Inflammatory pseudotumors of the kidney due to IgG4-related tubulointerstitial nephritis

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Abstract
The paper presents the case of a female patient who was admitted to our department because of prolonged febrile syndrome, altered general status and renal tumoral masses revealed by thoracic and abdominal CT. After thorough histological examination, including immunohistochemistry and in situ hybridization studies, we reached the diagnosis of renal pseudotumoral masses due to IgG4-related tubulointerstitial nephritis. The kidney is a distinct target organ affected by IgG4-related sclerosing disease, and the most frequent manifestation is tubulo-interstitial nephritis. We described the clinical, imagistic and histopathological features of kidney and urological involvement in IgG4-related sclerosing disease, especially focusing on IgG4-related tubulointerstitial nephritis. This is a rare case of IgG4-related sclerosing disease without extrarenal features, excepting lumboaortic lymphadenopathy.

Keywords: renal pseudotumoral masses, IgG4-related disease, tubulointerstitial nephritis, membranous nephropathy, retroperitoneal fibrosis.

Introduction
IgG4-related sclerosing disease (IgG4-RSD) is a recently recognized systemic autoimmune disease, which is characterized by presence of fibro-inflammatory masses in almost every organ of the body [1]. Sarles et al., in 1961, have described for the first time the autoimmune pancreatitis, the first recognized form of the disease. Since then, some form of IgG4-RSD has been described in nearly every organ system, including the kidney [1]. The renal manifestation of IgG4-RSD is in most cases tubulo-interstitial as IgG4-related tubulointerstitial nephritis (IgG4-RTIN), but sometimes may associate glomerular involvement, especially membranous nephropathy, which could be also found as an isolated lesion [2–4].

We report a rare case of IgG4-RTIN and describe the clinical, imagistic and histopathological features of kidney involvement in IgG4-RSD, especially focusing on IgG4-RTIN.

Patient, Methods and Results
A 55-years-old female patient was admitted to our unit because of persistent fever. The patient’s medical history had begun 10 years earlier. At the onset of the disease, the clinical picture was dominated by fever. Physical examination was normal. The laboratory data showed normal white blood cell count, no anemia, increased erythrocyte sedimentation rate 70 mm/1s hour, normal liver enzymes, normal renal function. No urinary abnormalities. No monoclonal components were found in serum or urine. Serology for autoimmunity and infectious diseases was negative. Procalcitonin was negative.

The abdominal and thoracic CT revealed multiple paraaortic-caval abdominal lymph nodes of approximately 1 cm in diameter. The histopathological examination of a lymph node showed just necrosis. The bone marrow biopsy was normal.

Under treatment with 20 mg Prednisolone/day, the outcome was apparently good, associated with improvement of clinical signs (disappearance of fever).

During these 10 years from the debut of the disease, the patient was periodically investigated hematologically, immunologically and imaging (including abdominal and thoracic CT scan). Until this year, no pathological alterations were found.

On admission to our unit, the clinical picture was dominated by fever, altered general status, and diffuse abdominal pain. Physical examination was normal. The laboratory data showed normal white blood cell count, mild anemia, increased inflammatory indices (C-reactive protein 40 mg/L, IL-6 23 pg/mL), normal renal function.

We have found no urinary abnormalities and normal urinary levels of β2-microglobulin and lipocalin-2. Serology for autoimmunity was negative (ANA, ANCA, anti ds-DNA, SS-A, SS-B, anti Sm, anti-RNP, anti-SCL70 auto-antibodies, C3, C4, immunoglobulin dosage, rheumatoid factor, cryoglobulins).

Serology for infections was negative, including HIV, HCV, HBV, CMV, EBV, and Toxoplasma.

The abdominal CT scan showed nodular masses in the right kidney associated with a large lumboaortic lymphadenopathic mass (Figure 1).
Renal biopsy revealed a fibro-inflammatory process, which extensively replaces normal renal interstitium (Figures 2 and 3). The borders of the sclerotic lesion were heavily infiltrated by lymphocytes and plasma cells (Figure 4, A and B).

Based on the morphology and anatomic distribution of the lesions, we have made the differential diagnosis of tubulointerstitial nephritis with a lymphoma or plasma cell dyscrasia. A lymphoproliferative process was excluded by immunohistochemistry and in situ hybridization studies (including CD3, CD20, CD68, CD138, lambda LC, kappa LC, PAX5, Desmin, ALK-1, AE1/AE3 Cytokeratin, HMB-45). CD20 and PAX5 highlight/disclosed well-formed follicles and occasional germinal centers, while CD3 stained mostly small, mature appearing T-cells. Abundant CD138+ plasma cells were observed, kappa/lambda ISH showing a polytypic distribution. Reed–Sternberg and/or Hodgkin cells were not identified on the HE-stained sections, although focally, eosinophils were prominent (Figure 5, A and B).

Additional diagnostic considerations (although unlikely), including inflammatory myofibroblastic tumors and metastatic carcinoma with florid inflammatory response, were not supported by IHC analysis. Nonetheless, IgG4 immunohistochemistry showed important increase in IgG4-positive plasma cells at the borders of the sclerotic lesions. We made a diagnosis of inflammatory pseudotumors of the kidney due to IgG4-RTIN. Following immunosuppressive therapy (Prednisone and Cyclophosphamide), evolution was favorable, with an important decrease in size of the lumboaortic adenopathic mass and the right kidney nodular masses, disappearance of fever and of the inflammatory syndrome.
Discussion

IgG4-related tubulointerstitial nephritis

IgG4-RTIN is the most common type of kidney involvement in IgG4-RSD. Kidney involvement in IgG4-RSD is not necessarily concomitant with involvement of other organs. However, some of the published studies on IgG4-RSD, reported extrarenal involvement (e.g., dacryoadenitis, sialadenitis, lymphadenopathy, autoimmune pancreatitis) in 80–90% of cases [5, 6]. Thirty percent of patients with autoimmune pancreatitis present tubulointerstitial kidney injury [1].

The great majority of patients with IgG4-RTIN present elevated plasma levels of IgG4 or of total IgG or hypergammaglobulinemia on electrophoresis of serum proteins (abnormalities present in 80% of cases) [5, 6]. Eosinophilia is present in almost one third of cases [1, 5, 6].

Abnormalities of the urinary sediment in IgG4-RTIN are present. In a study on 35 patients diagnosed with IgG4-RSD, proteinuria was present in 40% of cases [6]. The clinical picture of IgG4-RTIN is poor in the initial phases of the disease, with hypertension and edema occurring very rarely. In a study published by Raissian et al. on a group of 35 patients with IgG4-RSD, in 75% of cases the reason for performing kidney biopsy was kidney failure (acute, chronic or progressive), while in 25% of cases biopsy or nephrectomy were recommended due to renal tumoral masses [6].

Symptoms were usually associated with extrarenal manifestations, rather than with the renal abnormalities [5, 7–9].

Frequently, imaging examination of these patients reveal singular or multiple nodular masses affecting one or both kidneys, and can be mistaken for renal cancer, sometimes leading to nephrectomy for the exclusion of renal malignancy. In the study of Saeki et al., 70% of the patients presented abnormal renal CT-scan, the most common findings being renal hypertrophy, renal small lesions (cortical nodules), pseudotumoral lesions [5]. Sometimes, the diameter of these pseudotumoral masses might be greater than 8 cm [10]. Whenever the presence of these renal masses is accompanied by satellite lymphadenopathy, the differential diagnosis with renal cancer is difficult, many of these patients being nephrectomized. Moreover, histopathological diagnosis is challenging because differential diagnosis with lymphoma or plasma cell dyscrasia is difficult to be done [1, 2].

In optical microscopy, involvement of the renal cortex in IgG4-TIN may be focal, multifocal or diffuse [5]. The inflammatory infiltrate consists in mononuclear cells, many plasmocytes and sometimes-frequent eosinophils [5, 6]. As the disease progresses, plasma cells become dominant. The tubes are atrophic, with thickening of the basement membranes. Deposits of immune complexes at the level of the tubular basement membrane are identified in the majority of cases. Tubulitis with mononuclears (or plasmocytes) is frequently present. Inflammatory injury of the renal cortex is similar with the injury produced by IgG4-RSD to other organs [1, 2]. Even in the early phase of the disease, storiform sclerotic fibrosis is present [5, 6].

In immunofluorescence, granular deposits of IgG, C3, kappa and lambda light chains are identified in the tubular basement membrane. In some cases, fine granular deposits of IgM and C1q may be described in the tubular basement membrane. Occasionally, glomerular immune-complex deposits are seen, and membranous nephropathy is associated in these cases.

In electronic microscopy, amorphous electronodense deposits are identified at the tubular basement membrane level, which correspond to the changes seen in immunofluorescence.

IgG4 immunohistochemistry and IgG4 grading

In IgG4-RSD, IgG4+ infiltrates are divided into several categories, depending on the number of IgG4+ plasmocytes per field at a magnification of 40× HPF (high-power field) from the areas with the highest density of cells: 0–5 IgG+ plasmocytes, the number of IgG4+ plasmocytes is not increased; 5–10 IgG+ plasmocytes, minimal increase; 11–30, moderate increase; >30, important increase. In a study published by Raissian et al., the presence of a moderately increased level of IgG4+ plasmocytes used as a diagnostic criterion for IgG4-related tubulointerstitial nephropathy demonstrated a sensitivity of 100%, a specificity of 91% and a positive predictive value of 76% [6].
Commonly, the minimum requirement for making the diagnosis in case of most tissues is the presence of at least 30 IgG4-positive plasma cells/HPF. Still, in case of the kidney and other few organs, only 10 IgG4-positive plasma cells/HPF may be satisfactory.

The presence of interstitial infiltrates with IgG4+ plasmocytes could also be seen in other glomerular or tubulointerstitial nephropathies. Thus, moderate interstitial infiltrates with IgG4+ plasmocytes may occur in up to 25% of cases of ANCA-positive necrotizing glomerulonephritis [11]. Other tubulointerstitial nephropathies in which interstitial inflammatory infiltrate may contain IgG4+ plasmocytes are represented by: chronic pielonephritis, tubulointerstitial nephropathy associated with Sjögren syndrome (less than 10% of cases) and some drug-induced tubulointerstitial nephropathies [1, 11].

A multinational and multidisciplinary group of specialists on IgG4-RSD has established a consensus report, which describes the guidelines for diagnosing the disease and the most important histopathological criteria in formulating the diagnosis [12]. Previously, only for autoimmune pancreatitis, were recommended precise diagnostic criteria. There is no international consensus on the histopathologic diagnostic criteria for IgG4-RSD.

The following histopathological features are critical for making the diagnosis: a dense lymphoplasmacytic infiltrate, storiform fibrosis, obliterative phlebitis and mild tissue eosinophilia. These findings, in association with an increased number of IgG4-positive plasma cells are strongly suggestive for the diagnosis [1].

IgG4-related glomerular nephropathies

Glomerular nephropathies have also been described in patients with IgG4-RSD [1]. Glomerular nephropathies in patients with IgG4-RSD may be isolated or associated with tubulointerstitial nephritis lesions. Membranous nephropathy is the most common type of glomerulopathy associated with IgG4-RD, consisting in over half of these cases [5, 6, 13–15]. None of the patients with IgG4-RSD were positive for phospholipase A2 receptor on biopsy, although it is present in a majority of patients with primary membranous nephropathy [13–15].

In the most ample series of cases of IgG4-RSD with kidney injury reported by Saeki et al., six out of 23 patients with IgG4-RTIN (24%) presented concomitant glomerular disease: membranous glomerulonephritis in two cases, IgA nephropathy in one case and mesangial or endocapillary proliferative glomerulonephritis in the other three cases [5].

Other histological types of glomerular nephropathies described in IgG4-RSD include: membranoproliferative glomerulonephritis, minimal change disease and focal segmental glomerulosclerosis.

IgG4-related retroperitoneal fibrosis

Involvement of the extra-renal urinary tract, direct or secondary to retroperitoneal fibrosis, is relatively frequent in IgG4-RSD and may lead to hydronephrosis and obstructive nephropathy [16]. A study of patients diagnosed with autoimmune pancreatitis reported many cases with extra-pancreatic involvement, retroperitoneal fibrosis being found in 13% of the cases [17].

Conclusions

The case described in the paper draws attention to a rare case of kidney involvement in IgG4-RSD. The tumoral masses revealed on abdominal CT scan proved to be the consequence of IgG4-RTIN. The histopathological diagnosis was difficult, requiring immunohistochemistry and in situ hybridization studies in order to facilitate the differential diagnosis with lymphoma, plasma cell dyscrasia or inflammatory myofibroblastic tumors and metastatic carcinoma with florid inflammatory response. We described the clinical, imagistic and histopathological features of kidney involvement in IgG4-related sclerosing systemic disease, especially focusing on IgG4-RTIN.

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References

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