Small-vessel vasculitis with prominent IgG4 positive plasma cell infiltrates as potential part of the spectrum of IgG4-related disease: a case report

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ABSTRACT

IgG4-related disease (IgG4-RD) is a systemic entity characterised by multiorgan inflammatory lesions with abundant IgG4+ plasma cells, obliterative phlebitis, and storiform fibrosis. Involvement of several organs such as the pancreas, gastrointestinal tract, salivary glands, periorbital tissue and lymph nodes has been described. Up to now, vascular involvement by IgG4-RD has been thought to be essentially confined to large vessels.

We present a patient with small-vessel systemic vasculitis involving muscle, peripheral nerve and kidney (glomerulonephritis) in the context of IgG4-RD diagnosed on the basis of elevated serum IgG4+ concentrations and histologically consistent signs in all biopsied tissues. Thoracic and abdominal aortic aneurysms in addition to aortitis, suggestive of large-vessel involvement, were also present. This observation expands the spectrum of vascular involvement in the context of IgG4-RD and supports the inclusion of IgG4-RD in the category of vasculitis associated with systemic disorder.

Introduction

IgG4-related disease (IgG4-RD) is a fibroinflammatory condition characterised by dense lymphoplasmacytic infiltrates, mainly composed by IgG4+ plasma cells, with frequently increased serum IgG4+ concentrations. Other histopathological features of the disease include storiform fibrosis and obliterative phlebitis (1).

Most patients affected by IgG4-RD are male >50 years who present with subacute development of a mass or organomegaly (2). Lymph nodes, salivary glands and the pancreas are the most frequently involved tissues (3, 4), although the gastrointestinal and hepatobiliary tract, periorbital tissue, breast, kidney, lung and thyroid may also be affected (2). Multiple organs are involved in 60%–90% of patients (2).

Reported vascular involvement by IgG4-RD consists of thoracic aortitis, abdominal aortic aneurysms, and periaortitis with retroperitoneal fibrosis (5). Herein, we describe a patient with systemic small-vessel vasculitis in the context of IgG4-RD.

Case report

An 80-year-old man presented with malaise, fever and weight loss. Four months before, he underwent endovascular repair of an abdominal aortic aneurysm (AAA). The patient also had aneurysmal dilatation in the descending thoracic aorta (Fig. 1), detected two years before. Two months before admission, he developed progressive fatigue, 4 kg weight loss, low-grade fever, and numbness in his legs. Physical examination revealed mild oedema of the legs and healing purpura. Previous medical history included chronic obstructive pulmonary disease and bladder cancer, diagnosed and treated 12 years before.

Laboratory tests disclosed normocytic anaemia (Hb 8.8 g/L), an erythrocyte sedimentation rate of 132 mm/h (normal <20) and C-reactive protein of 14.83 mg/dL (normal <0.8). Serum creatinine was 1.3 mg/dl and mild peripheral eosinophilia was detected (970 cells/mm^3). Urinalysis revealed a protein excretion of 1.37 g/24 hrs, and 4–10 red blood cells/high-power field (HPF).

Blood and urine cultures remained sterile. Detection of antibodies against hepatitis B, hepatitis C or human im-

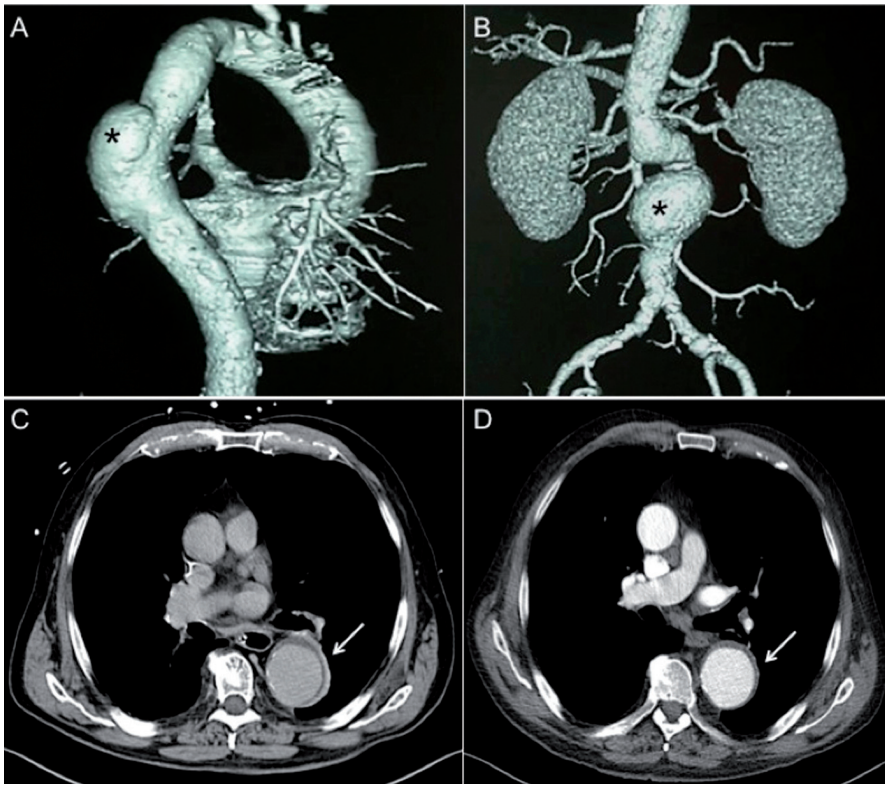

Fig 1. Computed tomography angiography of thoracic (**A**) and infra-renal abdominal (**B**) aortic aneurysms (*). Vessel wall thickening with contrast enhancement in the descending thoracic aorta, indicating aortitis, was identified before starting glucocorticoid treatment (**C**). After 2 years of treatment, reduction in the aortic wall thickening and disappearance of the contrast enhancement was observed (**D**).

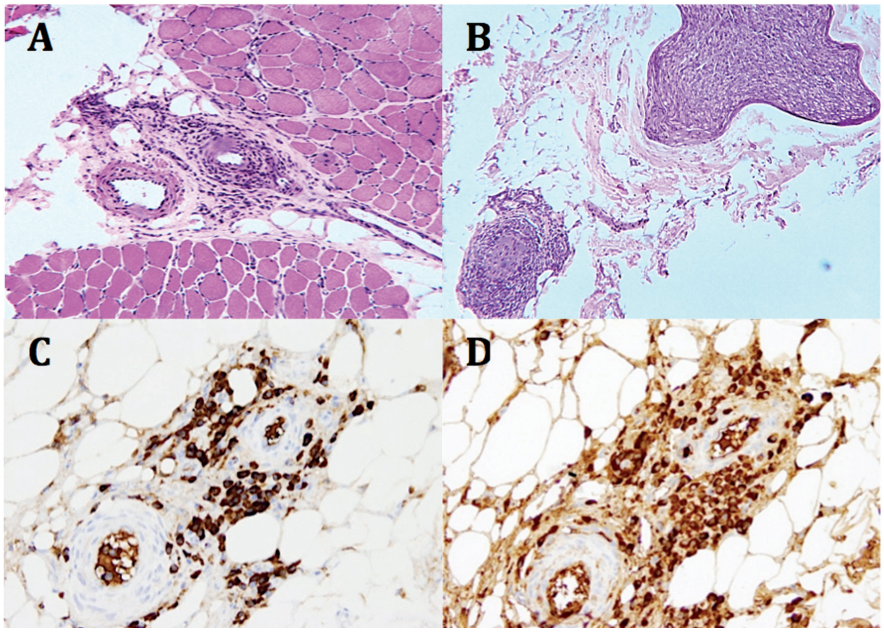

Fig. 2. Haematoxylin and eosin (H&E)-stained section of gastrocnemius muscle (**A**) and sural nerve (**B**) showing necrotising vasculitis of small vessels. Plasma cells stained for IgG4 (**C**), represent nearly 90% of IgG positive cells (**D**). (All images were taken at 200 x magnification).

munodeficiency viruses was negative. Thoracic and abdominal CT scans showed aortic wall thickening with contrast enhancement in the descending thoracic segment, indicative of aortitis (Fig. 1). Thoracic aneurysm remained stable in size.

Serum protein electrophoresis disclosed marked polyclonal hypergammaglobulinemia (48% of total serum protein) and a small monoclonal IgG *lambda* component was detected by immunofixation. Skeletal x-rays did not disclose lytic lesions. Bone marrow aspirate revealed 12% of plasma cells with normal phenotype as assessed by flow cytometry. Antinuclear antibodies determined by indirect immunofluorescence were positive (1:320) and rheumatoid factor was elevated (107 IU/ml). Extractable nuclear antigen antibodies, anti-DNA, ANCA (IIF and ELISA) and cryoglobulins were negative. Complement levels were normal. Serum total IgA and IgM concentrations were in the reference range but IgG was highly increased (32.6 g/L, normal <15.3).

Electromyography and nerve conduction studies evidenced distal symmetric axonal peripheral neuropathy involving the superficial peroneal, sural, median and ulnar nerves. Sural nerve and gastrocnemius muscle biopsies were performed.

Histological study of muscle and nerve disclosed small-vessel vasculitis with dense lymphoplasmacytic infiltrates and scattered eosinophils (Fig. 2). A kidney biopsy showed focal segmental necrotising glomerulonephritis (Fig. 3). Interstitial inflammatory infiltrates consisting of lymphocytes, scattered eosinophils and abundant plasma cells were evident.

The age and sex of the patient, the presence of aortic aneurysms and aortitis, as well as the finding of hypergammaglobulinemia led us to consider IgG4-RD. Determination of serum IgG subtypes demonstrated a remarkable elevation of IgG4 (24.1 g/L, normal <1.4) with an IgG4/IgG ratio of 74%. Immunohistochemical staining for IgG4+ plasma cells was evident in perineural vessels and in the kidney (Fig. 2-3). More than 10 IgG4+ plasma cells per HPF and an IgG4/IgG ratio >50% were found. These clinico-pathological findings were suggestive of a small-vessel systemic vasculitis associated with IgG4-RD (1).

Treatment with prednisone (1 mg/kg/day) and azathioprine (100 mg/d) was started with prompt improvement of all symptoms and abnormal blood tests.

Prednisone was slowly tapered and, after a 20-month follow-up, the patient remains asymptomatic with no recurrences. Of note, no findings suggestive of aortic inflammation were observed in the most recent CT scan (Fig. 1).

Discussion

IgG4-RD has been defined as a systemic entity characterised by multiorgan inflammatory involvement with tissue infiltration by abundant IgG4+ plasma cells. Additional findings may include storiform fibrosis and obliterative phlebitis (2). Here, we present a patient with systemic small-vessel vasculitis associated with IgG4-RD.

Vascular inflammation associated with IgG4-RD mainly involves large arteries, essentially the aorta, in the form of aortitis, inflammatory aneurysm or periaortitis (5-7). IgG4-RD can affect both the thoracic and abdominal aorta and usually occurs in men aged 55–75 years (5-7). Aortic lesions of IgG4-RD are characterised by extensive inflammatory infiltrates and fibrosis with remarkable thickening of the adventitia (7). In addition to the aortic involvement, anecdotic reports of other vascular territories affected by IgG4-RD include medium-small arteries in the lung (8, 9), the mesenteric and coronary circulation (10, 11).

The vasculitic lesions of our patient definitely included the major proposed hitopathological criteria for IgG4 disease: dense lymphoplasmacytic infiltration with the presence of >10 IgG4+ plasma cells/HPF and an IgG4+/IgG ratio >40% (1, 12). Slight eosinophilic infiltrates, present in our patient biopsies, are also frequent in IgG4-RD (1) Storiform fibrosis and obliterative phlebitis were not observed but the absence of these findings is common in several organs involved by IgG4-RD such as salivary glands, lymph nodes or lungs (1). In addition to the characteristic infiltration by IgG4 positive plasma cells our patient had additional relevant data (1), including elevated serum IgG4 concentration >13.5 g/dL, an effective response to glucocorticoid therapy and an additional typical organ, the aorta, was likely affected. Other reported features associated with IgG4-RD such mild eosinophilia, positive rheumatoid factor and antinuclear antibodies were also present in this patient (3).

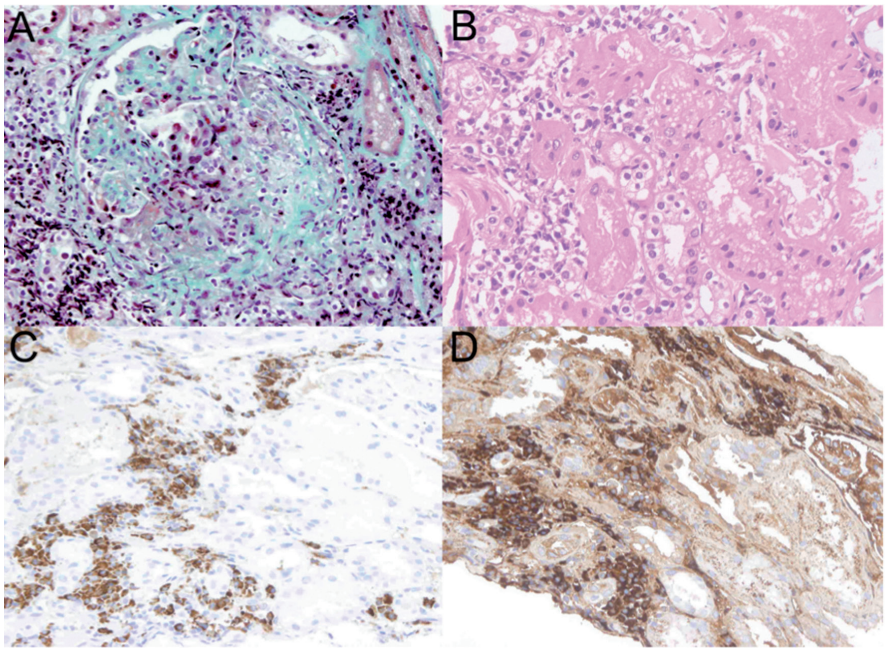

Fig. 3. Renal biopsy. Trichrome stain reveals focal segmental necrotising glomerulonephritis with small cellular crescent formation (**A**). Focal aggregation of plasma cells in the interstitium was also present (**B**) (H&E). Plasma cells stained for IgG4 (**C**), represent nearly 90% of IgG positive cells (**D**). (All images were taken at 200 x magnification).

In front of the evidence of vasculitis involving small vessels with glomerulonephritis, an ANCA-associated vasculitis (AAV) was initially suspected (13). In fact, there may be some overlapping features between AAV and IgG4-RD. Increased IgG4 levels may be found in AAV (14, 15). Elevated serum concentrations of IgG4 have been demonstrated in patients with active eosinophilic granulomatosis with polyangiitis (EGPA) (14). However, ENT biopsies obtained from 9 patients with active EGPA did not show increased IgG4+ plasma cell infiltration (14). By contrast, in a study of 23 patients with granulomatosis with poliangiitis (GPA) (16), serum IgG4 levels remained in reference range whereas increased IgG4+ plasma cells with elevated IgG4/IgG ratios were observed in 31% of biopsies obtained from sinonasal and orbital/periorbital regions. However, in our patient, ANCA detection, present in 95% of patients with severe generalised disease (17), was negative in two independent determinations. In addition, our patient did not have asthma, ENT manifestations or pulmonary infiltrates and his biopsies did not exhibit histological features such as granuloma, or extensive neutrophilic/eosinophilic infiltration suggesting the diagnosis of GPA or EGPA. He did not fulfil existing classification criteria for these diseases (18, 19).

In summary, the case presented here with prominent IgG4+ plasma cell infiltrates in all tissues biopsied, with negative ANCA testing and not fulfilling ACR classification criteria for GPA or EGPA, suggests that systemic small-vessel vasculitis may be part of the spectrum of IgG4-RD (1). Further studies are necessary to determine the complete spectrum of vascular involvement in IgG4-RD and to ascertain its underlying immunopathogenic mechanisms.

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