

[CASE REPORT]

Retroperitoneal Fibrosis Diagnosed as IgG4-related Disease after 35 Years

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Abstract:

In 1982, we reported a case of retroperitoneal fibrosis (RPF) exhibiting various clinical manifestations. Our current understanding of immunoglobulin G4 (IgG4)-related disease led us to consider it as a possible diagnosis because all of the patient's clinical features could be explained by this disease entity. To confirm our hypothesis, we investigated the histopathological findings of resected specimens that had been stored for 35 years postoperatively. Typical pathological findings together with predominant IgG4⁺ plasma cell infiltration confirmed a potential diagnosis of IgG4-related RPF. Furthermore, we observed positive immunohistochemical staining for several molecules associated with T regulatory and T follicular helper cells.

Key words: IgG4-related disease, retroperitoneal fibrosis, T regulatory (Treg) cells, T follicular helper (Tfh) cells

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Introduction

Retroperitoneal fibrosis (RPF) is a rare disease characterized by chronic inflammatory and sclerotic or fibrotic tissue in the periaortic or peri-iliac retroperitoneum that encases adjacent structures. RPF, first described by Ormond (1), was shown to occasionally involve idiopathic sclerosing lesions in other organs, such as the bile duct in the form of sclerosing cholangitis and salivary glands in the form of sclerosing sialadenitis, as a clinical presentation referred to as multifocal fibrosis. In the 21st century, accumulating evidence on autoimmune pancreatitis suggests that immunoglobulin G4 (IgG4)-positive plasma cell infiltration might be a common pathological feature of fibrotic lesions in many of the involved organs in RPF. Currently, IgG4-related disease is a recognized clinical entity (2, 3), of which RPF is considered a disease manifestation.

Among the organs involved in IgG4-RD, retroperitoneal tissue is particularly difficult to obtain for assessment. Specifically, retroperitoneal involvement has been considered as

a manifestation of IgG4-RD only based on radiographical findings, following the establishment of IgG4-RD as a clinical entity. Accordingly, compared with other organs that are relatively easy to obtain, such as lymph nodes and salivary glands, few studies have conducted histochemical analyses of RPF in IgG4-RD.

In 1982, long before IgG4-RD was recognized as a distinct clinical disease, we reported a case of RPF exhibiting various clinical manifestations involving multiple organs (4). Our current understanding of IgG4-RD prompted us to explore the possibility that these clinical features in that case could be explained by a diagnosis of IgG4-RD. In this report, in addition to a brief description of the clinical course of the case from the initial diagnosis in 1982 until death, we re-evaluated the histopathological specimens preserved since 1982. In the same tissue specimens, we also performed immunohistochemical staining for several molecules known to be involved in IgG4-RD pathogenesis.

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Immunohistochemical staining

The only tissue material available from the current case was a formalin-fixed paraffin-embedded block consisting of sub-centimeter biopsy fragments. For detection of CD3, forkhead P3 (FOXP3), and CD117 (c-Kit), immunoperoxidase staining was performed using antibodies against CD3 (mouse monoclonal, clone LN10; Leica Biosystems, Newcastle, UK), FOXP3 (mouse monoclonal, clone PCH101, 1:100; Bioscience, Hudson, USA), and CD117 (rabbit polyclonal, 1:500; Dako, Carpinteria, USA), respectively, according to the manufacturer's instructions. Tissue sections were visualized using the horseradish peroxidase-labeled polymer method (EnVision FLEX system; Dako). Alexa488-conjugated mouse monoclonal anti-human CD4 (clone GK 1.5) and mouse monoclonal anti-human B cell lymphoma 6 (BCL6; clone LN22) antibodies were purchased from Santa Cruz Biotechnology (Dallas, USA) and Nichirei (Tokyo, Japan), respectively. Alexa594-conjugated goat anti-mouse antibody (Thermo Fisher, Waltham, USA) was employed as a secondary antibody to detect mouse anti-BCL6 antibody, and TO-PRO-3 (Thermo Fisher) was used to visualize nuclei. For immunofluorescence microscopy to detect CD4⁺BCL6⁺ cells, tissue specimens were examined to capture images using an LSM780/ELYRAS.1 confocal microscope (Carl Zeiss, Oberkochen, Germany).

Case report

In 1981, a 72-year-old man was initially referred to our hospital for the presence of mediastinal shadows on thoracic radiographs. Computed tomography (CT) revealed soft tissue anteriorly surrounding the heart from the aortic arch. In addition, tumor-like shadows were noted in the region surrounding the aorta and vena cava, crossing the bifurcation from the region proximal to the second lumbar vertebra. Furthermore, left ureteral obstruction and hydronephrosis, dilated bladder, left common iliac vein occlusion, and thrombus formation were observed. Ga scintigraphic findings revealed an abnormal uptake in the region from the middle mediastinum, base of the heart, and upper abdomen to the left pelvic cavity. In addition, enlargement of the submandibular glands and supraclavicular lymph nodes and hardening of the testicles were noted. An endocrinological evaluation revealed central diabetes insipidus. Furthermore, low testosterone and high luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels, which increased after the administration of LH-releasing hormone, suggested that hypogonadism was caused by testicular dysfunction, likely due to direct invasion of fibrosis into the testis and/or artery and spermatic cord veins. While the underlying etiology of these clinical manifestations was ill-defined, a benign-looking retroperitoneal mass was surgically removed to alleviate hydronephrosis. A histological examination re-

vealed that the mass consisted of fibrous tissue with marked infiltration of lymphocytes, plasma cells, and histiocytes. The administration of prednisolone (PSL) resulted in the rapid amelioration of all of the abovementioned abnormalities. The details of the clinical course were reported in 1984 (4).

The PSL dose was gradually tapered to 10 mg/day over 3 months, and the patient did not experience relapse until 1987. In March 1987, 4 months after tapering PSL from 10 to 2.5 mg/day, the patient developed bilateral lower extremity edema. Echocardiography and CT revealed multiple fibrotic masses in the pericardium and right ventricle, which were considered to have caused the edema of the lower extremities. Increasing the daily PSL dose from 2.5 to 30 mg dramatically reduced the lower extremity edema, and the size of the fibrotic lesions in the pericardium and right ventricle was rapidly reduced. Until his sudden death in 1992, likely due to a cardiac event, the patient was treated with 20 mg/day PSL and did not exhibit symptoms in other organs suggestive of systemic fibrosis.

A re-examination of the pathological samples surgically resected in 1982

In 2017, we re-investigated the histopathological specimens preserved since 1982. The majority of cells involved in the tissues were mature lymphocytes and plasma cells, which were widely distributed within the tissue. Within these lymphoplasmacytic infiltrates, spindle cells resembling fibroblasts and myofibroblasts were found to form whorls, a typical indicator of storiform fibrosis (Fig. 1A and B). Venous channels were obliterated by a dense lymphoplasmacytic infiltrate within both the venous walls and lumen, suggestive of obliterative phlebitis (Fig. 1C and D). Arteries and arterioles were also occasionally inflamed (data not shown). Immunohistochemical staining for IgG4 revealed that a large majority of the infiltrated plasma cells were IgG4⁺ (>200/high-power field), and the IgG4⁺/IgG⁺ ratio was >70% (Fig. 1E-H).

Immunohistochemical staining for Tfh, Treg, and mast cells

We also performed immunohistochemical staining for several molecules proposed to be involved in the pathogenesis of IgG4-RD, including FOXP3, a transcriptional factor involved in the differentiation of Treg cells that are CD3⁺FOXP3⁺; CD117 (c-kit), a marker of mast cells; and BCL6, a marker of Tfh cells that are CD4⁺BCL6⁺. CD3⁺T cell infiltration was observed in areas with and without prominent fibrosis (Fig. 2A-C), which consisted of roughly equal numbers of CD4⁺ and CD8⁺T cells (not shown). There was also infiltration of many FOXP3⁺ lymphoid cells (Fig. 2B) and CD4⁺BCL6⁺ cells (Fig. 2E-H). Only a small number of CD117⁺ cells were found throughout the specimen (Fig. 2D). These findings are compatible with the pathological characteristics of IgG4-related disease.

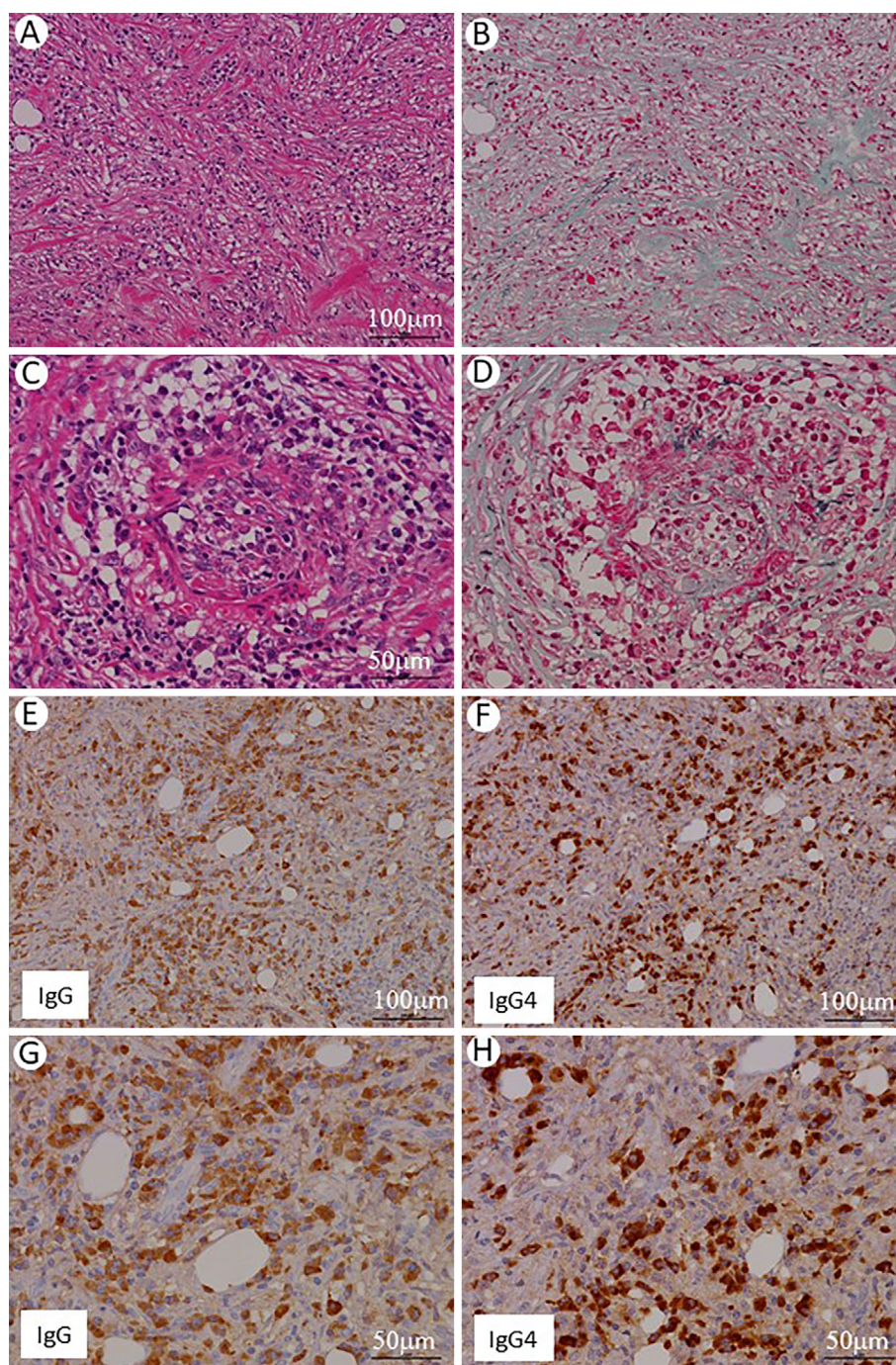


Figure 1. Histopathological findings of the surgically-resected retroperitoneal mass. A, B: Spindle cells resembling fibroblasts and myofibroblasts, organized in whorls that are typically observed in storiform fibrosis, are found within the lymphoplasmacytic infiltrate. (C, D) Venous channels are obliterated by a dense lymphoplasmacytic infiltrate within both the venous walls and the lumen, suggestive of obliterative phlebitis. (E-H) Immunohistochemical staining for IgG4 showing that the majority of the infiltrated plasma cells are IgG4⁺ (>200/high-power field), and the IgG4⁺/IgG⁺ ratio is >70%. A, C: Hematoxylin and Eosin staining; B, D: Elastica-Masson staining.

Discussion

The most significant impact of the establishment of IgG4-RD as a distinct and new disease entity is its unification of a large number of medical diagnoses that were previously considered to be idiopathic fibrosis confined to single organ

systems (2, 3). The re-evaluation of the pathological findings using stored specimens surgically resected 35 years ago revealed the typical findings of IgG4-RD, including storiform fibrosis, obliterative phlebitis, and predominantly IgG4⁺ plasma cell infiltration. These findings confirmed that the current case was consistent with IgG4-related RPF. Since its proposal as a distinct clinical entity, a number of studies

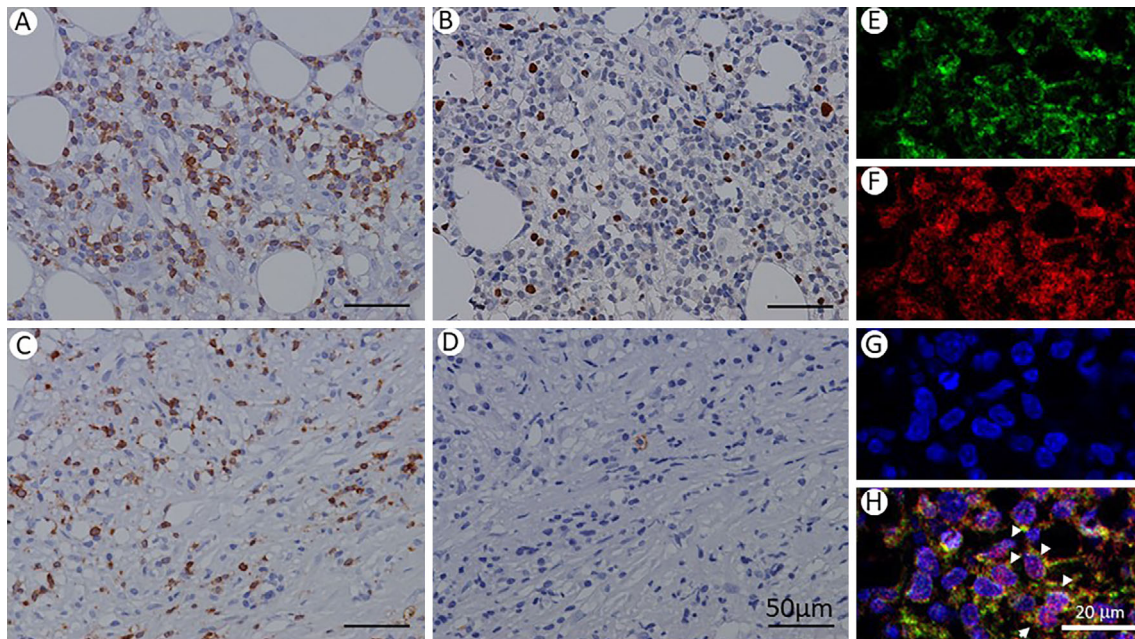


Figure 2. Immunohistochemical phenotypes of mononuclear cells. (A-D) In areas, FOXP3⁺ lymphoid cells constitute a significant proportion of CD3⁺ T cells (A, CD3; B, FOXP3). CD117⁺ mononuclear cells are rarely found in the fibrotic areas compared with CD3⁺ T cells (C, CD3; D, CD117). (E-H) Immunofluorescence confocal laser microscopy showing the expression of CD4 (green) and BCL6 (red) in cells of the retroperitoneal tissue using TO-PRO-3 (blue) to label nuclei.

have reported on the retrospective examination of stored specimens of several organs (5, 6). Although IgG4-RD might have developed in other patients long before its recognition as a distinct entity, to our knowledge, this might be the earliest pathologically confirmed case.

Following its establishment, retroperitoneal involvement tended to be diagnosed as a manifestation of IgG4-RD only by radiographical findings, due to the anatomic difficulty of obtaining biopsy specimens. Accordingly, compared with diseases involving other organs, relatively few studies have conducted histochemical analyses of IgG4-RPF. In the current case, we confirmed the presence of several molecules associated with Tfh and Treg cells, consistent with the findings of previous reports, including one from our group showing disease involvement in other organs (7-10), and further confirmed our diagnosis of a retroperitoneal mass, revisited 35 years after the initial diagnosis. In contrast, we found only a small number of CD117⁺ mast cells, which has been reported in a recent study on salivary glands (11). We speculate that this difference between the present and previous reports might be due to distinct microenvironmental features and/or the degree of disease progression within the involved organs.

Although not histologically confirmed, the clinical features observed in multiple organs in the current case, including the mediastinum, submandibular glands, and testicles/epididymis, may be explained as a manifestation of IgG4-RD. In addition, although brain CT did not reveal any abnormalities, the results of the endocrinological examination, including a low antidiuretic hormone level and increased

urinary osmolality after the administration of desmopressin, strongly suggest central diabetes insipidus, which might have been caused by IgG4-induced hypophysitis. Furthermore, low testosterone and high LH and FSH levels, which were increased after the administration of LH-releasing hormone, suggest that hypogonadism might be caused by testicular dysfunction, probably due to direct RF invasion of the testicles and/or arteries and veins of the spermatic cord. To our knowledge, there are no reports of hypogonadism due to IgG4-related orchitis/epididymitis.

A favorable response to systemic steroids lends further support to our hypothesis that all symptoms in the present case can be explained by IgG4-RD. However, it is now evident that there is a marked tendency to relapse during steroid tapering and that maintenance therapy is necessary in most cases. Indeed, tapering of the PSL dose to 2.5 mg/day in our patient led to the appearance of pericardial and intra-ventricular fibrotic masses, which dramatically improved after increasing the dose to 20 mg/day.

In contrast, laboratory and radiographical findings suggesting the presence of pancreatitis, the most frequently recognized manifestation of IgG4-RD, were not observed at any point in the clinical course. More sensitive techniques, such as magnetic resonance imaging and ¹⁸F-fluorodeoxyglucose-positron emission tomography, which were not clinically utilized 35 years ago, might have confirmed the involvement of other organs, including the pancreas.

Although IgG4-RD is currently recognized as a discrete disease entity, its pathogenesis remains poorly understood. Whether IgG4⁺ plasma cells play a central role or are only a

consequence of the fibro-inflammatory process remains unclear. IgG4-RD encompasses a wide spectrum of clinical presentations, from single to multiple organ involvement, and some cases fail to show a favorable response to steroids. In addition, pathologically, IgG4-RD can resemble other diseases, such as Castleman disease and mucosa-associated lymphatic tissue (MALT) lymphoma. Continued advances in medical research have led to the recognition of previously unknown disorders, such as IgG4-RD. Therefore, clinically relevant definitions that correlate more closely with the clinical course and treatment response might be established in the future.

Finally, we would like to emphasize the importance of re-evaluating previous cases in light of current medical knowledge of the disease. This concept, along with the long-term storage of specimens as in the current case, will aid in achieving further medical progress and effectively managing patients suffering from illnesses. We learned about the historical transition of IgG4-RD from this case and believe that our findings will contribute to the better understanding of the novel pathogenesis of IgG4-RD and further medical progress. This case well represents the concept of ‘visiting old, learning new’ as described by the Analects of Confucius.

In summary, this case illustrates the pathological diagnosis of IgG4-related RPF presenting with various clinical manifestations involving multiple organs using specimens stored for 35 years. Furthermore, this is the first case of IgG4-RPF with the confirmed involvement of Tfh and Treg cells.

The authors state that they have no Conflict of Interest (COI).

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