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【 CASE REPORT 】

Clinical Features of Fibrosing Mediastinitis in Japanese Patients: Two Case Reports and a Literature Review

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Abstract:
Fibrosing mediastinitis (FM) is a rare fibroinflammatory disease of the mediastinum with an etiology and clinical features that vary by world region. The characteristics of FM in Japan are still unknown. We herein report two Japanese patients with FM who were treated with corticosteroids and responded well. We also reviewed the Japanese literature on PubMed® and summarized the characteristics of 27 Japanese FM patients, including our two patients. In Japan, the predominant cases were those without a specific cause, were diffusely distributed, and responded well to corticosteroid therapy.

Key words: fibrosing mediastinitis, sclerosing mediastinitis, mediastinal fibrosis, corticosteroid therapy, Japanese

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Introduction

Fibrosing mediastinitis (FM), also known as sclerosing mediastinitis or mediastinal fibrosis, is a rare disease characterized by the proliferation of fibrous tissue within the mediastinum (1). Patients with FM may present with symptoms of compression and obstruction of the mediastinal structures including the superior vena cava (SVC), pulmonary vessels, tracheobronchial airways, and esophagus (2).

The etiology of FM can be divided into idiopathic and secondary. The causes of secondary FM include granulomatous infections (histoplasmosis, tuberculosis, aspergillosis, blastomycosis, or other fungal infections), sarcoidosis, and mediastinal irradiation (3). Many reviews from the United States show that the most common cause is histoplasmosis (4). The causes of FM differ depending on the world region. In some reviews, sarcoidosis was the most common cause in France (5), whereas in China, many cases were related to tuberculosis (6). Except in the United States, patients in the reviews were seldom associated with histoplasmosis. When no specific cause can be found, FM is classified as idiopathic. The pathogenesis of idiopathic FM is unknown, but many case reports describe the pathophysiology of FM as being related to autoimmune disease or idiopathic fibroinflammatory disorders (3). Examples of autoimmune disease include anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, Behçet disease, and large-vessel arteritis. Examples of idiopathic fibroinflammatory disorders include retroperitoneal fibrosis, sclerosing cholangitis, and Riedel thyroiditis, and these may coexist with IgG4-related disease (1, 3).

Depending on the etiology, the medical features of FM vary in terms of symptoms, extent of lesions, response, and outcome. It is believed that there is no curative treatment for FM, so the purpose of treatment is to relieve symptoms and avoid life-threatening situations by using vascular or airway stents or performing surgery (1, 7). Corticosteroid therapy is not considered to benefit the typical FM patient (1, 2, 8). Some cases of FM have been reported in Japan, but the characteristics of FM in Japan remain unknown.

We herein report two cases of FM and review the Japanese literature on FM to compare the features, etiologies, and treatments with those of other countries.

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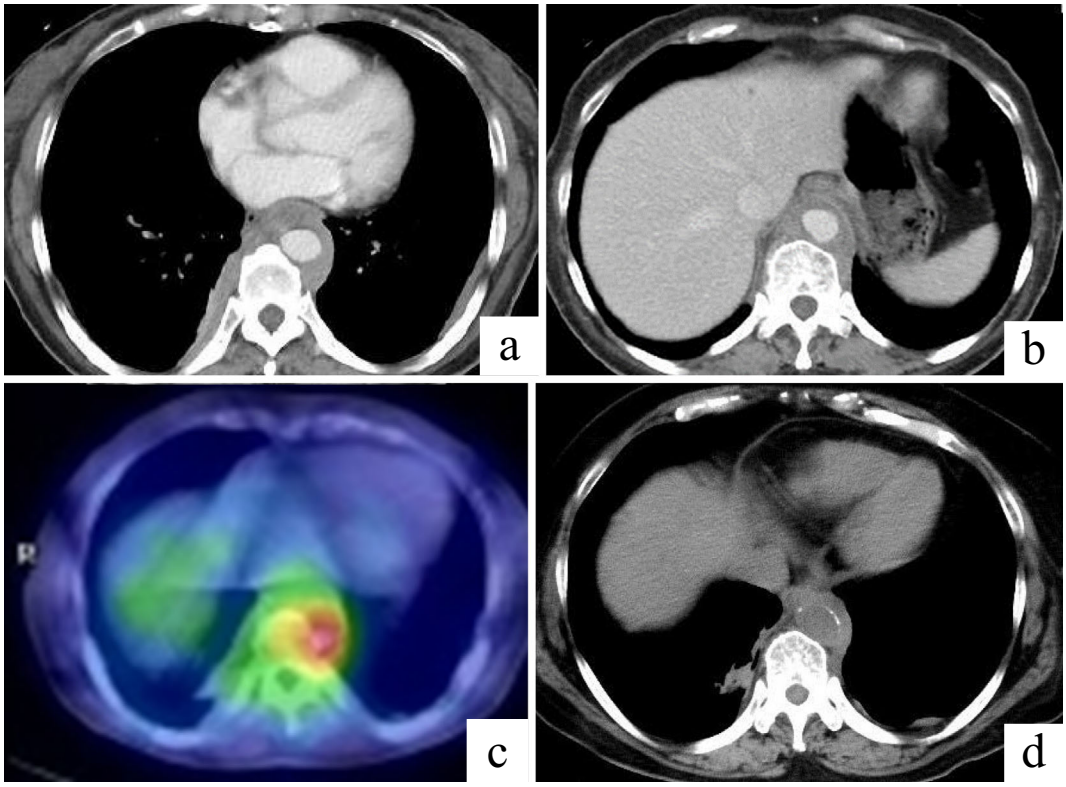

Figure 1. **(a, b) Chest computed tomography (CT) showed a diffuse mass surrounding the descending aorta and the thoracic and lumbar spine. (c) Gallium-67 scintigraphy showed accumulation in the mass. (d) CT showed the recurrence of lesions around the descending aorta 4 months after discontinuation of corticosteroids.**

Case Reports

Case 1

A 62-year-old woman was admitted to our hospital with a 3-month history of dull back pain. Her medical history was unremarkable. Her physical examination was normal, and she had no fever. Chest computed tomography (CT) showed a diffuse mass surrounding the descending aorta and the thoracic and lumbar spine (Fig. 1a, b). The lymph nodes were free of calcification. Gallium-67 scintigraphy showed accumulation in the mass (Fig. 1c). Laboratory examinations revealed an elevated erythrocyte sedimentation rate of 84 mm/h and C-reactive protein (CRP) level of 8.17 mg/dL. IgG4 and tumor markers were within the normal range. Her serologic tests were negative for anti-histoplasma antibody and interferon-γ release assay (IGRA).

A thoracoscopic surgical biopsy was performed to obtain a histological diagnosis. Biopsy specimens revealed diffuse fibrotic lesions with hyalinization and the focal infiltration of lymphocytes (Fig. 2a, b). No neoplastic lesions or granulomas were observed. Immunostaining for IgG4 is shown in Fig. 2c. The $IgG4^+/CD138^+$ plasma cell ratio was about 3%, so we judged the specimen to not be immunoreactive for IgG4. Therefore, the pathological diagnosis was FM.

Corticosteroid treatment (prednisolone 30 mg/day) was started. Thereafter, her back pain improved, and her CRP level returned to the normal range. CT showed a reduction in the size of the mediastinal mass. She continued on low-dose corticosteroids for about 3 years but discontinued them due to her good health condition. However, after 4 months, the lesions and symptoms recurred (Fig. 1d), and her CRP level rose to 2.67 mg/dL. Corticosteroid treatment (prednisolone 10 mg/day) was restarted, which relieved her symptoms and improved the mediastinal lesions. She then continued to take prednisolone 5 mg/day, and her symptoms have remained stable for about one year after restarting the corticosteroid treatment.

Case 2

A 77-year-old man was admitted to our hospital because a routine medical checkup revealed an abnormal mediastinal contour on his chest X-ray. His medical history was unremarkable. His medical examination was normal, and he was afebrile. CT showed a diffuse mass surrounding the aortic arch and thoracic vertebrae and a discontinuous retroperitoneal mass along the bilateral common iliac arteries (Fig. 3a-c). There were no calcifications in the lymph nodes. ^{18}F-fluorodeoxyglucose-positron emission tomography-CT showed accumulation in the mass (standardized uptake value max: 4.97) (Fig. 3d). Laboratory tests revealed elevated levels of IgG of 2,675 mg/dL and IgG4 of 487 mg/dL. CRP and tumor markers were within normal limits. Autoimmune

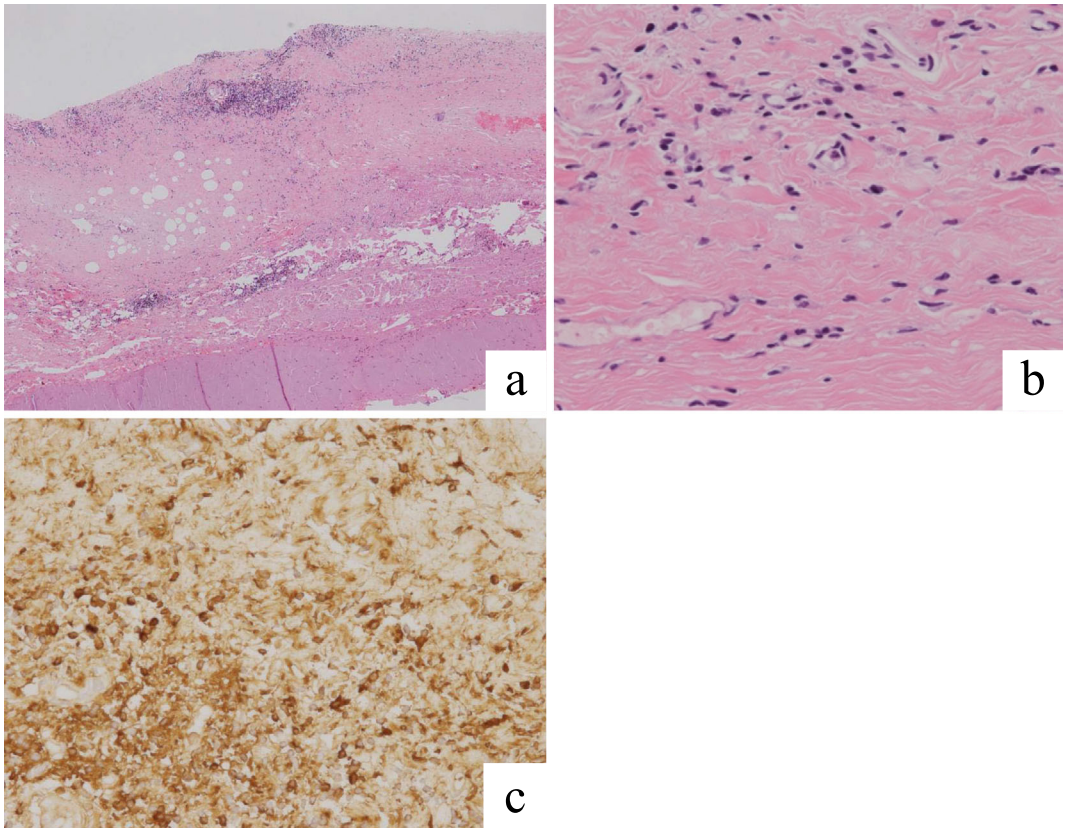

Figure 2. **(a, b) A thoracoscopic biopsy specimen revealed diffuse fibrotic lesions with hyalinization and focal infiltration of lymphocytes. Hematoxylin and Eosin staining (a: ×20, b: ×200). (c) The specimen was not immunoreactive for IgG4 (×200).**

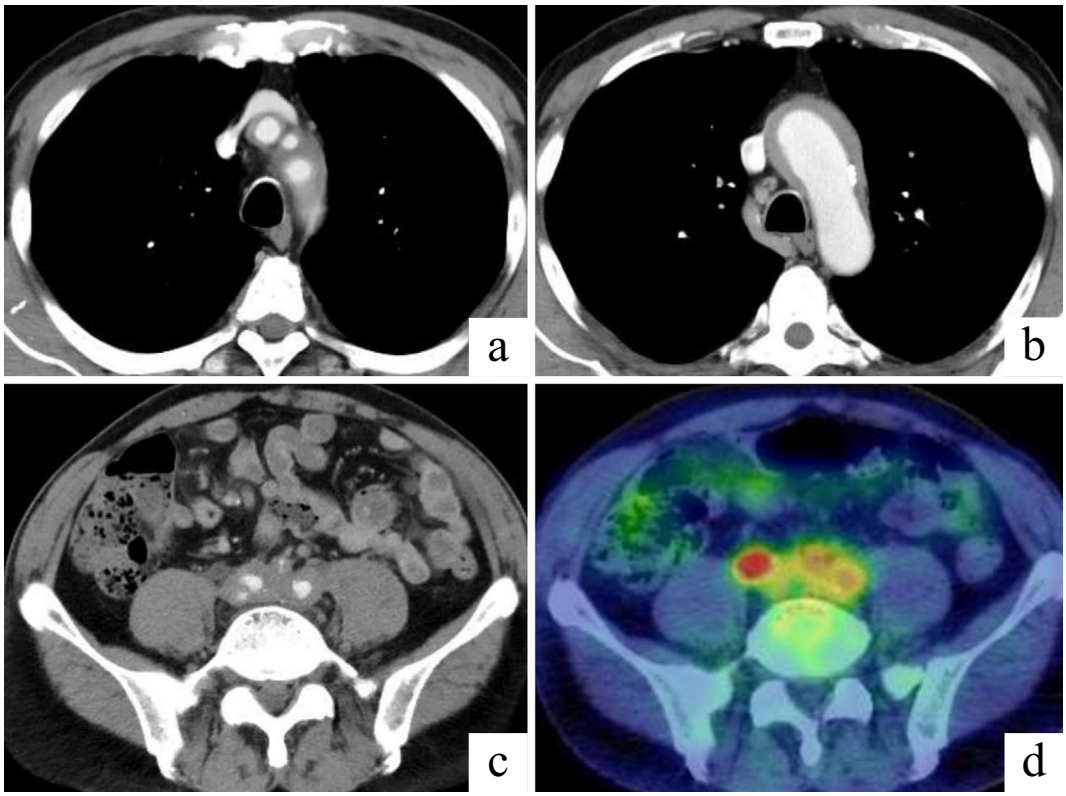

Figure 3. **(a, b) Chest computed tomography (CT) showed a diffuse mass surrounding the aortic arch and thoracic vertebrae. (c) Abdominal CT showed a discontinuous retroperitoneal mass along the bilateral common iliac arteries. (d) ^{18}F-fluorodeoxyglucose-positron emission tomography-CT showed accumulation in the mass.**

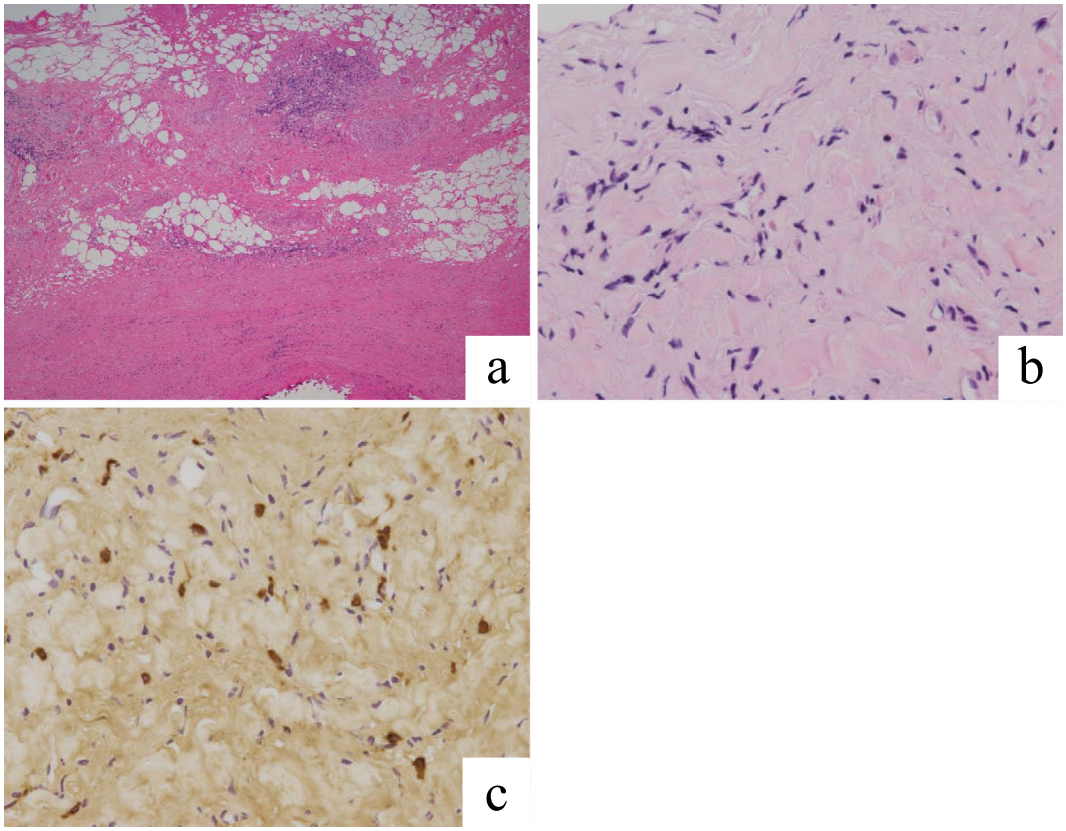

Figure 4. **(a, b) A thoracoscopic biopsy specimen revealed diffuse fibrotic lesions with hyalinization and focal infiltration of lymphocytes. Hematoxylin and Eosin staining (a: ×20, b: ×200). (c) The specimen was not immunoreactive for IgG4 (×200).**

antibodies were negative, as were his serologic tests for anti-histoplasma antibody.

A thoracoscopic surgical biopsy was performed to obtain a histological diagnosis. Biopsy specimens revealed diffuse fibrotic lesions with hyalinization and the focal infiltration of lymphocytes (Fig. 4a, b). No neoplastic lesions or granulomas were observed. Immunostaining for IgG4 is shown in Fig. 4c. The $IgG4^+/CD138^+$ plasma cell ratio was about 8%, so we judged the specimen to not be immunoreactive for IgG4. Therefore, the pathological diagnosis was FM.

Corticosteroid treatment (prednisolone 30 mg/day) was started. After that, CT showed a reduction in the size of the mediastinal and retroperitoneal lesions. Thereafter, the dose of prednisolone was reduced to 3 mg/day, and the mediastinal lesions have not relapsed for about 5 years after onset.

Discussion

We herein describe two cases of FM diagnosed by thoracoscopic biopsy. In both cases, the lesions were located along the aorta and spine, did not compress or obstruct mediastinal organs such as blood vessels, trachea, and esophagus, and responded well to corticosteroid therapy. The etiologies of both cases could not be identified.

FM is considered to be a clinicopathologic syndrome rather than a single disease (2). Many etiologies cause an excessive fibrotic reaction in the mediastinum. The cause of FM clearly relates to the area of the world from which it was reported, and each etiology can produce different phenotypic variations. Therefore, the FM characteristics may vary depending on the region. For example, a case series from the United States described 86 FM patients with 71 clinical and 15 histological diagnoses (2). The median age was 42 years and 54% were female. Only 5% were asymptomatic, and 83% had conclusive or suggestive evidence of histoplasmosis. Among the therapeutic interventions, 6% of patients received corticosteroids, 19% underwent nonsurgical intervention, and 21% underwent surgical treatment. Anti-inflammatory therapies including corticosteroids provided little benefit. In a French study reviewing 27 FM patients with pulmonary hypertension, the etiology was sarcoidosis in 13 (48%), confirmed or estimated tuberculosis in 9 (33%), and idiopathic in 3 (11%) (5). Twelve patients (44%) received corticosteroids. A case series in China reported on 20 FM patients (6). Their average age was 69.5 years and 60% were female. Among them, 40% had a history of old tuberculosis, 20% were diagnosed as having a latent tuberculosis infection based on the results of IGRA, with the strong involvement of tuberculosis, 45% received anti-tuberculosis drugs, and only 5% received corticosteroids. The therapeutic effect of corticosteroids was poor. As these examples illustrate, the clinical picture of FM depends on the area in which it occurs.

To date, the characteristics of Japanese FM patients are

still unclear. We therefore conducted a comprehensive search of the literature on MEDLINE®/PubMed® from 1992 to May 2020, using the terms "fibrosing mediastinitis", "sclerosing mediastinitis", and "mediastinal fibrosis". We thus found 25 case reports of Japanese patients with FM (9-32). The clinical characteristics of the 27 Japanese patients with FM, including the two present cases, are summarized in Table. We excluded some articles in commercial journals from medical publishers or case reports with an unclear clinical course. Regarding the distribution of the disease, we followed Sherrick's criteria (33), in which a pattern showing a localized soft-tissue mass is classified as localized type, and a pattern showing a diffuse homogenous soft-tissue process throughout the mediastinum is classified as diffuse type. The median age at diagnosis was 61 years, and 14 of the 27 patients (52%) were male. The main complaints were chest and back pain, face-to-arm swelling, dyspnea, and hoarseness, but 8 of the 27 (30%) were asymptomatic. Regarding distribution, 17 cases (63%) were of the diffuse type. Only one patient (case 6) had a history of old tuberculosis suffered 40 years ago, and the relationship between FM and tuberculosis was unknown. Four patients tested for IGRA received negative results. Nine of the 27 (33%) were tested for histoplasmosis, 5 had serological antibody tests, and 5 had immunostaining of histological specimens, but all results were negative. Six patients (22%) were serologically or histologically IgG4 positive. Serum IgG4 was measured in 9 patients and ranged from 7.9 to 1,940 mg/dL. When the serum IgG4 cutoff value was set at 135 mg/dL (34), 5 of the patients were positive. Of the 10 patients with histological staining of IgG4, 5 were pathologically diagnosed as having IgG4-related FM. In one patient (case 21), because serum myeloperoxidase-ANCA was positive, FM was suspected to be related to ANCA. A specific etiology was not detected in 20 of the 27 patients (74%). The main treatment was corticosteroid therapy, which was administered to 18 patients (67%), of whom 13 responded well, 3 partially responded (i.e., improvements in symptoms and lesion size were described as mild or partial), and 2 patients (case 2 and case 13 with chylous effusion) did not respond at all.

In Japan, although the possibility of IgG4-related disease was not investigated in more than half of the patients, there were many cases in which a specific cause could not be detected, so more cases were diagnosed as "idiopathic" than in other countries. The etiology of FM depends on the prevalence of each disease. As histoplasmosis is rarely detected in Japan, it is unlikely to cause FM. Although sarcoidosis is a common disease in Japan, it has a lower incidence than that in France, where sarcoidosis was the main cause of FM (5). The incidence of sarcoidosis per 100,000 person-years was reported to be 1.01 in Japan (35) and 4.9 in France (36). Japan is a country with a moderate prevalence of tuberculosis, but compared to China, where tuberculosis was the main cause of FM, as mentioned above (6), fewer people are affected. According to a World Health Organization report, the estimated incidence of tuberculosis per 100,000 person-years in 2018 was 61 in China and 14 in Japan (37). International comparisons of the prevalence of autoimmune diseases including IgG4-related diseases are not easy. In Japan, the prevalence of IgG4-related diseases was reported to be 0.28 to 1.08 per 100,000 (38), but, in fact, many potential cases may exist. It is unclear whether many FM cases in Japan are truly "idiopathic". Likely, the cause could not be identified because of the low prevalence of specific diseases that cause FM, resulting in the high rate of idiopathic cases.

It is worth noting that more Japanese patients were given corticosteroids and that their response to corticosteroid therapy was better than elsewhere in the world. In general, corticosteroid responsiveness is expected to be higher with a higher degree of infiltration of inflammatory cells and lower with a higher degree of fibrosis. Flieder et al. divided FM into three stages based on histological patterns such as cell infiltration and fibrotic changes (39): stage I with edematous fibrous mucinous tissue with inflammatory cells; stage II with a thick glassy band of collagen with focal stromal spindle cells, lymphocytes, and plasma cells; and stage III with dense acellular collagen interspersed with lymphoid follicles. Of the 27 FM cases in Japan, 6, including the present two, were evaluated by these criteria, and all were judged to be stage II. Among the other cases, lymphocyte infiltration was common in most of them. Meanwhile, in the US report, 13 of 30 (43%) patients were in stage III, with few inflammatory cells (39). Thus, we consider the cause for the good response to corticosteroid therapy in Japanese FM patients to be incomplete fibrosis and relatively high cell infiltration. In addition, more patients in Japan were diagnosed as being asymptomatic than in other regions, and it is possible that many patients were able to start treatment early before fibrosis progressed. This could be another reason why the steroid response was good in Japan. It is also thought that specific genotypes, including human leukocyte antigen (HLA)-A2 and HLA DQB1*04:02, contribute to the onset of FM (40, 41). Differences in genetic background may also be associated with clinical differences.

Our report is associated with several limitations. First, our review is a collection of published case reports, not a case series from a single center. There may be some selection bias in that the collected cases received good therapeutic effect from corticosteroids. Therefore, the Japanese case series cannot be easily compared to reports from the case series of other countries. However, in Japan, where the number of FM cases is small, it is difficult to create a case series with an adequate number of cases. Second, this review may have been insufficient in searching for the cause of FM. Screening for infectious diseases, including histoplasmosis, and autoimmune diseases, including IgG4-RD, was often insufficient. In particular, IgG4-RD is a relatively new disease concept and it has not been well investigated so far. There are many latent cases, which therefore need to be investigated actively in the future. To undertake international comparisons, it will be necessary to create diagnostic guidelines for FM and perform comparisons under the same conditions.

Table. **Characteristics of 27 Japanese Cases of Fibrosing Mediastinitis.**

Case	Age	Sex	Main symptoms	Location	Histological stage	Histoplasma (Serum Ab/ Tissue)	Serum IgG4 (mg/dL)	Immunostaining of IgG4	Serum CRP (mg/dL)	Symptomatic compressed organs	Main treatment	Outcome/ Recurrence	Ref
1	32	M	Facial swelling, neck tightening	Diffuse	NA	NA	NA	NA	2.23	SVC	Bypass surgery	Improved	9
2	54	M	Dyspnea, leg edema	Diffuse	NA	NA	NA	NA	Elevated	Thoracic duct	Steroid	Not improved	10
3	28	F	Chest pain, left shoulder pain, hoarseness	Diffuse	NA	NA	NA	NA	NA	Nerves	Resection, steroid, tranilast	Improved	11
4	51	F	Fever	Local	NA	NA	NA	NA	6.8	No	Resection	Improved	12
5	56	M	Dyspnea	Diffuse	NA	NA	NA	NA	7.66	No	Steroid	Partially improved	13
6	68	M	Hoarseness	Diffuse	II	NA/negative	NA	NA	6.69	Nerves	Steroid	Improved	14
7	63	F	Facial swelling	Local	NA	NA	NA	NA	NA	SVC	Resection, bypass surgery	Improved/partially recurred	15
8	62	M	Headache, face and right shoulder swelling	Local	NA	NA	NA	NA	NA	SVC	Balloon dilatation, stenting	Improved/partially recurred	16
9	7	M	None	Local	II	Negative/NA	NA	NA	NA	No	Medical observation	Stable	17
10	67	F	Fever	Local	NA	NA	NA	NA	NA	No	Resection	Improved	18
11	52	M	Back pain	Diffuse	NA	NA	392*	Positive	9.3	No	Steroid	Improved	19
12	65	F	Hoarseness	Diffuse	NA	NA/negative	NA	NA	0.4	Nerves	Steroid	Improved	20
13	61	M	None	Diffuse	NA	NA	583*	Positive	NA	Ureter	Steroid	Improved	21
14	75	F	Left neck swelling	Diffuse	NA	NA/negative	NA	NA	NA	Carotid artery	Steroid	Improved	22
15	56	F	Dyspnea	Diffuse	NA	NA	127	Positive	NA	Main bronchus	Steroid	Improved	23
16	54	M	None	Local	NA	NA	NA	NA	NA	No	Resection	Stable	24
17	68	M	Intermittent claudication	Diffuse	NA	NA	NA	NA	0.26	Iliac artery	Steroid, saireito	Partially improved	25
18	28	M	Dyspnea	Local	NA	Negative/ negative	20.9	Negative	NA	Thoracic duct	Steroid, octreotide	Improved (steroid ineffective)	26
19	36	M	Abdominal pain	Local	II	Negative/NA	NA	NA	5.2	No	Resection	Improved	27
20	54	M	Chest pain, dyspnea	Diffuse	II	NA	NA	Negative	0.07	Pulmonary artery, main bronchus	Steroid	Partially improved	28
21	52	F	Malaise, weight loss	Diffuse	NA	NA/negative	NA	NA	12.6	No	Steroid, CPA	Improved	29
22	61	F	None	Local	NA	NA	7.9	Negative	NA	No	Resection, bypass surgery	Stable	30
23	68	F	None	Local	NA	NA	NA	NA	NA	No	Resection, steroid	Improved	31
24	66	F	None	Diffuse	NA	NA	276*	Positive	4.11	No	Steroid	Improved	32
25	78	F	None	Diffuse	NA	NA	1940*	Positive	0.03	No	Steroid	Improved	32
26	62	F	Chest pain	Diffuse	II	Negative/NA	97.5	Negative	8.17	No	Steroid	Improved/recurred	Present Case
27	77	M	None	Diffuse	II	Negative/NA	487*	Negative	0.27	No	Steroid	Improved	Present Case

Ab: antibody, NA: not available, SVC: superior vena cava, CPA: cyclophosphamide

* Cutoff value of serum IgG4>135 mg/dL

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In conclusion, we reviewed 27 cases of FM in Japan whose cause could not be identified and found that corticosteroid therapy was effective in treating many of them. In patients with incomplete fibrosis or suspected autoimmune disease, it may therefore be worthwhile to try corticosteroid therapy.

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

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