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From the Clinic

ANCA-positive pauci-immune glomerulonephritis and febuxostat treatment

The approval of febuxostat, a non-purine analogue inhibitor of xanthine oxidase, by the European Medicines Agency and US Food and Drug Administration, heralds a new era in the treatment of gout [1]. The most commonly reported adverse drug reactions were liver function abnormalities, diarrhoea, headache, nausea, and dizziness and/or altered taste. Only one case of cutaneous leukocytoclastic vasculitis has been reported with febuxostat [2]. In this report, we provide the first case of anti-neutrophil cytoplasmic antibody (ANCA)-positive pauci-immune glomerulonephritis (PIGN) during febuxostat treatment.

A 63-year-old African man was hospitalized for acute kidney injury (AKI). He was a known hypertensive patient controlled on calcium channel inhibitors who had a six-month history of allopurinol-uncontrolled chronic asymptomatic hyperuricaemia. Allopurinol was stopped in June 2011 with normal renal parameters (serum creatinine, 0.80 mg/dL [70.4 µmoL/L], negative urine albumin and bland urine sediment) at this date. He had begun treatment with febuxostat in July 2011. In December 2011, he developed AKI characterized by acute renal failure (serum creatinine 2.47 mg/dL [217.36 µmoL/L]); nephrotic syndrome (serum albumin, 1.7 g/dL [17 g/L], proteinuria, 6 g per 24 h), microscopic haematuria (500RBC/hpf) and aseptic leukocyturia (50WBC/hpf). Constitutional symptoms, arthralgias and skin findings were not present. There was no eosinophilia or evidence of hemolysis. Tests for cryoproteins, rheumatoid factor, hepatitis B and C virus antibodies and HIV antibodies were all negative. Measurements of serum complement components and serum immunoelectrophoresis were within normal limits. On ultrasonography, both kidneys were slightly enlarged.

Febuxostat was stopped. Within 48 h of discontinuation of the drug, the nephrotic syndrome remained although serum creatinine improved to 2.27 mg/dL [199.75 µmoL/L]. High concentrations of antimyeloperoxidase (anti-MPO) pANCA type ab (768 IU) and anti-DNA (1/640 IU) type ab were noted. Native anti-DNA and anti-Sm antibodies were negative. A percutaneous renal biopsy was performed, which revealed diffuse crescentic necrotizing glomerulonephritis (Figure 1), no mesangial proliferation and negative immunofluorescence, consistent with ANCA-positive PIGN. Methylprednisolone pulse (500 mg/day) was given for 3 days, followed by institution of prednisone 1 mg/kg body weight/day and an IV dose of cyclophosphamide (1000 mg) was given at this stage.

The aetiology of this ANCA-positive PIGN case remains unknown. The triggers for ANCA-positive vasculitis are largely unknown. In a minority of cases, however, the disease appears to be medication-induced [3]. We are not aware of any previous reports linking febuxostat to ANCA-positive PIGN. However, the temporal relationship between the febuxostat therapy and the onset of clinical signs of renal disease, the higher titre of anti-MPO pANCA antibodies [3] as reported with several other drugs in the literature [4] were suggestive of a drug-induced disease. The evidence is considered sufficient to make it unethical to reintroduce febuxostat even if high MPO-ANCA binding levels do not exclude a conventional 'idiopathic' ANCA vasculitis.

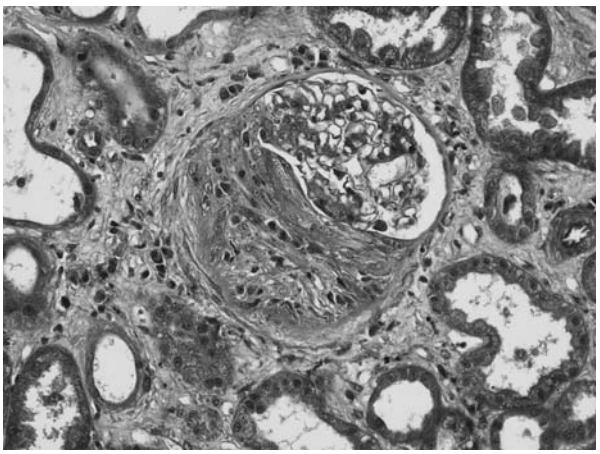

Fig. 1. Crescentic glomerulonephritis with fibrocellular crescent formation and collapsed glomerular tuft.

Patients being administered such a drug should be tested for ANCA.

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