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Exceptional Case

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Membranous nephropathy associated with immunoglobulin G4-related disease successfully treated with obinutuzumab

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ABSTRACT

Immunoglobulin G4 (IgG4)-releated disease is typically associated with interstitial nephritis, but rare cases of idiopathic membranous nephropathy as a renal manifestation have been described. Obinutuzumab was successfully used in refractory membranous nephropathy, but evidence for the treatment of IgG4-related disease with obinutuzumab is lacking. We report one patient's case with membranous nephropathy associated with IgG4-related disease who was treated with obinutuzumab following an anaphylactic reaction to rituximab. Obinutuzumab treatment resulted in a sustained complete remission of membranous nephropathy and a decrease of IgG4 to the normal range. This case demonstrates that membranous nephropathy associated with IgG4-related disease can be treated successfully with obinutuzumab.

Keywords: B lymphocytes, IgG4-related disease, kidney disease, membranous nephropathy

BACKGROUND

Renal manifestations of immunoglobulin G4 (IgG4)-releated disease are common and patients typically present with interstitial nephritis [1]. There have been few cases of IgG4-related disease associated with idiopathic membranous nephropathy reported so far [2]. Thus the diagnosis of IgG4-related disease is challenging and needs careful evaluation [1].

In most cases, IgG4-related disease is treated effectively with rituximab [3], showing response in 97% of patients [3]. However, only 42% of patients with high IgG4 levels achieve normal values [3]. Obinutuzumab has been reported as an alternative treatment in cases where rituximab was not able to induce clinical remission of idiopathic membranous nephropathy [4]. So far, no available evidence exists that obinutuzumab is effective in treating IgG4-related disease. We here in report on a patient's case with IgG4 disease-related membranous nephropathy who was successfully treated with obinutuzumab.

CASE REPORT

In May 2017, a 55-year-old male was referred to the hospital because of dyspnea and swelling of the lower extremities. Laboratory investigations showed increased levels of urinary albumin:creatinine ratio [ACR; 5601 mg/g (normal 0–30)] and urinary protein:creatinine ratio [PCR; 6421 mg/g (normal –110)] as well as serum IgG4 [8.369 g/L (normal 0.030–2.010)] elevation. Kidney function was within the normal range as depicted by the estimated glomerular filtration rate. Kidney biopsy showed

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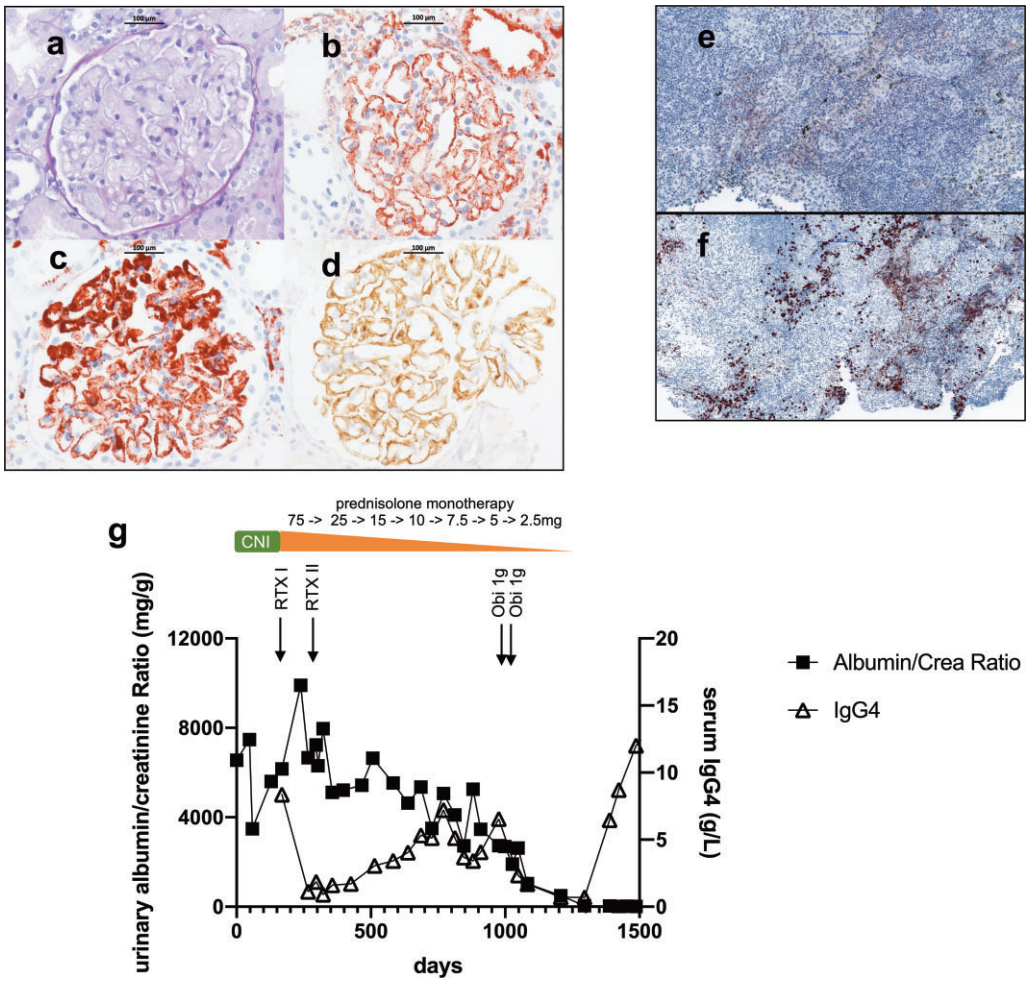

FIGURE 1: Histopathologic evaluation and laboratory findings of our patient. Histopathologic evaluation of the kidney shows (**a**) perimembranous nephropathy in periodic acid–Schiff–stained kidney sections with (**b**) IgG, (**c**) IgG4 and (**d**) PLA-2R positivity. Representative pictures are shown. Magnification ×200. (**e**) IgG and (**f**) IgG4 staining of lymph nodes show massive infiltration of IgG4-positive plasma cells and an $IgG4^+$:IgG^+ plasma cell ratio >40%. Representative pictures are shown. Magnification ×100. (**g**) Urinary albumin:creatinine ratio and serum IgG4 levels over the course of the disease are shown. The therapy was started using a CNI and prednisolone, followed by the first rituximab dose (RTX I, 860 mg) and the second reduced dose (RTX II, 430 mg), which needed to be stopped due to an anaphylactic reaction. We then continued with steroid monotherapy slowly tapering the dosage. 1 g obinutuzumab (Obi) was given twice, on day 1 and 15.

perimembranous nephropathy with IgG4 and phospholipase A2 receptor (PLA-2R) antibody positivity (Figure 1a–d). Anti-PLA-2R antibodies in the serum were negative. Thus idiopathic membranous nephropathy was diagnosed.

Radiological examination showed multiple enlarged bilateral mediastinal lymph nodes and well-circumscribed pulmonary nodules. Subsequently a mediastinoscopy and biopsy did not detect malignant cells. Immunohistochemical examination revealed a high expression of IgG4 in the lymph nodes and an $IgG4^+$:IgG^+ plasma cell ratio >40%, compatible with IgG4-related lymphadenopathy (Figure 1e–f).

Based on elevated serum IgG4 concentrations and clinical and radiological involvement of a typical organ (in our case kidneys and lung), the clinical diagnosis of IgG4-related disease was established according to the classification criteria of the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) [1].

Our patient was initially treated with a calcineurin inhibitor (CNI) and corticosteroids, but showed no signs of renal remission even though IgG4 levels initially decreased. Therefore treatment with rituximab was started but was not tolerated by the patient, causing an anaphylactic reaction.

In November 2019, our patient presented high levels of albuminuria (2700 mg/g) and the IgG4 concentration increased again (2.340 g/L), prompting us to start therapy with obinutuzumab (2 × 1000 mg on day 0 and 14; Figure 1g). Complete clinical and laboratory remission was reached. The patient did not show an allergic reaction or any other side effects to treatment with obinutuzumab. ACR, PCR and IgG4 serum concentration reached normal levels after the implementation of therapy (Figure 1g). Interestingly, serum IgG4 concentrations started to increase significantly 1 year after the obinutuzumab therapy without having an effect on ACR, which was still within the normal range.

DISCUSSION

Membranous nephropathy as a renal manifestation of IgG4-related disease is rare [2]. We here in report on one patient with membranous nephropathy as a renal manifestation of IgG4-related disease. Rituximab has been shown to be effective in IgG4-related disease [3] as well as in membranous nephropathy. Even though the patient received only a minimal dose of rituximab, due to anaphylaxis, IgG4 concentrations and albuminuria decreased. Obinutuzumab has several advantages

compared with rituximab. It is a humanized, type II anti-CD20 monoclonal antibody and has greater antibody-dependent cellular cytotoxicity, superior direct B-cell killing and less reliance on complement-dependent cytotoxicity than type I anti-CD20 antibodies such as rituximab [5]. The clinical superiority of obinutuzumab versus rituximab has been shown for lupus nephritis [6] and membranous nephropathy [4]. To our knowledge, data on the effectiveness of obinutuzumab in IgG4-related disease are lacking. We decided to treat our patient with 1 g obinutuzumab twice within 14 days according to the NOBILITY trial (NCT02550652) protocol [6]. Treatment with obinutuzumab resulted in a rapid and sustained complete response over >1 year of membranous nephropathy and an initial decrease of IgG4 levels to the normal range. Still, serum IgG4 levels significantly increased starting 1 year after the obinutuzumab therapy, which suggests that one course of obinutuzumab is not sufficient to reach long-term laboratory and clinical remission, thus repeated infusions as maintenance therapy are needed.

In conclusion, this case shows the rare combination of membranous nephropathy and IgG4-related disease and suggests that obinutuzumab is a possible alternative treatment of IgG4-related membranous nephropathy in cases where rituximab does not result in complete clinical or laboratory remission.

PATIENT CONSENT

This case report was approved by the Institutional Review Board of the Medical University of Graz, Austria (34-037 ex 21/22). The patient gave his informed consent for the study.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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