# Immunoglobulin G4-related disease with recurrent uveitis and kidney tumor mimicking childhood polyarteritis nodosa

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## ABSTRACT

**Introduction:** Immunoglobulin G4-related disease (IgG4-RD) is an condition rarely reported in children. Additionally, IgG4-RD may rarely mimic vasculitis in adults and may infrequently present with uveitis. In our service, 6,198 patients were followed-up and only one (0.0001%) of them had IgG4-RD. To our knowledge, the present IgG4-RD case was the first described case mimicking childhood polyarteritis nodosa (c-PAN) with recurrent uveitis and kidney tumor.

**Case Report:** We describe herein a 7-year-old boy that presented intermittent fever. He developed arthralgia, weight loss, myalgia, skin lesions and recurrent uveitis. Skin biopsy revealed necrotizing vasculitis in medium/small sized vessels associated with septal panniculitis suggesting c-PAN. Prednisone and azathioprine were administered with improvement. At 11 years, he had persistent fever and abdominal angiotomography revealed a large tumor in left kidney and he was then submitted to nephrectomy. The renal histopathology showed lymphoplasmacytic and histiocytic proliferation with extensive areas of fibrosis, and lymphomonocitic phlebitis with presence of IgG4 in 43 plasmocyte cells, suggesting IgG4-RD.

**Discussion:** We present a unique case of a male pediatric patient with IgG4-RD with rare ocular, cutaneous and renal manifestations.


**Keywords:** Immunoglobulin G4-related disease; Polyarteritis nodosa; Vasculitis; Uveitis; Tumor; Children.

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## INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is an condition characterized by tissue IgG4-positive plasma cells infiltration[1]. This systemic disease may affect glands, periorbital tissues, kidneys, lungs, meninges and skin[1-3].

The majority of IgG4-RDs were described in adult patients, particularly in middle age.[2] There are few cases reported in pediatric populations and the most frequent manifestation was orbital involvement[2]. Additionally, IgG4-RD may rarely mimic vasculitis, never before associated with anti-neutrophil cytoplasmic antibody (ANCA) in adults[4], and may rarely present with uveitis[5].

From January 1983 to December 2016, 6.198 patients were followed-up at the Pediatric Rheumatology Unit of the Instituto da Criança da Faculdade de Medicina da Universidade de São Paulo. Only one (0.0001%) of them had IgG4-RD. To our knowledge, the present IgG4-RD case was the first described case mimicking childhood polyarteritis nodosa (c-PAN) with recurrent uveitis and kidney tumor.

## CASE REPORT

An 11-year-old boy presented with intermittent fever for nine consecutive months at the age of seven. At 7 years and 9 months he was admitted to our tertiary hospital due to arthralgia in ankles, knees, wrists and right elbow. Concomitantly, he presented with weight loss, diffuse myalgia and painful nodules in calves, left forearm and feet. At that moment, his laboratory tests revealed hemoglobin 8.4 g/dL, hematocrit 27% and white blood cell count 7,100/mm$^3$ (63% neutrophils, 33% lymphocytes, 1% eosinophils and 3% monocytes). Erythrocyte sedimentation rate was 59 mm/1$^{st}$ hour,

C-reactive protein 41.1 mg/dL (normal range <5.0), C3 134mg/dL (normal range 79-172), C4 21 mg/dL (normal range 16-38) and 24-hour proteinuria 0.18 mg/day. Antinuclear antibody was 1:160. Anti--dsDNA, ANCA, anti-cardiolipin IgG and IgM autoantibodies, lupus anticoagulant and rheumatoid factor were negative. Anti-RNP, anti-Sm, anti-Ro/SSA and anti-La/SSB autoantibodies were negative. Serum IgA level was 249.9 mg/dL (normal range 45-234), serum IgG was 1358 mg/dL (normal range 970-1710) and serum IgM was 142.4 mg/dL (normal range 53-145). Ophthalmoscopy and slit-lamp biomicroscopy showed a bilateral uveitis. Serologies for parvovirus B19, measles, hepatitis (A, B and C), Human Immunodeficiency Virus (HIV), Epstein Barr virus, cytomegalovirus and toxoplasmosis were also negative. Tuberculosis skin test was 0 mm. Bone marrow aspirate was normal. Echocardiogram and Doppler ultrasound of renal arteries were normal. Thoracic and abdominal magnetic resonance angiographies were also normal. Skin biopsy revealed necrotizing vasculitis in medium and small-sized vessels associated with septal panniculitis without granulomas, suggesting c-PAN. No immune deposition was observed in direct immunofluorescence. Therefore, c-PAN was diagnosed according to the European League Against Rheumatism (EULAR)/Peadiatric Rheumatology International Trials Organisation (PRINTO)/Paediatric Rheumatology European Society (PRES) criteria[6]. Prednisone (1.0 mg/kg/day) and azathioprine (1.0 mg/kg/day) were administered with improvement of skin lesions, fever and uveitis. At 9 years, after a prednisone dose reduction (2.5 mg/day), he presented with a recurrence of bilateral anterior uveitis. This ophthalmological complication was treated with prednisone (1.0 mg/kg/day) and cyclosporine (5.0 mg/kg/day). At 11 years, he presented with persistent fever and increased acute phase reactants. In order to exclude features of c-PAN, an abdominal angiotomography was performed and revealed a tumor in left kidney without retroperitoneal fibrosis (Figure 1). The patient was submitted to left nephrectomy. Renal histopathology showed lymphoplasmocytic inflammatory infiltrate involving renal parenchyma with different stages of fibrosis (Figure 2). The Figure 3 revelead stromal fibrosis with plasmocytic infiltration. This fibrosis envolving particularly the intima-media thickness of medium--size vessels, with lymphomonocitic phlebitis and presence of IgG4 in 43 plasmocyte cells, suggesting IgG4-RD. No vasculitis was observed in this histopathology exam. At that moment, uveitis was improved with combination of prednisone (1.0 mg/kg/day), cyclosporine (5.0 mg/kg/day) and mycophenolate mofetil (2 g/day).

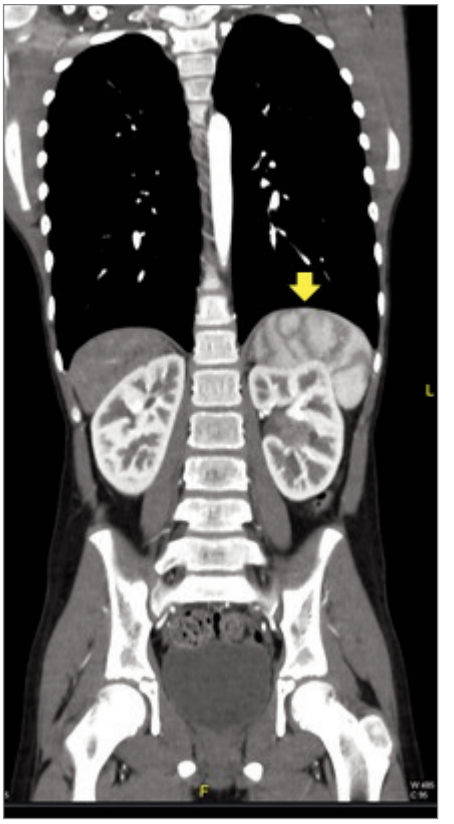

**FIGURE 1.** Abdominal angiotomography revealed in the left kidney a tumor with irregular septations and without retroperitoneal fibrosis.

## DISCUSSION

We present herein a unique case of a male pediatric patient with IgG4-RD associated with rare ocular, cutaneous and renal manifestations. This was also the only IgG4-RD case observed over 34 years at our university and tertiary hospital.

IgG4-RD is a rare pediatric disease, showing a large spectrum of different clinical presentations, such as articular, renal, and orbital involvement, pancreatitis, cholanghitis, and thyroiditis[2]. Most cases were described in adults affecting glands, periorbital tissues, kidneys, lungs, meninges and skin[1-3].

Histopathology demonstrating presence of IgG4 in

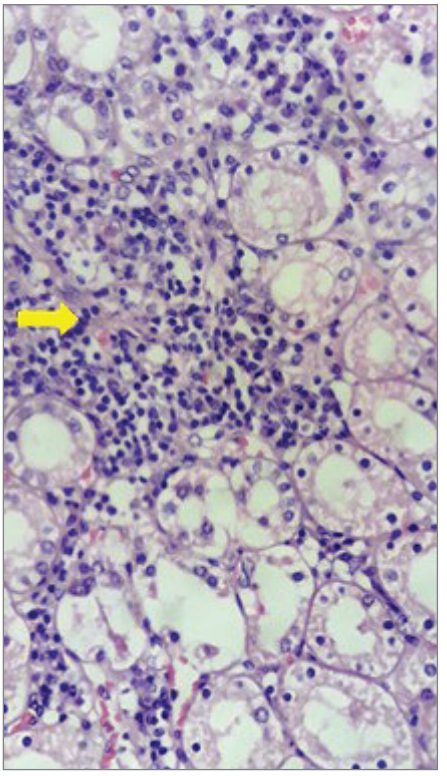

**FIGURE 2.** Histopathological examination shows lymphoplasmocytic inflammatory infiltrate involving renal parenchyma with different stages of fibrosis (100x magnification)

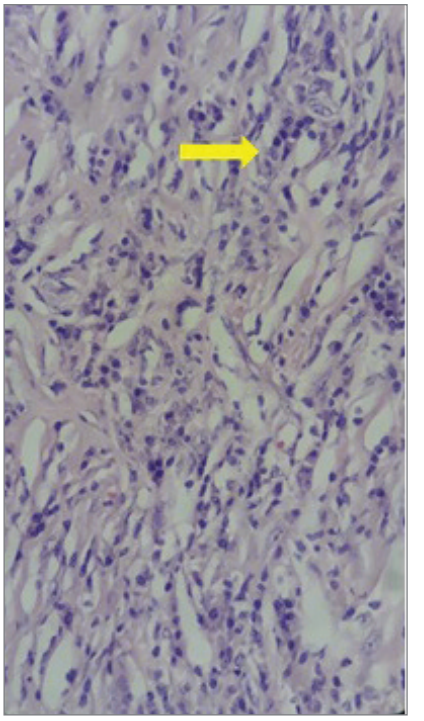

**FIGURE 3.** Histopathological analysis of the tumor revealed stromal fibrosis with plasmocytic infiltration (100x magnification)

any organ is the gold standard for IgG4-RD diagnosis, as evidenced in the present case. Elevated serum IgG4 concentration is not necessary for its diagnosis[7,8], and this test was not performed in the present case.

Our patient had cutaneous involvement with necrotizing vasculitis associated with septal panniculitis at disease onset, and the first diagnosis was c-PAN. In fact, the presence of necrotizing vasculitis in medium or small-sized arteries in cutaneous biopsy associated with two clinical criteria (skin nodules and myalgia/muscle tenderness) fulfilled the EULAR/PRINTO/ /PRES c-PAN criteria. Sensitivity and specificity to c-PAN diagnosis according to these criteria were 89.6 and 99.6, respectively, when compared to other vasculitides[6]. Interestingly, nephritis is frequently reported in c-PAN.

The biopsy of the entire kidney did not evidence necrotizing vasculitis and confirmed IgG4-RD. Granulomatosis with polyangiitis, Churg-Straus syndrome, Behcet's disease and undifferentiated vasculitis has been rarely reported as a first manifestation or associated with IgG4-RD in adults[4,7,9,10].

On the other hand, the presence of recurrent uveitis combined with a large kidney tumor indicated that the initial picture was from a case of IgG4-RD rather than a c-PAN. The potential mechanisms and links between IgG4-RD and cPAN are unknown, and possible related with a Th-response predominance in both diseases with marked levels of IgG4 plasma cell infiltration in the former, as previously reported in other systemic vasculitis[11].

This patient was evaluated by pediatric oncologist and pediatric surgery, which both suggested left nephrectomy to exclude neoplasia. However, this procedure could have been avoided if a renal biopsy was performed, since the gold standard for IgG4-RD diagnosis is histopathological findings with the presence of IgG4 [7].

Our patient also had bilateral anterior uveitis and a lymphoplasmacytic infiltrate rich in IgG4 plasma cells that resemble a kidney tumor. This ocular manifestation was rarely reported in adult patients with IgG4--RD concomitantly with orbital pseudotumor[5]. Therefore, it is also important to consider IgG4-RD as a dif-

ferential diagnosis of a malignant kidney tumor.

The first-line therapy for IgG4-RD is glucocorticoids. Surgical approaches may be indicated for 10% of IgG4-RD patients. Immunosuppressive agents and/or biological agents may be indicated for refractory cases[8]. The use of mycophenolate mofetil partially improved the recurrent uveitis in our case.

In conclusion, we reported a rare case of IgG4-RD mimicking c-PAN with recurrent uveitis and a kidney tumor.

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