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 m^2), 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 macrohaematuria. Suspecting rapid-progressive glomerulonephritis, we performed additional laboratory testing. According to the international consensus on testing of anti-neutrophilic cytoplasmic antibodies (ANCAs) (2), we firstly used enzyme-linked immunosorbent assays (ELISA) to detect myeloperoxidase (MPO) or proteinase 3 (PR3) antibodies. The immunoassay was positive for MPO-ANCAs (26.39 IU/ml). Indirect immunofluorescence (IFT) for ANCAs though was 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).

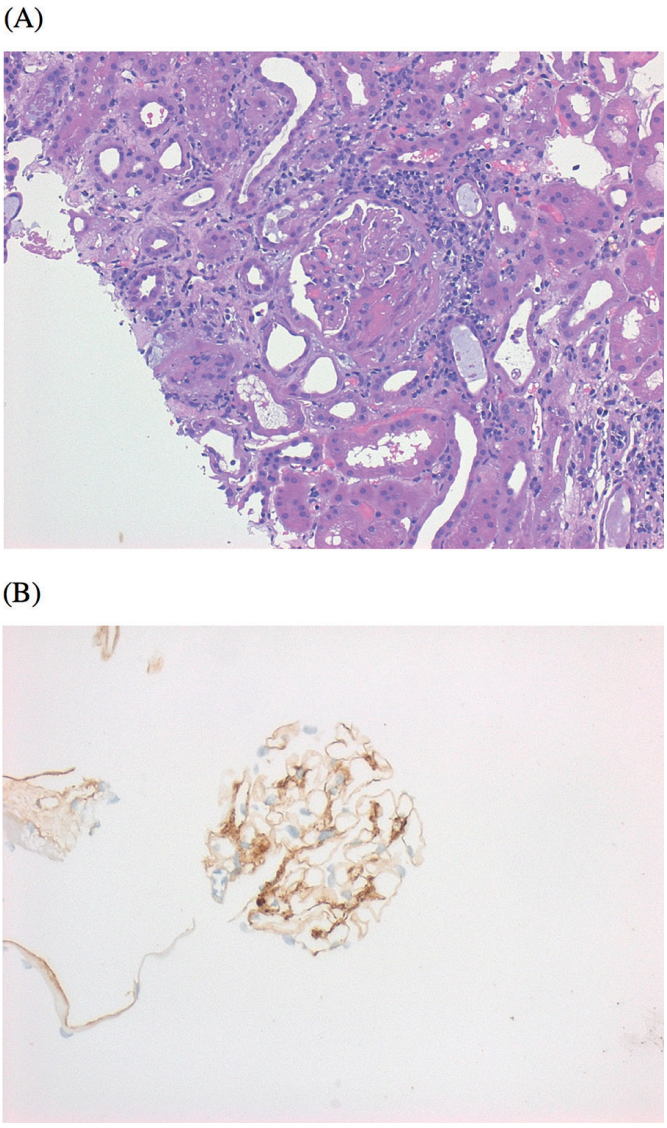

Fig. 1. A: Kidney biopsy of the young patient exemplarily showing one glomerulus with fibrinois necrosis and crescent formation with peri-glomerular accumulation of leukocytes (**A**) and one glomerulus with positive IgA stain (**B**).
HE – x20.

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 aetiological 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 autoimmune (5) or the polyglandular 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). Bantis *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

crescents, positive IgA stain in the glomerular mesangium and MPO-ANCA positivity), we diagnosed an ANCA-positive IgAN. The MPO titre was rather low, but ≥ four times the upper limit which has been demonstrated to be a reasonable cut-off point for diagnosing AAV (9). The origin and relevance of both, ANAs and dsDNA antibodies, remains elusive. However, as outlined above, we hypothesise an autoantibody induction caused by the former adalimumab therapy. In the light of the established diagnose, the coincidence of the multiple autoimmune diseases within our patient was interpreted as being random.

Consequently, treatment to induce remission was initiated using oral prednisolone (1 mg/kg) and rituximab (RTX) (375 mg/m^2) according to the RAVE (10) and RITUXVAS trials (11). RTX is a known option for adult-onset IgA vasculitis, too (12). Our decision was also driven by the underlying RA (RTX has been shown to be highly effective in RA therapy) and the relatively young age of this female patient (potential risk of ovarian failure and secondary haematologic malignancy under cyclophosphamide therapy). Cotrimoxazole was prescribed for pneumocystis jiroveci pneumonia prophylaxis as long as applying prednisolone >15 mg qd. Since the results of the PEXIVAS trial, published in 2018 in abstract form, showed no favourable outcome regarding renal function after plasma exchange (PLEX), PLEX was not used as an additional treatment (13). Following the induction therapy, prednisolone was tapered to 5 mg per day. The renal function slightly improved to an eGFR of 47 ml/min/1.73 m^2 while MPO-ANCAs significantly decreased to 2.25 IU/ml.

Fortunately, RA remained in stable clinical remission under well-tolerated RTX maintenance therapy every 6 months (14). In this context, RTX has been shown to be cost-effective for maintenance treatment (15).

The presented case emphasizes the difficulties arising from multiple autoimmune phenomena (RA, ANCA-positive IgAN and type 1 diabetes mellitus) in one patient. Rheumatologists should always be open-minded for the possibility of another autoimmune disease, even though such coincidences do not appear very often.

All procedures performed in this survey were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Data obtained in this study did not interfere with the course of treatment for patients included.

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