Non-IgG4-related Multifocal Fibrosclerosis

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Abstract

Multifocal fibrosclerosis (MFS), which causes systemic and chronic connective tissue inflammation, has been associated with IgG4 and regarded as an identical entity with “IgG4-related disease (IgG4-RD)”. Although a few cases of MFS mimicking IgG4-RD histopathologically, despite the absence of a serum IgG4 elevation and IgG4-positive plasma cell infiltration, have been reported, there is, so far, little information regarding such exceptional cases. We herein demonstrate a case of non-IgG4-related MFS presenting with periaortitis and parotiditis, whose histological findings were consistent with IgG4-RD despite the absence of elevated serum and tissue IgG4 levels.

Key words: multifocal fibrosclerosis, IgG4-related disease, periaortitis, retroperitoneal fibrosis, parotiditis, sialadenitis

(Intern Med 55: 2497-2502, 2016)
(DOI: 10.2169/internalmedicine.55.6297)

Introduction

Multifocal fibrosclerosis (MFS), first proposed by Comings et al. in 1967, is a rare entity with an unknown cause, which is characterized by systemic inflammatory fibrosis (1). Its common manifestations include retroperitoneal fibrosis (RPF), sclerosing cholangitis, sclerosing pancreatitis, Riedel thyroiditis, orbital pseudotumor, sialadenitis, and hypertrophic pachymeningitis. A number of studies have shown an association of MFS with IgG4 since Hamano et al. reported elevated serum IgG4 levels and tissue infiltration by IgG4-positive plasma cells in autoimmune pancreatitis around the early 2000s (2, 3). Thereafter, a new clinical disease entity, IgG4-related disease (IgG4-RD), became widely accepted (4-6). Most reports have regarded IgG4-RD as a disease entity that is identical with MFS, and there is no doubt that IgG4 is one of the most characteristic features in MFS (2, 7).

It is still obscure as to whether both disease entities are completely identical or partially overlaps. The diagnosis of IgG4-RD is, in principle, based on the histopathological findings such as IgG4-positive/IgG-positive cell ratio or IgG4 cell count in the affected organ tissue, which is included in the comprehensive diagnostic criteria (8). Moreover, there are three distinguishing morphological features except for the infiltration of IgG4-positive cells, including 1) dense lymphoplasmacytic infiltrate, 2) fibrosis arranged at least focally in a storiform pattern, and 3) obliterative phlebitis (9). On the other hand, there are sporadic case reports describing systemic MFS mimicking IgG4-RD histopathologically despite the absence of any serum IgG4 elevation and IgG4-positive plasma cell infiltration has also been reported (10-13), although little information is available about IgG4-unrelated cases. We herein report a case of non-IgG4-related MFS presenting with RPF and swelling of the left parotid gland.

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Received for publication August 3, 2015; Accepted for publication December 27, 2015
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A 57-year-old Japanese male, who had previous histories of hypertension, dyslipidemia, diabetes mellitus, smoking-related emphysema and pneumothorax, presented at a neighborhood clinic with fever and a swollen left parotid gland in September, 2013. Two weeks later, he was referred to the Department of Otolaryngology in our hospital because his symptoms persisted in spite of the administration of both oral hydrocortisone at 100 mg/day, which was tapered and discontinued in five days, and oral antibiotic therapies. On admission, he received intravenous antibiotic chemical treatment for the diagnosis of cellulitis around the left auricle without any beneficial effects. He underwent a surgical biopsy on the left parotid gland, which revealed thickening of the small vascular wall, narrowed lumen, perivascular inflammatory cell infiltration and concentrically fibrosis, suggesting vasculitis. Moreover, because acute renal failure also developed, he was thereafter transferred to our department.

On physical examination, the patient was well-oriented but his body temperature was slightly high (37.2°C) under oral administration with a non-steroidal anti-inflammatory drug. He had anorexia and had experienced a weight loss of 5 kg over the past 9 months. He had the left parotid gland swelling with heat, redness, and pain. Otherwise, there was no abnormal finding on physical examination, except for tenderness in the left costovertebral angle.

Urinalysis revealed no abnormal findings including proteinuria, hematuria, and casts. Complete blood counts revealed leukocytosis with neutrophilia (WBC 10,300/mm³, neutrophils 79.0%), mild anemia (Hb 9.5 g/dL), and thrombocytosis (Plt 717,000/mm³). Biochemistry showed increased levels of hepatobiliary enzymes [aspartate aminotransferase (AST) 35 U/L, alanine aminotransferase (ALT) 63 U/L, alkaline phosphatase (ALP) 435 U/L, and γ-GTP 271 U/L] and renal dysfunction [blood urea nitrogen (BUN) 12 mg/dL, serum creatinine 2.13 mg/dL, and 24-hour Ccr, 21.0 mL/min/1.73 m²]. Protein fraction revealed decreased total protein (6.9 g/dL) and albumin (2.7 g/dL) levels in addition to elevated IgG (1,789 mg/dL) and IgE (311 IU/mL) levels, but with a normal range for IgG4 (18.8 mg/dL). In serology, C-reactive protein (CRP) was 13.85 mg/dL and angiotensin-converting enzyme (ACE) was 14.7 IU/L, whereas no autoantibodies including antinuclear antibody, antineutrophil cytoplasmic antibodies, rheumatoid factor, anti-SS-A and anti-SS-B antibodies were detectable. No abnormality was found in the complement system (C3 74 mg/dL, C4 33 mg/dL, and CH50 45.7 U/mL). The T-SPOT.TB test was negative.

Computed tomography (CT) demonstrated left parotid gland swelling and irregular-shaped retroperitoneal massive lesions with sporadic calcification, which involved the abdominal aorta, bilateral common iliac arteries, and ureters, leading to hydronephrosis of the left kidney. These lesions were accompanied by an abnormal incorporation of 18F-fluorodeoxyglucose (FDG) in positron emission tomography (PET)-CT (Fig. 1A and B). The maximum standardized uptake value (SUV) of FDG was 4.7 and 6.2 in the left parotid gland and the periaortic abdominal mass lesion, respectively.

A histopathological examination of the left parotid gland revealed lymphoplasmacytic infiltration, fibrosis including a storiform pattern and fibrin accumulation (Fig. 2A). Elastica van Gieson stain revealed hyperplasia of collagen fibers and obliterative phlebitis (Fig. 2B). A flow cytometric analysis of the parotid gland tissue showed no abnormal findings including κ/λ ratio of free light chain. Similarly, lymphoplasmacytic infiltration and mild fibrosis were also found in a biopsy specimen of the retroperitoneal mass. These findings...
were compatible with MFS. However, immunohistochemistry revealed that up to 20% of the plasma cells were IgG4 positive and the number of IgG4-positive cells per high-power field was under 10, thereby not fulfilling the diagnostic criteria for IgG4-RD in both biopsy samples (Fig. 2C-F). Although epithelioid granulomas and infiltration of neutrophils and eosinophils were observed around the small vessels in the left parotid gland and the surrounding tissue, there was no infiltration of inflammatory cells in the vessel wall, disruption of the internal and external elastic lamina, or fibrinoid degeneration. The clinical manifestations were therefore far from that of small vessel vasculitis as defined by the 2012 International Chapel Hill Consensus Conference (CHCC2012), including microscopic polyangitis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, and immune complex small vessel vasculitis (14). Accordingly, we diagnosed the patient with non-IgG4-related MFS.

Ureteral stents were immediately inserted bilaterally, resulting in a drastic improvement of the renal function as the serum creatinine level decreased to 1.03 mg/dL within 10 days after performing ureteral catheterization. After carrying

Figure 2. Histopathological findings of left parotid gland and retroperitoneal mass. (A) Hematoxylin and Eosin staining for left parotid gland demonstrates lymphoplasmacytic infiltration, fibrosis and fibrin accumulation. The arrow indicates fibrosis in a storiform-like pattern. (B) Elastica van Gieson stain for the left parotid gland reveals hyperplasia of collagen fiber and obliterative phlebitis (arrow). (C, E) Immunohistochemical staining of IgG for the left parotid gland (C) and retroperitoneal mass (E). (D, F) Immunohistochemical staining of IgG4 for the left parotid gland (D) and retroperitoneal mass (F). Only 20% of plasma cells are IgG4 positive both in the left parotid gland and in a retroperitoneal mass. In (A)-(F), bars indicate 50 μm.
out a retroperitoneum biopsy, we started treatment with 60 mg of prednisolone (PSL) daily, corresponding to 1 mg/kg weight per day (Fig. 3). The fever immediately subsided followed by gradual diminishing of the left parotid gland. In parallel, most of laboratory data, including CRP and biliary enzymes were normalized, suggesting the coexistence of sclerosing cholangitis as another lesion of MFS. After successful remission induction at 4 weeks from starting the initial therapy, the dose of PSL was gradually tapered without any recurrent signs and symptoms. Five months later, a follow-up PET-CT scan confirmed that both lesions of the left parotid gland and retroperitoneal soft tissue were remarkably diminished with only a slight FDG uptake (Fig. 1C and D). The serum IgG4 level remained within the normal limit during the course of treatment.

Discussion

The present case showed a systemic fibrotic and inflammatory condition with multiple organ involvement similar to that of IgG4-RD in spite of the absence of a serum IgG4 elevation and increased IgG4-positive plasma cell infiltration. The case mimicked IgG4-RD both symptomatically and pathologically because the patient had periaortitis and parotiditis, which were characterized by lymphoplasmacytic infiltration, storiform fibrosis and obliterative phlebitis. On the other hand, there were some data incompatible with IgG4-RD in this case. First, the serum IgG4 level was far under 135 mg/dL. Second, the IgG4/IgG ratios of the infiltrating plasma cells were far under 40% in the involved tissues. Furthermore, numbers of the IgG4-positive cells were under 10 in high power fields. Therefore the case met neither the comprehensive diagnostic criteria for IgG4-RD nor the criteria for IgG4-related Mikulicz’s disease (8, 15), and we diagnosed him with non-IgG4-related MFS. To our knowledge, this is the first case of non-IgG4-related MFS presenting with both periaortitis (or RPF) and parotiditis.

In this case, there was no known causative agent inducing RPF among agents which the patient was receiving for hypertension and other complications when MFS developed (16). It was necessary to rule out a possibility of vasculitis, because elevated serum CRP level and fever are rarely seen in IgG4-RD. First, the clinical manifestations were far from the criteria established by the CHCC 2012 (14). Second, a histopathological examination revealed epithelioid granulomas and infiltration of neutrophils around the small vessels in addition to lymphoplasmacytic infiltration. But there was no infiltration of the inflammatory cells in the vessel wall, a disruption of the internal and external elastic lamina, or fibrinoid degeneration. Third, storiform fibrosis and obliterative phlebitis were observed in the parotid gland. Taken together, these are much more compatible with IgG4-RD than with vasculitis. Malignant lymphoma, sarcoidosis, and tuberculosis are also important differential diagnoses, because unilateral swelling of the parotid gland is atypical in IgG4-RD. However, these disorders were less compatible based on the results of histopathological examinations and blood tests.

The patients with RPF often have constitutional symptoms, such as fever, fatigue and elevated erythrocyte sedimentation and CRP levels (17). In a retrospective study, there was no significant difference in the CRP level between the IgG4-related periaortitis group and the non-IgG4-related periaortitis group [3.060 (interquartile range 0.63-5.49) vs. 6.225 (0-13.8) mg/dL, p=0.057] (18). This case continuously showed a high level of CRP before starting PSL administration. CRP was highly positive even after the improvement in the urinary findings by antibacterial drugs and ureteral stent.
insertion. Thereafter, CRP was immediately normalized after starting PSL and it maintained a low level. Thus, although pyelonephritis due to obstruction of the ureter by a retroperitoneal mass could have temporarily contributed to the high CRP level, the inflammation by RPF should have been the main cause of CRP elevation.

So far, four previous case reports recently described patients having typical MFS without meeting the diagnostic criteria for IgG4-RD (10-13) (Table). The first case presented with intracardiac involvement and a retroperitoneal mass, which showed lymphoplasmacytic infiltration and fibrosis in the biopsied specimen (10). The second showed tubulointerstitial nephritis (TIN), sclerosing sialadenitis in the submandibular gland, a retroperitoneal mass, and pancreatitis (11). The third showed a systemic fibroinflammatory condition including TIN, systemic lymphadenopathy, sialadenitis, and interstitial pneumonitis (12). In the second and third cases, the renal biopsy revealed lymphoplasmacytic infiltration with fibrosis mimicking IgG4-related TIN, a few infiltrating eosinophils, and storiform fibrosis. The latest case report described three cases with autoimmune pancreatitis which all had the characteristic histology of IgG4-related pancreatitis, except for the presence of IgG4 abnormalities (13). These cases had evidence of other organ involvements, including the biliary tree, kidneys, and RPF. All the 6 cases described in the previous reports did not satisfy the diagnostic criteria for IgG4-RD because the serum IgG4 levels did not exceed 135 mg/dL, and IgG4/IgG-producing cell ratios were less than 40%, or the number of IgG4-positive cells in high power field was under 10 in the affected tissues. They responded well to oral glucocorticoid therapy, in which the described initial doses of PSL ranged from 30 to 60 mg/day.

It is still unknown why the serum IgG4 levels and IgG4-positive plasma cells in the tissue increase in IgG4-RD, and whether IgG4 is a key player of inflammation or just a consequence of inflammation induced by other causes (19). In the case that IgG4 is a cause of inflammation, our case and the previous cases support the possible existence of non-IgG4-related MFS as an independent entity from IgG4-RD. Even if IgG4 is a result of IgG4-RD, a causal substance can exist upstream of IgG4 production and thus be different from that of non-IgG4-related MFS. Kasashima et al. showed that an IgG4-related inflammatory abdominal aortic aneurysm (AAA) was pathologically characterized by the frequent infiltration of eosinophils, lymphoid follicle formation, perineural inflammatory extension, obliterator phlebitis, and infrequent infiltration of neutrophils as compared with non-IgG4-related inflammatory AAA (20). As for RPF, Khosroshahi et al. demonstrated that IgG4-related RPF was identified in 57% of the total cohort, and that the IgG4-related RPF patients had lymphoplasmacytic infiltrate, storiform fibrosis, or tissue eosinophilia in retroperitoneal biopsies at a significantly higher rate than observed in non-IgG4-related RPF patients (21). Koo et al. also compared IgG4-related RPF with non-IgG4-related RPF, and reported the recurrence rate of IgG4-related RPF to be significantly higher than that of non-IgG4-related RPF (22). In this case, some histopathologic features, such as epithelioid granulomas and infiltration of neutrophils around the small vessels, were incompatible with IgG4-RD, possibly suggesting a difference in non-IgG4-related MFS from IgG4-RD.

It is also still unclear whether the sensitivity to glucocorticoid differs between IgG4-related and non-related MFS. The distinction between IgG4-related and unrelated diseases may be important in sclerosing cholangitis, because IgG4-related cholangitis has been reported to respond well to glucocorticoid therapy in contrast to primary sclerosing cho-

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**Table. The Cases of Non-IgG4-related MFS Reported Previously.**

<table>
<thead>
<tr>
<th>Case</th>
<th>Clinical manifestations</th>
<th>Laboratory data</th>
<th>Pathology</th>
<th>Treatment</th>
<th>Reference #</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 F</td>
<td>Intracardiac mass Periaortitis</td>
<td>CRP (mg/dL)</td>
<td>7.42 N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>56 M</td>
<td>Lymphadenopathy</td>
<td>IgG (mg/dL)</td>
<td>1,969 N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>74 M</td>
<td>Lymphadenopathy</td>
<td>IgG4 (mg/dL)</td>
<td>782 4,193</td>
<td>7.5</td>
<td>547 N/A</td>
</tr>
<tr>
<td>63 F</td>
<td>Cholangitis</td>
<td>IgE (IU/mL)</td>
<td>0.20 1,475</td>
<td>5,593</td>
<td>10</td>
</tr>
<tr>
<td>70 M</td>
<td>Cholangitis</td>
<td>IgG4/IgG ratio (IU/mL)</td>
<td>0.30 1,040</td>
<td>80.8</td>
<td>N/A</td>
</tr>
<tr>
<td>68 M</td>
<td>Periaortitis</td>
<td>PSL dosage (mg/day)</td>
<td>0.20 1,020</td>
<td>40.1</td>
<td>N/A</td>
</tr>
<tr>
<td>57 M</td>
<td>Periaortitis</td>
<td>Outcome</td>
<td>13.85 350</td>
<td>1,789</td>
<td>18.8</td>
</tr>
</tbody>
</table>

N/A: not available, TIN: tubulointerstitial nephritis
The authors state that they have no Conflict of Interest (COI).

Acknowledgement
We thank Mr. Tom Kiper for his review of the manuscript.

References


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