

# Clinical characteristics of IgG4-related retroperitoneal fibrosis versus idiopathic retroperitoneal fibrosis: a retrospective study of 132 patients

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## Research article

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# Abstract

**Background** Retroperitoneal fibrosis (RPF) is a condition characterized by the presence of inflammation and fibrosis in the retroperitoneal space. More than two-thirds of all cases of RPF are idiopathic retroperitoneal fibrosis (IRPF), while the remaining one-third stem from different secondary causes. Many studies suggest that IgG4-related RPF is a secondary form of RPF. We undertook this study to compare detailed demographic, clinical and laboratory characteristics of IgG4-related RPF and IRPF in a large China cohort.

**Methods** We carried out a retrospective review of the medical records of 132 cases of RPF diagnosed at Peking University People's Hospital between March 2010 and March 2018. We divided the patients into two groups, IgG4-related RPF group and IRPF group. A standardized case report form was used for data collection. All statistical analyses were performed by SPSS 24.0.

**Results** Among the 132 patients, the mean age at disease onset was 54.8 years. IgG4-related RPF group showed greater male predominance compared to IRPF group. IgG4-related RPF patients showed a longer interval between symptom onset and diagnosis, and allergic diseases were more common in this group. Sixty-four patients (48.4%) had lower back pain, which was more common in IRPF group than that in IgG4-related RPF patients. In terms of organ involvement, although 42 of 47 patients (89.3%) with IgG4-related RPF had other organ involvement, there were no patients in the IRPF group with other organ involvement. In addition, the serum IgG4 level, elevated eosinophils counts and IgE level were significantly higher in IgG4-related RPF patients.

**Conclusions** We have revealed demographic, clinical and laboratory differences between IgG4-related RPF and IRPF patients, which indicated potential differences in pathogenesis and important implications for the diagnosis and management of these two phenotypes.

## Introduction

Retroperitoneal fibrosis (RPF) is a rare disease characterized by the presence of chronic inflammation and fibrosis in the retroperitoneal space[1]. It usually involves the adventitia of the abdominal aorta and the iliac arteries and the adjacent structures, resulting in flank pain, lower extremity oedema, hydronephrosis, ureteral obstruction and other clinical symptoms[2]. More than two-thirds of all cases of RPF are idiopathic, while the remaining one-third stem from secondary causes, such as infections, trauma, tumor, autoimmune diseases, drugs, radiation therapy, and surgery[3, 4].

During the last decade, the concept of IgG4-related disease (IgG4-RD) has emerged: IgG4-RD embraces fibro-inflammatory disorders affecting different structures (e.g, pancreas, biliary tract, lymph nodes, retroperitoneum) and is characterized by lympho-plasmacytic inflammation, irregular and pronounced fibrosis, and infiltration by IgG4<sup>+</sup> plasma cells[5, 6]. Recently, many cases have been reported, suggesting that IgG4-related RPF is a secondary form of RPF, and it is thus now included within the IgG4-related spectrum of sclerosing disease[7–10].

Previous researches have suggested that IgG4-related RPF patients may present different pathogenesis compared to idiopathic retroperitoneal fibrosis (IRPF) patients[11–13]. However, Choi[14] found that clinical and laboratory characteristics of IgG4-related RPF are similar to those of IRPF except for a striking male predominance, older age, and higher incidence of postrenal AKI in IgG4-related RPF. Therefore, we conducted this study to compare the demographic, clinical and laboratory characteristics of IgG4-related RPF and IRPF patients in a large Chinese

cohort. Defining the characteristics of these two groups might facilitate advanced recognition of the condition, help to identify risk factors and develop a treatment strategy specific for each cluster.

## Patients And Methods

### Patients

We retrospectively reviewed the medical records of RPF patients who were treated at Peking University People's Hospital between March 2010 and March 2018. A total of 132 cases were diagnosed during this time with RPF, excluding RPF from other secondary causes such as malignancy, infection, drugs, surgical injury, and radiation therapy. Patients who did not undergo serum IgG4 detection were also excluded. The diagnosis of RPF was based on radiologist reports of Computed tomography or magnetic resonance imaging. The typical image showed soft-tissue mass surrounding the aorta and/or adjacent tissues. Retroperitoneal biopsies were not performed routinely. They were usually performed in cases with atypical localization or when the clinical picture was highly suggestive of malignancy. Allergic disease was diagnosed according to the criteria from the European Academy of Allergy and Clinical Immunology (EAACI), and diagnosis was made by experienced specialists. All patients in the study were followed up until death or 31 March 2019, whichever came first.

We divided the patients into two groups, IgG4-related RPF and IRPF, based on the comprehensive diagnostic criteria published by Umehara et al [15] in 2011. While, patients with RPF of unknown origin are labelled as having IRPF[1].

### Clinical and Laboratory data

A standardized case report form was used for data collection. Age at disease onset, age at diagnosis, gender, follow up time, clinical symptoms, smoking history, biopsy status, complication of allergic disease were included in the forms. The location of the retroperitoneal fibrotic mass was classified as periaorta, renal pelvis and ureter by image. For patients who had undergone biopsy, the pathology reports were reviewed.

Laboratory index comprised haemoglobin, eosinophil count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum creatinine before the initial treatment, complement 3 (C3) and complement 4 (C4), immunoglobulin E (IgE), immunoglobulin G4 (IgG4) and autoantibodies.

### Statistical analysis

All statistical analyses were performed by SPSS 24.0. Data were analyzed using descriptive methods, with standard summary statistics including mean  $\pm$  SD, median, interquartile range (IQR) and proportions. Differences for continuous, normally distributed data were performed using the Student's *t*-test; continuous, non-normally distributed data were analyzed by the Mann–Whitney test. Categorical variables were processed by chi-square or Fisher's exact tests, as appropriate. A *P*-value less than 0.05 was considered statistically significant.

## Results

### Patients' demographic characteristics

A total of 132 patients diagnosed as RPF were enrolled in this study. Among the 132 cases in our cohort, 47 patients (35.6%) were classified as having IgG4-related RPF (19 definite, 5 probable, 23 possible), and 85 patients

were classified as having IRPF. The demographic features of all cases are shown in **Table1**. The mean age at disease onset was 54.8 years, and 70% patients were male. Sixty-four patients (48.4%) underwent biopsies. Among them, 24 cases were identified as IgG4-related RPF, and 40 cases were identified as IRPF. Established allergic diseases were found in fourteen cases (10.6%). Cardiovascular disease risk factors, i.e. hypertension, diabetes mellitus, and smoking, were found in 40 (30.3%), 21 (15.9%), and 60 (45.4%) patients, respectively.

We compared the demographic features of patients with IgG4-related RPF against cases of IRPF in **Table2**. The gender ratio (Male:Female) of IgG4-related RPF group and IRPF group were 4.8:1 and 1.7:1, respectively ( $P=0.012$ ). The time from disease onset to diagnosis was 26 months in IgG4-related group, which was significantly longer than that in IRPF group (12 months) ( $P=0.001$ ). The mean follow-up time of IgG4-related RPF group and IRPF patients was 20 months and 24 months, respectively. In terms of allergic disorders, IgG4-RD RPF patients (21.2%) had a higher frequency of allergic diseases (allergic rhinitis, urticaria, asthma) than that in IRPF patients (4.7%) ( $P=0.006$ ).

### Clinical features

Clinical symptoms varied from patient to patient. Pain was the most common presenting symptom. Sixty-four patients (48.4%) had lower back pain, which was more common in IRPF group ( $P=0.035$ ). Thirty-five patients (26.5%) had flank pain and twenty-seven (20.4%) had abdominal pain, respectively. Hydronephrosis occurred in 85 of 132 patients (64.3%), with 35 bilateral and 50 unilateral involvement; however, there was no statistical difference between this two groups. Other constitutional symptoms were fever, weight loss, lower limb edema, venous thrombus, and anorexia (**Table 3**). Organ involvement was evaluated by systematic standards including symptoms, signs, radiographic or other image examinations. Although 42 of 47 patients (89.3%) with IgG4-related RPF had other organ involvement, with the pancreas being the most commonly affected organ, there were no patients in the IRPF group with other organ involvement ( $P<0.001$ ). However, there was no significant difference in incidence of mass location ( $P=0.482$ ).

### Laboratory findings

We further compared the laboratory tests between these two groups (**Table 4**). The levels of inflammatory markers such as ESR and CRP were not statistically different between groups, while the number of patients with elevated CRP was significantly higher in the IRPF group (61.1% vs 42.5%,  $P=0.04$ ). Hypocomplementemia was a common finding in both IgG4-related RPF (21.2%) and IRPF group (18.8%) ( $P=0.734$ ), and the number of patients with low serum C4 was significantly higher in IgG4-related RPF group ( $P=0.024$ ). The serum IgG4 level and IgE level were significantly higher in IgG4-related RPF group. IgG4-related RPF patients were more commonly associated with elevated eosinophils counts (23.4% vs 7.05%,  $P=0.007$ ).

### Treatment

Treatment strategies are reported in **Table 5**. However, there was no significant difference in both groups. As shown, fifteen patients (11.4%) received no treatment, whereas other patients received medical therapy (31.8%), surgical

therapy (9.1%), or both (47.7%). Glucocorticoids are the first-line medical therapy, with initial doses of 0.75–1 mg/kg per day of prednisone in our study. About 79.5% of all our patients were initially treated with prednisone. Immunosuppressants used in our cohort comprised cyclophosphamide alone in 46 patients (34.8%), Methotrexate alone in 3 (2.2%) patients, and mycophenolate mofetil in twenty (15.1%) patients. Eleven patients (8.3%) experienced immunosuppressant replacement during the period, because of either side effects or poor efficacy. Two patients received rituximab combined with glucocorticoids, due to disease relapse. Tamoxifen was used alone in twelve (9.0%) patients.

With regard to surgical interventions, 55 patients (41.6%) had ureteral stents to help alleviate the symptoms. Ureterolysis was carried out in 18 of 132 patients. Fourteen patients (10.6%) underwent percutaneous nephrostomy.

## Discussion

We compared herein the demographic, clinical and laboratory features between 47 IgG4-related RPF patients and 85 IRPF patients, differences in the above aspects were found. To our knowledge, this is the first research on such two phenotypes of RPF in China, and the sample size is large.

In our current study, male predominance has been described in both groups. However, IgG4-related RPF group showed greater male predominance compared to IRPF group. This is comparable to several previous studies [14, 16–18]. It was found that IRPF patients got a diagnosis at an earlier age than IgG4-related RPF patients, although the comparison between the two groups fell short of statistical significance. More patients in IRPF group complain lower back pain initially than that in IgG4-related RPF, which is easily noticed even in the absence of other symptoms. Maybe it could explain time from onset to diagnosis of IRPF patients was shorter than that in IgG4-related RPF patients. Moreover, IgG4-related RPF is a newly known disease, and it takes time for doctors to identify it.

Most reports of IgG4-related RPF describe extraperitoneal involvement of IgG4-related disease with RPF [9, 18, 19]. Sialadenitis, autoimmune pancreatitis periaortitis of the thoracic aorta, and reticular lung lesions can exist simultaneously, while other lesions are not identified in IRPF patients. Similar to previous reports [12, 17], other organ involvement was much more frequent in IgG4-related RPF (89.3% vs. 0%).

Serum IgG4 level, IgE level, eosinophilia as well as allergic diseases were higher or more commonly observed in IgG4-related RPF patients. Such findings indicate that different pathogenesis involved in these two phenotypes. High serum IgG4 levels have been linked to IgG4-related RPF [1, 18]. CD4 + T cells are abundant in IRPF biopsies [20], while in IgG4-related RPF they show a T-helper 2 (Th2)-polarization [21]. Th2 cytokines such as interleukin-4 and interleukin-13 enhance the production of both IgG4 and IgE [22]. Additionally, Th2 cytokines may induce the enrichment of the IgG4 + plasma cell [23]. Eosinophilia and elevated serum IgE levels, both observed in approximately 40% of patients with IgG4-related disease, are also mediated by Th2 cytokines [3, 23]. We consider that maybe our finding could supply evidence that IgG4-related RPF is induced preferentially in the setting of a Th2-cell dominant immune reaction.

CRP levels are increased in the majority of patients in our cohort (54.5%), which is consistent with previous studies [24, 25]. The proportion of elevated CRP patients in IRPF group was higher than that in IgG4-related RPF group. CRP is often used to monitor the clinical course of the disease, though they do not always reliably mirror disease activity [26]. Additionally, more research is needed to confirm whether IRPF patients is more active in inflammatory response.

Steroid therapy is the main treatment option for IgG4-related and IRPF patients. Although there are currently no standard treatment regimens, moderate to high dose of steroids with slow tapering are recommended[27, 28]. In our study, tamoxifen and immunosuppressants (cyclophosphamide, mycophenolate mofetil, and methotrexate ) are used as glucocorticoid-sparing agents or remission-maintenance drugs. For patients with recurrent or refractory disease, B-cell depletion with rituximab appears to be a useful approach[29]. With regard to patients with ureteral compression, the first goal of treatment is the relief of ureteral obstruction[2].

Strengths include that it's a real-world study and we compared the differences between the two groups in a large sample size. The limitations of this study include the fact that it was retrospective in nature, and that retroperitoneal biopsies were not available from all participants. As it was known that retroperitoneal biopsy is a high-risk and invasive procedure, patients and even some doctors cannot accept it or refuse to do that.

## Conclusion

In conclusion, we have analyzed demographic, clinical and laboratory differences between IgG4-RD RPF and IRPF patients. IgG4-RD RPF patients were associated with longer time from onset to diagnosis and showed greater male predominance compared to IRPF patients. Allergic diseases and multi-organ involvement were more commonly observed in IgG4-RD RPF group. IgG4-RD RPF phenotype showed higher level of IgG4 and IgE. These findings indicated potential differences in pathogenesis and important implications for the diagnosis and management of these two phenotypes.

## Abbreviations

RPF Retroperitoneal fibrosis

IRPF idiopathic retroperitoneal fibrosis

IgG4-RD IgG4-related disease

CRP C-reactive protein

IgG4 immunoglobulin G4

IgE immunoglobulin E

## Declarations

**Ethics approval and consent to participate:** This study was approved by the Medical Ethics Committee of Peking University People's Hospital (Beijing, China).

**Consent for publication:** Not applicable.

**Availability of data and materials:** The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interests:** The authors declare that they have no competing interests.

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**Authors' contributions:** Yanying Liu and Kunkun Wang analyzed, interpreted the patient dataset, and wrote the manuscript. Zhenfan Wang completed the statistical analysis related to this manuscript. Qiaozhu Zeng, Lijuan Zhu, Jingyuan Gao, Ziqiao Wang, Yanyan Zhang, Shanshan Zhang, Fei Yang, Danhua Shen, Guangyan Yu, and Yi Wang shared the data collection and interpretation. Zhanguo Li directed the study. All authors read and approved the final manuscript.

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## Tables

**Table 1** Demographic and clinical characteristics of 132 RPF patients

Characteristics	Value
Number of cases, n	132
Gender (Male:Female)	2.38:1
Mean age at disease onset (years±SD)	54.8±12.4
Mean age at diagnosis (years±SD)	56.8±12.6
Time from onset to diagnosis ,median (IQR)	15(6-26)
Follow up time (months),median (IQR)	20(12-48)
Biopsy,n (%)	64(48.4)
Complication of allergic disease, n (%)	14(10.6)
Hypertension, n (%)	40 (30.3%)
Diabetes mellitus, n (%)	21 (15.9%)
Smoking, n (%)	60(45.4)

**Table 2** Differences in demographic characteristics between IgG4-related RPF and IRPF patients

Characteristics	IgG4-related RPF	IRPF	<i>P</i> -value
Number of cases, n	47	85	
Gender (Male:Female)	4.8:1	1.7:1	0.012
Mean age at disease onset (years±SD)	55.7±12.0	54.3±12.7	0.532
Mean age at diagnosis (years±SD)	59.4±12.3	55.4±12.7	0.082
Time from onset to diagnosis , median (IQR)	26(14-38)	12(6-16)	0.001
Follow-up time (months), median (IQR)	20(12-36)	24(12-48)	0.251
Complication of allergic disease, n (%)	10(21.2)	4(4.7)	0.006
Biopsy, n (%)	24(51%)	40(47%)	0.659

**Table 3** Differences in Clinical characteristics between IgG4-related RPF and IRPF patients

Characteristics	Total	IgG4-related RPF	IRPF	<i>P</i> -value
Clinical symptom				
Abdominal pain, n (%)	27(20.4)	12(25.5)	15(17.6)	0.282
Flank pain, n (%)	35(26.5)	15(31.9)	20(23.5)	0.296
Lower back pain, n (%)	64(48.4)	17(36.1)	47(55.2)	0.035
Lower limb edema, n (%)	12(9.0)	5(10.6)	7(8.2)	0.754
Anorexia, n (%)	6(4.5)	2(4.2)	4(4.7)	0.905
Weight loss, n (%)	8(6.0)	5(10.6)	3(3.5)	0.132
Fever, n (%)	7(5.3)	2(4.2)	5(5.8)	1.000
Oliguria or anuria, n (%)	6(4.5)	3(6.3)	3(3.5)	0.666
Venous thrombus, n (%)	2(1.5)	1(2.1)	1(1.1)	1.000
Bilateral hydronephrosis, n (%)	35(26.5)	16(34.0)	19(22.3)	0.145
Unilateral hydronephrosis, n (%)	50(37.8)	19(40.4)	31(36.4)	0.654
Mass location				
Aorta, n (%)	56(42.4)	22(46.8)	34(40)	0.482
Renal pelvis, n (%)	11(8.3)	5(10.6)	6(7.0)	
Ureter, n (%)	65(49.2)	20(42.5)	45(52.9)	
Other organ involvement n (%)	42(31.8)	42(89.3)	0(0)	<0.001

**Table 4** Laboratory findings in IgG4-related RPF and IRPF patients

<b>Parameter</b>	<b>Total</b>	<b>IgG4-related RPF</b>	<b>IRPF</b>	<b>P-value</b>
ESR (mm/h), median (IQR)	31(13-61)	39(18-72)	30(12-57)	0.186
Elevated ESR, n (%)	91(68.9)	35(74.4)	56(65.8)	0.307
CRP(mg/L), median (IQR)	9(3-19)	5.93(2.4-16.2)	10(3.15-20)	0.075
Elevated CRP, n (%)	72(54.5)	20(42.5)	52(61.1)	0.040
Eosinophilia, n (%)	17(12.8)	11(23.4)	6(7.05)	0.007
ANA (+), n (%)	17(12.8)	6(12.7)	11(12.9)	0.977
Anemia, n (%)	69(52.2)	26(55.3)	43(50.5)	0.602
Serum creatinine at onset [μmol/L]	95(73-130)	90(65-120)	100(74.5-160)	0.145
Hypocomplementemia, n (%)	26(19.6)	10(21.2)	16(18.8)	0.734
Reduced serum C4, n (%)	16(12.1)	11(23.4)	5(5.8)	0.003
Reduced serum C3, n (%)	25(18.9)	8(17.0)	17(20.0)	0.676
Serum IgG4 level (mg/dL), median (IQR)	67(26-203)	300(171-877)	35.8(20-70)	0
Serum IgE (IU/ml), median (IQR)	64(40-157)	98.8(68-282)	50(22.2-103.7)	0

**Table 5** Type of medical and surgical therapy in IgG4-related RPF and IRPF patients

Type	Total	IgG4-related RPF	IRPF	P-value
No treatment, n (%)	15(11.4)	5(10.6)	10(11.7)	0.845
Medical therapy alone, n (%)	42(31.8)	18(38.2)	24(28.2)	0.235
Surgical therapy alone, n (%)	12(9.1)	2(4.2)	10(11.7)	0.211
Combination (medical and surgical therapy ) ,n(%)	63(47.7)	22(46.8)	41(48.2)	0.875
GCs only, n (%)	11(8.3)	5(10.6)	6(7.0)	0.520
GCs+Tamoxifen, n (%)	12(9.0)	1(2.1)	11(12.9)	0.055
GCs+cyclophosphamide, n (%)	46(34.8)	18(38.2)	28(32.9)	0.536
GCs+Mycophenolate Mofetil, n (%)	20(15.1)	10(21.2)	10(11.7)	0.144
GCs+Methotrexate, n (%)	3(2.2)	1(2.1)	2(2.3)	0.934
GC+Rituximab, n (%)	2(1.5)	1(2.1)	1(1.1)	0.668
GCs+two or more immunosuppressants, n(%)	11(8.3)	4(8.4)	7(8.2)	0.956
Percutaneous nephrostomy, n (%)	14(10.6)	2(4.2)	12(14.1)	0.137
Ureterolysis , n (%)	18(13.6)	4(8.4)	14(16.4)	0.234
Ureteral stents, n (%)	55(41.6)	16(34.0)	39(45.8)	0.257
Resection of retroperitoneal mass, n (%)	6(4.5)	2(4.2)	4(4.7)	0.905

GCs = glucocorticoids.