No specific imaging pattern can help differentiate IgG4-related disease from idiopathic retroperitoneal fibrosis: 18 histologically proven cases

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Abstract

Objective

Retroperitoneal fibrosis (RPF) is a rare disease, with unknown aetiology (idiopathic RPF: iRPF) in two-thirds of cases. A subset of iRPF may be a manifestation of IgG4-related disease (IgG4-RD). Thus, recognition of IgG4-RD-RPF is crucial to optimise patient's care with iRPF. The current study aimed to examine imaging specific patterns, which could help differentiate between IgG4-RD-RPF and iRPF, and thus skip performing biopsies.

Methods

This analysis included patients with iRPF and a retroperitoneal biopsy at the Lille University Hospital, France. We reviewed their baseline characteristics, clinical presentation, biological results and imaging features. Patients were classified in 3 groups according to histopathological characteristics of IgG4-RD as follows: highly suggestive of IgG4-RD, possible IgG4-RD, or non-evocative of IgG4-RD.

Results

Of the 18 patients analysed in the study, 4 (22%) patients had highly suggestive IgG4-RD-RPF, 8 (44%) possible IgG4-RD-RPF and 6 (33%) non-evocative IgG4-RD. We found no clinical, biological features nor specific imaging pattern that could help differentiate between the 3 groups.

Conclusion

After ruling out all known causes of RPF, retroperitoneal biopsy is still necessary to ascertain the diagnosis of IgG4-RD-RPF. No specific pattern can be used to distinguish between IgG4-RD-RPF and iRFP.

Key words
IgG4 related disease, retroperitoneal fibrosis, imaging

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Introduction

Retroperitoneal fibrosis (RPF) is a rare disease characterised by inflammation and fibrosis spreading along the retroperitoneal space, the infrarenal aorta and the ureters (1). Many conditions can be associated with RPF: malignant diseases such as, lymphomas, carcinomas, sarcomas, Erdheim-Chester disease (2), abdominal or pelvic surgery postoperative complication, radiotherapy (3), and some medications, *e.g.* dopamine agonists or ergot alkaloids (4). In two thirds of the cases, the aetiology remains unknown and RPF is then defined as idiopathic (iRPF) (5). Recently, several reports suggested that iRPF may be one expression of the IgG4-related disease (IgG4-RD) (6-8). IgG4-RD is an immune-mediated fibroinflammatory disease, characterised by inflammation and fibrosis of various anatomic sites: pancreas, salivary or lachrymal glands, thyroid, kidneys, and the retroperitoneal space (9). The diagnosis of IgG4-RD can not be definite without identification of distinctive histological features on a tissue sample pathological examination, *i.e.* dense lymphoplasmacytic infiltrate with numerous IgG4 positive plasma cells, storiform fibrosis, and obliterative phlebitis (10). Recognition of RPF associated with IgG4-RD (IgG4-RD-RPF) requires a retroperitoneal biopsy, but is crucial to optimise patient care. Indeed the way IgG4-RD-RPF is treated might differ from iRPF with the use of rituximab for instance (6, 9, 11). However, retroperitoneal biopsy remains invasive and alternative tools to identify IgG4-RD-RPF would be of great interest. No study specifically focused on discriminant radiologic findings to distinguish IgG4-RD-RPF from other causes of RPF (6, 12). Our group previously reported a magnetic resonance imaging (MRI)-based algorithm to distinguish between malignant RPF and non-malignant RPF (13). We analysed the retroperitoneal biopsies from our cohort, looking at IgG4-RD-RPF and aimed to describe any clinical or radiologic specific pattern that could help discriminate IgG4-RD-RPF from other RPF and may spare patients needless biopsies.

Patients and methods

Study design and population

Among eligible patients with RPF, as documented by MRI from 1994 to 2012 in the radiology department of our university hospital (13), 42 had iRPF, but 24 had to be excluded due to missing data or material. Therefore, 18 patients were analysed.

Data collection

We retrieved the patients' characteristics, clinical and laboratory findings at diagnosis by complete review of their medical records. The following definitions were used: smoker (current or stopped within the last 5 years); cardiovascular disease (prior stroke, coronary artery disease, and/or peripheral arterial disease); hypertension, diabetes, and hyperlipidaemia (mentioned or if antihypertensive drug, oral antidiabetic, or lipid-lowering agent were prescribed); venous thromboembolism (prior deep vein thrombosis or pulmonary embolism); poor general condition (anorexia, asthenia, or weight loss preceding RPF diagnosis). The following biological data: C-reactive protein (CRP), fibrinogen, serum creatinine were collected. Serum IgG4 subclass concentration was available for 2 patients only, and was normal. Follow-up focused on drug prescribed and ureteral stenting for upper urinary tract obstruction.

Histopathologic classification

Original haematoxylin and eosin-stained slides have been reviewed and new immunohistochemistry performed with anti-IgG4 antibody (ABCyst Abc117-5754 Mouse clone HP6025, 1:100 dilution) and anti-IgG antibody (Dako, 1:400 dilution). Lymphoplasmacytic infiltrate, storiform-type fibrosis, obliterative phlebitis were recorded as major features of IgG4-RD (10). Other features such as increased number of eosinophils, granulomas, and neutrophilic micro-abscesses were also noticed. The IgG4-to-IgG ratio (IgG4+/IgG+) was calculated after counting separately the IgG-positive plasma cells and the IgG4-positive plasma cells in three high power fields. Patients were classified as follows: histologically highly suggestive of IgG4-RD if pres-

ence of at least two out of three major features and IgG4+/IgG+ >40%, possible IgG4-RD if presence of at least two out of three major features and IgG4+/IgG+ ≤40%, or non-evocative of IgG4-RD if not matching with one of the definitions above. The pathologist (DB) who examined the tissue samples was blinded to the patients' characteristics.

Imaging characteristics

Morphologic criteria were collected as previously described (13). The radiologist (PP) who examined each MRI was blinded to the patients' characteristics.

Statistical analysis

Continuous variables are expressed as medians (25^{th}–75^{th} percentiles), and compared with the Mann-Whitney U-test or the Kruskall-Wallis test for 2 or 3 groups comparisons, respectively. Categorical variables are expressed as number (%) and compared with the chi-square test or the Fisher exact test when appropriate. Statistical computations were performed using SPSS software v. 13.0 (SPSS Inc., Chicago, IL), with two-sided *p*-values <0.05 considered significant.

Results

Histopathology

Six patients had surgical biopsy and 12 had computed tomography-guided biopsy. The histopathological review of the cases classified 4 (22%) patients in the highly suggestive IgG4-RD group, 8 (44%) in the possible IgG4-RD group and 6 (33%) were non-evocative of IgG4-RD (Table I).

Baseline characteristics, clinical presentation and biological parameters

There was no statistical difference between the 3 groups in terms of age, sex, smoking history, hypertension, diabetes, dyslipidaemia or venous thromboembolism (Table II). Median age of the highly suggestive IgG4-RD-RPF patients was 69.6 (63.0–73.7) years with 75% of men. Clinical findings in the highly suggestive IgG4-RD-RPF group were poor general condition, abdominal, lumbar and scrotum pain, lower limbs oedema, constipation, and there was no statistical difference with the other groups. Highly suggestive IgG4-RD-RPF patients were more likely to have BMI over 30 kg/m^2 (p=0.012) than the 2 other groups, but BMI as a continuous variable did not differ between groups. Among biological parameters, only the CRP tended to be higher in the highly suggestive IgG4-RD-RPF patients (p=0.053).

Table I. Histopathology features of each group according to the IgG4-related disease consensus.

	IgG4-related-disease histology		
	Non-evocative n=6	Possible n=8	Highly suggestive n=4
Lymphoplasmacytic infiltrate	1 (17)	7 (86)	4 (100)
Storiform fibrosis	4 (67)	8 (100)	4 (100)
Phlebitis	0	2 (25)	1 (25)
IgG4+ plasma cells per field	9.5 (6.0–28.0)	46.5 (26.5–72.5)	105.0 (38.5–380.0)
IgG4+/IgG+	40.8 (25.3–45.4)	25.5 (18.8–32.1)	81.7 (60.8–91.7)

Results are number (percentage) or median (25^{th}–75^{th} percentiles); IgG4+: IgG4 positive staining; IgG4+/IgG+: IgG4-to-IgG ratio (%).

Table II. Baseline characteristics and biological parameters according to histology groups.

	IgG4-related-disease histology			
	Non-evocative n=6	Possible n=8	Highly suggestive n=4	*p*-value
Baseline characteristics				
Female n (%)	1 (16.7)	2 (25.0)	1 (25.0)	0.923
Age (years)	71.1 (59.3–77.5)	58.6 (43.0–70.4)	69.6 (63.0–73.7)	0.172
Follow-up (month)	57.01 (5.82–97.94)	32.23 (16.36–137.87)	8.53 (4.39–35.03)	0.524
Smoker	4 (66.7)	5 (62.5)	3 (75.0)	0.908
Hypertension	3 (5.0)	1 (12.5)	2 (5.0)	0.221
Diabetes	1 (16.7)	1 (12.5)	1 (25.0)	0.867
Hyperlipidaemia	2 (33.3)	2 (25.0)	1 (25.0)	0.934
Venous thromboembolism	0	3 (37.5)	1 (25.0)	0.136
Clinical presentation				
Poor general condition	4 (66.7)	4 (5.0)	3 (75.0)	0.660
Abdominal pain				
unilateral	1 (16.7)	1 (12.5)	0	0.570
bilateral	1 (16.7)	1 (12.5)	1 (25.0)	0.867
Lumbar pain				
unilateral	2 (33.3)	2 (25.0)	0	0.296
bilateral	3 (5.0)	2 (25.0)	3 (75.0)	0.233
Scrotum pain				
unilateral	1 (16.7)	0	0	0.314
bilateral	2 (33.3)	1 (12.5)	1 (25.0)	0.636
Lower limb oedema	2 (33.3)	2 (25.0)	1 (25.0)	0.934
Constipation	0	1 (12.5)	0	0.428
BMI (kg/m^2)	25.6 (24.2–27.3)	24.3 (22.1–26.9)	30.5 (27.1–32.6)	0.121
BMI ≥30 kg/m^2	1 (16.7)	0	3 (75.0)	0.010
Biological parameters				
C-reactive protein (mg/L)	39.0 (27.0–142.0)	23.3 (8.4–29.7)	94.0 (68.0–125.5)	0.053
Fibrinogen (g/L)	5.9 (5.4–6.4)	6.1 (4.7–6.2)	5.0 (3.7–6.6)	0.294
serum creatinine (mg/dL)	1.0 (8.0–14.0)	9.0 (8.5–11.0)	29.5 (9.0–78.0)	0.421
Cockcroft clearance (mL/min)	91.7 (6.0–94.3)	95.0 (67.0–104.7)	55.0 (12.3–105.3)	0.726
Renal failure	1 (2.0)	1 (14.3)	2 (5.0)	0.427

Results are number (percentage) or median (25^{th}–75^{th} percentiles); BMI: body mass index.

Radiology findings

Highly suggestive and possible IgG4-RD-RPF exhibited slight different patterns on peri- and pre-aortic infiltrations, extension below the aortic bifurcation or above the renal arteries (Table III). We found a higher frequency of RPF infiltration circumscribed by the renal arteries and the aortic bifurcation

Table III. Imaging parameters according to histology groups.

	IgG4-related-disease histology			
	Non-evocative n=6	Possible n=8	Highly suggestive n=4	*p*-value
Peri-aortic RPF infiltration	1 (16.7)	2 (25.0)	1 (25.0)	0.923
Pre-aortic RPF infiltration	2 (33.3)	1 (12.5)	1 (25.0)	0.643
Other RPF infiltration pattern	3 (5.0)	6 (75.0)	2 (5.0)	0.557
Layer between RPF and the anterior intervertebral body wall	4 (66.7)	4 (5.0)	4 (100.0)	0.223
RPF between the renal arteries and the aortic bifurcation	4 (66.7)	1 (12.5)	4 (100.0)	0.010
RPF above the renal arteries	1 (16.7)	3 (37.5)	0	0.312
RPF below the aortic bifurcation	1 (16.7)	4 (5.0)	0	0.144
RPF above the renal arteries to below the aortic bifurcation	0	0	0	
widest RPF (mm)	17.0 (1.0–21.0)	26.5 (17.0–35.5)	22.0 (15.5–31.0)	0.469
thinnest RPF (mm)	5.0 (3.0–5.0)	7.0 (6.0–1.0)	7.0 (3.5–1.5)	0.160
Aorta lumen to posterior RPF limit (mm)	2.5 (2.0–3.0)	2.5 (.0–7.5)	2.5 (2.0–4.0)	0.911
Aorta lumen to anterior intervertebral body wall (mm)	3.0 (3.0–4.0)	4.0 (2.5–9.0)	3.0 (3.0–6.0)	0.710
Aorta thickness	2.0 (1.0–3.0)	1.0 (.8–2.5)	1.3 (1.0–1.8)	0.448
Aorta lumen	14.0 (1.0–15.0)	14.5 (14.0–19.5)	15.5 (14.0–16.5)	0.271
Inferior vena cava compression	0	4 (50)	1 (25.0)	0.117
Aorta compression	0	1 (12.5)	0	0.516
Urinary tract involvement	5 (83.3)	6 (75.0)	4 (100.0)	0.549
Medial ureteral attraction	5 (83.3)	5 (62.5)	4 (100.0)	0.312
Absence of ureteral obstruction	2 (33.3)	5 (62.5)	0	0.105

Results are number (percentage) or median (25^{th}–75^{th} percentiles); RPF: retroperitoneal fibrosis.

in highly suggestive IgG4-RD-RPF, than in possible IgG4-RD-RPF but not compared to the non-evocative group. Globally, no specific patterns could differentiate highly suggestive or possible IgG4-RD-RPF from non-evocative IgG4-RD-RPF.

Outcome in IgG4-RD-RPF patients

Follow-up of the highly suggestive and possible IgG4-RD-RPF patients varied from 4 to 14 years. Among the 4 highly suggestive IgG4-RD-RPF patients, one presented other organ involvement: a lung plasma cell granuloma. He relapsed when corticosteroids were tapered, leading to the introduction of methotrexate. Three out of 4 were only treated by corticosteroids, and 2 still needed bilateral ureteral stenting. None of the eight possible IgG4-RD-RPF patients had another organ involvement. Three out of eight relapsed when corticosteroids were tapered, leading to the introduction of immunosuppressor (azathioprine n=2, methotrexate n=1).

Discussion

In this study, we reported 18 patients with initial diagnosis of iRPF for whom retroperitoneal biopsies have been reviewed, in the light of the histopathological characteristics of IgG4-RD. This allowed to reclassify 4 iRPF as highly suggestive IgG4-RD and 8 as possible IgG4-RD. Unfortunately analysis of their clinical presentation, biological parameters, and imaging features did not identify any specific pattern that could help differentiate IgG4-RD-RPF from iRPF.

Our study led us to determine an IgG4-RD-RPF prevalence among iRPF of 22%, which is quite consistent with other studies showing prevalence between 13% and 50%. Zen *et al*. reviewed 17 patients with RPF: 10 of them had actually IgG4-RD-RPF based on their pathologic features: diffuse IgG4-positive plasma cell infiltration and an IgG4+/IgG+ >30%. All patients with IgG4-RD-RPF in that study were men above 50 years old (8). Vaglio *et al*., in a prospective trial, found 4 IgG4-RD-RPF from the 14 studied cases (29%), based on a high IgG4-positive plasma cell infiltrate (14). Khosroshahi *et al*. reviewed 23 iRPF with retroperitoneal biopsies and 10 IgG4-RD-RPF using an IgG4+/IgG+ cut-off of 40%. Mean age was 57 years with 77% of men (6). In a Spanish cohort of 24 cases with iRPF, 3 (13%) were highly suggestive IgG4-RD-RPF (15), this prevalence rising up to 47% in the South Korean cohort of 19 patients (16). We failed to identify any specific pattern that could help differentiate IgG4-RD-RPF from iRPF. But despite our small sample, neither Khosroshahi *et al*. (6) despite there being a larger number of north American cases retrospectively reviewed (n=23), nor Zen *et al*. (8) with 17 Japanese cases described any difference between IgG4-RD-RPF and iRPF. This was consistent with other studies in which the mean age, sex ratio, comorbidities and clinical symptoms were not different (6, 16, 17). All patterns of iRPF are possibly found in IgG4-RD-RPF: it mostly involves the peri-aortic region or near the renal hilum, can spread from the superior mesenteric artery to the bifurcation of the aorta, and can lead to aneurysm formation (12, 18). It is worth noting in our study that only one patient had another organ involvement in the spectrum of IgG4-RD. This highlights the fact that IgG4-RD-RPF can be isolated to the retroperitoneum and to base its diagnosis on clinical features only would be inaccurate.

Study limitations

Our study had a retrospective design, but the published studies on IgG4-RD-RPF had the same design, and worked on small sample size too. This is one of the pitfalls inherent in rare diseases such as IgG4-RD.

Conclusions

This study confirmed the high prevalence of IgG4-RD-RPF in patients previously considered as iRPF, but no clinical or radiologic criteria could help distinguish IgG4-RD-RPF from iRPF. Therefore, based on the current knowledge, it remains mandatory to perform a tissue biopsy in case of iRPF, in order not to jeopardise the diagnosis of IgG4-RD-RPF, especially when considering the promising results of rituximab therapy in IgG4-RD (11, 19, 20).

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