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Immunoglobulin G4-related disease associated with extensive granulomatous changes

Rheumatology key message

- Extensive granulomatous changes may rarely be encountered in otherwise typical IgG4-related disease.

SIR, IgG4-related disease (IgG4-RD) is a relatively newly described condition characterized classically by the triad of lymphoplasmacytic inflammation, storiform-type fibrosis and obliterative phlebitis, with prominence of IgG4-positive plasma cells and an IgG4/IgG ratio of $>40\%$ on immunohistochemistry [1]. The presence of granulomas generally excludes the diagnosis of IgG4-RD [2]. Herein, we describe a markedly rare case of IgG4-RD associated with extensive granulomatous changes.

A 61-year-old man was admitted to our hospital with enlargement of the submandibular glands. He had never had previous exposure to tuberculosis, Bacillus Calmette–Guérin vaccination and organic solvents. One year previously, non-contrast CT had shown dilatation of the aortic root to a diameter of 53 mm, but not right hydronephrosis. Five months before admission, he had noticed enlargement of the right submandibular gland. Physical examination demonstrated a palpably enlarged right submandibular gland. ^{18}F-Fluorodeoxyglucose (FDG)-PET/CT revealed increased uptake in the right submandibular gland, around the outside of the aortic root and in foci adjacent to the common iliac arteries (Fig. 1A–D; arrow). Contrast-enhanced CT demonstrated a mass lesion corresponding to the FDG uptake partly surrounding the aortic root (Fig. 1E–G; arrow). Contrast-enhanced CT and FDG-PET/CT showed no hilar lymphadenopathy. The uptake along the common iliac arteries corresponded to a mass causing right ureteral obstruction and hydronephrosis. Laboratory results included elevated serum IgG4 (198 mg/dl), IgG (1963 mg/dl) and IgE (392.1 IU/ml), and showed normal hepatic function tests and negative tests for anti-SS-A/Ro, SS-B/La antibodies and ANCA. Submandibular gland biopsy demonstrated an extensive inflammatory infiltrate, rich in plasma cells with occasional lymphoid follicles (Fig. 1H and I). Obliterative phlebitis was also observed (Fig. 1J). Immunostaining revealed more than 100 IgG4-bearing plasma cells per high-power field (Fig. 1K) and $>40\%$ of IgG4/IgG-positive cell ratio (Fig. 1L and M). Extensive non-necrotizing granulomatous changes with CD68-positive Langhans-type giant cells were also noted against the background of storiform fibrosis (Fig. 1N and O). Ziehl–Neelsen staining for *Mycobacterium tuberculosis* and Grocott staining for fungus were negative. There was no evidence of lymphoma or vasculitis. Moreover, *M. tuberculosis* culture and PCR from submandibular gland tissue were negative. We diagnosed IgG4-RD with extensive granulomatous changes. The patient was treated with oral prednisolone 0.6 mg/kg, which dramatically reduced the prominence of the IgG4-RD lesions on CT and also lowered the serum IgG4 and IgG.

Our case illustrated clinically, serologically and histopathologically typical IgG4-RD except for many multinucleated giant cells (MGCs) and granulomas. A good response to CS contradicted the possibility of a granulomatous infectious disease, such as tuberculosis or ANCA-associated vasculitis, including granulomatosis with polyangiitis. In addition, the association of sarcoidosis was also very unlikely because of the unusual organ distribution that included the periaorta and retroperitoneum. Granulomas and MGCs are exceptional in IgG4-RD, and their presence would previously have made this diagnosis very unlikely [2]. However, some cases with typical IgG4-RD accompanied by MGCs have been recently reported [3, 4]. Some of these had a history of tuberculosis or RA, indicating that immune reactions to tuberculosis or rheumatoid nodules might be related to the disease initiation. It is thought that IL-4 and IFN-γ are crucial for MGC formation [5, 6]. The involvement of IL-4 is well known in the pathophysiology of IgG4-RD [7]. Furthermore, it was recently reported that lesional CD4$^+$ cytotoxic T lymphocytes secreted IFN-γ in IgG4-related dacryoadenitis and sialoadenitis [8]. Therefore, IL-4 and additional Th1 stimulation, which induces IFN-γ, might generate MGCs in patients with IgG4-RD.

In conclusion, extensive granulomatous changes may rarely be encountered in otherwise typical IgG4-RD. Close clinicopathological correlations are required to exclude the possibility of true granulomatous diseases mimicking IgG4-RD (e.g. sarcoidosis, granulomatosis with polyangitis) or coincidental development of the two conditions.

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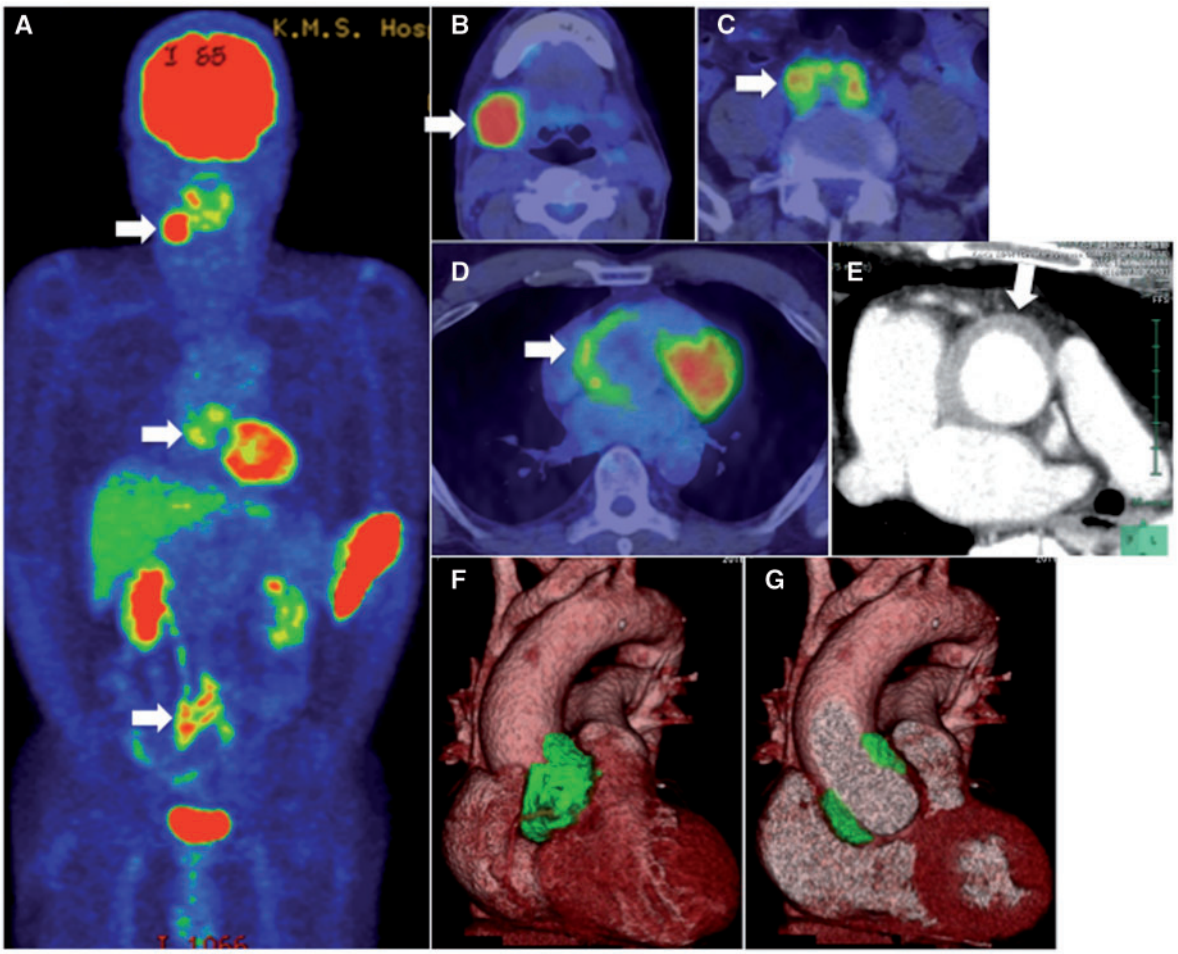
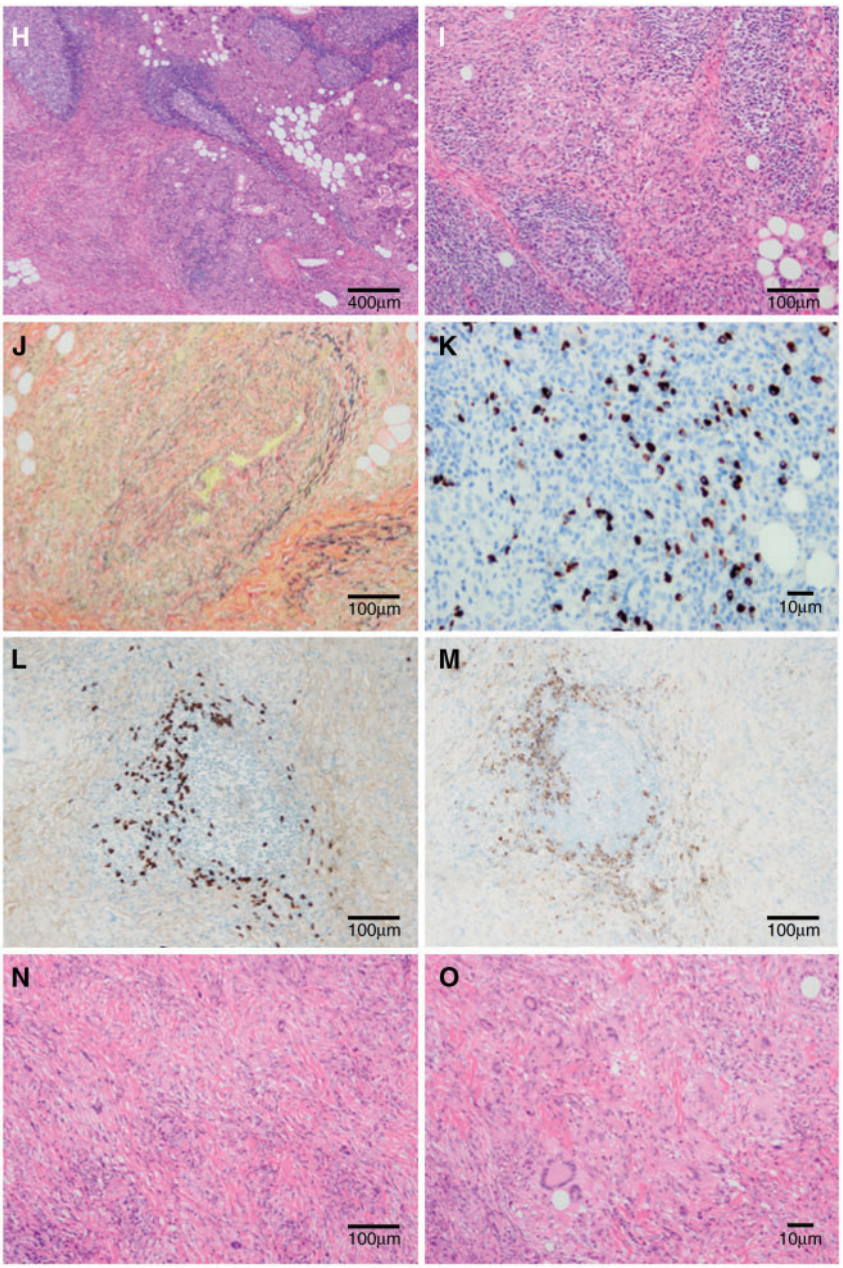
FIG. 1 The imaging and histological findings of IgG4-related disease lesions



(**A**–**G**) ^{18}F-Fluorodeoxyglucose-PET/CT and contrast-enhanced CT at admission. (**A**–**D**) PET/CT images show abnormal uptake in the right submandibular gland (arrows in **A** and **B**; maximum standard uptake value (SUVmax) 9.8), along the common iliac arteries (arrow in **C**; SUVmax 6.7) and around the aortic root (arrow in **D**; SUVmax 5.5). (**E**–**G**) Sagittal (arrow in **E**) and three-dimensional (**F** and **G**) contrast-enhanced CT demonstrates the mass (shown in green in **F** and **G**) around the outside of the aortic root. (**H**–**O**) Histological findings of the submandibular gland. (**H**) The gland is involved in a severe fibro-inflammatory process (400μm). (**I**) The inflammatory infiltrate is associated with many plasma cells and lymphoid follicles (100μm). (**J**) Elastica–van Gieson staining reveals obliterative phlebitis (100μm). (**K**) Immunostaining for IgG4 shows many IgG4-positive plasma cells (100μm). (**L** and **M**) The ratio of IgG4/IgG-positive plasma cells appears to be $>$ 40% (**L**: IgG4 immunostaining; **M**: IgG immunostaining; both 100μm). (**N** and **O**) Extensive granulomatous changes with multinucleated giant cells are observed against the background of storiform fibrosis (**N**: 100μm; **O**: 10μm).

FIG. 1 continued



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Failure of rivaroxaban to prevent thrombosis in four patients with anti-phospholipid syndrome

Rheumatology key message

- Rivaroxaban does not seem to be efficient and safe in all APS patients.

Sir, APS is an acquired autoimmune disorder characterized by the association of vascular thrombosis or pregnancy morbidity and the presence of persistent aPL [1]. Current management of thrombosis in APS is based on long-term vitamin K antagonists (VKAs) to prevent recurrences. Recently, direct oral anticoagulants have been shown to be non-inferior to VKAs for the secondary prevention of venous thromboembolism [2]. Small case series have indicated either a good safety and efficacy profile or thrombosis recurrence in APS patients on rivaroxaban [3, 4]. Here we report four new cases of recurrent thrombosis in APS patients treated with rivaroxaban.

The first patient was a 33-year-old man who presented with unprovoked superficial vein thrombosis of the right great saphenous vein who was treated with a therapeutic dose of s.c. low molecular weight heparin over 3 weeks and then switched to rivaroxaban 20 mg/day. A few days after the switch, he experienced dyspnoea leading to the diagnosis of pulmonary embolism. Laboratory testing revealed a high-risk aPL profile (triple positivity [5]: the presence of LA, aCL and anti-β_2-glycoprotein I antibodies). The patient improved after switching rivaroxaban to heparin and a VKA. One year later the patient was asymptomatic.

The second patient was a 21-year-old female diagnosed with SLE-associated APS based on skin involvement, arthritis, deep vein thrombosis (DVT) and triple aPL positivity. She was treated with acenocoumarol before switching to rivaroxaban for patient preference. Three months later she developed a lupus flare together with purpuric and necrotic skin lesions on the upper and lower limbs. The lupus flare was diagnosed based on arthritis associated with thrombocytopenia, antinuclear and dsDNA antibodies and decreased complement. A skin biopsy confirmed small vessel thromboses without any lupus vasculitis. Clinical and laboratory abnormalities disappeared rapidly after the introduction of low molecular weight heparin, aspirin, HCQ and i.v. pulse steroids. Thereafter, heparin was bridged to warfarin and there was no thrombotic recurrence for the next 2 years.

The third patient was a 26-year-old man diagnosed with a primary thrombotic APS (recurrent unprovoked distal DVT with triple positivity) treated with rivaroxaban. Nine months later, despite the anticoagulant treatment, an unprovoked bilateral proximal pulmonary embolism was diagnosed without DVT. However the patient confirmed suboptimal compliance to anticoagulant treatment with rivaroxaban.

The last case was a 58-year-old female diagnosed with SLE-associated APS (history of venous, arterial and small vessel thrombosis before the diagnosis of APS and triple positivity). Rivaroxaban was started in October 2015 for a second DVT of her right leg. Rivaroxaban was then stopped and warfarin was initiated because of the worsening of skin lesions 3 months after starting rivaroxaban. The patient did not experience any further thrombotic recurrence after 5 months.

Recently, Cohen *et al.* [6] reported the impact of rivaroxaban on thrombin generation in APS patients [Rivaroxaban in Anti-phospholipid Syndrome (RAPS) study]. APS patients included were at low risk, with at least one venous thrombosis during no or subtherapeutic anticoagulant therapy. Indeed, patients with previous arterial thrombosis or recurrent venous thromboembolism (VTE) while on a therapeutic dose of warfarin were not included. Overall, patients treated with rivaroxaban had a significant 2-fold increased thrombin potential, suggesting a higher thrombotic risk, compared with warfarin users. However, the authors concluded that rivaroxaban was a safe alternative to warfarin in APS patients since no clinical event occurred during the follow-up (210 days).

Our case reports illustrate four cases of rivaroxaban failure for preventing secondary thrombosis in APS patients (Table 1). In accordance with the RAPS study, our patients had a previous VTE. Only one had a history of arterial and small vessel thrombosis as well, which is considered a higher risk for thrombosis. Furthermore, all patients in this report have a high-risk aPL profile (triple positivity). In the RAPS study, a lower frequency of persistent triple-positive patients was included (12% in the rivaroxaban group). Differences in the patients' characteristics in terms of history of arterial thrombosis or aPL profile may have produced a higher rate of thrombosis recurrence in our patients.

The third case illustrates the drawback of the absence of biological monitoring, which does not allow an objective compliance assessment. Long-term VKA can be difficult for some patients, because the treatment requires repeated monitoring, but this can also be an advantage in APS patients. Thanks to their long half-life, the risk of thrombotic recurrence in case of a missed treatment dose may be lower than in patients on rivaroxaban, which has a shorter half-life, especially in patients with a high thrombotic risk [5].

In conclusion, rivaroxaban does not seem to be efficient and safe in all APS patients, especially those with a history of arterial thrombosis or triple positivity [7]. Therefore, it is urgent to perform randomized controlled trials to clarify in which subgroups rivaroxaban is a safe alternative to warfarin [8].