

Clinical Report

Membranous nephropathy with repeated flares in IgG4-related disease

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Abstract

IgG4-related disease (IgG4-RD) is associated with the infiltration of IgG4-positive plasma cells into various organs. Nephropathy of IgG4-RD is generally interstitial nephritis and glomerulonephritis is rare. We describe a case of membranous nephropathy (MN) without interstitial nephritis associated with IgG4-RD symptoms including lymphadenopathy and pulmonary and pleural lesions. Treatment with steroids improved these clinical symptoms, but withdrawal of steroids induced the repeated relapse of MN. Finally, flaring of MN was prevented by the combination of steroids and cyclosporine. This is the first report of the successful treatment of MN associated with IgG4-RD by this combination therapy.

Keywords: cyclophosphamide; cyclosporine A; flares; IgG4-related disease; membranous nephropathy

Background

IgG4-related disease (IgG4-RD) is characterized by an elevated serum IgG4 level and the infiltration of IgG4-positive plasma cells into various organs. With regard to renal involvement, interstitial nephritis is mainly observed in patients with IgG4-RD [1, 2]. Recently, glomerular lesions in IgG4-RD have been reported, although such reports are still scarce [1, 3–5]. We describe a patient with IgG4-RD who developed membranous nephropathy (MN) with repeated flares but who was successfully treated with a combination of a steroid and cyclosporine A (CyA).

Case report

In August 1999, a 50-year-old Japanese man with a 6-month history of bilateral submandibular and lacrimal gland enlargement was admitted to our hospital. The serum concentration of IgG was elevated to 6227 mg/dL, whereas antinuclear antibody and SS-A/B antibodies were negative. The histological features of a submandibular gland specimen revealed acinar atrophy, infiltration of ductal lymphocytes and plasmacytes and focal fibrosis, which suggested chronic sialadenitis. Chest-computed

tomography revealed interstitial pneumonia, pleural effusion and thickening and enlargement of mediastinal and hilar lymph nodes. Pathological findings of the mediastinal lymph node biopsy included lymphoplasmacytic infiltration and lymphoid follicular hyperplasia. The lung specimen obtained by a video-associated thoracic surgery revealed lymphoplasmacytic infiltration in the alveolar interstitium around the bronchi and artery. Since other diseases could be excluded because of the negative findings, we made a diagnosis of lymphoproliferative disorder including Mikulicz disease and started prednisolone (PSL) at 40 mg/day. Steroid therapy was effective for improving these symptoms and PSL was maintained at 10 mg/day.

In August 2004, pretibial and eyelid edema were observed. Laboratory findings were as follows: albumin 1.7 g/dL, creatinine (Cr) 0.87 mg/dL, IgG 1273 mg/dL and IgG4 447 mg/dL. Urinalysis showed the following data: 20–50 red blood cells/high-power field, the presence of poikilocyte and granular casts, protein 11.019 mg/gCr (9.4 g/day), *N*-acetyl- β -D-glucosaminidase 16.6 mg/gCr and α -1-microglobulin 28.0 mg/gCr. A renal biopsy was performed (Figure 1A–C). The specimen for light microscopy contained eight glomeruli, which was almost unremarkable. Infiltration of inflammatory cells, fibrosis and tubular injury were not shown in the interstitium. A routine immunofluorescence study revealed diffuse and global IgG and C3 deposition along the glomerular

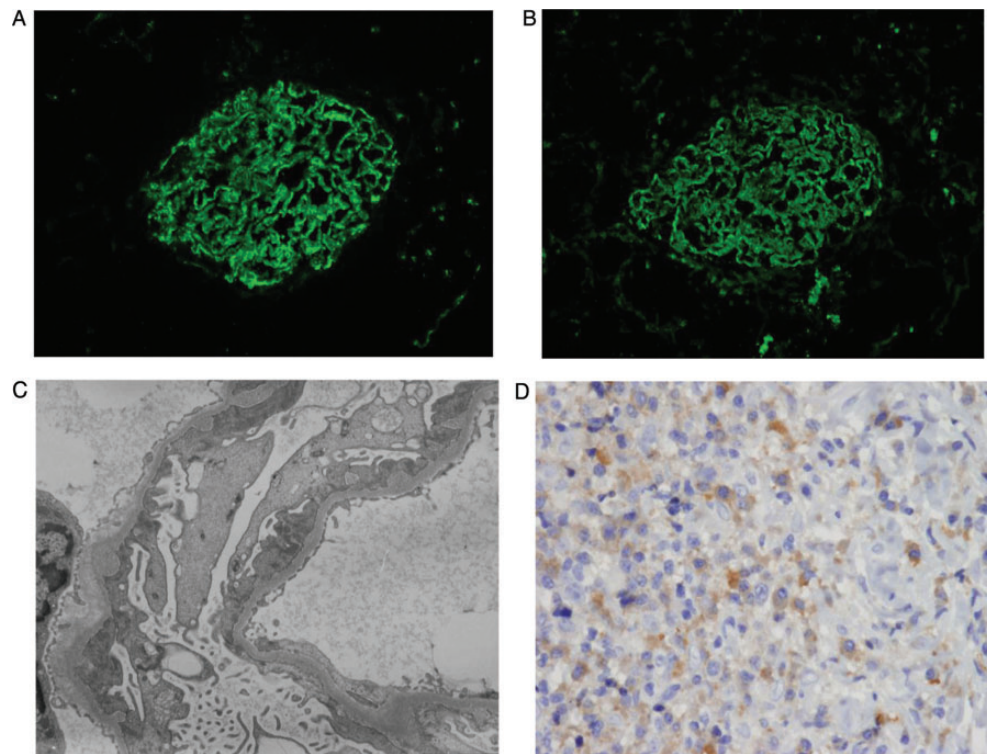


Fig. 1. Pathological findings of specimens obtained by renal (A–C) and pleural (D) biopsy. (A) Immunofluorescence of IgG1 staining, (B) immunofluorescence of IgG4 staining, (C) electron microscopy and (D) immunohistochemistry of IgG4 staining (magnification $\times 400$).

capillary walls. In addition, immunofluorescence staining for IgG1 and IgG4 showed granular global positivity in a capillary wall distribution. Electron microscopy showed electron-dense subepithelial deposits on the glomerular basement membrane and tubular basement membranes. We also performed immunohistochemical staining of the pleural specimen that had been obtained 5 years before and found a strongly positive staining of IgG4 (IgG4-positive/IgG-positive cells $>60\%$) on the cytoplasm of infiltrated plasma cells (Figure 1D). Moreover, a strongly positive staining of IgG4 (IgG4-positive/IgG-positive cells $>80\%$) was observed in fat tissue surrounding the kidney. Therefore, we changed the diagnosis to MN associated with IgG4-RD. He was treated with intravenous pulse methyl-PSL therapy followed by oral PSL at 60 mg/day. Six weeks later, cyclophosphamide was added at 100 mg/day because of worsening proteinuria. He achieved complete remission (CR) of MN, defined as decreased urinary protein excretion to ≤ 0.2 gCr with normalized serum creatinine 5 months later. At the same time, cyclophosphamide was stopped because of alopecia, and only PSL at 5 mg/day was continued.

In May 2008, he developed a flare of MN with increased proteinuria at 2150 mg/gCr (2g/day) and an elevated serum IgG4 level (414 mg/dL). However, flares of extra-renal lesions were not observed. We increased the dose of PSL to 30 mg/day and started CyA at 150 mg/day. After 4 months, CR of MN was achieved and treatment was maintained with PSL at 5 mg/day and CyA at 150 mg/day (trough blood concentration of CyA: 100–200 mg/dL).

In June 2010, he developed sepsis and pneumonia due to *Streptococcus* infection and CyA was discontinued. The nephrotic syndrome relapsed after 1 month, but extra-renal lesions did not relapse. The combination of PSL,

increased to 30 mg/day, with CyA was effective and CR was achieved 5 months later. He has remained in CR with PSL and CyA (Figure 2).

Discussion

MN is a rare renal manifestation of IgG4-RD [1, 3–5]. The histological characteristics of MN in IgG4-RD include strongly positive IgG4 staining on infiltrated plasma cells and diffuse staining of glomerular capillary walls or tubular basement membranes. However, the relationship between glomerular lesions and IgG4-RD is poorly understood. The predominant IgG4 staining in the glomerular capillary walls is similar to the immunofluorescence pattern of idiopathic MN [6]. In addition, the predominance of T-helper (Th) 2 cytokines in both idiopathic MN and IgG4-RD has been reported [6]. Zen *et al.* [7] demonstrated that IgG4-related pancreatitis is characterized by an immune reaction that is mediated predominantly by not only Th2 cells but also Foxp3+ regulatory T cells (T_{reg} s). Recently, interleukins (IL)-4 secreted by Th2 cells and IL-10 secreted by Foxp3+ T_{reg} s have been reported to induce the differentiation of B cells to produce IgG4 [8].

The next question is whether MN associated with IgG4-RD is 'primary MN' or 'secondary MN'. Recently, M-type phospholipase A2 receptor (PLA2R) was identified as a target antigen in idiopathic MN, but not in secondary MN. The sensitivity and specificity of positive serum anti-PLA2R antibodies were reported to be >75 and 100%, respectively [9, 10]. Fervenza *et al.* [4] did not detect circulating anti-PLA2R antibodies in any of their patients with MN associated with IgG4-RD, which suggested that

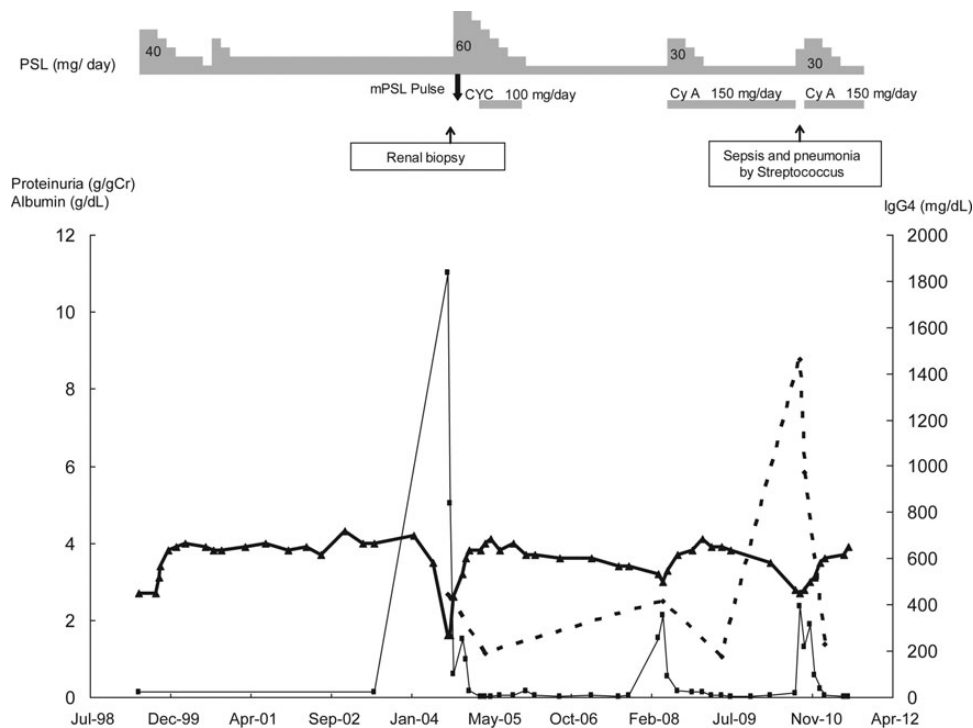


Fig. 2. Changes in serum albumin levels (bold line and triangles), proteinuria (thin line and squares) and serum IgG4 level (dashed line and diamonds) since the first clinical signs of IgG4-related systemic disease. CYC, cyclophosphamide; CyA, cyclosporine A.

it is secondary MN. Therefore, the examination for anti-PLA2R antibodies may be useful to distinguish primary and secondary MN. Unfortunately, the recombinant PLA2R that is required to detect PLA2R antibodies by western blotting was not commercially available and therefore it was impossible to test for the presence of PLA2R antibodies in the current patient. However, we considered that the patient had secondary MN, since the other symptoms of IgG4-RD preceded the development of MN by 5 years and the infiltration of most IgG4-positive cells was observed in fat tissue surrounding the kidney. The probability of coincidental development of primary MN in patients with IgG4-RD is extremely rare considering the incidence of these diseases.

The natural course of idiopathic MN can be variable. About one-third of the patients achieve spontaneous remission, another third remain active with fluctuating proteinuria, and the remaining third progress to end-stage renal disease (ESRD) [11]. Several reports with a follow-up duration of more than 10 years reported that 50–60% of untreated patients died or progressed to ESRD [12]. Therefore, patients with risk factors for progression to ESRD, such as a presence of interstitial lesions at initial renal biopsy, renal insufficiency at presentation and the magnitude and persistence of proteinuria, should be treated with steroids and immunosuppressive agents [11]. Two regimens have been shown to be superior to steroids for the treatment of idiopathic MN in randomized controlled trials: the Ponticelli regimen of six alternating months of steroid and alkylating agents and the Cattran regimen of low-dose steroids and cyclosporine [11]. However, only the Ponticelli regimen protected renal function [11]. On the other hand, IgG4-RD generally shows a good response to steroid treatment [12]. However, the relapse rate is ~30% and refractory or

recurrent IgG4-related pancreatitis usually requires treatment with immunosuppressive agents [12]. In this case, we first started a treatment with PSL but after failure of this treatment, we added cyclophosphamide. Although the combination of PSL and cyclophosphamide induced remission of MN that persisted for 4 years, we could not continue cyclophosphamide because of a side effect, and therefore we next used CyA based on the Cattran regimen. The combination of CyA and PSL successfully prevented relapses. There was no correlation between the activity of nephrotic syndrome and the extra-renal manifestations at several relapses in this case. We considered that PSL at a maintenance dose was effective for extra-renal manifestations, but was not enough to suppress MN. This speculation is supported by the report of Watson *et al.* [3] that steroid therapy improved extra-renal manifestations but did not improve proteinuria in MN associated with IgG4-RD. With regard to the comparison between cyclophosphamide and CyA, we could not make a definitive conclusion, as the doses of steroid concurrently used with these agents were different.

In conclusion, we treated a patient who developed repeated relapses of MN without interstitial nephritis associated with IgG4-RD. The combination of a steroid and CyA was effective for the induction and maintenance of remission. In 2011, the guidelines for the diagnosis of IgG4-RD were proposed by the organizing committee comprising 35 IgG4-RD experts [13]. We have to verify these guidelines and accumulate reports on various treatments, including cyclophosphamide, cyclosporine and azathioprine. A prospective study is warranted to evaluate the efficacy of this combination therapy for patients with frequently relapsed IgG4-RD. In addition, the ideal duration of maintenance therapy should also be investigated in the future.

Conflict of interest statement. None declared.

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