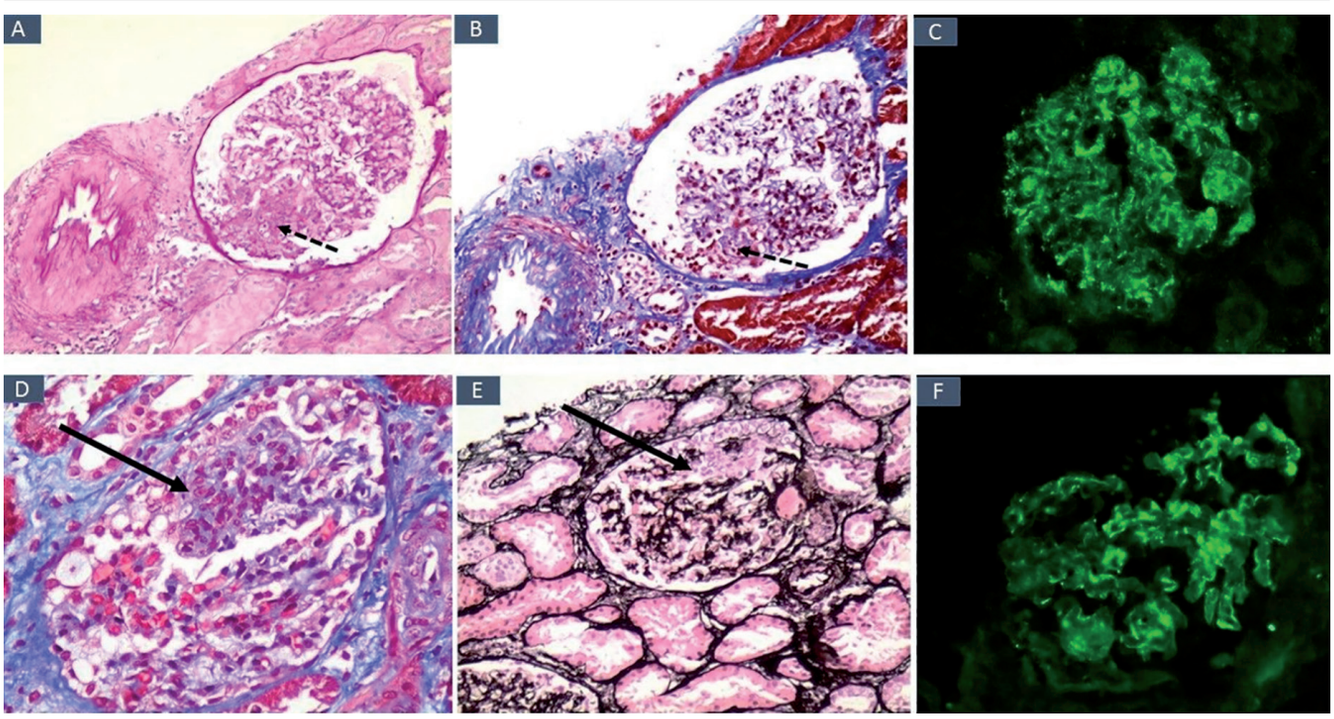

Fig.1. Renal biopsy findings. A glomerulus with segmental endocapillary hypercellularity (square dot arrow), PAS X 200 (**A**). The same glomerulus as in A, exhibiting a small cellular crescent overlying the segmental endocapillary proliferative lesion (square dot arrow), Masson's trichrome X 200 (**B**). Intense IgA immunofluorescence in the mesangial regions and along the capillary walls with a granular pattern (x200) (**C**). A glomerulus displaying mesangial and segmental endocapillary hypercellularity with an overlying cellular crescent (solid arrow), Masson x 400 (**D**). A glomerulus with a cellular crescent (solid arrow), JMS x 200 (**E**). Strong C3 immunofluorescence in mesangium and along the capillary walls with a granular pattern (x200) (**F**).

are found in about 30% of the cases (2, 8). IASAG is treated with antibiotics, while steroid use remains controversial (1, 2, 4).

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