ANCA-positive IgA nephropathy in a patient with ANA-positive long-standing rheumatoid arthritis and type 1 diabetes

Sirs,
a 40-year-old woman has been under care for severe anti-citrullinated protein antibody (ACPA)-positive rheumatoid arthritis (RA) at our clinic for 18 years. She received different synthetic and biologic disease modifying anti-rheumatic drugs (methotrexate, leflunomide, adalimumab) with either insufficient response or intolerable side effects. In 2017, a monotherapy with tofacitinib was initiated, leading to complete disease remission. From the medical history, a type 1 diabetes mellitus was known since childhood. To date, insulin is applied using an insulin pump.

During a routine blood sampling in 2019, creatinine was found to be more than three times elevated (52 → 173 mmol/l, eGFR according to CKD-EPI at 31 ml/min/1.73 m²), indicating acute kidney injury (AKI) stage 3 (1). In addition, urea was slightly above the upper normal value (9.8 mmol/l), C-reactive protein (CRP) was increased (35.24 mg/l) and a blood cell count exhibited normochromic anaemia (haemoglobin 10.0 g/dl). The patient’s history and clinical examination revealed a poor general condition, fatigue and a weight increase of 3 kg within the last two weeks. The blood pressure at the subsequent hospital admission was 189/99 mmHg and urine analysis showed new onset proteinuria of 734 mg/day (albumin 429.2 mg/day, alpha1-microglobulin 28.1 mg/day, immunoglobulin G 52 mg/day) with detection of some leukocytes as well as dysmorphic erythrocytes without macrohematuria. Suspecting rapid-progressive glomerulonephritis, we performed additional laboratory testing. According to the international consensus on testing of anti-neutrophilic cytoplasmic antibodies (ANCA) (2), we firstly used enzyme-linked immunosorbent assays (ELISA) to detect myeloperoxidase (MPO) or proteinase 3 (PR3) antibodies. The immunoassay was positive for MPO-ANCA (26.39 IU/ml). Indirect immunofluorescence (IFT) for ANCA was though negative. Consequently, we considered an ANCA-associated vasculitis as being causative for the assumed glomerulonephritis. Of interest, anti-nuclear antibodies (ANA) were found to be highly positive (1:5120) with a low double-strand (ds) DNA antibody titre (20.6 IU/ml). Nucleosome antibodies were unsuspicious (15 U/ml) and screening for extractable nuclear antigens was negative.

To confirm an ANCA-associated vasculitis (AAV), a kidney biopsy was performed after informed consent. Histopathological workup not only showed 50 % crescents, but also mesangial IgA deposits (Fig. 1).

Fig. 1. (A) Kidney biopsy of the young patient exemplarily showing one glomerulus with fibrinoid necrosis and crescent formation with peri-glomerular accumulation of leukocytes (A) and one glomerulus with positive IgA stain (B). HE – x20.

(B) Granular IgA staining in the glomerular mesangium – x40

Due to the coincidence of MPO positivity, crescents and deposition of IgA, we wondered whether an ANCA-associated vasculitis or an IgA nephropathy with ANCA positivity (3) was the underlying disease. The etiological interpretation was further complicated by ANA and dsDNA antibody positivity. Taking the long-standing, highly ACPA-positive RA and the type 1 diabetes into account, the accumulation of autoimmune phenomena was even more puzzling. The ANA and dsDNA antibody positivity could be explained by the former use of adalimumab which is known (besides other TNF inhibitors) to possibly induce ANAs as well as dsDNA antibodies without pathogenic relevance (4). Nevertheless, the patient still exhibits at least three autoimmune diseases not belonging to the known patterns of the multiple autoimmunity (5) or the polyglottalicular autoimmune syndromes (6). Since we cannot proof a connection between these diseases, this accumulation also could be random. The entity of an ANCA-positive IgA nephropathy (IgAN) has been described before (3, 7, 8). It seems to be a rather rare condition and the patients tend to be older than in ANCA-negative IgAN. Furthermore, ANCA-positive IgAN takes a more severe course regarding systemic disease features (3, 7). Banis et al reported a worse kidney function at presentation with a more severe deterioration in kidney function during the first three months in ANCA-positive (n=8) compared to ANCA-negative (n=26) IgAN. In contrast, Yang et al showed a better renal outcome (i.e. the prevention of end-stage renal disease) for ANCA-positive crescentic IgAN (n=20) compared to ANCA-negative crescentic IgAN (n=40) after six months (7). The histological features also tend to differ with ANCA-positive IgAN exhibiting fibrinoid necrosis significantly more often than ANCA-negative IgAN (7). Notably, in the study of Yang et al., 30 % of ANCA-positive IgAN patients showed ANA positivity and four out of 20 patients had a coincidental RA (7).

Taking the findings together (AKI, renal...
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