IgG4-related disease with renal and orbital involvement: a clinical case

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ABSTRACT

Introduction: IgG4-related disease (IgG4-RD) is characterized by the growth of pseudotumors, which can affect almost every organ. Elevated serum IgG4 levels are present in only two-thirds of the patients and are not specific. Diagnosis is difficult and is usually based on a biopsy.

Clinical Case: A 39-year-old man presented complaints of low back pain and fever. A renal computed tomography (CT) scan revealed a voluminous mass next to the right kidney and a biopsy showed an inflammatory process and excluded a neoplasm. A follow-up CT scan at four months revealed total regression without any treatment. Three years later, the patient presented with diplopia and right proptosis. MRI of the orbits revealed a retro-ocular mass; biopsy excluded a malignant process. Infectious, autoimmune or paraneoplastic diseases were also excluded. Although the patient's IgG4 serum levels were normal, histopathological reobservation of the renal biopsy revealed IgG4-positive plasma cells, thus confirming the diagnosis. The patient was prescribed a daily dose of 40 mg of prednisolone and regression of the right orbital lesion was observed.

Discussion: IgG4-RD is a rare and recently described condition. Most anatomic pathology laboratories do not routinely test for it. Spontaneous pseudotumor remission is possible, even when associated with the renal phenotype, although this has not been described until now.

Keywords: Immunoglobulin G; Neoplasm.

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INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is a rare and recently recognized clinical, radiological, and pathological condition[1]. The pathogenesis is not completely understood, but it is probably due to a combination of autoimmune and allergic factors[2-4]. The main characteristic of IgG4-RD is the growth of pseudotumors, which can affect almost every organ (most frequently, the pancreas, salivary glands, orbit or kidney)[5]. Lymphadenopathy is also common and can be the only clinical sign[8]. The prevalence of IgG4-RD is not known, partly because it remains underdiagnosed. The disease affects mainly middle-aged to elderly men[1].

A diagnosis of IgG4-RD can be made using a combination of histologic, clinical, serologic, and radiologic data[10], and international guidelines have been proposed[12]. Notably, serum IgG4 levels are elevated in only two-thirds of cases[5,11] and even patients with active disease can have normal serum IgG4 levels[7,11]. The histology hallmarks include lymphoplasmacytic infiltrate with IgG4-positive cells, storiform fibrosis pattern, obliterative phlebitis, and eosinophilia[6,10].

CLINICAL CASE

39-year-old man with chronic arterial hypertension controlled with olmesartan (20 mg) and amlodipine (5 mg). The patient was admitted to the emergency department complaining of fever (38.3°C) and lower right back pain. Blood and urine tests revealed normochromic normocytic anemia (hemoglobin 12 g/dL), acute kidney injury (creatinine 1.25 mg/dL), increased C-reactive protein (13.72 mg/dL), an increased erythrocyte sedimentation rate (108 mm) and normal urinalysis. Abdominal and renal computed tomography (CT) scans showed a big mass next to the right kidney (Figure 1) which the radiologist described as signs of lymphoma; moreover, there were multiple adeno—

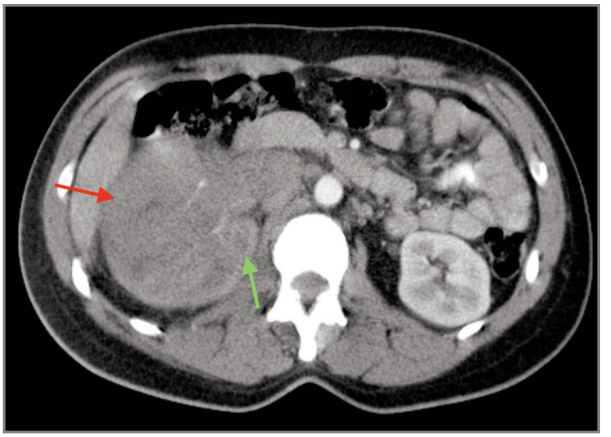

FIGURE 1. CT: Infiltrative and hypovascular mass occupying the lower two-thirds of the right kidney and extending to the upper third of the ureter, with a size of 10 × 9 × 9 cm (red arrow). It is possible to see the kidney structure in the lower and medial regions (peri-vertebral; green arrow).

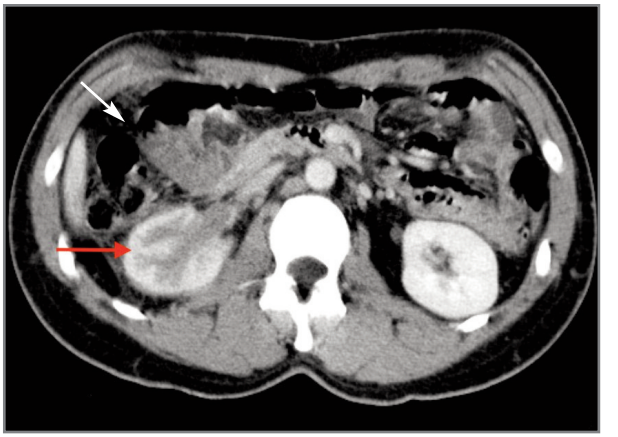

FIGURE 2. CT: Almost complete regression of the mass. Densification of peri-renal fat and thickening of the urothelium (red arrow) can be observed.

pathies. A core biopsy was performed with a Tru-Cut 18 G needle to complement the diagnostic study. The histopathology showed an inflammatory process and excluded neoplastic entities. The microbiological and mycobacteriological cultures and the immunophenotyping of the biopsy were negative.

The rest of the investigation was inconclusive, and therefore an excisional surgery was scheduled four months later. The patient remained asymptomatic in that period. A follow-up CT scan before the procedure revealed spontaneous regression of the right kidney

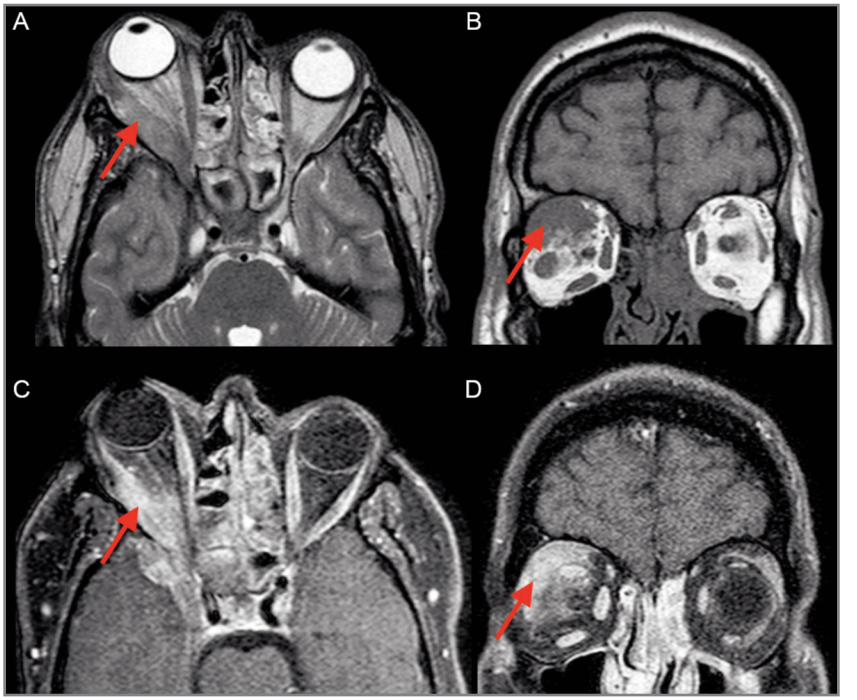

FIGURE 3. MRI of the orbits at presentation. Axial T2-weighted imaging (A), coronal T1-weighted imaging (B), and axial (C) and coronal (D) contrast-enhanced T1-weighted imaging showed a T1 and T2 isointense right intra- and extraconal mass extending toward the ipsilateral cavernous sinus and with adjacent intracranial pachymeningeal thickening and enhancement (red arrow).

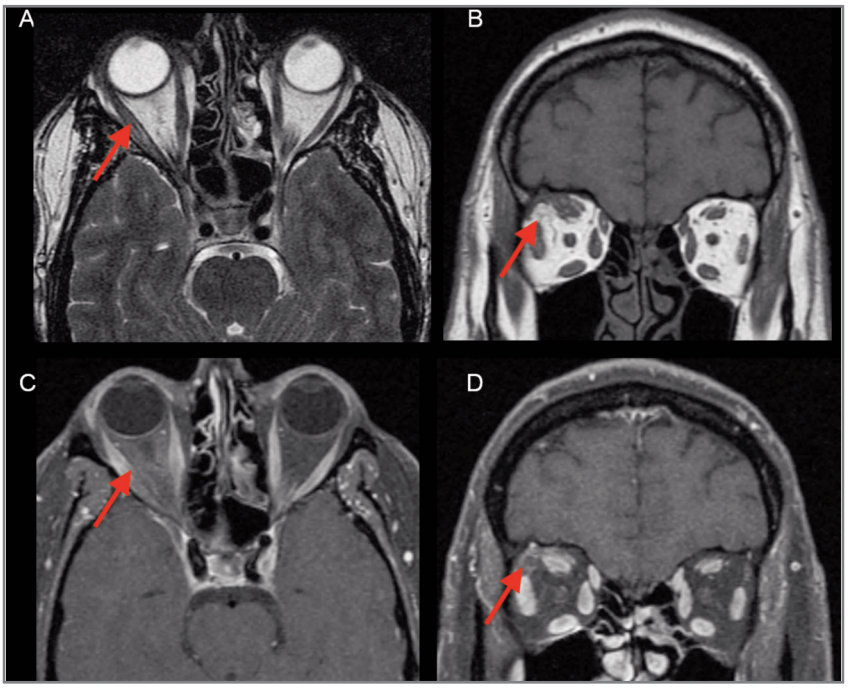

FIGURE 4. Follow-up MRI of the orbits. Axial T2-weighted imaging (A), coronal T1-weighted imaging (B), and axial (C) and coronal (D) contrast-enhanced T1-weighted imaging performed 2 months after treatment demonstrated sub-total regression of the previously identified right orbital, cavernous and pachymeningeal soft tissue mass (red arrow).

mass (Figure 2).

The patient was closely followed, with imaging performed every three months. The imaging revealed some loss of the normal structure of the right kidney; however, the function was normal, and there were no signs of recurrence of the kidney mass.

Three years later, the patient presented with right periorbital edema, erythema, and proptosis associated with diplopia; visual acuity was normal. Magnetic resonance imaging (MRI) showed an ipsilateral intra-orbital, cavernous and pachymeningeal soft tissue mass (Figure 3). An orbital biopsy was subsequently performed. Histopathology again excluded a malignant process, namely lymphoma; microbiological and mycobacteriological cultures and immunophenotyping were all negative.

Blood test results revealed normal C3 (109 mg/dL), C4 (22.9 mg/dL), and IgE (113 IKU/L) levels and an increased eosinophil count (0.83 x 10E3/uL). Autoimmunity tests were also negative for antineutrophil cytoplasmic antibodies (ANCA). Other complementary etiological investigations were negative for infectious or paraneoplastic processes (including full-body CT, endoscopy, colonoscopy, and blood and urine immunofixation). Although IgG4 serum levels were normal (117 mg/dL) as other conditions were excluded, a diagnosis of IgG4-RD was then considered.

A histopathological reevaluation of the kidney and orbital biopsies was requested, considering this new diagnostic possibility. Indeed, the kidney biopsy revealed fibrosis, lymphoplasmacytic infiltrate, and eosinophilia, with more than 10 IgG4-positive plasma cells per high-power field (HPH). The orbital biopsy specimen showed up to 50 IgG4-positive plasma cells/HPH, although it was not possible to identify the characteristic fibrosis or lymphoplasmacytic infiltrate in this location.

The diagnosis of IgG4-RD was therefore credited and the patient initiated 40 mg of prednisolone once daily. Clinical and imaging follow-up demonstrated significant improvement in the orbital lesion after two months of treatment (Figure 4) which allowed us to gradually taper the dose of glucocorticoid until it was stopped two weeks later. The patient has been closely followed up, and no relapse has been observed over the past three years since remission; there has been no need to restart glucocorticoid treatment.

DISCUSSION

IgG4-RD is a rare and recently described condition and is often misdiagnosed as a neoplastic, inflammatory or infectious condition[15]. Many histological laboratories only test for IgG4-RD if the diagnosis is clinically suggested. The disease mainly affects men who are middle aged or older, as in this case. Pseudotumours are the hallmark of the disease, so doctors must consider IgG4-RD as a possible diagnosis when faced with such a finding.

Recently, two consensus statements for the diagnosis and treatment of IgG4-RD have been published[6,12]. According to those publications, IgG4 serum concentrations can be easily measured and help to diagnose this condition. However, there have been other reports stating that IgG4 levels are not elevated in up to one-third of patients[5,11], a finding that our results reflect. Therefore, normal IgG4 serum levels do not exclude a diagnosis of IgG4-RD. On the other hand, serum IgG4 levels can be elevated in other conditions, such as neoplastic, infectious, and autoimmune diseases, and analytic errors are also possible[15]. Hypocomplementemia of C3 and C4 and increased IgE are also common, but not specific[10], and our patient did not have any of these. Also, eosinophilia can be present, as we saw in this case.

Histological examination remains the main way to definitively diagnose IgG4-RD, although optimal biopsy samples can be difficult to get[10,15]. The number of IgG4-positive plasma cells/HPH necessary to diagnose this condition varies based on the analyzed tissue[10]: most tissue samples need to have 30–50 IgG4-positive cells/HPH to make the diagnosis. However, 10 IgG4-positive plasma cells/HPH in kidney tissue samples is sufficient. The histological pattern is also essential; it comprises lymphoplasmacytic infiltrate with IgG4-positive cells, storiform fibrosis pattern, obliterative phlebitis, and eosinophilia[6]. In our case, both histological features needed for the diagnosis of IgG4-RD were fulfilled using kidney biopsy, although not in the orbital specimen because of the small biopsy sample. The negative ANCA result also allowed us to exclude the possible diagnosis of an orbital pseudotumor of ANCA vasculitis.

Recent literature, including the American College of Rheumatology/European Alliance of Associations For Rheumatology (ACR/EULAR) classification criteria[16], divides IgG4-RD into different phenotypes: pancreato-hepatobiliary disease (31%) retroperitoneal fibrosis with or without aortitis (24%) head and neck-limited disease (24%) and classic Mikulicz's syndrome with systemic involvement (22%). However, our patient did not fit into any of these phenotypes, which probably reflects one of the limitations of the classification.

It is also important to highlight that the kidney lesion, which was the presentation form of the disease in our patient, spontaneously disappeared after four months without any treatment. Indeed, on a follow-up CT scan, besides the change in the normal renal architecture, the mass had already disappeared. Scientific literature confirms this possibility, despite being rare and only associated with the pancreato-hepatobiliary[17] and retroperitoneal phenotypes[18]. To our knowledge, there are no scientific data confirming spontaneous remission associated with the renal phenotype. The mechanism of the previously described spontaneous remission is unclear[18].

IgG4-RD treatment is based on glucocorticoids: 0.6 mg/kg/day of prednisolone[13]. Usually, patients respond to treatment within two to four weeks; however, relapses are common, and second-line agents such as rituximab, azathioprine or mycophenolate mofetil can be used[13]. Here, the orbital lesion showed marked improvement after initiation of prednisolone (0.6 mg/kg once daily for two months) and there were no subsequent relapses during the three years of follow-up (to date).

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