Case Report

Severe non-proliferative lupus nephritis with predominant sub-endothelial IgA deposits

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Introduction

Systemic lupus erythematosus (SLE) involves the kidney in a large majority of patients with a spectrum of glomerular pathology. It has been suggested that a renal biopsy be performed in all SLE patients even in the absence of overt renal involvement, to classify the biopsy following the World Health Organization (WHO) recommendation and to treat those with proliferative glomerulonephritis [1–3]. Here we report the case of a girl suffering from SLE with a nephrotic syndrome. The renal biopsy findings showed an unusual form of non-proliferative lupus nephritis characterized by predominant large subendothelial deposits of IgA. Despite immunosuppressive therapy the patient developed end-stage renal failure 1 year later.

Case

A 12-year-old girl was referred to our renal clinic because of persistent fatigue, malaise, arthralgia, and oedema during the previous 2 months. Her past history was unremarkable. On examination there was a facial erythema and the major joints showed swelling and tenderness. She presented generalized oedema, fever, and splenomegaly. Her blood pressure was normal.

White blood count was 7.1 x 10⁷/l, haemoglobin 6.3 mmol/l, haematocrit 29%. Erythrocyte sedimentation rate was 60 mm/h. Chemistry values showed blood urea nitrogen 14 mmol/l, creatinine 50 μmol/l, and albumin 26 g/l. Creatinine clearance was 110 ml/min/1.73 m². Electrolytes and liver enzymes were normal. The serological examination revealed circulating IgG 15.80 g/l (normal range 5.2–15.6 g/l); IgM 2.85 g/l (normal range 0.28–2.4 g/l); IgA 3.30 g/l (normal range 0.70–3.60 g/l); IgAI 3.18 g/l (normal range 0.65–2.9 g/l); IgA2 0.14 (normal range 0.10–0.51 g/l) as well as a dramatic decrease of serum complement levels (C1q 20 kiloUnits/l, normal range 88–128 kiloUnits/l; C3 0.18 g/l, normal range 0.9–1.89 g/l; C4<0.06 g/l, normal range 0.1–1.89 g/l). Antinuclear antibody was strongly positive (anti dsDNA antibodies by Farr assay 14400 IU/ml). By immunofluorescence, IgG, IgM, and IgA anti dsDNA antibodies were detected. IgG and IgM anticardiolipin antibodies were also present. Urine examination revealed a proteinuria in the nephrotic range (4.8 g/24 h). The sediment contained 0–3 red cells and 5–10 white cells per high-power field. Radiographs of the chest were normal. The clinical manifestations in combination with antinuclear antibodies (anti-native DNA antibodies) and hypocomplementaemia were diagnostic for SLE. Since the histological type of lupus nephritis may not be predicted with certainty on the basis of the clinical and laboratory findings, a renal biopsy was performed in order to establish the adequate therapy.

By light microscopy, all glomeruli showed massive PAS-positive, homogeneous hyaline material in sub-endothelial position resembling diffuse wire-loops (Figure 1A). Focally in the silver staining, the formation of subendothelial spikes was observed (Figure 1B). Surprisingly, no significant proliferation or influx of inflammatory cells was present. Along this line, there was neither extracapillary proliferation nor fibrinoid necrosis. In the interstitium, a mild inflammatory infiltrate mixed with a large amount of apoptotic bodies was focally present. Immunofluorescence staining revealed ribbon-like deposition of IgA without C3 in subendothelial location (Figure 1C) whereas IgM and C1q were predominantly seen in mesangial areas. Staining for IgG and

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C3 (Figure 1D) was chiefly positive in subepithelial positions. Electron microscopy confirmed these findings. Massive electron-dense deposits were found in subendothelial positions in combination with sparse and small subepithelial deposits (Figure 1E). Numerous spikes were observed at both sides of the glomerular basement membrane and diffuse effacement of the podocytes was also present. The electron-dense deposits did not display a particular ultrastructure. As frequently seen in lupus nephritis tubuloreticular inclusions were present in endothelial cells. Altogether this patient suffered from lupus nephritis characterized by predominant diffuse subendothelial deposits of IgA with a positive immune reaction for IgG and C3 restricted to the subepithelial position in the absence of significant cellular proliferation or inflammation.

Despite the absence of proliferative changes, this unusual case of lupus nephritis has to be considered as a class IV lupus nephritis of the WHO classification (see Discussion) and has therefore to be treated aggressively. Because of the young age of the patient and the normal renal function, azathioprine was preferred to cyclophosphamide. The patient received three pulses of methylprednisolone (one per day for
3 days) followed by a combination of prednisone at a dosage of 20 mg/day and azathioprine (80 mg/day). Eight days after the start of the therapy, the patient was discharged in good condition. She was re-hospitalized for a new administration of three methylprednisolone pulses (according to the treatment protocol of our institution) and discharged again. Prednisone and azathioprine were continued at the same dosage. Serum C3 increased progressively without complete normalization (maximum level 0.89 g/l), whereas C4 finally normalized (0.10 g/l). Anti-DNA antibody levels rapidly decreased and normalized after 1 month of treatment. However, proteinuria remained higher than 5 g/24 h and hypoalbuminaemia persisted. Therefore enalapril was added to the immunosuppressive treatment but still without success in normalizing serum albumin (maximum level 30 g/l). Six months after commencing therapy the patient presented with a flare up (skin rash, diminished C3, and increased anti-dsDNA antibody levels), which was successfully treated by temporarily increasing the daily prednisone dosage to 40 mg/24 h. However, proteinuria remained important and hypoalbuminaemia persisted. One year after the initial biopsy, the patient developed end-stage renal failure. A second renal biopsy was performed and showed extensive glomerulosclerosis and tubulo-interstitial damage (WHO class VI). Haemodialysis was started.

Discussion

From this observation, different questions arise. Firstly, how to classify and to treat this patient? The pathological distinction between proliferative and membranous lupus glomerulopathies should be straightforward because it determines the mode of treatment and the renal prognosis. According to the recommendations of Churg et al. [4] class IV lupus nephritis is defined by diffuse distribution of subendothelial deposits regardless of the pattern of proliferation. Therefore this unusual case of lupus nephritis should be considered as a class IV lupus nephritis, because the substantial subendothelial deposits dominated the histological picture, even though numerous subepithelial deposits were seen and significant proliferation was absent. Patients with lupus nephritis combining subendothelial deposits with membranous features at renal biopsy have a poor prognosis, even worse than uncomplicated diffuse proliferative lupus nephritis, and must be treated as having class IV nephritis. The presence of large subendothelial deposits of immunoglobulins without activation of the complement system and proliferation is exceptional. In order to support the decision to treat this young patient aggressively, the renal biopsy was stained for the TNF family member CD134 ligand (CD134L) and for TNF receptor 1 (TNFR1). Recently, a strong and selective glomerular localization of CD134L and TNFR1 was found in proliferative lupus nephritis (WHO class IV) but not in any other classes [5]. The distribution of CD134L and of TNFR1 was similar to that of the immune complexes. Our case of lupus nephritis showed significant staining for CD134L as well as for TNFR1, mainly in subendothelial locations (Figure 1F). These results support the diagnosis of lupus nephritis class IV.

Secondly, what may be the pathogenesis of this lupus nephritis with predominant IgA deposits? The IgA subclasses were measured in the serum of our patient at different time points and were not abnormal (before treatment, IgA 3.30 g/l, normal range 0.70–3.60 g/l; IgA1 3.18 g/l, normal range 0.65–2.9 g/l; IgA2 0.14, normal range 0.10–0.51 g/l). We analysed the protein profile as well as the molecular size distribution of IgA by gel filtration using high-pressure liquid chromatography. Except for the albumin peak, the profiles of the serum proteins were comparable to those observed in healthy controls. Moreover, as in control sera, the IgA fraction was essentially composed of monomers of IgA. We looked for the specificity of the serum IgA. A positive reaction of IgA to dsDNA was found by immunofluorescence before steroid treatment, but disappeared rapidly. In IgA nephropathy and in lupus nephritis the presence of IgA reactive to endothelial cells has been observed and correlated with the severity of the disease [6,7]. This may be also the case in our patient. As in IgA nephropathy, the deposited IgA was almost completely restricted to the IgA1 subclass. In ‘conventional’ lupus nephritis deposits consist of IgA1 as well as IgA2. It has been proposed that under-galactosylated IgA1 could directly deposit in the mesangium and subsequently interact with C3 in IgA nephropathy [8]. However, at this time, substantial experimental evidence to support these hypotheses for IgA1 deposition is lacking. Moreover, this hypothesis does not elucidate the preferential distribution of IgA in subendothelial areas in the present case, and the lack of co-localization with C3 staining. As stated above, the relative absence of C3 in subendothelial areas explains the absence of inflammation.

Finally, is this case of lupus nephritis with predominant IgA deposits unique? To our knowledge, there is no other description in the literature of lupus nephritis characterized by preferential deposition of IgA. A few cases of patients with a well-established clinical diagnosis of SLE in whom the renal biopsy findings are diagnostic for IgA nephropathy have been reported [9,10]. In all these cases the renal biopsy showed a mild mesangial hypercellularity with almost exclusively deposits of IgA and C3 in the mesangium, a completely different phenotype from our case. Moreover, the follow-up confirmed a rather indolent renal disease.

In conclusion, this patient may represent a rare case of severe non-proliferative lupus nephritis with predominant subendothelial IgA deposits, which illustrates the value of classifying the biopsy as a class IV lupus nephritis on the basis of immune-deposit localization, despite the absence of proliferation.
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References

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