IgG4-related fibrosing mediastinitis: clinical presentation, treatment efficacy and comparison with IgG4-RD without fibrosing mediastinitis

P. Zhang[1], X. Han[2], J. Li[1], Z. Liu[1], H. Lu[1], X. Luo[1], C. Liu[3], L. Peng[1], Y. Fei[1], X. Zeng[2], W. Zhang[1], X. Zeng[1]

[1]Department of Rheumatology, Peking Union Medical College Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Key Laboratory of Rheumatology and Clinical Immunology, Ministry of Education & National Clinical Research Center for Dermatologic and Immunologic Diseases (NCRC-DID), Beijing, China; [2]Department of General Internal Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Beijing, China; [3]Department of Rheumatology, The Second Hospital of Dalian Medical University, Beijing, China.

Abstract

Objective

This study aimed to investigate the clinical characteristics and treatment efficacy of immunoglobulin G4 (IgG4)-related fibrosing mediastinitis (IgG4-RFM) and to compare IgG4-RFM patients with IgG4-related disease (IgG4-RD) patients without fibrosing mediastinitis (FM).

Methods

Twenty IgG4-RFM patients and 60 randomly matched IgG4-RD patients without FM from a prospective cohort at the Peking Union Medical College Hospital (PUMCH) were enrolled from 2011 to 2019. Patient demographic data, clinical characteristics, laboratory parameters and treatment efficacy were analysed.

Results

The prevalence of IgG4-RFM in our cohort was 2.8%. The average age was 51.7±14.8 years, and the patients were predominantly male (60.0%). Periaortic masses (75.0%) and paravertebral masses (35.0%) were the most common characteristic imaging findings of IgG4-RFM. Compared with male patients with IgG4-RFM, a lower percentage of female patients had abdominal aorta involvement ($p=0.015$). IgG4-RFM patients had a shorter disease duration; lower percentage of allergy history, submandibular gland involvement, and pancreas involvement; lower serum IgG4; higher erythrocyte sedimentation rate (ESR) and high-sensitivity C-reactive protein (hsCRP) levels; and a higher percentage of single organ involvement than patients without FM ($p<0.001$, $p=0.008$, $p=0.033$, $p=0.001$, $p=0.027$, $p=0.007$, $p=0.004$ and $p=0.047$, respectively). After treatment, 94.7% of patients achieved a mediastinal soft tissue reduction of >30%.

Conclusion

IgG4-RFM is a distinct fibrotic subtype of IgG4-RD. Periaortic masses and paravertebral masses were the most common characteristic imaging findings of IgG4-RFM. Most IgG4-RFM patients respond well to glucocorticoid (GC) and immunosuppressant treatments.

Key words

IgG4-related disease, fibrosing mediastinitis, treatment

*Panpan Zhang, MD**
*Xinxin Han, MD**
Jieqiong Li, MD
Zheng Liu, MD
Hui Lu, MD
Xuan Luo, MD
Changyan Liu, MD
Linyi Peng, PhD
Yunyun Fei, MD, PhD
Xuejun Zeng, MD, PhD
Wen Zhang, MD, PhD
Xiaofeng Zeng, MD

**These authors contributed equally.*

Please address correspondence to:
Wen Zhang,
Department of Rheumatology,
Peking Union Medical College Hospital.
No. 1 Shuai Fu Yuan,
Dong Cheng District.
Beijing, 100730, China.
E-mail: zhangwen91@sina.com

Xuejun Zeng
E-mail: zxjpumch@126.com

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Introduction

Immunoglobulin G4 (IgG4)-related disease (IgG4-RD) is a fibroinflammatory disease that presents a distinctive histopathological appearance of dense lymphoplasmacytic infiltrate with abundant IgG4-positive plasma cells and characteristic fibrosis (1). IgG4-RD can involve one or more organs, such as the lacrimal glands, salivary glands, pancreas and retroperitoneum, with the appearance of inflammatory swelling or tumefactive lesions (1-4).

Fibrosing mediastinitis (FM) is a rare disease characterised by an aggressive fibroinflammatory process within the mediastinum (5-7). Progressive fibrosis caused by the proliferation of invasive fibrous tissue within the mediastinum frequently results in compression and functional compromise of vital mediastinal structures (6, 7). Consequently, FM can lead to substantial disease-related morbidity and perhaps even increased mortality (6). Increasing evidence suggests that IgG4-RD could affect the mediastinum, manifested as IgG4-related fibrosing mediastinitis (IgG4-RFM). In a recent study, a histopathological overlap between IgG4-RD and FM was described. FM may appear as an isolated lesion of IgG4-RD (8). Due to the low incidence of IgG4-RFM, the published studies were mainly case reports describing the clinical manifestations, imaging characteristics and treatment efficacy of patients. IgG4-RFM is now classified as a fibrotic subtype of IgG4-RD, differing from the proliferative subtype in many aspects (9). Therefore, large prospective studies may help clarify the complete clinical picture of IgG4-RFM. In this study, we aimed to analyse the clinical characteristics and evaluate the treatment efficacy of patients with IgG4-RFM. In addition, we also validated differences between IgG4-RFM and the proliferative subtype of IgG4-RD.

Methods

Patient enrolment

In our prospective cohort of IgG4-RD carried out at the Peking Union Medical College Hospital (PUMCH; registered with the ClinicalTrials.gov ID: NCT01670695), 710 new-onset IgG4-RD patients have been enrolled since January 2011 who fulfilled the 2011 comprehensive diagnostic criteria (10). The diagnosis of IgG4-RD was based on the following criteria: (1) a clinical examination showing characteristic diffuse/localised swelling or masses in a single organ or multiple organs; (2) an elevated serum IgG4 concentration (>135 mg/dL); and (3) a histopathologic examination showing (a) marked lymphocytic and plasma cell infiltration and fibrosis or (b) infiltration of IgG4+ plasma cells [a ratio of IgG4+/IgG+ cells >40% and >10 IgG4+ plasma cells per high power field (HPF)]. Patients with antineutrophil cytoplasmic antibody-associated vasculitis were excluded. In our cohort, 540 patients were classified as the proliferative type, 170 patients belonged to the fibrotic type (including IgG4-RFM, retroperitoneum fibrosis, aortitis, pachymeningitis, sclerosing mesenteritis) or a mixture of both (11). In order to avoid confounding factors, the control groups consisted of randomly selected patients with the proliferative type of IgG4-RD, with three controls matching one case.

The study was conducted in compliance with the Declaration of Helsinki and was approved by the Ethics Committee of PUMCH. All patients provided written informed consent.

Diagnosis of IgG4-RFM

A patient was diagnosed with IgG4-RFM needs to meet the following criteria: 1) a mediastinal mass surrounding adjacent structures such as the aorta, airway, oesophageal, pericardium, thoracic vertebra or nervous within mediastinum (12) (13); 2) other causes, such as malignant tumours, granulomatous vasculitis or infections, were excluded; and 3) a good response to glucocorticoid (GC) therapy. Patients who only presented as aortitis (vessel wall thickening or vascular dilation) without perivascular soft tissue were not included.

Clinical data and laboratory and imaging examinations

Patient data, including age, sex, disease duration, history of allergies, treatment

Table I. Demographic features of patients with/without IgG4-related FM.

Demographic features	IgG4 related FM (n=20)	IgG4-RD without FM (n=60)	*p*-value
Age at disease onset(years)	51.7 ± 14.8	54.4 ± 13.4	0.296
Disease duration (month), M (Q_1-Q_3)	8 (0-12)	28 (6-36)	<0.001*
Male (n, %)	12 (60)	40 (67)	0.79:1
Baseline IgG4-RD RI	9.2 ± 6.0	11.3 ± 6.5	0.186
Baseline PGA	5.6 ± 2.8	6.4 ± 2.5	0.226
Number of organs affected	3.4 ± 2.1	3.5 ± 1.9	0.818
Single organ involvement (n, %)	7 (35)	8 (13)	0.047*
History of allergy (n, %)	3 (15.0)	30 (50.0)	0.008*

FM: fibrosing mediastinitis; IgG4-RD RI: IgG4-RD responder index; PGA: physician's global assessment; * statistical significance.

strategy, symptom onset, affected organs, and follow-up time, were collected. The IgG4-RD responder index (IgG4-RD RI, 2015 version) (14) and physician global assessment (PGA) were evaluated at baseline and each follow-up. Laboratory parameters included routine blood analysis; liver function; kidney function; serum IgG, A, and M; serum IgG subclass; total serum IgE; C3 and C4; erythrocyte sedimentation rate (ESR); and high-sensitivity C-reactive protein (hsCRP) tests. CT, MRI, or PET/CT were performed to measure and evaluate organ involvement, including IgG4-RFM.

Treatment efficacy assessment

The therapeutic response of IgG4-RFM patients was defined as the shrinking of mediastinal soft tissues and reduced vessel wall thickness. To evaluate the alleviation of FM, the reduction in soft tissue or vessel wall thickness was classified into three categories: 0–30%, 31–70%, and >70%. Three standard

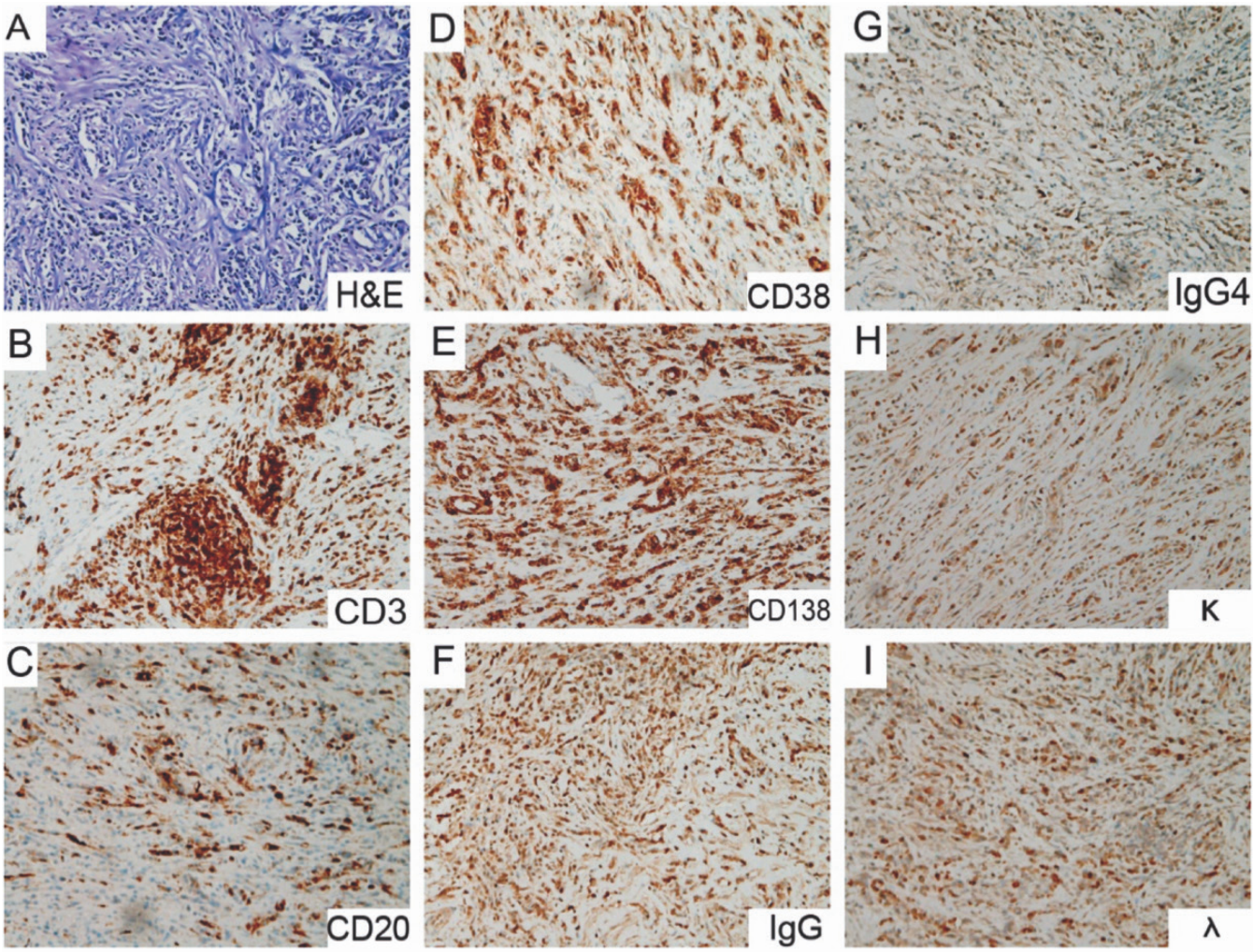

Fig. 1. Characteristic pathological features of 1 IgG4-RFM patient.
A: Haematoxylin and eosin staining showed dense lymphoplasmacytic infiltration and storiform fibrosis (20×); **B**: CD3 staining, dense infiltration of CD3+ T cells (20×); **C**: CD20 staining, scattered CD20+ B cells infiltration (20×); **D**: CD38 staining (20×); **E**: CD138 staining (20×); **F**: IgG staining, dense infiltration of IgG+ plasma cells (20×); **G**: IgG4+ staining, massive IgG4+ plasma cells infiltration (20×); **H**: Lambda chain staining (20×); **I**: Kappa chain staining (20×).

slices were made of anatomical structures which are typically involved in FM: 1) the transection of three major branches of the aortic arch (left subscapular artery, left common carotid artery and brachiocephalic trunk); 2) the transection of the aortic arch; 3) the thoracic vertebral body with greatest trans-axial area of involvement. 2D measurement of the area of the soft tissue surrounding the vessels, trachea and vertebral body was made in the standard slices. As shown in Supplementary Figure 1, by making small 5mm grids on the CT image, the amorphous soft tissue area could be estimated by counting the total number of grids involved (grids with more than 1/2 involvement were counted as 1, and those with less than 1/2 involvement were counted as 0). The reduction percentage after treatment was calculated as: (soft tissue area of the previous scan - soft tissue area of the current scan)/soft tissue area of the previous scan. If a patient has more than 1 standard slice of involvement, the reduction percentage of each slice was averaged.

The overall treatment response was assessed by the changes in IgG4-RD RI scores (14) and PGA scores (15). Clinical relapse was defined as the reappearance of clinical symptoms or imaging findings that worsened with or without elevated serum IgG4 levels (1, 7, 8).

Statistical methods

Statistical analyses were performed using IBM SPSS Statistics version 24.0 software (IBM, Armonk, NY, USA), Adobe Illustrator CC 2015 (Adobe, Cal, USA) and Prism software version 6.1 (GraphPad Software, La Jolla, CA, USA). Data are reported as the means ± standard deviation or median (Q1-Q3). Normally distributed data between two groups were analysed using independent-samples t-tests or paired-samples t-tests, and one-way analysis of variance was used to compare groups. Categorical data were analysed using the chi-square test or Fisher's exact test, while nonnormally distributed data were analysed using the rank sum test. A two-tailed *p*-value <0.05 was considered statistically significant.

Table II. Onset symptoms and organs affected of IgG4-RD patients with/without FM.

Symptoms and organs affected at baseline	IgG4 related FM (n=20)	IgG4-RD without FM (n=60)	*p*-value
Symptoms at disease onset (n, %)			
Back pain	5 (25.0)	1 (1.7)	0.003*
Cough	4 (20.0)	10 (16.7)	0.741
Hoarseness of voice	4 (20.0)	0 (0)	0.003*
Lymph node swelling	4 (20.0)	13 (21.7)	1.000
Abdominal pain	4 (20.0)	14 (23.3)	1.000
Chest pain	4 (20)	0 (0)	0.003*
Submandibular gland enlargement	3 (15.0)	26 (43.3)	0.031*
Arthralgia	3 (15.0)	4 (6.7)	0.358
Nasal congestion	3 (15.0)	9 (15.0)	1.000
Lower limb oedema	2 (10.0)	3 (5.0)	0.594
Lacrimal gland enlargement	2 (10.0)	26 (43.3)	0.007*
Fever	2 (9.5)	3 (5.0)	0.594
Dysphagia	1 (5.0)	0 (0)	0.250
Organs affected (n, %)			
Pleura	8 (40.0)	5 (8.3)	0.002*
Lymph node	7 (35.0)	23 (39.7)	0.505
Submandibular gland	5 (25.0)	31 (52.5)	0.033*
Lacrimal gland	5 (25.0)	29 (48.3)	0.057
Lung	3 (15.0)	21 (35.0)	0.076
Kidney	3 (15.0)	10 (20.0)	0.585
Prostate	3 (23.1)	7 (17.9)	0.403
Parotid gland	2 (10.0)	9 (15.5)	0.445
Bile duct	1 (5.0)	14 (24.1)	0.060
Pancreas	1 (5.0)	27 (45.0)	0.001*
Paranasal sinus	1 (5.0)	16 (27.6)	0.033

* statistical significance.

Table III. Laboratory parameters of IgG4-RD with/without FM.

Parameters	IgG4-related FM (n=20)	IgG4-RD without FM (n=60)	*p*-value
HgB (g/L)	133 ± 20	136 ± 15	0.461
WBC (10^9/L)	7.99 ± 2.85	6.50 ± 2.06	0.015*
PLT (10^9/L)	278 ± 76	219 ± 64	0.001*
Eos (%)	3.0 ± 3.2	4.4 ± 5.2	0.336
ESR (mm/h), M (Q_1-Q_3)	47 (13-73)	26 (6-36)	0.007*
hsCRP (mg/L), M (Q_1-Q_3)	16.23 (2.31-14.30)	5.60 (0.32-4.34)	0.004*
IgG (g/L)	22.35 ± 7.52	21.93 ± 13.48	0.896
IgA (g/L)	2.93 ± 1.01	2.12 ± 1.58	0.044*
IgM(g/L)	1.30 ± 0.90	0.90 ± 0.97	0.130
IgG1 (mg/L), M (Q_1-Q_3)	11488 (9780-13100)	10504 (7668-11100)	0.057
IgG2 (mg/L), M (Q_1-Q_3)	6401 (3920-8500)	6500 (4235-7550)	0.692
IgG3 (mg/L), M (Q_1-Q_3)	539 (206-806)	685 (292-1018)	0.361
IgG4 (mg/L), M (Q_1-Q_3)	8065 (1130-5540)	16573 (2743-20550)	0.027*
T-IgE (KU/L), M (Q1-Q3)	381.7 (44.6-553.0)	387.8 (13.4-508.5)	0.500
C3 (g/L)	0.845 ± 0.353	0.885 ± 0.305	0.718
C4 (g/L)	0.145 ± 0.089	0.156 ± 0.076	0.688
Cr (μmol/L)	88 ± 43	73 ± 19	0.315

* statistical significance.

Results

Demographic characteristics of IgG4-RFM

Among 710 IgG4-RD patients, 20 patients had IgG4-RFM, which included 7 (35.0%) with only FM and 13 (65.0%) with multiple organ involvement. Demographic features of IgG4-RFM are shown in Table I. The age was 51.7±14.8 years, with a male to female ratio of 1.5:1. The IgG4-RD RI and PGA scores were 9.2±6.0 and 5.6 ± 2.8 at baseline, respectively, and were comparable between male and female IgG4-RFM patients. Moreover, 3 (15.0%) IgG4-RFM patients had an

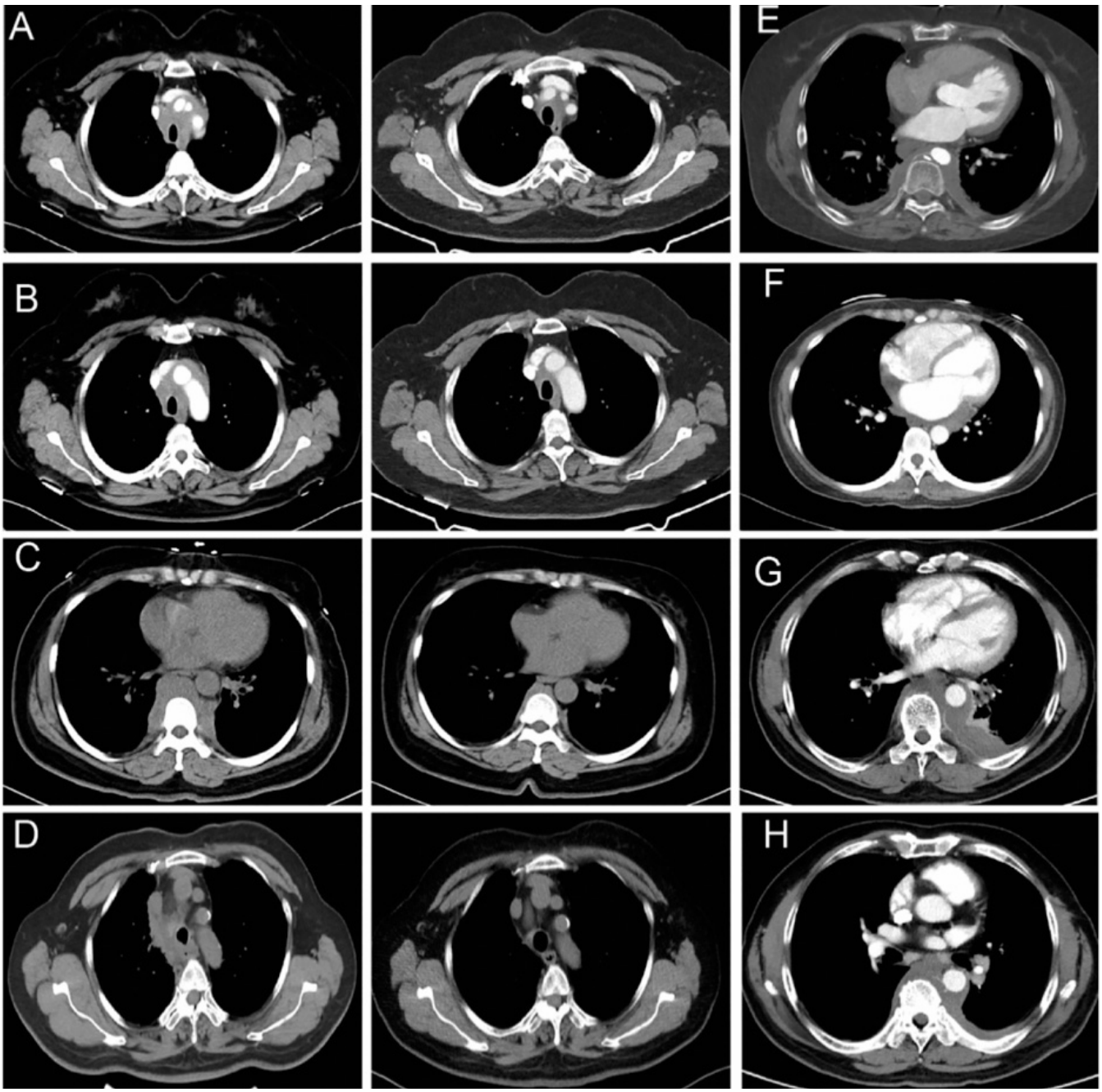

Fig. 2. Characteristic imaging findings of IgG4-RFM.
A-D: Different types of mediastinum involvement. From A to D are soft tissues around aortic branch, aortic arch, thoracic vertebra and oesophagus, respectively), before and after treatment (left and right). **E-H**: Soft tissue entraps aorta, thoracic vertebra, and oesophagus, respectively.
F: Soft tissue surrounds the descending aortic root. Contrast-enhanced computed tomography (A-B, E-H), Computed tomography (C-D).
IgG4-RFM: IgG4-related fibrosing mediastinitis.

allergy history. The median follow-up time was 15 (6-41) months.

Pathological diagnosis was performed in 11 patients; among them, 9 patients underwent mediastinal biopsy, and 2 patients had biopsy of the lacrimal gland and submandibular gland. The characteristic pathological features of the mediastinum of 1 patient are shown in Figure 1. Histological findings showed dense lymphoplasmacytic infiltration along with storiform fibrosis (Fig. 1A). Immunohistochemical staining showed dense $CD3^+$ T cells, $CD20^+$ B cells, $CD38^+$, $CD138^+$, IgG^+, and $IgG4^+$ plasma cell infiltration, as well as lambda chain and kappa chain staining (Fig. 1B-I). The ratio of $IgG4^+$ plasma cells/IgG^+ plasma cells was >40%, and there were >10 $IgG4^+$ plasma cells/HPF.

Symptoms of IgG4-RFM at disease onset

Symptoms at disease onset in IgG4-RFM patients are shown in Table II. Back pain (25.0%), chest pain (20.0%), hoarseness of voice (20.0%) and cough (20.0%) were the most prevalent symptoms at disease onset. Other symptoms included lymph node swelling (4, 20.0%), submandibular gland enlarge-

ment (3, 15.0%), nasal congestion (3, 15.0%), arthralgia (3, 15.0%), lacrimal gland enlargement (2, 10.0%), lower limb oedema (2,10.0%) and dysphagia (1, 5.0%) (Table II).

Laboratory parameters of IgG4-RFM patients

Among IgG4-RFM patients, the baseline ESR and hsCRP were 47 (13-73) mm/h and 16.23 (2.13-14.30) mg/L, respectively. Serum IgG, IgG4 and total IgE (T-IgE) were 22.35±7.52 g/L, 8065 (1130-5540) mg/L and 381.7 (44.6-553.0) KU/L, respectively.

In order to elucidate the differences and similarities in laboratory parameters of IgG4-RFM patients with only FM and those with FM plus multi-organ involvement, comparison was performed between these two groups. IgG4-RD patients with only FM showed lower serum IgG and T-IgE levels than those with multiple organ involvement (p=0.024 and p=0.043, respectively) (Supplementary Table S1).

Comparison between IgG4-RD patients with and without FM

Compared with IgG4-RFM patients, non-FM IgG4-RD patients had a longer disease duration, a higher percentage of allergy history and a lower percentage of single organ involvement (p<0.001, p=0.008, and p=0.047, respectively; Table I). Age at onset, male/female ratio, number of organs involved, and IgG PGA and IgG4-RD RI scores were comparable in the two types of IgG4-RD patients.

Of note, submandibular gland enlargement and lacrimal gland enlargement were less common in IgG4-RFM patients than in those without FM (p=0.031 and p=0.007, respectively), while pleural involvement was more prevalent in FM patients than non-FM patients(p=0.002) (Table II).

Compared with non-FM IgG4-RD patients, IgG4-RFM patients had higher levels of white blood cells (WBC), platelets (PLT), ESR, hsCRP and IgA (p=0.015, p=0.001, p=0.007, p=0.004 and p=0.044, respectively) (Table III) but lower levels of serum IgG4 (p=0.027) (Table III).

After 6 months of treatment, IgG4-RFM patients had a higher percentage of serum IgG4 returned to normal range than non-FM IgG4-RD patients (75.0% *vs*. 37.5%, p=0.019). No statistical significance was noted in the percentage of patients whose serum IgG and IgE were reduced to normal levels after treatment between the non-FM IgG4-RD patients and the IgG4-RFM patients (79.2% *vs*. 100%, 43.2% *vs*. 66.7%; p=0.101, p=0.199; respectively).

Table IV. Regions affected of IgG4-related FM.

Regions affected in mediastinum	IgG4 related FM (n=20)	Female (n=8)	Male (n=12)	p-value
Soft tissue around the descending aorta	9 (45.0)	2 (25.0)	7 (58.3)	0.197
Soft tissue around aortic arch	7 (35.0)	3 (37.5)	4 (33.3)	1.000
Soft tissue around ascending aorta	3 (15.0)	1 (12.5)	1 (8.3)	1.000
Paravertebral soft tissue	7 (35.0)	3 (37.5)	4 (33.3)	1.000
Esophageal entrapped	1 (5.0)	1 (12.5)	0 (0.0)	0.400
Pericardium thickening	1 (5.0)	1 (12.5)	0 (0.0)	0.368
Soft tissue around atrial	1 (5.0)	1 (12.5)	0 (0.0)	0.368
Recurrent laryngeal nerve entrapped	4 (20.0)	1 (12.5)	3 (25.0)	0.619
Aneurysmal dilatation	2 (10.0)	0 (0)	2 (16.7)	0.495
Thickening of blood vessel wall	7 (35.0)	1 (12.5)	6 (50.0)	0.158
lymph node enlargement	10 (50.0)	4 (50.0)	6 (50.0)	1.000

* statistical significance.

Lesion distribution of IgG4-RFM patients

IgG4-RFM lesions were frequently seen in the posterior and superior mediastinum. Characteristic imaging findings of IgG4-RFM are shown in Figure 2, displaying soft tissue entrapping the aorta, surrounding thoracic vertebra, oesophagus, etc. In regard to para-aortitis, of the 20 IgG4-RFM patients, it was most common to find a soft tissue mass around the descending aorta (9, 45.0%), followed by the aortic arch (7, 35.0%) and the ascending aorta (3, 15.0%). 12 patients had either aorta arch, ascending aorta or descending aorta involvement. One patient had aortic arch and ascending aorta involvement. One patient had aortic arch and descending aorta involvement. Specifically, ascending aorta to descending aorta involvement was found in 1 patient with large mediastinum mass. Notably, the para-vascular lesions extended to the abdominal aorta in 7 patients (35.0%) and to the iliac artery in 3 patients (15.0%).

In addition to periaortic masses, paravertebral masses (7, 35.0%) were also common in IgG4-RFM patients, followed by soft tissues around the oesophagus (5.0%) and pericardium (5.0%) and atrium (5.0%). As a consequence of aortitis/periaortitis, 10.0% of patients developed aneurysmal dilation (Table IV). Compared with male patients with IgG4-RFM, a lower percentage of female patients had abdominal aorta involvement (p=0.015). Notably, 4 of 8 patients with FM in superior mediastinum suffered hoarseness of voice, and improved after GC therapy, suggesting recurrent laryngeal nerve was entrapped.

To clearly demonstrate features of the 20 IgG4-RFM patients, demographics (including age, sex), disease duration, symptoms, organ involvement, baseline serum IgG, serum IgG4, serum IgE, serum CRP, results of organ biopsy, treatment strategy and therapeutic outcome were shown in Table V. IgG4-RD is a systemic disease with multiple organ involvement. Extra-mediastinal involvement was evaluated, and 13 (65.0%) IgG4-RFM patients had other organ lesions, which included lesions in the submandibular gland (5, 25.0%), lacrimal gland (5, 25.0%), lung (3, 15.0%), kidney (3, 15.0%), prostate (3, 25.0%), parotid gland (2, 10.0%) and pancreas (1, 5.0%) (Table II). In addition, 8 patients (40.0%) had pleural thickening, which was another common manifestation of IgG4-RFM.

Treatment efficacy in IgG4-RFM patients

All 20 IgG4-RFM patients were treated with GCs (40–50 mg/d for 4 weeks and then gradually tapered to a main-

Table V. Clinical features of 20 IgG4-RFM patients

Patient no.	Age (years)	Sex	Disease duration (months)	Symptoms at disease onset	organs involvement	Serum IgG (g/L)	Serum IgG4 (mg/L)	Serum IgE (KU/L)	Serum hsCRP (mg/L)	Biopsy organ	Treatment strategy	Therapeutic outcome
PA1	31	M	2	Hoarseness of voice, lymph node swelling, cough, nasal congestion	Mediastinum, LN, PAO/PA (thoracic)	17.82	250	23.4	10.91	Mediastinum	GCs 50mg qd +TMX	Remission
PA2	50	M	10	Chest pain, abdominal pain	Mediastinum, PAO/PA (thoracic+ abdominal)	26.94	5630	840	43.03	NA	GCs 50mg qd+CTX	Remission
PA3	34	F	12	Chest pain	Mediastinum, PAO/PA (thoracic)	23.65	1990	43.4	0.29	NA	GCs 40mg qd	Remission
PA4	46	F	9	Dysphagia, lymph node swelling	Mediastinum, LN, PAO/PA (thoracic)	15.02	1060	NA	0.70	Mediastinum	GCs 60mg qd+ CTX+TMX	Remission
PA5	46	F	0	LG enlargement	Mediastinum, SMG, LG, PG, paranasal sinus, pleura	24.35	18900	451	5.42	NA	GCs 50mg qd+ CTX+TMX	Remission
PA6	68	F	2	Cough	Mediastinum, Lung, pleura, PAO/PA (thoracic)	15.66	1340	258	NA	Mediastinum	GCs 40mg qd+CTX	Remission
PA7	71	M	3	Hoarseness of voice	Mediastinum, PAO/PA (thoracic)	13.84	1060	16.7	2.32	Mediastinum	GCs 40mg qd+CTX	Remission
PA8	65	F	36	SMG enlargement	Mediastinum, SMG, LG, kidney, breast	38.12	44800	864	2.52	Mediastinum	GCs 30mg qd+ CTX +TMX	Remission
PA9	66	M	12	Hoarseness of voice	Mediastinum, SMG, LG, PG, PAO/PA (abdominal), lung, prostate, pleura	31.13	80	149	9.79	SMG	GCs 40mg qd+CTX	Remission
PA10	55	M	2	SMG enlargement	Mediastinum, SMG, LG, kidney, LN, pleura	28.79	30200	520	0.56	Mediastinum	NA	NA
PA11	63	M	0	LG enlargement, SMG enlargement and nasal congestion	Mediastinum, SMG, LG, lung, LN, prostate, pleura	28.05	27900	2348	2.47	LG	GCs 40mg qd	Remission
PA12	64	M	0	Back pain, abdominal pain, lower limb edema, lymph node swelling	Mediastinum, LN, prostate, PAO/PA (thoracic+abdominal), pleura	24.81	3190	125	24.48	NA	GCs 50mg qd+TMX	Remission
P A13	20	F	0	Back pain, lower limb edema, nasal congestion, arthralgia, fever	Mediastinum, Kidney, PAO/PA (thoracic)	19.04	3200	180	NA	Mediastinum	GCs 30mg qd	Remission
PA14	59	F	0	Fever, arthralgia, cough	Mediastinum, PAO/PA (thoracic), bile duct, pleura	26.9	5270	NA	2.26	NA	GCs 30mg qd+LEF	Remission→ relapse
PA15	63	M	24	Chest pain	Mediastinum, PAO/PA (thoracic+abdominal), pleura	30.69	1440	147	55.93	Mediastinum	GCs 50mg qd+ CTX+TMX	Remission
PA16	53	M	36	Chest pain, cough	Mediastinum, Pancreas, PAO/PA (thoracic)	8.37	918	70.8	10.00	Mediastinum	GCs 50mg qd+ LEF+TMX	Remission
PA17	51	F	1	Hoarseness of voice	Mediastinum, PAO/PA[#]	18.72	1510	8.9	8.61	NA	GCs 50mg qd+CTX	Remission
PA18	30	M	0	Abdominal pain, arthralgia, lymph node swelling, back pain	Mediastinum, PAO/PA (abdominal+thoracic), LN	18.90	4600	45	5.13	NA	GCs 60mg qd+TMX	Remission
PA19	36	M	1	Abdominal pain, back pain	Mediastinum PAO/PA (thoracic+abdominal)	20.56	3190	125	105.25	NA	GCs 50mg qd+MMF	Remission
PA20	63	M	0	Back pain	Mediastinum, PAO/PA (thoracic+abdominal)	13.91	4770	655	2.55	NA	GCs 40mg qd+CTX	Remission

PA: patient. 0 = FM was found by physical examination or IgG4-RD with other organs affected so chest CT was performed and FM found accidentally.
LN: lymph node; SMG: submandibular gland; LC: lacrimal gland; PG: parotid gland; PAO/PA: aortitis/periaortitis and periarteritis.
[#] innominate artery, left common carotid artery and left subclavian artery involvement. Serum IgG, IgG4, IgE and hsCRP represented baseline levels of the above parameters.
GCs: glucocorticoids. CTX: cyclophosphamide; TMX: tamoxifen; LEF: leflunomide; NA: not applicable.
Patient 14 suffered a relapse during lose dose glucocorticoids maintenance therapy.
Daily dose of CTX: 50–100mg qd; daily dose of TMX: 10mg bid.

tenance dosage of 10 mg/d or less). Among these patients, 8 received combined immunosuppressant agents (IMs), which included cyclophosphamide (CTX) (6, 75.0%), leflunomide (LEF) (1, 12.5%) and mycophenolate mofetil (MMF) (1, 12.5%); 3 received GCs combined with tamoxifen (GCs + TMX); and 5 received GCs combined with IMs and TMX (GCs + IM + TMX). All patients except 1 were regularly followed up. The median follow-up time was 23 (6–39) months. After treatment, 9 patients achieved a reduction in mediastinal soft tissues >70%, 9 patients achieved a reduction between 31–70%, and 1 patient had a reduction <30%.

Overall IgG4-RD RI and PGA scores and ESR, hsCRP and serum IgG4 levels significantly decreased after treatment. After 6 months of treatment, the IgG4-RD RI score decreased from 9.2±6.0 to 1.4±0.5 (p<0.001), the PGA score decreased from 5.6±2.8 to 1.3±0.7 (p<0.001), serum IgG4 levels decreased from 8065 (1130–5540) mg/L to 2049 (413–2770) mg/L (p=0.046), hsCRP levels decreased from 16.23 (2.31–14.30) mg/L to 3.07 (0.68–3.25) mg/L (p=0.030), and ESR levels decreased from 47 (13–73) mm/h to 5 (2–7) mm/h (p<0.001).

During a follow-up of 57 months, 1 patient suffered clinical relapse with growth of the periaortic mass because of drug withdrawal.

Discussion

FM is one of the manifestations of IgG4-RD, accounting for 2.8% of all IgG4-RD patients in our cohort. Symptoms of FM were mainly dyspnoea, cough, chest pain, hoarseness of voice and dysphagia due to the compression of the aorta and airway by fibrotic tissues. Periaortic masses and paravertebral masses were the most common characteristic imaging findings of IgG4-RFM. Dense fibrosis but relatively less ectopic germinal centre formation were typical pathologic manifestations of IgG4-RFM. IgG4-RFM patients responded well to GCs. By comparison with non-IgG4-RFM patients, differences were identified in the spectrum of organs involved and the laboratory parameters in patients with IgG4-RFM, indicating IgG4-RFM is a distinctive type of IgG4-RD belonging to the fibrotic subset.

Many aetiologies, including granulomatous (tuberculosis, sarcoidosis, and histoplasmosis infections) and non-granulomatous (radiation therapy and IgG4-RD), can cause FM (16). Previous studies on IgG4-RFM were cases or case series, with an onset age of 63±15 years and a male/female ratio of 3:1 (12, 16, 17). However, in our cohort, the age of disease onset was lower and there was a less prominent male/female ratio. The lesion distribution of FM varies, including the hilum, airway, pulmonary vessels, aorta, etc. In this study, IgG4-RFM patients did not have pulmonary vessel involvement, which was different from FM patients with other aetiologies (18-20). FM lesions caused by tuberculosis were soft tissue processes throughout the mediastinum and hila that compressed the bronchial and pulmonary vessels. Calcification and pulmonary hypertension are common complications of FM caused by tuberculosis infection (21). However, unlike FM caused by infection, we found that soft tissues around the aorta/vertebra and periaortitis were typical characteristics of IgG4-RFM patients. Compression of bronchial and pulmonary vessels was relatively rare in IgG4-RD. Akiyama et al. conducted a literature review of IgG4-related pulmonary hypertension and identified a total of 7 patients meeting the IgG4-RD comprehensive diagnostic criteria (pulmonary hypertension caused by IgG4-RFM was found in 3 patients) (22). IgG4-related pulmonary hypertension is a rare clinical manifestation which may be related to IgG4-RFM or IgG4-RD patients with lung involvement. The incidence of pulmonary artery in IgG4-RD need to be further investigated. Unlike FM caused by other aetiologies, FM patients with IgG4-RD also had extra-mediastinal involvement, including of the pancreas, lacrimal glands, lymph nodes and submandibular glands. It is worth noting that the oesophagus could also be involved in IgG4-RFM (5% of our cohort).

Consistent with previous studies (7), 9 patients with IgG4-RFM in our cohort were asymptomatic. Thoracic radiological examinations were recommended for IgG4-RD patients with the above symptoms for early detection and treatment. Considering that the delayed diagnosis of FM results in irreversible organ damage and poor prognoses, biopsy to identify the aetiology of FM is essential for the initiation of early, appropriate treatment.

In large-vessel vasculitis, such as Takayasu arteritis or giant cell arteritis, the elevation of ESR and hsCRP was an indicator of vascular wall inflammation (23, 24). Our data demonstrated that IgG4-RFM patients had higher ESR and hsCRP but lower serum IgG4 levels than IgG4-RD patients without FM, suggesting that the prominent elevation of ESR and hsCRP in IgG4-RFM may be mainly caused by aortic inflammation. In addition, IgG4-RD patients with the fibrotic subtype had higher ESR and hsCRP levels than patients with the proliferative subtype (11), and our study was consistent with this finding.

According to the latest research, an intuitive approach to classifying IgG4-RD on the basis of a patient's clinicopathological involves differentiating two overlapping subtypes of the disease: the proliferative and fibrotic subtypes (11). IgG4-RFM was classified as a fibrotic type of IgG4-RD by a recent study. The fibrotic subtype of IgG4-RD tended to have a lower percentage of atopy but a higher percentage of single organ involvement than the proliferative subtype of IgG4-RD (11). Our study of IgG4-RFM was consistent with this. In addition, we demonstrated that IgG4-RFM patients differed from those without FM in the types of organ involvement. Therefore, IgG4-RFM might be a distinct type of IgG4-RD, as it is characterised by prominent fibrosis, sparse lymphoplasmacytic infiltration, fewer extra-nodal germinal centres, and mildly elevated serum IgG4 concentrations. Notably, our study also revealed that IgG4-RFM patients were likely to achieve normal serum IgG4 levels after treatment than those without RFM (75.0% *vs*. 37.5%). The differences in organ involvement may reveal that the pathogenesis of the fibrotic subtype

may differ from that of the proliferative subtype.

FM patients are often treated with medium to high-dose GCs with/without immunosuppressants (8). According to case reports, prednisone monotherapy had better outcomes in IgG4-RFM (25), but there was a lack of evidence based on relatively long-term follow-up (17). In our study, GCs was effective in the treatment of IgG4-RFM, with a low recurrence rate. All IgG4-RFM patients improved after treatment based on the shrinking of the soft tissue mass in the mediastinum. The significant reduction in ESR, hsCRP, and serum IgG4 levels after treatment also supported the treatment efficacy of IgG4-RFM (17). However, clinical practice is highly variable in terms of the agent choice and dosing strategy and is largely based on an individual clinician's preference and/or experience (26). The use of rituximab as a rescue and, less frequently, an induction therapy is also widely reported (15, 26, 27). The use of other biological therapies targeting B- and T-cells or other molecular targets are in the preliminary stages.

This study had some limitations. First, this was a single-centre study. Second, the follow-up time was relatively short. Third, since this is a rare type of IgG4-RD, the sample size was relatively small.

Conclusion

IgG4-RFM is a distinct spectrum of the fibrotic subtype of IgG4-RD. Periaortic masses and paravertebral masses were the most common characteristic imaging findings of IgG4-RFM. Most IgG4-RFM patients respond well to GC and immunosuppressant treatment. The different disease origins, clinical manifestations and laboratory parameters may indicate that the pathogenesis of IgG4-RFM differs from that of the proliferative subtype of IgG4-RD.

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