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# IgG4-Related Disease: Results From a Multicenter Spanish Registry

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**Abstract:** IgG4-related disease (IgG4-RD) is a rare entity consisting of inflammation and fibrosis that has been described in multiple organs. Concrete diagnostic criteria have been established recently and there is a lack of large series of patients.

To describe the clinical presentation, histopathological characteristics, treatment and evolution of a series of IgG4-RD Spanish patients.

A retrospective multicenter study was performed. Twelve hospitals across Spain included patients meeting the current 2012 consensus criteria on IgG4-RD diagnosis.

Fifty-five patients were included in the study, 38 of whom (69.1%) were male. Median age at diagnosis was 53 years. Thirty (54.5%) patients were included in the Histologically Highly Suggestive IgG4-RD group and 25 (45.5%) in the probable IgG4-RD group. Twenty-six (47.3%) patients had more than 1 organ affected at presentation. The most frequently affected organs were: retroperitoneum, orbital pseudotumor, pancreas, salivary and lachrymal glands, and maxillary sinuses.

Corticosteroids were the mainstay of treatment (46 patients, 83.6%). Eighteen patients (32.7%) required additional immunosuppressive agents. Twenty-four (43.6%) patients achieved a complete response and 26 (43.7%) presented a partial response (<50% of regression) after 22 months of follow-up. No deaths were attributed directly to IgG4-RD and malignancy was infrequent.

This is the largest IgG4-RD series reported in Europe. Patients were middle-aged males, with histologically probable IgG4-RD. The systemic form of the disease was frequent, involving mainly sites of the head and abdomen. Corticosteroids were an effective first line treatment, sometimes combined with immunosuppressive agents. Neither fatalities nor malignancies were attributed to IgG4-RD.

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**Abbreviations:** DMARDs = disease modifying antirheumatic drugs, GEAS = Group of Autoimmune Diseases, IgG4-RD = IgG4-related disease, IQR = interquartile range, REEIGG4 = Spanish Register of IgG4-related disease, SEMI = Spanish Society of Internal Medicine.

## INTRODUCTION

IgG4-related disease (IgG4-RD) is a fibro-inflammatory disorder that is often characterized by the presence of a pseudotumor(s) with locally expansive behavior. Such patients are often misdiagnosed initially as having a malignancy. Other patients present with systemic symptoms including fever, malaise, and weight loss.<sup>1</sup> These different presentations, which recapitulate only some of the ways in which IgG4-RD can present, are not mutually exclusive.

IgG4-RD includes many previously recognized conditions that affected single organs such as Mikulicz's disease or Ormond's disease. Since 2001, when high levels of IgG4 were described in some patients with autoimmune pancreatitis,<sup>2</sup> the knowledge on this entity has increased dramatically. In the following years, several authors described series of patients with multiple organs involved<sup>3</sup> and the name "IgG4-related sclerosing disease" was adopted. The first diagnostic consensus was established in 2009 by Japanese experts.<sup>4</sup> They also established the current name of the disease: IgG4-RD. Many case reports and short series, with a myriad of inclusion criteria can be found in the literature. Approximately three-quarters of the patients reported in the literature to date were Japanese.<sup>5</sup> Because of those methodological biases, it is difficult to extract solid evidence. In 2012, an international consensus determined the current IgG4-RD diagnostic criteria,<sup>6</sup> based on pathologic characteristics, leaving IgG4 serum elevation as a complementary finding. The organ-specific involvement has also been defined, withdrawing eponyms and old terms.<sup>7</sup> The largest work available is a Japanese multicenter study published in 2014, which included 122 patients, but only 76 of them met the current diagnostic consensus.<sup>8</sup> The only European multicenter

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study available included 25 patients from a French nationwide cohort and used the Japanese expert's criteria.<sup>9</sup>

In order to apply the new diagnostic criteria and to deepen in the understanding of the clinical course, treatment and evolution of IgG4-RD, a Spanish nationwide multicenter register was created. Here we report the results of the 55 patients included.

## METHODS

### Spanish Register of IgG4-Related Disease (REEIgG4)

In 2009, we reported the prevalence of IgG4 infiltration among patients affected with idiopathic retroperitoneal fibrosis (IRPF), and therefore of IgG4-related retroperitoneal fibrosis.<sup>10</sup> In October 2013, after the publication in the previous year of the new IgG4-RD diagnostic criteria, the need of a nationwide register in order to unify the management of those patients emerged. The register was approved and created within the Spanish Society of Internal Medicine (SEMI) and its Group of Autoimmune Diseases (GEAS).

### Register Management

The respective institutional review boards from the different centers approved the study. A standardized form was given to every contributor. Once filled, the forms were returned and all personal data from the patients were removed. Each one was assigned a register number.

### Inclusion Criteria

The recruitment period ranged from November 2013 to November 2014. Patients eligible for the study could be introduced retrospectively or prospectively. The basic inclusion criteria was to meet the 2012 international diagnostic consensus on IgG4-RD by Deshpande et al,<sup>6</sup> based on pathology findings and clinical correlation. The technical procedures recommended were the same (IgG4 staining with monoclonal antibodies, preference for surgical biopsies, cell counts at 400× calculating the mean cell counts in at least 3 high power fields or hpf in 3 different hot spots). Pathologic evaluations were performed at every center separately. This classification included 3 categories as described elsewhere. Only patients with Histologically Highly Suggestive IgG4-RD or Probable Histological Features of IgG4-RD were included in this study.

### Epidemiological Study

The following data were collected: the hospital center at which the patient was evaluated, sex, birth date, age at diagnosis, date of the first and last control and the presence of other autoimmune conditions.

### IgG4-RD Study

The extent of the disease was defined as systemic if there were 2 or more organs affected. Otherwise it was considered localized. The specific organs included were those already cited previously in the literature. IgG4 serum determinations were made by nephelometry or by enzyme immunoassay, considering normal values 5 to 135 mg/dL.

### Treatment and Evolution

The use of corticosteroids, with maximum doses, time under maximum doses, time of dosage decrease, and current

dose were noted. Other treatments like radical surgery, immunosuppressive agents, and biologic therapies were also recorded. Regarding evolution, resolution after treatment was divided into 3 subsets: complete (complete regression of the fibrotic mass/masses and systemic symptoms), partial (<50% of regression of the mass/masses and cease of the systemic symptoms) and none (no response). During follow-up, the appearance of malignancies or deaths and the cause of the decease were reported, as well as previous cancers.

### Statistical Analysis

Descriptive statistics included median, quartile 25 and quartile 75. Comparisons between variables were performed using Chi-square tests. The statistical study was performed with SPSS (version 18.0; SPSS, Inc., Chicago, IL).

## RESULTS

### Patients

Fourteen medical centers across Spain sent eligible patients for the study. Sixty-four cases were referred for evaluation but only 55 were included. All 9 patients who did not meet the inclusion criteria had almost 2 IgG4-RD pathologic criteria but the immunohistochemical study including IgG4 cell count and/or IgG4<sup>+</sup>/IgG<sup>+</sup> ratio was not available.

Regarding the patients included in the study, 38 (69.1%) were male, with an approximate male to female ratio 3:1. The median age at diagnosis was 53 years (interquartile range [IQR] 41–64). The diagnosis of previous autoimmune diseases was reported in 9 (16.4%) patients: 5 (5.7%) had been diagnosed of Hashimoto's thyroiditis, and 4 of rheumatoid arthritis, antineutrophil cytoplasmic antibodies-negative systemic vasculitis, ankylosing spondylitis and Graves' disease, once (1.8%) each.

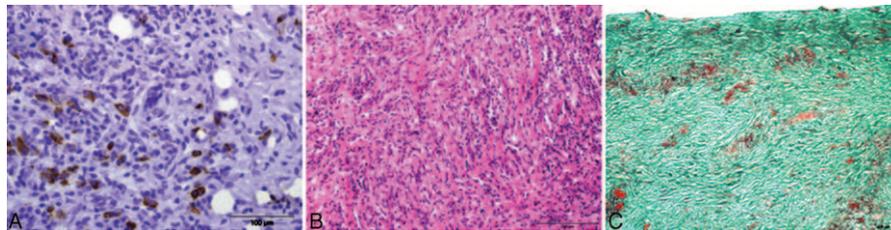
### Pathology and Distribution of Involvement by Organs

Samples of biopsies of IgG4-RD patients are exposed in Figure 1. Fifty patients (90.9%) had surgical biopsy specimens and 5 (9.1%) had needle aspiration samples. Thirty patients (54.5%) were included in the Histologically Highly Suggestive IgG4-RD histological group and 25 (45.5%) in the Probable Histological Features of IgG4-RD group. The histopathological characteristics and serum IgG4 levels are summarized in Table 1. Twenty-six patients (47.3%) had systemic IgG4-RD with more than 1 organ affected at presentation. The different tissues involved and the frequencies are described in Figure 2. There were no statistically significant differences between systemic and localized IgG4-RD regarding organ involvement, except for maxillary sinus involvement, more associated to the systemic form ( $P = 0.001$ ).

### Treatment

Forty-seven patients (85.5%) received corticosteroids. The median maximum dose was 55 mg/day (IQR 30–60) during 1 month (IQR 0.75–1.5). Corticosteroid tapering lasted a median of 8 months (IQR 4–11.25). Twelve patients (21.12%) were maintained on a mean dose prednisone of 7.5 mg/day (IQR 5–10).

Nineteen patients (34.5%) received immunosuppressive agents due to corticosteroid resistance (sustained disease activity, progression of clinical symptoms or flares when down-scaling steroids) or secondary effects. Mofetil mycophenolate/



**FIGURE 1.** Microscopic samples of IgG4-related disease. Panel A shows immunostaining for IgG4-positive plasma cell infiltrate in a retroperitoneal mass, at 400×. Panel B illustrates an important lymphoplasmacytic infiltrate in a retroperitoneal mass sample, stained with hematoxylin and eosin at 200×. Finally, Panel C, stained with Masson's trichrome, depicts the storiform fibrosis at 100× in a sample of pleura.

mycophenolic acid was prescribed in 6 patients (10.9%), azathioprine in 9 (16.4%), azathioprine followed by methotrexate in 2 (3.6%), and azathioprine followed by cyclophosphamide in 2 patients each (2.9%). Three subjects (5.5%) received biologic treatment with rituximab. Finally, 16 individuals (29.1%) underwent radical surgery in the context of the diagnostic process and/or local compression. They were all performed before the IgG4-RD diagnosis was made.

In summary, 35 (63.6%) patients received medical treatment only, 4 (7.3%) underwent surgery alone, and 12 (21.8%) received a combination of medical and surgical interventions. In addition, 4 (7.3%) patients did not receive any treatment. One because she was asymptomatic, and the other 3 because they were diagnosed just near the inclusion period ending, and no therapeutic decision had been made at that moment. Patients with systemic IgG4-RD were more likely to receive immunosuppressive agents than those with localized disease ( $P = 0.004$ ).

**Evolution and Survival**

The median follow-up was 23.03 months (IQR 8.08–55.06). Calculations were made with 52 patients at risk. Twenty-four individuals (46.2%) presented a complete response and 26 (50%) presented a partial response. One patient (1.9%) did not respond to the treatment and in another, the lesion was too small to evaluate the response. Within the 19 subjects who only took prednisone, 10 had a complete resolution and 14 were able to discontinue the medication. The comparison between systemic IgG4-RD and localized IgG4-RD, discarding the 2 nonresponders, showed that localized IgG4-RD significantly presented more complete responses than the first group (8 vs. 16,  $P = 0.24$ ). Twenty subjects (38.5%) presented recurrences. Systemic forms of IgG4-RD had a

statistically significant tendency to flare when compared with localized IgG4-RD forms (15 cases vs. 5 cases,  $P = 0.00$ ).

During the follow-up, 2 fatalities were reported (3.6%), 1 due to a car accident and another due to a sepsis secondary to an episode of pneumonia. No deaths were directly attributed to IgG4-RD. Appearance of malignancy or premalignant conditions were reported in 5 occasions, corresponding to 4 patients. The following conditions were reported: monoclonal gammopathy of unknown significance in twice, prostate cancer once, breast cancer once and 1 patient developed a cervix cancer previously to IgG4-RD.

**DISCUSSION**

We have presented a multicenter observational study including 55 Spanish patients with IgG4-RD. It is the first non-Japanese study using the current IgG4-RD diagnostic criteria, and the largest European series by the moment. Also, the fact that it comes from a single country adds homogeneity to the population and accuracy to the data recruitment. There was a male predominance, typical of what has been reported by other investigators. Middle-aged individuals were the most affected. The disease tended to affect multiple organs and it had an acceptable response to treatment with corticosteroids, immunosuppressive agents and biologics. Flares and incomplete response to the treatment were associated to the systemic form of IgG4-RD. No deaths were directly related with the disease and the malignancy rate was low.

There is limited data in the literature in order to compare our findings with other studies. We chose the 2 widest series published in the literature to do so, but limitations emerged rapidly. On one hand, the French National Society of Internal Medicine's register,<sup>9</sup> involving 25 patients. This study described in 2012 a cohort of patients in the vicinity of our

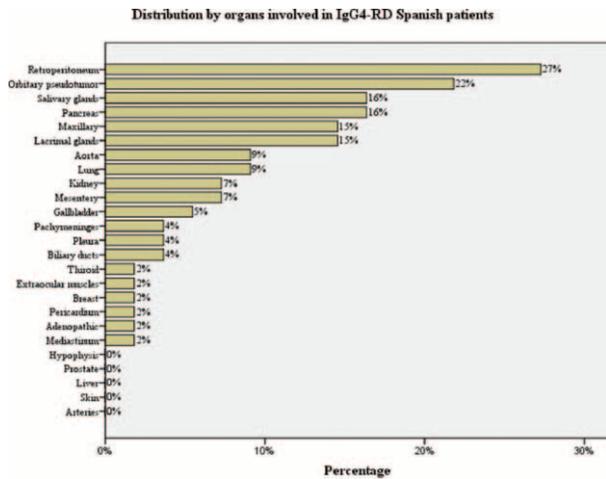
**TABLE 1.** Histopathological Characteristics and Serum IgG4 Levels of Spanish Patients With IgG4-Related Disease

	Highly Suggestive IgG4-RD	Probable IgG4-RD
Lymphoplasmacytic infiltrate	100% (30)	100% (25)
Storiform fibrosis	93.3% (28)	100% (25)
Obliterative phlebitis	43.3% (13)	48% (12)
Median IgG4 cells*	56 (Q1 43.2, Q3 99.3)	26.4 (Q1 10.25, Q3 38.8)
Median IgG4/IgG ratio*	126.7 (Q1 80.2, Q3 180.5)	77.4 (Q1 22.2, Q3 350)
Median serum IgG4 mg/dL <sup>†</sup>	223 (Q1 123.5, Q3 1145.2)	93 (Q1 30.8, Q3 494.7)

IgG4-RD = IgG4-related disease.

\* Per high power field at 400×.

<sup>†</sup> Thirty-eight serums available; serum IgG4 normal range 5 to 145 mg/dL.



**FIGURE 2.** Distribution by organs involved in IgG4-related disease Spanish patients. Total recount by organs: retroperitoneum 15; orbital pseudotumor 12; pancreas and salivary glands 9; maxillary and lacrimal glands 8; aorta and lung, kidney and mesentery 4; gallbladder 3; pachymeninges, pleura and biliary ducts 2; thyroid, extraocular muscles, breast, pericardium, adenopathic and mediastinum 1; hypophysis, prostate, liver, skin, and arteries 0.

country. The main bias as a comparator was the use of comprehensive diagnostic criteria, what left patients outside the study. Otherwise, regional differences in the incidence and presentation of autoimmune pancreatitis type I,<sup>11</sup> the cornerstone from which studies on IgG4-RD started, may be a strong point of this paper. On the other hand, we chose the SMART<sup>8</sup> database, a Japanese study, recently published, including 122 patients. This work included 76 patients fulfilling the 2012 international consensus,<sup>6</sup> mixed with 66 patients diagnosed with the older comprehensive diagnostic criteria.<sup>12</sup> This issue constitutes another bias because the reliance of these criteria on IgG4 serum levels and the difficulty to make comparisons with mixed cohorts. The role of increased serum IgG4 levels in diagnosis has been heavily questioned.<sup>13,14</sup>

The 3 reports agree that the age of presentation is between 60 and 53 years. There are differences between the sex ratio, where the Asian cohort showed a 1:1 ratio, while the French cohort showed a male predominance (2.6:1), as well as ours (3:1). A systematic review of the literature<sup>5</sup> including 3366 cases, but with different sets of IgG4-RD diagnostic classifications, also suggested a trend toward increased male to female ratios, matching with our results. We found 9 patients over 55 with diverse associated inflammatory diseases. No rheumatologic condition has been solidly associated with the presence of IgG4-RD. Similarly, 4 patients over 25 in the French study also presented other immune disorders.

The pathological examination showed that all the subjects had almost 2 of the classical histological features. All patient reports included the IgG4 cell count and/or the IgG4/IgG ratio. Probably, in the next years, with the validation and introduction of new biomarkers like serum plasmablast determinations,<sup>15</sup> diagnostic criteria will adapt more to the everyday clinicians reality with its material limitations.

Regarding the current international classification, nearby one-half of the patients presented Histologically Highly Suggestive IgG4-RD, while the rest presented Probable Histological Features of IgG4-RD. Patients with incomplete histological features (ie, disclosing fibrotic changes only) were excluded in

order to grant more cohesion. Twenty-six patients, nearby the half of our sample, had IgG4-RD with more than 1 organ affected at presentation. These data were close to the 61.4% of patients with organ involvement different from dacryoadenitis and/or sialadenitis reported by the SMART authors. The French group reported 22 over 25 patients with more than 1 organ involved. We think that a figure between the 2 first studies may be the right estimation due to the larger size of both samples. If we review the most frequently affected organs, all patients in the Japanese study had IgG4-related dacryoadenitis or sialadenitis because it was the main inclusion criteria. Among those patients, retroperitoneal fibrosis (20%) and type I autoimmune pancreatitis (15.7%) were the following in frequency order. Meanwhile, in the French report the most common tissues involved were lymph nodes (76%), pancreas (52%) salivary glands and kidney (44%), biliary duct and retroperitoneum (32%). Getting back to our results, retroperitoneum was the most commonly altered organ, probably overrepresented because the main recruiting center had conducted previous investigations on IRPF. Twenty-eight over 55 cases, representing more than the half of our sample, presented almost one infiltrated tissue located in the head (lacrimal and salivary glands, orbital pseudotumor, extraocular muscles, maxillary sinuses, and pachymeninges). This numbers are comparable to the other European study. Likewise, a compilation of the cases reported in the literature with unselected IgG4 organ involvement also showed lacrimal and salivary glands involved in 40% and 29% of the cases, respectively.<sup>5</sup> The tropism of IgG4-RD for the head is currently unexplained. Active search for new lesions in this area must be conducted by clinicians at diagnosis and during follow-up because of the systemic nature of IgG4-RD.

In the field of the therapeutic management, although patients did not follow any defined treatment scheme, unlike in the SMART study, results were similar. In the same way, French cohort treatments were alike. Corticosteroids were the most commonly prescribed drug. All prescriptions are based on autoimmune pancreatitis experiences.<sup>16</sup> There seems to be consensus on maintaining high doses of steroids for nearby a month. The differences appear in the long-term steroid treatment: complete withdrawal or maintenance dose? Most of the SMART patients received a maintenance dose, with a mean dose of 4.8 mg/day of prednisolone to control the disease. The French cohort reported a complete withdrawal rate of 30%. Only the 20% of our patients were put on a long-term low steroid maintenance regime. The use of rituximab was anecdotic in the 3 series (9 patients in total) but with positive results. In our study, surgical treatment accounted for nearly 30% of the patients. The initial management by other specialists, diagnostic aggressiveness and treatment of complications may justify the use of this procedure.

Immunosuppressive agents were more used in both European series (48% in the French and 32.7% in ours), opposite to the Japanese series (9%). Disease modifying antirheumatic drugs (DMARDs) have been reported to be useful in a few patients with IgG4-RD<sup>17</sup> and in similar conditions like in IRPF<sup>18,19</sup> or in autoimmune pancreatitis.<sup>20</sup> In our experience, DMARDs seem an effective treatment, although directed trials are needed to strengthen this limited evidence. Otherwise, they may be an option instead of rituximab. Rituximab has been described as a highly effective treatment in IgG4-RD combined or not with steroids in a study including 10 patients.<sup>21</sup> Experience is still short but B-cell depletion seems the cornerstone of future therapeutic strategies against IgG4-RD. Our 3 patients

treated with rituximab had systemic involvement, with 2 or more target tissues affected. All of them had damaged tissues located in the head (maxillary, lachrymal and salivary glands, orbital pseudotumor, and pachymeninges) and only 1 had pleural involvement. In 2 patients, 2 courses of rituximab 1000 mg were administered separated by 14 days. The third one received 375 mg/m<sup>2</sup>/week for 4 weeks. One of the patients had just received the first dose when this proof was sent while the other 2 patients did not relapse during follow-up.

There is no outcome measurement tool validated for IgG4-RD at the moment, but a prototype of activity index was proposed in 2012.<sup>22</sup> This item will be basic for any future trials. Different composite scores including symptoms, clinical and radiological items were used to define the outcomes of the 3 compared cohorts. In the Japanese cohort, there was an 11.5% annual relapse rate and symptoms were controlled initially in all patients. Half of the patients relapsed after 7 years. Our total rate of relapses was 38.5%. Patients with systemic IgG4-Rd received more DMARDs, responded worse and relapsed more than the ones with localized IgG4-RD. Patients with systemic IgG4-RD should be strictly monitored and treated more aggressively. Symptom control was almost a constant, but 47.3% of the patients kept with a residual inactive fibrotic mass. The available treatments still have limitations in order to eradicate all the remains of the disease, especially in the cases with a long period of evolution and more fibrosis. Mortality was anecdotic, and not linked to IgG4-RD, with only a dead patient in the French cohort and another 2 in ours (the SMART study did not mention mortality).

The link between IgG4-RD and neoplasm is still controversial.<sup>23</sup> We found that only 7.2% of the patients developed cancer (solid or hematological) or premalignant conditions after IgG4-RD diagnosis, all of them with a low level of aggressiveness, what matches with the SMART group results (7.4%).

The retrospective character of this study is a clear limitation for the interpretation of the data. Also, conclusions about treatment regimes and evolution should be taken in consideration but the design of the study was not directed to elucidate this questions. We expect to give a depiction of IgG4-RD in our environment with the strength of the latest diagnostic criteria and the participation of multiple centers.

In conclusion, we described a series of patients with IgG4-RD in Spain. The disease had preference for head structures, retroperitoneum and pancreas. There was a good response to treatment but systemic IgG4-RD is more difficult to treat and more relapsing. Rituximab introduction may start a new treatment era. Malignancy and mortality were infrequent. International collaborative studies and randomized clinical trials could help clarifying these areas of uncertainty.

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