IgG4-Related Systemic Disease

Features and Treatment Response in a French Cohort: Results of a Multicenter Registry

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Abstract: IgG4-related systemic disease is now recognized as a systemic disease that may affect various organs. The diagnosis is usually made in patients who present with elevated IgG4 in serum and tissue infiltration of diseased organs by numerous IgG4+ plasma cells, in the absence of validated diagnosis criteria. We report the clinical, laboratory, and histologic characteristics of 25 patients from a French nationwide cohort. We also report the treatment outcome and show that despite the efficacy of corticosteroids, a second-line treatment is frequently necessary. The clinical findings in our patients are not different from the results of previous reports from Eastern countries. Our laboratory and histologic findings, however, suggest, at least in some patients, a more broad polyclonal B cell activation than the skewed IgG4 switch previously reported. These observations strongly suggest the implication of a T-cell dependent B-cell polyclonal activation in IgG4-related systemic disease, probably at least in part under the control of T helper follicular cells.

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Abbreviations: Fc = constant fragment, FITC = fluorescein isothiocyanate, IgG4-RSD = IgG4-related systemic disease, mAb = monoclonal antibody, SD = standard deviation, Th2 = T helper 2.

INTRODUCTION

IgG4 is under normal conditions one of the less abundant IgG subclasses in blood. Because IgG4 poorly binds Fc (constant fragment) receptors and does not activate the complement classical pathway, its role in humoral immune responses is unclear. Some reports suggest that the relative expression of the IgG4 isotype among antibodies increases with iterative antigenic challenges,[1] and that IgG4 displays antiinflammatory properties.[19] A polyclonal and moderate increase of blood IgG4 has been reported in allergic disease, parasitic infection, and several inflammatory or lymphoproliferative conditions.[2] To our knowledge, the relation between inflammatory organ lesions and elevated IgG4 levels was first reported by Hamano et al[8] in patients with "autoimmune" pancreatitis. Of note, hypergammaglobulinemia was noted several years before in such conditions by Sarles et al,[16] although they did not assess the repartition of IgG subclasses. Since these first descriptions, several types of inflammatory organ involvement have been recognized as manifestations of IgG4-related systemic disease (IgG4-RSD).[9] However, few series have been reported from Western countries.

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The diagnosis of IgG4-RSD or IgG4+ multiorgan lymphoproliferative syndrome (MOLPS)[11] is now used for patients presenting with elevated polyclonal IgG4 blood levels and organ involvement including sclerosing pancreatitis, sclerosing cholangitis, retroperitoneal fibrosis, mediastinal fibrosis, Küttner tumor, and inflammatory pseudotumors. To date there are no internationally recognized diagnostic criteria for IgG4-RSD. Criteria have been proposed for autoimmune pancreatitis, and a cutoff value of 1.35 g/L serum IgG4 (by single radial immunodiffusion or nephelometry) resulted in a high rate of specificity (97%) and sensitivity (95%), allowing the differentiation of autoimmune pancreatitis from other pancreatic diseases.[6–8,12,14] This cutoff value has been extended for the diagnosis of IgG4-RSD. Characteristic pathologic features include an inflammatory cell infiltrate dominated by lymphocytes and plasmocytes sometimes with lymphoid follicle formations. Other characteristic findings are fibrosis with a storiform pattern and obliterative phlebitis. A marked IgG4+ plasma cell infiltration with an IgG4+/IgG+ plasma cell ratio >0.4 on immunohistology, usually observed in these patients, has also been proposed to ascertain the diagnosis.[5]

Both the mechanisms of IgG4 plasma cell infiltration and IgG4 production, and the role of IgG4 in the disease remain unknown. To better define the characteristics of patients with IgG4-RSD, we created a multicenter registry in France. We report here on the clinical, laboratory, and histologic characteristics of 25 patients.

PATIENTS AND METHODS

Ascertainment of Patients

Patients were ascertained in several ways. In February 2009, all members of the French National Society of Internal Medicine were sent an e-mail describing characteristics of IgG4-RSD and inquiring if they were or had previously been following patients with IgG4-RSD, and if they would agree to enter them in the registry. Another description of the disease and the registry was presented in June 2009, during the national congress of the Society. Nephrologists were invited to include patients in the registry through an announcement on the website of the French Society of Nephrology. Two investigators who were performing serum IgG subclass measurements were asked to provide the names of physicians who had sent blood samples from patients with IgG4 elevation >1.35 g/L in the context of clinical suspicion of IgG4-RSD. Physicians were sent a 3-page clinical data entry form requesting detailed information on the demographic and clinical characteristics of the patient; the laboratory, radiologic, and histologic findings at diagnosis; treatments and corresponding responses; and the patients' latest status. The first patient was registered in February 2009, and between then and October 2010, 25 patients were entered into the registry. In May 2010, a 2-page follow-up form was sent to each physician who had entered patients in the registry up to that date, requesting information on the status of the patients at their last follow-up and the date of that last follow-up.

Construction of Registry

To maintain patient anonymity, the only identifying data collected were the patients' initials, birth date, and sex. The names, addresses, phone numbers, social security numbers, and/or hospital numbers were not provided. Duplicate entries from different physicians were avoided by cross-checking the patients' initials and birth dates.

Inclusion Criteria

There is no international consensus regarding IgG4-RSD diagnostic criteria to date. In the current study, patients were considered to have IgG4-RSD if they had 1) sclerosing and inflammatory involvement of 1 or more organ, including sclerosing pancreatitis, sclerosing cholangitis, inflammatory pseudotumors, retroperitoneal or mediastinal fibrosis, interstitial nephritis, hypophysitis, sclerosing dacryoadenitis, sialadenitis (Mikulicz disease and Küttner tumor), inflammatory aortic aneurysm, lymphadenopathy, or other inflammatory conditions; and 2) elevated serum IgG4 (>1.35 g/L) (measured by nephelometry or by ELISA); with 3) histopathologic features of fibrosis and/or lymphocytic and polyclonal plasma cell infiltration (and IgG4+ plasma cells on immunohistology when performed); and 4) exclusion of other diseases.

Evaluation of Treatment Response

In the clinical data entry form and the follow-up form, physicians were asked to answer yes or no to the following questions regarding the disease evolution: Did the clinical status improve? Did the IgG4 level significantly decrease? Did the radiologic abnormalities improve? Treatment was considered effective if at least 2 of these criteria improved based on the physician's evaluation.

Histologic Analysis

Tissue biopsies were all analyzed by conventional microscopy with Masson trichrome and hematoxylin-eosin staining. When performed, staining by anti IgG, IgG4, IgG3, IgG2 and IgG1-fluorescein isothiocyanate (FITC) monoclonal antibody (mAb) (all from The Binding Site, Birmingham, UK) were analyzed by immunofluorescence. IgG4+ plasma cell infiltration was assessed by a semi-quantitative evaluation from the pathology examination: no (-), present (+), abundant (++), or intense (+++) IgG4+ plasma cell infiltrate. When the number of

TABLE 1. Clinical Features of Patients With IgG4-RSD at Presentation

Feature	No. (%) (n = 25)
Symptom	
Asthenia	14 (56)
Weight loss	11 (44)
Abdominal pain	10 (40)
Xerostomia	8 (32)
Xerophthalmia	6 (24)
Cough or dyspnea	5 (20)
Diarrhea	3 (12)
Pruritus	3 (12)
Fever	3 (12)
Visual disorder	1 (4)
Examination	
Lymphadenopathy	11 (44)
Jaundice	5 (20)
Salivary gland swelling	5 (20)
Hepatomegaly	3 (12)
Abnormal pulmonary auscultation	3 (12)
Splenomegaly	2 (8)
Lacrimal gland swelling	1 (4)

TABLE 2. Organ Involvement of Patients With IgG4-RSD

Organ Involvement	No. (%) (n = 25)
Adenopathy	19 (76)
Sclerosing pancreatitis	13 (52)
Sialadenitis	11 (44)
Interstitial nephritis	11 (44)
Sclerosing cholangitis	8 (32)
Retroperitoneal fibrosis	8 (32)
Aortic involvement	6 (24)
Abdominal aorta	6 (24)
Thoracic aorta	3 (12)
Dacryoadenitis	3 (12)
Interstitial pneumonitis	3 (12)
Hypophysitis	2 (8)
Inflammatory pseudotumor	4 (16)
Orbital	1 (4)
Hepatic	2 (8)
Meningeal	1 (4)

IgG4+ plasmocytes per high-power field or the IgG4+/IgG+ plasma cell ratio were available, they were noted.

Statistical Analysis

IgG4 levels were expressed as geometrical means and standard deviations (SD). Correlations of IgG4 with IgG1, IgG2, and IgG3 levels were performed with the Spearman rank test, using GraphPad Prism v. 4.0.

RESULTS

Patient Characteristics

Among 50 cases reported, 25 patients fulfilled the inclusion criteria and were retained for the study. Most were recruited through the French Society of Internal Medicine, others from nephrologists and a few from gastroenterologists and rheumatologists. Among cases excluded from the study (n = 25), 12 patients had typical organ involvement but IgG4 levels <1.35 g/L, 5 patients had typical organ involvement and high serum IgG4 but insufficient available data, and 8 patients had serum IgG4 levels >1.35 g/L but no characteristic organ involvement and another diagnosis (Gougerot-Sjögren in 2 patients, and relapsing

TABLE 3. Characteristics of 25 Patients With IgG4-RSD

Patient	Age/Sex (yr)	IgG4-RSD Manifestation	Allergy*	Associated Inflammatory Condition
1	70/F	AIP, IN, hepatic IPT, LN	Yes	No
2	50/F	AIP, orbital IPT, dacryoadenitis, sialadenitis, LN	Yes	No
3	54/M	RPF	No	No
4	54/M	Meningeal IPT	No	No
5	66/M	IN, LN	Yes	No
6	72/M	AIP, SC, IN, LN	No	No
7	74/F	AIP, sialadenitis, LN	No	Ankylosing spondylarthritis
8	45/M	RPF	No	No
9	72/M	AIP, SC, sialadenitis, IN, LN, aortitis	No	No
10	50/F	RPF, mediastinal and pleural fibrosis, Riedel thyroiditis, aortitis, coronary inflammatory lesions	No	No
11	53/F	AIP, SC	No	No
12	61/M	RPF, AIP, sialadenitis, LN	No	No
13	24/F	SC, LN, splenomegaly	No	No
14	56/M	IN, ADP, interstitial pneumonitis	No	No
15	83/M	IN, RPF, AIP, sialadenitis, LN, splenomegaly	No	No
16	26/M	Sialadenitis, AIP, SC, LN	No	No
17	79/F	AIP, LN, interstitial pneumonitis	No	Sarcoidosis
18	50/M	IN, sialadenitis, LN, hypophysitis	Yes	No
19	69/M	RPF, aortitis, dacryoadenitis, sialadenitis, LN	No	Rheumatoid arthritis
20	54/M	RPF, aortitis, iliac, carotid and intracerebral inflammatory aneurysms, hypophysitis	No	No
21	49/M	AIP, SC, LN, renal IPT	No	No
22	69/M	AIP, IN, hepatic IPT, LN	Yes	No
23	41/M	Dacryoadenitis, sialadenitis, LN, interstitial pneumonitis	Yes	Rectocolitis
24	55/M	AIP, SC, RPF, aortitis, sialadenitis, renal IPT, LN	No	Anterior granulomatous uveitis?
25	77/M	Sialadenitis, IN, pararenal IPT	No	No

Abbreviations: AIP = autoimmune pancreatitis, IN = interstitial nephritis, IPT = inflammatory pseudotumor, LN = lymph node involvement, RPF = retroperitoneal fibrosis, SC = sclerosing cholangitis.

*Allergic manifestations were allergic rhinitis and/or bronchial asthma.

polychondritis with membranous glomerulonephritis, Henoch-Schönlein purpura, cystic fibrosis, hypogammaglobulinemia with recurrent infections and scleritis, eosinophilic fasciitis, and post-streptococcal uveitis in the other 6 patients). Of note, 3 of the 12 patients with normal IgG4 blood levels presented with typical pathologic findings including IgG4+ plasmocyte infiltration.

In the study group, the male to female ratio was 2.6:1. The mean age at onset was 58 years (range, 24–83 yr). The mean delay to diagnosis, corresponding to the delay between the first symptoms and the discovery of elevated IgG4 blood levels or typical histologic findings, was 3.8 years. However for some patients the delay to diagnosis was very long, up to 18 years for 1 patient. Only 6 (24%) patients presented with a history of allergic disease. Four of 25 patients presented with other associated inflammatory disease: 1 with ankylosing spondylarthritis, 1 with rheumatoid arthritis, 1 with sarcoidosis, and 1 with rectocolitis.

Clinical Features and Organ Involvement

The clinical features of patients at presentation are reported in Table 1. The most frequent symptoms were asthenia (56%), weight loss (44%), abdominal pain (40%), sicca syndrome (32% and 24% for xerostomia and xerophthalmia, respectively) and cough or dyspnea (20%). Fever was uncommon (12%) but lymphadenopathy was frequent on examination (44%). All 25 patients presented with typical organ involvement as shown in Table 2. The most common tissues involved were lymph nodes (76%), pancreas (52%), salivary glands (44%), kidney (44%), biliary duct (32%), and retroperitoneum (32%). As many as 6 (24%) patients presented with arterial wall inflammatory lesions. All 6 had aortitis, associated in 1 case with coronary inflammatory lesions and in another case with carotid and intracerebral inflammatory aneurysms. Most patients presented with involvement of more than 1 organ (range, 2–7 organs) (Table 3). The 3 patients with isolated organ involvement presented with retroperitoneal fibrosis (n = 2) or meningeal pseudotumor (n = 1).

TABLE 4. Laboratory Characteristics of Patients With IgG4-RSD*

	Value (n = 25)
IgG (g/L)	25.5 (1.8)
IgG4 (g/L)	7.2 (3.3)
IgG1 (g/L)	12.1 (1.8)
IgG2 (g/L)	4.0 (2.4)
IgG3 (g/L)	1.1 (3.2)
Low CH50	33% (5/15)
Low C3	44% (7/16)
Low C4	40% (6/15)
ANA	16% (4/25)
A-SSA	0% (0/23)
A-SSB	0% (0/23)
Elevated IgE (>100k UI/L)	40% (2/5)
Elevated CRP (>10 mg/L)	56% (14/25)

Abbreviations: ANA = antinuclear antibodies, A-SSA = anti-SS-A/Ro antibodies, A-SSB = anti-SS-B/La antibodies, CH50 = 50% hemolytic unit of complement, CRP = C-reactive protein.

*Values are provided as geometrical means (geometrical SD) for IgG, IgG1, IgG2, IgG3, and IgG4. Incidence rates (numbers of positive patients) are shown for ANA, A-SSA, A-SSB; elevated IgE, elevated CRP; and low CH50, C3, and C4. IgE, A-SSA, A-SSB, and CH50/C3/C4 were examined in 5, 23, 23, and 15/16/15 patients, respectively (not all).

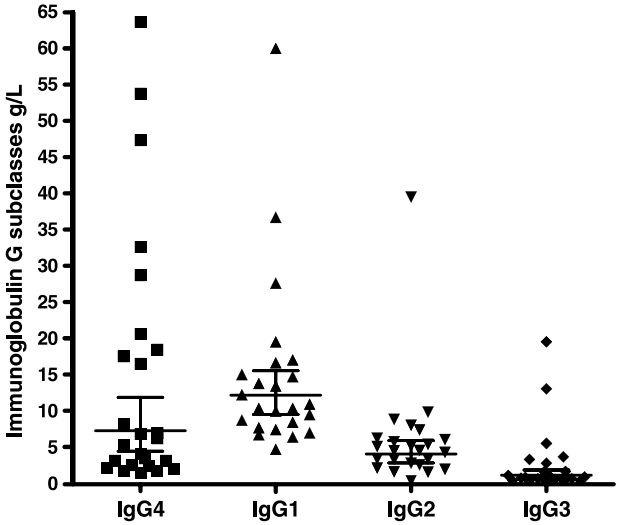

FIGURE 1. Distribution of IgG subclass levels in patients with IgG4-RSD. The horizontal bars show the geometrical mean and 95% confidence interval.

Laboratory Characteristics

Mean IgG and IgG subclass levels are shown in Table 4; a graphic representation is shown in Figure 1. IgG4 geometrical mean level was 7.2 (SD 3.3) g/L (range, 1.4–63.7 g/L). Eleven of 24 patients had elevated IgG1 levels (>11.4 g/L) (range, 12.2–36.7 g/L); 5 had elevated IgG2 levels (>6.4 g/L) (range, 7.31–39.5 g/L); and 9 had elevated IgG3 levels (>1.1 g/L) (range, 1.13–19.5 g/L). Only 3 patients presented with all IgG subclasses elevated (Patients 6, 13, 25). Patient 17, with associated sarcoidosis, had only mild IgG1 elevated levels (14.5 g/L) with normal IgG2 and IgG3 levels. Analysis by the Spearman correlation test of patients' IgG4 levels showed no correlation with IgG1 ($p = 0.58$) and IgG2 ($p = 0.36$), but a positive correlation with IgG3 levels ($p = 0.03$, $r = 0.43$). Polyclonal hypergammaglobulinemia on standard serum protein electrophoresis was noticed in 80% (20/25), and hyperproteinemia (>80 g/L) in 48% (12/25) of the cases. IgE levels were elevated in 2 of 5 analyzed patients. Antinuclear antibodies were positive at dilutions over 1:100 in 4 of 25 patients. None of the 23 patients examined had anti-SSA or anti-SSB antibodies. Elevated C-reactive protein levels (>10 mg/L) were observed in 56%, with a mean of 30.89 mg/L (range, 11–148 mg/L). C3 and/or C4 complement fraction serum levels were decreased in 9 of the 16 analyzed patients. Of these, 7 had nephritis.

Histologic Findings

For all patients at least 1 histologic tissue examination was performed (range, 1–4 different tissue biopsies per patient). Results of conventional histologic examination on hematoxylin-eosin and/or Masson trichrome staining were available for all, but immunofluorescence or immunohistochemical staining with anti-IgG4 mAb was performed in only 12 patients. Table 5 depicts the histologic findings for each tissue analyzed. Taken together, lymphocytic infiltration and polyclonal plasma cell infiltration were the most frequent findings, each in 92% of patients. Fibrosis was noticed in 80% and extranodal lymphoid

TABLE 5. Histologic Results for 25 IgG4-RSD Patients*

N	Organ	Fibrosis	Lymphocytic Infiltration	Lymphoid Follicle Formation	Polyclonal Plasmocyte Infiltration	Immunohistologic Staining
1	Liver	+++	+	+	No	NA
	Kidney	++	+++	+	+++	IgG4 ++
2	LG	++	++	+++	++	NA
	SG	++	++	No	+	NA
	LN	No		FH		NA
3	RPF	++	No	No	++	NA
4	Meningeal	++	+	+	+++	IgG4+ plasma cells +++
5	Kidney	++	++	No	+++	IgG4+ plasma cells +++
	SG	++	++	No	No	No IgG4+ plasma cell
6	LN	No			IF ++	NA
	Bile duct	++	++	No	++	NA
	Pancreas	+++	++	No	++	NA
7	SG	+++	++	+	++	NA
	Pancreas	++	++	No	++	NA
	Bile duct	++	++	No	++	NA
8	RPF	+++	++	No	++	
9	Parotid	No	+	++	++	No predominant IgG4 expression
	Liver	+	+	No	No	NA
	Pancreas	++	No	No	No	NA
10	Pleura	++	++	No	No	NA
	Thyroid	++	++	No	No	NA
11	Liver	+	+	No	No	NA
	Bile duct	++	++	No	+	NA
12	Pancreas	+++	++	+	+++	NA
	Aortic wall	++	++	No	++	NA
	LN	No		FH	IF ++	NA
	SG	+	+++	++	No	NA
13	Liver	++	++	No	++	NA
	LN	++		FH	IF ++	IgG4+ plasma cells +++
	Bile duct	+	++	No	+	NA
14	LN	No		FH	IF ++	NA
	Kidney	No	++	No	+++	NA
15	LN	++		FH	IF ++	IgG3+ and IgG4+ plasma cells +++
	Kidney	No	+	No	+++	IgG3+ and IgG4+ plasma cells +++
	SG	++	++	++	+	NA
16	SG	No	+	No	+++	NA
	Parotid	No	++	No	+	NA
	LN	No		FH	IF	NA
17	SG	++	++	No	No	NA
	LN	No		EF	No	NA
	Pancreas	+++	+	No	+	NA
18	SG	++	++	++	+	IgG4 staining + but no IgG4+ plasma cells
	Kidney	+++	+	++	+++	IgA+ plasma cells+++, IgM plasma cells++
19	SG	No	++	++	No	NA
	FRP	NA	NA	NA	NA	NA
20	LN	No			+++ (>150/hpf)	IgG4+ plasma cells+++ (60%)
	SG	No	No	No	No	NA
	RPF	NA	NA	NA	NA	NA
21	LN	NA	NA	NA	NA	NA
	Pancreas	++	+	No	+	NA
22	Kidney	+++	+++	No	+++	IgG4+ plasma cells+++ and IgA+ plasma cells++
	Liver	+	+	No	+	NA
	Pancreas	++	++	+	++	NA
	LN	+		FH	No	

(Continued on next page)

TABLE 5. *(Continued)*

N	Organ	Fibrosis	Lymphocytic Infiltration	Lymphoid Follicle Formation	Polyclonal Plasmocyte Infiltration	Immunohistologic Staining
23	SG	No	+++	++	No	NA
	Nasal mucosa	No	++	No	No	NA
	Bronchial mucosa	No	++	No	++	NA
	Stomach	No	++	No	++	NA
	Ileum	No	++	++	No	NA
	Colon	+	+	No	+	NA
	Nasal mucosa					
24	SG	++	+++	++	++	IgG4+ plasma cells +++
25	Pararenal IPT	+++	+	+	+++	IgG4+ plasma cells ++ (50/hpf)
	Kidney	+++	++	+	++	IgG4+ plasma cells ++ (50/hpf)
	SG	+	+	No	No	NA

Abbreviations: EF = epithelioid follicles, FH = follicular hyperplasia, hpf = high-power field, IF = interfollicular infiltration, IPT = inflammatory pseudotumor, LG = lachrimal gland, LN = lymphadenopathy, N = patient number, NA = data not available, RPF = retroperitoneal fibrosis, SG = salivary gland.

*Scale: no = not present, present (+), abundant (++), or intense (+++).

follicle formation in 52% of patients. The degree of these histologic changes was variable in the same patient depending on the organ analyzed. Staining with an anti-IgG4 mAb on tissue sections was performed in only 12 of 25 patients; 8 showed numerous IgG4+ plasma cells. In 1 patient (Patient 9) IgG4+ plasma cells were detected but did not predominate among IgG+ plasma cells. In another patient, the salivary gland lacked IgG4+ plasma cells (Patient 18). In Patient 18, who presented with typical renal interstitial lymphoid and plasma cell infiltration with extensive storiform fibrosis, IgG4+ and IgG+ cells were not detected despite serum IgG4 through levels of 20.6 g/L. In this patient, further immunostaining with anti-IgA and anti-IgM mAbs showed diffuse infiltration with IgA+ plasma cells and, to a lesser extent, with IgM+ plasma cells. Staining for immunoglobulin light chains with an anti-kappa and an anti-lambda mAb showed a polyclonal pattern, and bone marrow biopsy was normal. Serum IgA and IgM levels were normal in this patient. In another patient (Patient 15) with increased IgG4 and IgG3 blood levels, immunohistologic analysis on kidney and lymph node biopsy showed diffuse infiltration by both IgG4+ and IgG3+ plasma cells. Bone marrow biopsy was performed in 13 patients and was normal in 7 (54%). In 2 patients a polyclonal mature lymphocytic infiltration was observed, and polyclonal plasma cell infiltration was noted in 6 patients, but no IgG4+ staining was available.

Follow-Up and Response to Treatment

Patient follow-up and histories were recorded with a mean follow-up of 60.4 months (range, 4–224 mo). Only 1 patient (Patient 10) died, from a probable rupture of thoracic aortic aneurysm. Treatments are shown in Table 6. Treatment efficacy was determined based on clinical, laboratory, and radiologic global evaluation by the physician. Most patients (92%, n = 23) received prednisone (median, 0.6 mg/kg per d; mean, 0.67 mg/kg per d, SD = 0.3; range, 0.12–1). Two patients did not receive prednisone as a consequence of mild disease (Patient 6) or contraindication to steroids (Patient 15, pulmonary tuberculosis under treatment and chronic osteitis). Efficacy

TABLE 6. Treatment and Efficacy

	Patients Treated	Treatment Effective	Side Effects
Treatment	**No. (%)**	**No. (%)**	**No. (%)**
Corticosteroids	23 (92)	19/21* (90)	14/21* (67)
Azathioprine	6 (24)	3/4* (75)	1/4* (25)
Rituximab	3 (12)	2/3 (67)	0/3 (0)
Cyclophosphamide	3 (12)	1/3 (33)	1/3 (33)
Methotrexate	2 (8)	1/2 (50)	0/2 (0)
Other			
Surgery	4 (16)	1/4 (25)	1/4 (25)
Hepatic transplantation	1 (4)	0/1 (0)	1/1 (100)
Vinblastine	2 (8)	0/2 (0)	0/2 (0)
Tamoxifen	1 (4)	0/1 (0)	1/1 (100)
Tocilizumab	1 (4)	1/1 (100)	0/1 (0)
Imatinib	1 (4)	0/1 (0)	0/1 (0)

*Recent treatment for 2 patients, response and tolerance not yet evaluable.

was noticed in 90% of cases. Corticosteroids could be stopped in 30% of treated patients. Second-line treatments were used in 12 (48%) patients because of steroid dependence and/or steroid side effects (n = 10), or because of insufficient response under steroids (n = 2). Azathioprine was used in 6 patients. Rituximab was used in 3 patients, with an estimated good response in 2 (Patients 16, 20) and no response in 1 (Patient 14). (For more about rituximab treatment for IgG4-RSD, see the article by Khosroshahi et al[10a] in this same issue.) Cyclophosphamide was used in 3 patients, methotrexate in 2, imatinib in 1, and tocilizumab in 1.

DISCUSSION

We report here 25 patients with IgG4-RSD recorded in a French national registry. To date no well-recognized international diagnosis criteria for IgG4-RSD have been defined. Numerous reports indicate that the association of high serum IgG4 levels with organ infiltration by polyclonal lymphocytes and IgG4+ plasma cells enables IgG4-RSD to be distinguished from well-characterized autoimmune or inflammatory disease, lymphoproliferative malignant diseases, and other conditions previously associated with increased IgG4 levels.[11] We have included in the current study only patients presenting with IgG4 serum levels >1.35 g/L associated with "classical" organ involvement with fibrosis and polyclonal lymphocytic and plasma cell infiltration without evidence of other diseases. Of note, none of the patients presented with anti-SSA or anti-SSB, and only 4 had low titers of antinuclear autoantibodies. Unfortunately, in this retrospective multicentric study the immunohistologic analysis for IgG4+ plasma cell infiltration was lacking for a significant number of patients. Moreover, when performed, no accurate quantitative analysis for IgG4+ plasmocyte infiltration was available in most cases. However all the patients satisfied the clinical and laboratory (IgG4 >1.35) criteria as recently proposed.[13] All patients were shown to have characteristic pathologic findings with either polyclonal plasma cell and/or lymphocytic infiltration (100%) or storiform fibrosis (80%).

Males were significantly more frequent in our cohort (18 of 25 patients). Allergic conditions were noticed in only a few of our patients despite a high frequency in some previous cohorts.[11] Lymph node enlargement on examination was the most frequent sign, which might suggest a primary defect that could involve secondary lymphoid events.

As noted previously, xerostomia was less frequent (32%) than expected considering the frequency of sialadenitis (44%).[11] Most patients presented with multiple organ involvement. Organ involvement in the current series is in accordance with previous reports with lymph node (76%), pancreas (52%), and salivary glands (44%) involvement as the most frequent manifestations. In the current study renal involvement was relatively more frequent (44%) than previously reported in IgG4-RSD (17%).[11] Sclerosing cholangitis was less frequent (32%). The observed differences may be related to the patients' recruitment through the registry. Moreover it must be taken in account that IgG4-RSD is under-recognized, and that patients included in the registry are those probably presenting with a severe disease, which may account for the high frequency of multiple organ involvement observed. Of note, 6 patients presented with aortitis, associated with other arterial inflammatory lesions in 2 of them. This confirms the association of IgG4-RSD with large-vessel vasculitis, as recently reported.[10,17,18]

Laboratory findings for patients in the current study were comparable to those reported previously in patients with IgG4-RSD. Elevation of serum IgG4 levels was extremely variable, ranging from 1.4 to 63.7 g/L. Remarkably high IgG4 levels were found especially in patients with interstitial nephritis. There was no correlation between serum IgG4, IgG1, and IgG2 levels, but there was a positive correlation between IgG4 and IgG3 levels. In only 3 cases, all IgG subclasses were increased. IgG4 and IgG3 levels were significantly higher in IgG4-RSD patients with renal involvement than in IgG4-RSD patients without renal involvement ($p = 0.0048$ and $p = 0.0034$, respectively). Moreover, in 7/8 (88%) patients with interstitial nephritis, C3 and/or C4 complement fractions were decreased (only 29% of patients without renal involvement). A high frequency of hypocomplementemia was already reported in IgG4-RSD tubulointerstitial nephritis.[15] As IgG4 does not activate the complement classical pathway, these findings may suggest that IgG3 could participate in immune complex formation.

Some of our patients presented with atypical findings on immunohistology despite "typical" histologic abnormalities on conventional hematoxylin-eosin staining. In 3 patients immunohistologic analysis of plasma cell infiltration was surprising. In Patient 15, IgG4+ plasma cells were associated with numerous IgG3+ plasma cells in lymph node and kidney; in Patient 22, numerous IgA+ plasma cells were associated with IgG4+ plasma cells in the renal interstitium, and in Patient 18 only IgA+ and IgM+ plasma cells were found in the kidney. The observations that other IgG subclasses are also elevated in the blood of more than half the patients, and that numerous infiltrating plasma cells actually express Ig isotypes other than IgG4, indicate a more broad polyclonal B lymphocyte activation than the skewed IgG4 switch reported to date in IgG4-RSD. However most tissues analyzed in the current study with an anti-IgG4+ mAb showed abundant IgG4+ plasma cells (8/12). These findings confirm the importance of characterizing all the immunoglobulin isotypes of the plasma cell infiltration in IgG4-RSD to clarify these observations and the nature of plasmocyte infiltration in IgG4-RSD.

Five patients were excluded from the current series because of the lack of available pathologic analysis despite elevated IgG4 levels and typical organ involvement. Pathologic features in our patients also showed that the degree or the presence of lymphocytic and plasma cell infiltration and fibrosis could vary within the same patient depending on the tissue analyzed. The usual absence of fibrosis in lymph nodes was not surprising and was in accordance with previous reports. Some patients presented with typical clinical organ involvement and typical pathologic features including IgG4+ plasma cell infiltration but normal IgG4 blood levels (n = 3). These patients were excluded from the study but raise the question of the importance accorded to the elevation of IgG4 in blood for the diagnosis of IgG4-RSD. In fact, these patients probably presented with a "seronegative" IgG4-RSD as proposed in the clinical diagnostic criteria for IgG4-RSD proposed by the Japanese Research Committee for "systemic IgG4-related sclerosing disease".[13]

The current retrospective analysis of response to treatment in patients with IgG4-RSD was based on very basic response criteria that did not allow strong conclusions. We observed the efficacy of corticosteroids in IgG4-RSD, but also the frequent need for second- or third-line treatments. This indicates the urgent need for a better understanding of the pathogenesis of IgG4-RSD to help define new and more specific therapeutic strategies. Importantly, it is still unknown whether IgG4-secreting plasma cells merely result from an upstream pathogenic immunologic event, or if they do participate in the pathogenesis. Our findings also suggest direct or indirect implication of other Ig classes and subclasses in the disease. To date only a few studies have analyzed modifications of T-cell subsets in IgG4-RSD.[4] T helper 2 (Th2) and regulatory T cells

were demonstrated in tissues and in the blood from some of these patients.[3,20,21] Other T-cell subsets, such as follicular helper T cells, may certainly participate in the pathogenesis of IgG4-RSD by enhancing Ig isotype switching and B-cell terminal differentiation. Further clinical, laboratory, and histologic studies are needed to better define IgG4-RSD and to validate diagnostic criteria.

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