Scientific Research Publishing

Open Journal of Internal Medicine, 2024, 14, 329-336
https://www.scirp.org/journal/ojim
ISSN Online: 2162-5980
ISSN Print: 2162-5972

IgG4 Disease Revealed by Renal Damage: Report of a Series of Cases

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How to cite this paper: Konan, N.M., Sanou, P., Wognin, M.E.A., Ouattara, T.R., Koffi, G.S., Abbot, J.-F.L., Koffi, C.Z.R.M., Gonan, A.Y., Kpan, K.J., Yao, A.N.S., Tia, W.M., Kouamé, Y.H., Ouattara, B. and Rostaing, L. (2024) IgG4 Disease Revealed by Renal Damage: Report of a Series of Cases. *Open Journal of Internal Medicine*, **14**, 329-336.
https://doi.org/10.4236/ojim.2024.144029

Received: September 6, 2024
Accepted: November 10, 2024
Published: November 13, 2024

Abstract

IgG4 disease is an immune-mediated disorder characterized by fibroinflammatory masses that can infiltrate multiple organ systems. Renal involvement is considered one of the key features of this disease. Report 02 cases of IgG4 disease with renal manifestations revealing the disease such as extramembranous glomerulonephritis and tubulointerstitial nephritis rich in polytypic IgG4+ plasma cells. Associated renal parenchymal lesions concomitant with multiple organ involvement should help improve early recognition of IgG4-RKD disease (IgG4-RKD). In our case series, prednisone was the treatment of choice; the use of rituximab in extramembranous glomerulonephritis had resulted in remission of the disease.

Keywords

IgG4 Disease, Extramembranous Glomerulonephritis, Tubulo-Nephritis Interstitial, Corticotherapie, Rituximab

1. Introduction

IgG4 disease is a systemic disease identified by different organ specialists under many names (Mikulicz syndrome, Riedel thyroiditis, retroperitoneal fibrosis).

The incidence and prevalence of IgG4 disease are poorly known. It was in the early 2000s that the disease was identified in patients with autoimmune pancreatitis (AIP) [1]. It is often associated with an increase in serum IgG4 levels greater than 1.35 g/L. The histopathological appearance is that of an increase in the volume, sometimes pseudo-tumorous, of the affected organs and this is due to a lymphoplasmacytic infiltration with a predominance of IgG4-positive plasma cells and progressive fibrosis and lesions of thrombophlebitis obliterans [2]. Renal involvement is very common in IgG4 disease and is a hallmark of the disease; it is called IgG4-related renal disease (IgG4-RKD), which was first reported in 2004 [3]. The most common histological feature observed on renal biopsy is tubulointerstitial nephritis (IgG4-TIN); glomerular lesions have recently been described, including membranous nephropathy, membranoproliferative glomerulonephritis, and mesangial proliferative glomerulonephritis [4]. Here, we present two cases of IgG4 disease with multiple organ involvement but revealed by major renal involvement, namely extramembranous glomerulonephritis and tubulointerstitial nephritis; The first case was successfully treated with a combination of prednisone and rituximab and the second case was treated with prednisone alone.

2. Case Report

2.1. Case 1

80-year-old patient, whose reason for hospitalization was nephrotic syndrome associated with a deterioration in his general condition for about 2 months. Biology noted a pure deep nephrotic syndrome marked by massive proteinuria at 10 g/24 H. We also noted a normocytic aregenerative anemia, hypereosinophilia with eosinophilic PN at 1.9 Giga/l. The immunological assessment showed an increase in IgG4 to 14.6 g/l on immunophenotyping, a decrease in complement C3, antinuclear antibodies and rheumatoid factors came back strongly positive as well as cryoglobulinemia. Viral serologies were negative. The brain scan showed a thickening of the pituitary brain stem. A complete filling of almost all the sinuses. A bilateral type 1 exophthalmos by infiltration. The TAP scan had revealed thickening of the arterial walls of all supra-aortic trunks and the aorta associated with multiple moderate adenomegaly. Some irregularities of the slightly thickened bronchial walls with a calcified gallbladder stone of approximately 9 mm with significant infiltrative thickening of the pancreatic tail. The thickening of the aortic wall extends over the entire abdominal aorta of approximately 6 mm. Presence of 3 left renal stones with preservation of corticomedullary differentiation. The FDG-TEP/SCAN had revealed hyperfixation of the pancreas in its corporeo-caudal portion associated with adenopathies of the BARETY lodge and the hilum.

The renal biopsy was in favor of extra-membranous glomerulonephritis (EMG) associated with interstitial fibrosis and tubular atrophy of less than 25% of the cortical surface (**Figure 1** and **Figure 2**). Direct immunofluorescence (DIF) examination found pseudo-linear parietal deposits of IgG, lambda and C3. Following these clinical and paraclinical data, the diagnosis of an IgG4 disease with

multiple organ involvement, including renal, bronchial, hepatic, pancreatic and cerebral. The patient had received corticosteroid therapy based on Cortancyl 1 mg/kg then decreased according to the response to treatment associated with adjuvant measures to corticosteroid therapy. The evolution had been favorable after the association of rituximab with D1, D15 continued according to the protocol in force.

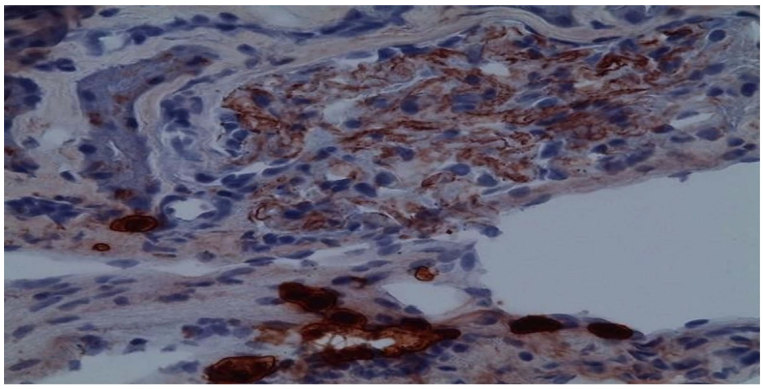

Figure 1. Segmental and focal extramembranous granular deposits.

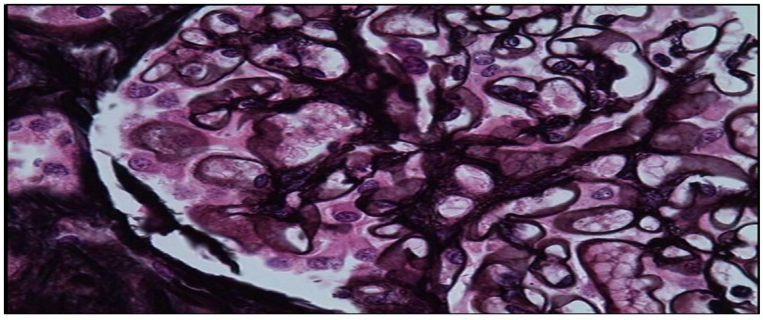

Figure 2. GEM spicules with Jones silver impregnation.

2.2. Case 2

72-year-old patient admitted to hospital for a deterioration in his general condition in a context of asthenia, weight loss with loss of 7 kg in one month and episodes of diarrhea. Biology noted an alteration of renal function with a creatinine level of 175 µmol/l with GFR of 25 ml/min/1.73 m^2 associated with a low 24-hour proteinuria estimated at 0.28 g/24 on 900 ml of urine. We also noted moderate anemia at 9.8 g/l, a collapse of complement C3 at 0.29 g/l; C4 at 0.2 g/l and CH50 < 10%, polyclonal hypergammaglobulinemia with IgG at 36.20 g/l with IgG4 at 7.663 g/l. The autoimmune assessment was negative. The renal biopsy had highlighted in direct immunofluorescence (DIF) an absence of glomerular deposits of immune complexes. Histopathological lesions of the type of severe and diffuse tubulointerstitial nephritis rich in polytypic IgG4+ plasma cells (**Figure 3** and **Figure 4**). In addition, the TAP scanner had highlighted poly-adenopathies above and below the diaphragm with pulmonary nodules. The FDG-TEP/SCAN had

shown intensely hypermetabolic poly adenopathies above and below the diaphragm, splenic and pancreatic hypermetabolism, hypermetabolism of several of the pulmonary nodules, intense parotid and left submaxillary fixation, hyperfixation of the rectosigmoid hinge of the vaginal region. Given these clinical and paraclinical arguments, the diagnosis of an IgG4 disease with renal involvement associated with multiple organ involvement (kidney, spleen, pulmonary pancreas, parotid) was retained. He had benefited from corticosteroid therapy (Cortancyl) at a rate of 1 mg/kg then decreased according to the response to treatment with adjuvant measures.

The evolution was marked by the occurrence of an acute coronary syndrome complicated by cardiogenic shock treated medically, the normalization of the complement, of the serum dosage of IgG4 after 03 months of management. An improvement in renal function was noted with creatinine at 106 µmol/l against 175 µmol/l at the beginning of the disease but persistence of the urinary sediment.

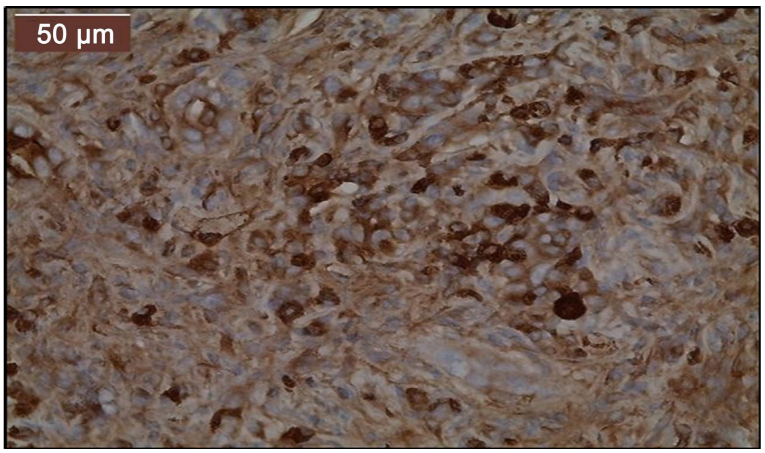

Figure 3. IgG+ plasma cells.

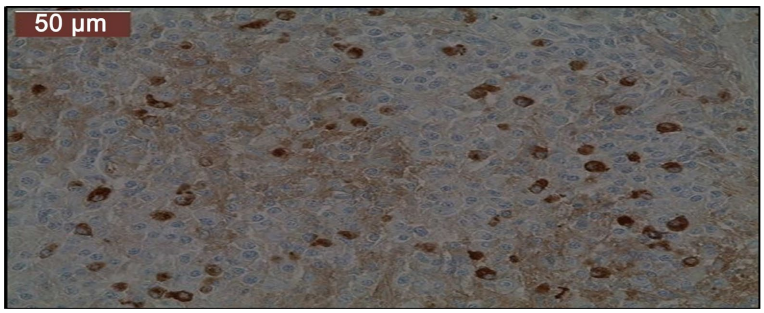

Figure 4. IgG+ plasma cell.

3. Discussion

The clinical, paraclinical and histopathological characteristics of ML-IgG4 have been the subject of an international consensus adopted in 2011 [5] [6]. It can affect one or more organs synchronously or delayed, in the form of a mass or diffuse enlargement of the affected organs. The histopathological aspect is that of

lymphoplasmacytic infiltration and progressive fibrosis. The most frequently affected organs are the pancreas, biliary tract, salivary glands, lacrimal glands, mediastinal lymph nodes, retroperitoneum, aorta, lungs and kidneys [7]. Renal involvement in IgG4+ disease is usually associated with multiple organ involvement. Saeki *et al.*, in 2010, reported that renal parenchymal lesions are associated with organ involvement in the following proportions: autoimmune pancreatitis in all patients, sialadenitis in 82.6% of cases, pulmonary lesions in 26% of cases; other organ involvement in variable proportions (liver, prostate, peritoneum, etc.). [8] The plasma cell-rich tubulointerstitial nephritis observed in our clinical case 2 dominates the renal histological lesions in IgG4 disease [9]. In the series of Saeki *et al.*, TINs represent more than 90% of renal histological lesions in IgG4 disease [10]. It was first described in 2003 by Kamisawa *et al.*, during autoimmune pancreatitis [1]. In 2015, Pradhan D and colleagues in a literature review also reported that NTI is the most common renal histological lesion observed during IgG4+ disease [11]. Positive IgG4 immunohistochemistry is 100% sensitive and 92% specific in the diagnosis of NTI during IgG4+ disease; according to the series of Raissian *et al.* [12]. Extramembranous glomerulonephritis is the renal histological lesion described in our clinical case1 in a context of persistent major nephrotic syndrome. According to the literature, glomerular involvement during IgG4 disease is rare but has a poor prognosis. It is always necessary to ensure that a primary glomerulopathy is ruled out by the absence of phospholipase A2 receptors on immunohistochemistry, which was the case in the clinical case 1. Saeki *et al.* found 7% of glomerular lesions in their series [8]. Mohamad Z *et al.* also found a low proportion of glomerular lesions in a study on uro-nephrological lesions linked to IgG4+ disease [13]. Wehrlen G *et al.* described in 2018 a case of GEM revealing IgG4+ disease [12]. The renal vascular histological lesions observed in our two observations correspond to those reported during IgG4 disease. Although obliterative phlebitis is the classic vascular lesion of MAG4, the arteritis described in case 2 is also reported in the literature.

Shree G *et al.* in 2012, described lymphoplasmacytic infiltrations rich in IgG4+ reaching the media, intima and adventitia of small and medium diameter arteries causing arteritis. Untreated and at a more advanced stage, fibrinoid necrosis sets in with hardening and loss of elasticity of the arteries causing the arteriosclerosis found in case 1 [13]. Corticosteroid therapy is the mainstay of induction treatment with a very high response rate [7] but its schedule varies according to schools and the Japanese authors who have the most experience in this condition propose the following treatment consensus [7]: prednisolone at a dosage of 0.6 to 1 mg/kg per day for two to four weeks. After this attack dose, the dosage will be reduced by 5 to 10 mg/day every 1 to 2 weeks to a daily dose of 20 mg, followed by a gradual reduction of 5 mg every 2 weeks until stopping. The duration of total remission treatment should generally last 12 weeks. In our clinical case 2, the patient seems to have a good response to corticosteroid therapy in view of the clinical-biological and radiological improvement of the disease markers. Thus, tubulointerstitial nephritis seems to have a better response to corticosteroid therapy and a better

prognosis. The series of Saeki *et al.* shows a rapid improvement in renal function after 4 weeks of corticosteroid therapy in 18 out of 19 patients, *i.e.* more than 90% [8]. Similar results were found by Raissian *et al.* with 90% of patients showing rapid remission after 4 weeks of corticosteroid therapy. Relapse after corticosteroid therapy is possible but associated with complex immunological and histochemical factors including high serum IgG4 levels, the presence of circulating eosinophils, TNF factor, persistent severe hypocomplementemia [14]. According to the literature, GEM during IgG4 disease would be associated with a poor therapeutic and evolutionary prognosis. Our clinical case 1 presents a persistence of clinical, biological and radiological symptoms with failure of corticosteroid therapy and recourse to an immunosuppressant, Rituximab [15] [16]. In case of corticosteroid dependence or especially in case of side effects in patients who may already have osteoporosis or diabetes, immunosuppressants or other treatments may be used: Rituximab, Azathioprine (2 to 2.5 mg/kg per day), Mycophenolate mofetil (750 mg per day) [7]. These are the two most commonly used immunosuppressants. Due to the high rate of recurrence, especially in cases of biliary involvement, monitoring is recommended. Predictive factors for relapse include a markedly elevated serum IgG4 level (such as > x4 UNL) before treatment and persistence of a consistently elevated level after steroid treatment; the presence of diffuse pancreatic enlargement, proximal cholangitis, and multiple organ involvement [17]. Monitoring is as follows: a serum IgG4 dosage every 3 months for 2 years and a pancreatic and biliary MRI every year for 2 years.

4. Conclusion

IgG4 disease is a new entity that includes autoimmune pancreatitis type 1. It is characterized by multiorgan involvement with histological features including a dense lymphoplasmacytic infiltrate (positive by immunohistochemistry for IgG4), organ fibrosis and obliterating venules. This autoimmune disease is called systemic IgG4 because of its highly elevated serum levels. It should be suspected in the presence of any subacute clinical picture of inflammation or fibrosis with a pseudotumoral radiological appearance of the organs involved. Suspicion is all the greater if the serum IgG4 level is increased. The diagnosis is confirmed by a characteristic histopathological appearance of biopsies. The pathophysiological process of this disease is not yet completely elucidated and requires in-depth studies, particularly concerning the link between histopathology, the increase in serum IgG4 levels, and the increased quantity of IgG4-positive plasma cells; the role of IgG4 in ML-IgG4 and the response to the different treatments proposed. Rituximab is an interesting therapeutic alternative currently being validated in the management of renal damage during IgG4-associated disease.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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