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IMMUNOGLOBULIN G4-RELATED RETROPERITONEAL FIBROSIS

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Abstract Some patients diagnosed with idiopathic retroperitoneal fibrosis could be reclassified as IgG4-related disease (IgG4-RD). Classification criteria have not been uniform and prevalence of IgG4-related retroperitoneal fibrosis (IgG4-RPF) is unknown in our region. We aimed to describe IgG4-RPF frequency relying on criteria published recently and comparing clinical, histopathologic and radiologic features with non-IgG4-RPF. From January, 2005 to December, 2020, nineteen adults with histopathologic diagnosis of idiopathic retroperitoneal fibrosis were included in a dynamic retrospective cohort at *Hospital Italiano de Buenos Aires*. Pathology slides were reviewed and immunohistochemistry was performed and assessed for each case. We used classification criteria described in 2019 American College of Rheumatology/European League Against Rheumatism to identify IgG4-RD cases. Ten of 19 patients met criteria for IgG4-RPF. Median age was similar in two subsets (61 versus 55, p = 0.2) and both had male predominance. Three out of 10 patients (p = 0.2) featured other manifestations of IgG4-RD in the IgG4-RPF group, and periaortic fibrosis was the most significant finding in images (p = 0.01). Corticosteroids were mostly used as therapy, followed by azathioprine and rituximab. Most patients did not receive specific treatment. IgG4-RPF patients had dense lymphocytic infiltrate and 8 out of 10 showed storiform fibrosis (p = 0.02). IgG4+ cells/hpf and IgG4/IgG ratio were significantly higher (p = 0.01). Over half of the patients in our cohort met the criteria of IgG4-RPF. New criteria may harmonize the identification of IgG4-RD. As IgG4-RD may be reversible at initial stages, these findings may lead to early recognition, treatment and integral follow-up.

Key words: IgG4, retroperitoneal fibrosis, chronic renal insufficiency, ureteral obstruction, autoimmunity

Resumen ***Fibrosis retroperitoneal relacionada con IgG4.*** Muchos pacientes con diagnóstico de fibrosis retroperitoneal idiopática (FRI) pueden ser reclasificados como enfermedad relacionada con IgG4 (ER- IgG4). Los criterios diagnósticos no han sido uniformes y la frecuencia de fibrosis retroperitoneal relacionada con IgG4 en nuestra región es desconocida. El objetivo fue describir la frecuencia de ER-IgG4 en pacientes clasificados como FRI y comparar características clínicas, histopatológicas y de laboratorio con aquellos que no reunían criterios de la enfermedad. Se incluyeron 19 adultos en un estudio de cohorte retrospectiva dinámica con diagnóstico anatomopatológico de FRI, en el Hospital Italiano de Buenos Aires, desde enero de 2005 hasta diciembre de 2020. Se revisaron las biopsias y se realizó inmunohistoquímica en cada una. Se consideró caso al paciente que reunía los criterios de la *American College of Rheumatology/European League Against Rheumatism* 2019. Diez pacientes reunieron criterios de ER-IgG4. La mediana de edad fue similar en ambos grupos (61 vs. 55, p = 0.2) y en ambos hubo predominio masculino. Tres de 10 pacientes (p = 0.2) tuvieron otras manifestaciones de ER-IgG4 y la fibrosis periaórtica fue el hallazgo más significativo en los estudios por imágenes (p = 0.01). Los corticoides fueron las drogas más utilizadas seguidos por azatioprina y rituximab, pero la mayoría no recibió tratamiento específico. Todos los pacientes con fibrosis retroperitoneal relacionada con IgG4 presentaron infiltrado linfocitario denso y 8/10 fibrosis estoriforme (p = 0.01), así como las células IgG4+/hpf y ratio IgG4/IgG fueron significativamente mayores (p = 0.01). Más de la mitad de los pacientes con FRI cumplieron criterios de ER-IgG4. Los nuevos criterios diagnósticos podrían contribuir a homogeneizar la identificación de ER-IgG4. Dado que esta enfermedad puede ser reversible en estadios tempranos, estos resultados promueven aumentar el conocimiento de la entidad para tratamiento precoz y seguimiento integral.

Palabras clave: IgG4, fibrosis retroperitoneal, insuficiencia renal crónica, obstrucción ureteral, autoinmunidad

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KEY POINTS

- Some patients diagnosed with idiopathic retroperitoneal fibrosis could be reclassified as IgG4-related disease. Classification criteria have been heterogeneous during the last years and IgG4-related retroperitoneal fibrosis frequency is unknown in our region. This etiology of retroperitoneal fibrosis may be responsive to treatment.
- More than a half of patients in our cohort met criteria of IgG4-RPF using last published classification criteria. Diagnosis and treatment has not been uniform, which may reflect lack of awareness of this entity. We highlight the importance of considering clinical, laboratory, histopathological and imaging features in order to identify patients accurately in a multidisciplinary setting.

IgG4-related disease (IgG4-RD) encompasses multiorganic fibroinflammatory lesions with similar histopathologic features, including dense lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis[1]. It was first recognized in 2003 in patients with autoimmune pancreatitis with extrapancreatic manifestations, either synchronous or metachronous. IgG4-RD is a relapsing-remitting disorder that has been described to affect almost every anatomic site. Furthermore, many diseases that have long been understood as conditions confined to single organs are now part of the spectrum of IgG4-RD [e.g. Mikulicz's syndrome, Riedel's thyroiditis or idiopathic retroperitoneal fibrosis (IRF), also known as the Ormond's disease]. The pathophysiology has not been completely understood, but an inflammatory phase followed by a fibrotic phase has been identified[3].

Retroperitoneal fibrosis is characterized by chronic inflammation and sclerosing lesions that encase retroperitoneal structures. The most common manifestations are generally subacute, including abdominal pain and hydronephrosis. Retroperitoneal fibrosis is idiopathic in most cases, yet it can also be secondary to drugs, malignancies, infections, injuries, radiotherapy or surgery[4].

A few studies, including mainly small patient cohorts, analyzed retroperitoneal involvement since IgG4-RD was recognized. Criteria to identify IgG4-RD cases have not been uniform among different studies and data available are of variable nature. Retrospective cohorts from Japan and USA proved that over 50% of patients with IRF showed the spectrum of IgG4-RD histopathological findings. A nationwide Danish study identified IgG4-RD in nearly half of the cases, with more possible rather than definite diagnosis[5-7]. On the other hand, an IRF-focused controlled trial reported only a small proportion of IgG4 among these patients and other recent studies about IRF do not consider this potential relation[5-8]. IgG4-RD prevalence is unknown in Latin America. Lack of knowledge and the absence of reclassification of "idiopathic" conditions probably lead to underdiagnosis. Therefore, IgG4-RPF's frequency in our region has not been reported.

Classification criteria have not been homogeneous over the last few years and IgG4-related retroperitoneal fibrosis prevalence is unknown in our country. We aim to describe IgG4-related retroperitoneal fibrosis (IgG4-RPF) frequency according to the criteria described in 2019 *American College of Rheumatology (ACR) /European League Against Rheumatism (EULAR)* and to compare clinical, histopathological and radiologic features with non-IgG4-RPF[6].

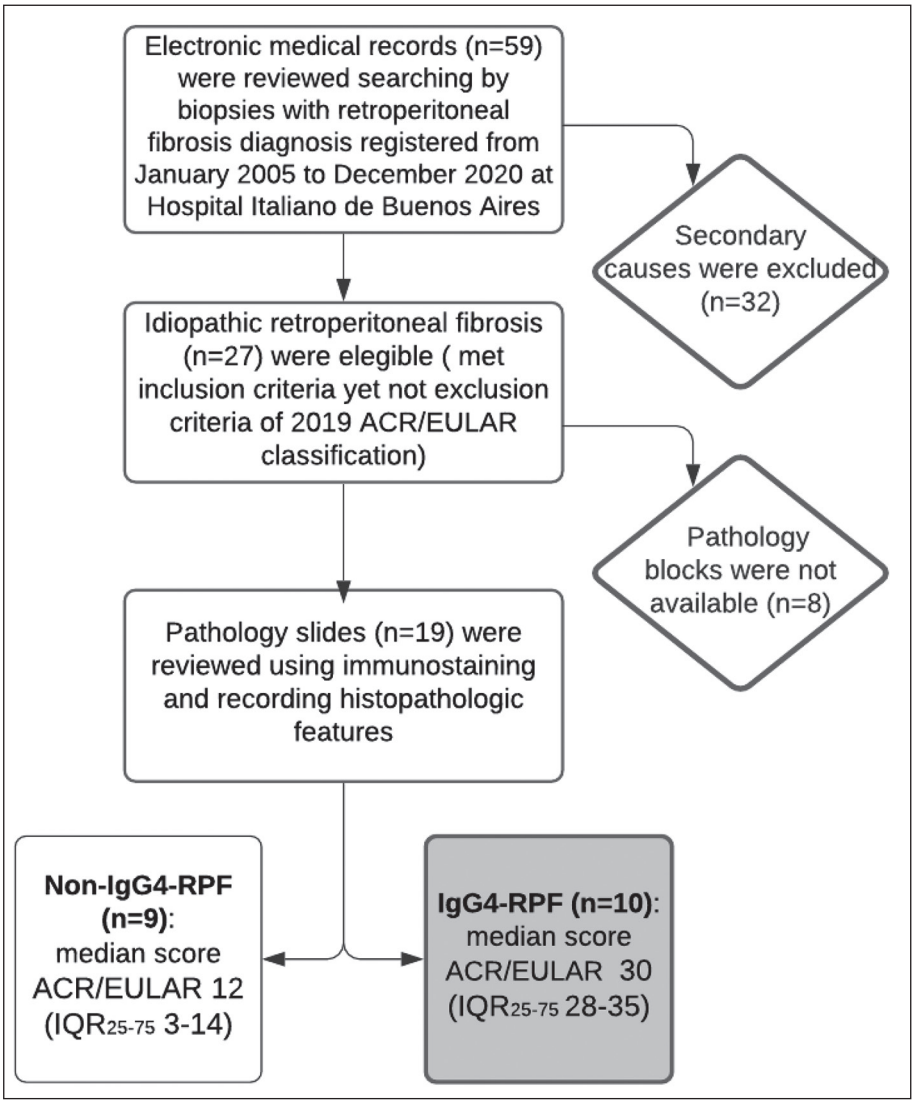
Materials and Methods

From January, 2005 to December, 2020, we reviewed 59 electronic medical records searching for biopsies with diagnosis of retroperitoneal fibrosis at Hospital Italiano de Buenos Aires (Fig. 1). After excluding secondary causes (neoplastic, post radiotherapy and surgery), 27 IRFs were eligible for IgG4-RD according to 2019 ACR/EULAR classification criteria (they met inclusion yet not exclusion criteria[6]). Eight pathology blocks were not available. Finally, 19 adults histopathologically diagnosed with IRF at Hospital Italiano de Buenos Aires were included in a dynamic retrospective cohort.

Pathology slides were reviewed by experienced pathologists to register histopathological features, including lymphoplasmacytic infiltrate, storiform fibrosis, obliterative or non-obliterative phlebitis, presence of eosinophils and germinal centers. The presence of neutrophilic infiltrates, prominent necrosis and granulomas was considered as histopathological exclusion criteria[6]. Immunohistochemistry for IgG4 (Roche, clone: MRQ-44) and IgG (Cell Marque, polyclonal) was conducted using the Benchmark XT (Ventana) automated system and assessed for each case. The biopsy date matched the date of IRF's diagnosis and the time elapsing from biopsy to revision was recorded. We used 2019 ACR/EULAR classification criteria to identify IgG4-RPF cases. After a three-step classification criteria process, IgG4-RD was identified if the entry criteria were met (involvement of at least 1 of 11 possible organs in a manner consistent with IgG4-RD) and no exclusion criteria were present (32 clinical, serologic, radiologic, and pathologic items). In the third step, the total points had to be $\geq$ 20 after applying 8 weighted criteria domains addressing clinical and radiology findings, serologic results and pathology interpretation, including histopathology and immunohistochemistry. Only the highest-weighted item in each domain was scored[6].

Clinical, serologic and imaging data were collected from electronic medical records. We reported the following clinical features: age, sex, allergic disease, hypertension, diabetes, collagen tissue disease, cardiovascular events, thromboembolic events, presenting symptoms, drug therapy, invasive treatment, hemodyalisis requirement, number of hospitalizations and death. Other IgG4-related manifestations were recognized by thoroughly analyzing specialist records, biopsies and image descriptions. Renal failure was defined as a glomerular filtration rate < 60 ml/min: we consider it acute renal failure if it was determined at the time of IRF diagnosis and chronic renal failure if it was present for more than 3 months. We included eosinophilia (defined as > 500 cells/ul in peripheral blood at any time of evolution), serum acute-phase reactants concentrations (erythrosedimentation rate and protein reactive C) at diagnosis and IgG4 serum levels, when available. In all cases, patients had at least one abdominal and pelvic image. Twelve contrast-enhanced computed tomography of the abdomen and pelvis, 3 computed tomography urography, 6 contrast-enhanced magnetic resonance of the abdomen and

Fig. 1.– Overview of patient selection



pelvis, 2 magnetic uro-resonances and 3 positron-emission tomography/computed tomography images were available. The location of soft tissue in the retroperitoneum and hydronephrosis presence (either uni- or bilateral) were recorded.

Data are presented as median values and as interquartile ranges for continuous variables and absolute frequencies for categorical variables. Mann Whitney U test (as non-parametric test for two independent samples) and the Fisher exact test were used to compare continuous and categorical variables, respectively. We consider a statistically significant p value <0.05. All the analyses were conducted using STATA software version 13 (Stata Corp, College Station, TX, USA).

This study was approved by the Ethics Committee for Research Projects (*Comité de Ética de Proyectos de Investigación;* Project number 3353*)* of *Hospital Italiano de Buenos Aires*. Written informed consent for research purposes is always secured before conducting biopsies at the abovementioned institution and we pledged to contact patients whose diagnosis had changed.

Results

Ten out of 19 patients met the criteria for IgG4-RPF with a total score > 20 (median of 30, IQR_{25-75} 28-35, $p < 0.001$), while 9 were considered non IgG4-RPF, as shown in Figure 1. Among the IgG4-RPF subset, 7/10 were male and the median age at the time of the biopsy was 61.5 years (IQR_{25-75} 55 -64). It was similar in non IgG4-RPF ($p = 0.2$). Time elapsing from biopsy to revision was 10 years in IgG4-RPF (IQR_{25-75} 1.3-11.8) and 6 years in non-IgG4-RPF (IQR_{25-75} 3- 11). Clinical and radiological features of IgG4- related and non-IgG4-RPF are detailed in Table 1.

There were no significant differences between such groups regarding the pattern of comorbidities. Allergic disease did not have predominance among IgG4-RPF

TABLE 1.– *Clinical and radiologic features of IgG4- related and non-IgG4-related retroperitoneal fibrosis (IgG4-RPF)*

	IgG4-RPF (n = 10)	Non IgG4-RPF(n = 9)	*p-value*
Male sex*	7	9	0.21
Age#	61.5 (55-64)	55 (48-58)	0.28
Allergic disease*	1	2	0.57
Hypertension*	4	5	0.63
Diabetes*	1	3	0.29
Cardiovascular events*	2	1	0.57
Thromboembolic events*	1	2	0.57
Other IgG4-RD manifestation*	3	0	0.21
Presenting symptoms*			
– Anorexia	2	1	0.57
– Low back pain	4	2	0.62
– Abdominal pain	0	2	0.47
– Weight loss	2	1	0.57
– Anuria	1	0	1.00
– Acute heart failure	1	0	1.00
– Incidental finding	0	2	0.47
Renal failure*			
– Acute	5	3	0.65
– Chronic	5	3	0.65
Hemodialysis*	2	1	0.57
Location mass*			
– Infrarrenal	10	6	0.08
– Periaortic	10	4	0.01
– Periiliac	7	5	0.65
– Mesenteric	1	0	1.00
– Presacral	1	2	0.57
Hydronefrosis*			
– Unilateral	2	4	0.62
– Bilateral	5	2	0.35
Erythrosedimentation rate (mm^2)#	66 (57-76)	31(23-44)	0.14
Drug therapy*			
– Corticosteroids	5	2	0.35
– Azathioprine	1	1	1.00
– Mycophenolate	0	1	1.00
– Metotrexate	0	1	1.00
– Rituximab	1	0	1.00
– Cyclophosphamide	0	1	1.00
– Tamoxifen	0	1	1.00
Double J stenting	8	7	1.00
Nephrostomy	2	2	1.00
Ureterolysis with intraperitonization	7	5	0.65
Number of hospitalizations#	3 (1-3)	2 (2-3)	0.95

**Absolute frequency, #median (IQR_{25-75}). IgG4-RD: IgG4 related disease*

patients. No collagen tissue diseases were reported. Three patients featured other manifestations of IgG4-RD in the IgG4-RPF group, including lung septal thickening, lung pseudotumor, mediastinal lymph node enlargement, hypertrophic pachymeningitis and hypophysitis with central insipid diabetes (p = 0.21). Three out of 10 had inflammatory abdominal aortic aneurysms as part of the spectrum of retroperitoneal fibrosis. One patient in the

IgG4-RPF group had been diagnosed with tubulointerstitial nephritis according to the biopsy conducted at the onset. Yet, this biopsy was conducted at a different hospital and the IgG4- related origin could not be determined.

Both acute and chronic renal failure and bilateral hydronephrosis were slightly more common among IgG4-RPF patients but renal failure, hydronephrosis and requirement of renal replacement therapy did not differ among groups statistically. One patient in the IgG4-RPF group was on the national transplant waiting list at the time when data were collected.

The median erythrosedimentation rate at the onset in the IgG4-RPF group was higher than in the non-IgG4-RF-group (66 mm/h versus 31 mm/h, p = 0.14). None of the patients had eosinophilia when IRF was diagnosed. Serum IgG4 levels at the time of diagnosis were not available, except for two patients in the IgG4-RPF group with normal measurements.

Thirteen contrast-enhanced computed tomography (IgG4-RPF = 7 - non-IgG4-RPF = 6), 3 computed tomography urography (IgG4-RPF = 2 - non-IgG4-RPF = 1), 8 contrast-enhanced magnetic resonance (IgG4-RPF = 3 - non-IgG4-RPF = 5), 2 magnetic uro-resonance (IgG4-RPF = 1-non-IgG4-RPF = 1), and 5 positron-emission tomography/computed tomography (IgG4-RPF = 3 -non-IgG4-RPF = 2) images were available. All of the IgG4-RPF had infrarenal and circumferential retroperitoneal extension along the aorta on different images but this was only significant in statistical terms for periaortic distribution (p = 0.01).

Among IgG4-RPF, corticosteroids were mostly used as drug therapy, followed by azathioprine and rituximab . However, most patients did not receive specific treatment. Eight out of 10 and 7/9 patients needed surgical or endoscopic intervention in both IgG4-RPF and non-IgG4-RPF groups, respectively. Double-J ureteral stenting was the most common invasive procedure, followed by ureterolysis with intraperitonization of the ureter; yet no statistical differences between groups were revealed. Eight patients in each subset were admitted to hospital with a similar median number of hospitalizations (3 in IgG4-RPF versus 2, p = 0.9). No deaths were reported with a median follow-up of 4 years in IgG4-RPF (IQR_{25-75}1 - 8) and of 1.5 years in non-IgG4-RPF (IQR_{25-75} 1-2.5).

Table 2 shows histopathological features of IgG4-related and non-IgG4-related retroperitoneal fibrosis. We included 3 needle biopsies in both groups and 7 surgical biopsy specimens in IgG4-RPF and 6 in non-IgG4-RPF subset. The mean biopsy area was greater for IgG4-RPF patients but no statistical differences were recorded (144 mm^2 versus 73.5 mm^2, p = 0.21). All IgG4-RPF patients had dense lymphocytic infiltrate (p = 0.21), 8/10 had storiform fibrosis (p = 0.02) and 6/10 had eosinophils (p = 0.17). IgG4+ cells/hpf and IgG4/IgG ratio were significantly higher than in patients with non-IgG4-RPF (p = 0.002 and p = 0.01, respectively) (Fig. 2). Spearman's correlation test revealed significant and accurate correlation between ACR/EULAR score and IgG4/IgG ratio (Rho = 0.68, p = 0.001) or IgG+ cells/hpf (Rho = 0.67, p = 0.001).

We summarize the ACR/EULAR score obtained for each patient in Table 3.

Discussion

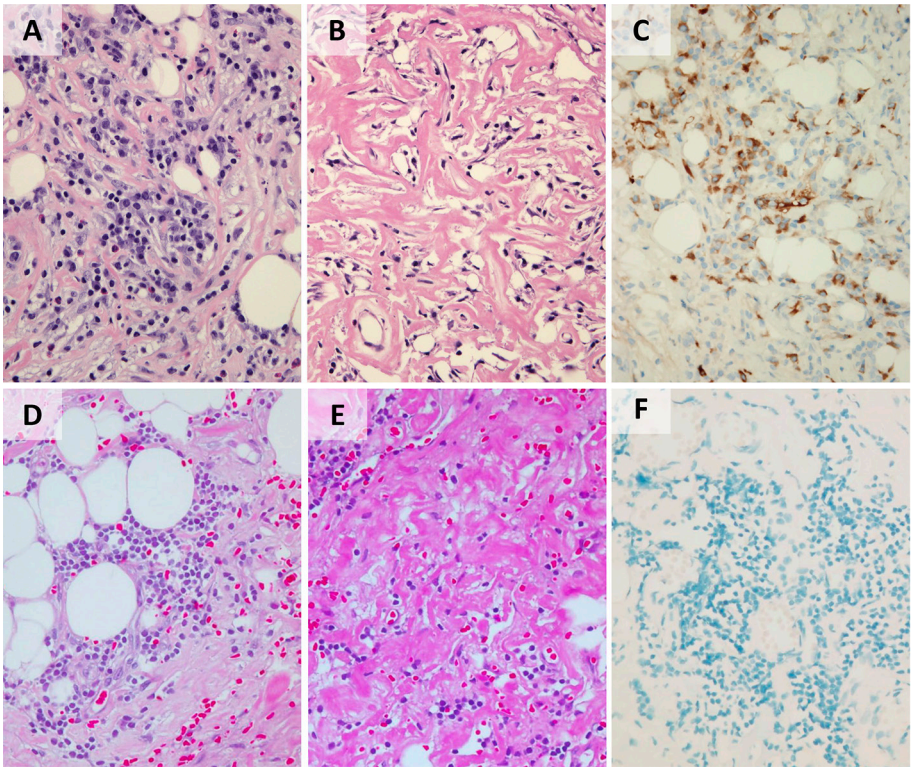
Over half of the patients included in our IRF retrospective cohort met criteria of IgG4-RPF. There are no series published in Latin America in this regard, then it is not possible to compare our findings with those from other countries in

TABLE 2.– *Histopathological features of IgG4- related and non-IgG4-related retroperitoneal fibrosis (IgG4-RPF)*

	IgG4-RPF (n = 10)	Non IgG4-RPF (n = 9)	*p-value*
Biopsy area (mm^2)#	144 (101.5-300)	73.5 (14-136)	0.21
Storiform fibrosis*	8	1	0.02
Non storiform fibrosis*	2	8	0.02
Dense lymphocytic infiltrate*	10	7	0.21
Obliterative phlebitis*	4	1	0.29
Non-obliterative phlebitis*	2	1	0.57
Eosinophils*	6	2	0.17
Germinal centers*	3	2	0.57
IgG4+ cells/hpf#	18.5 (16-33)	1 (0-11)	0.002
IgG4/IgG ratio#	46 (20-56)	10 (0-20)	0.01

**Absolute frequency, #median (IQR_{25-75})*

Fig. 2.– HE staining of an IgG4-RF case featuring dense lymphoplasmacytic infiltrate with eosinophils (A) and storiform fibrosis (B). IgG4 IHC staining of the same case, showing more than 30 IgG4+ cells per HPF (C). HE staining of a non-IgG4-RF case with predominant lymphocytic infiltrate (D) and hyaline fibrosis (E). IgG4 IHC staining of the same case showing no IgG4+ cells (F)



the region. Compared to worldwide reports, our prevalence in IgG4-RPF gets close to the 57% reported by Khosroshahi et al in 2013 in Boston, where IgG4-RD were identified with a IgG4/IgG ratio cutoff >40/HPF[7]. In 2009, Zen et al described a prevalence of 58% identifying IgG4-RD in a Japanese cohort, considering an IgG4/IgG ratio cutoff of >30/HPF[5]. The Danish nationwide study was based on the 2012 consensus statement's criteria and documented 45% definite or possible IgG4-RF (only 17% with definite diagnosis)[8]. Diagnosis relied on strict histopathologic criteria and different disease definitions, inclusion criteria or ratio cutoffs might hinder the interpretation of results. ACR/EULAR criteria confirm IgG4-RD diagnosis in patients with lower ratios as increasing points are assigned according to histopathologic and immunohistochemistry findings. They also consider clinical, radiologic and serologic features. In our study, 3 patients meeting the recently-established ACR/EULAR criteria would have been excluded as confirmed cases if only the IgG4/IgG ratio cutoff > 40/HPF criterion was considered.

The diagnosis in retroperitoneum may not be straightforward given the extensive fibrosis which makes the detection of dense cellular infiltrates unlikely. One of our potential sources of bias is the small size of tissue excised for pathology assessment because of their retrospective acquisition. Most samples were surgical biopsies, but the biopsy area available for histopathological analysis was greater in IgG4-RPF with a non-significant difference in comparison with non-IgG4-RPF. Misclassification bias may occur if a larger sample could allow us to consider non-IgG4-RPF as IgG4-RD cases. Small biopsies are common and an increased IgG4/IgG ratio has been suggested as the most sensitive pathologic feature, even in the absence of other typical histologic features[9]. New criteria assess not only histopathological or immunohistochemical features, reducing this potential source of bias. Although advanced fibrosis may be present in most cases, a storiform pattern is clear-cut and could be differentiated from hyaline fibrosis in non-IgG4-RPF. Khosroshahi et al and Zen et al described a high proportion of lymphoplasmacytic infiltrate and storiform fibrosis. In our cohort, all of IgG4-RPF showed these core histopathologic features (with a significant difference regarding storiform fibrosis) compared with non-IgG4-RPF. As ACR/EULAR criteria take into account many aspects other than mere histological and immunohistochemical findings, it may contribute to harmonizing the identification of IgG4-RD.

TABLE 3.– *ACR/EULAR score for each patient (n: 19)*

Patient	Histopathologic	IHQ	Retroperitoneum (images)	Other IgG4 manifestation (considered in score)	Other IgG4 manifestation (not considered in score)	Final score
1	4	7	8	–	–	19
2	13	14	8	–	–	35
3	4	0	8	–	–	12
4	13	7	8	Inflammatory aneurysm	–	28
5	4	7	8	–	–	19
6	6	0	8	–	–	16
7	13	0	0	–	–	13
8	13	14	8	–	–	35
9	13	16	8	–	Lung pseudotumor/ mediastinal lymphadenopathies	37
10	0	0	0	–	–	0
11	13	7	8	–	–	28
12	13	7	8	4 (lung septal thickening)/ Inflammatory aneurysm	–	32
13	13	14	8	–	Hypertrophic pachymeningitis and hypophysitis	35
14	0	0	0	–	–	0
15	13	7	8	–	–	28
16	0	0	0	–	–	0
17	4	7	0	–	–	11
18	4	14	8	Inflammatory aneurysm	–	26
19	6	7	8	–	–	21

IHQ: Immunohistochemistry

IgG4- RD in our cohort has male predominance, as published in most series. The median age at the time of diagnosis matches international reports. As Khosroshahi' s cohort, we described extra retroperitoneal manifestations in 30% of IgG4-RPF, especially lung involvement. Due to the lack of suspicion, some patients might not have complete evaluation. Retrospective design could have incomplete recordings but each patient had at least abdominal imaging. However, the retroperitoneal fibrosis phenotype has less organic features than other IgG4-RD presentations[10]. Infrequent manifestations of IgG4-RD are not included in ACR/EULAR criteria for the purpose of identifying homogeneous populations but they represent key points at the time of clinical evaluation and approach to classification as IgG4-RD cases. In our cohort, those infrequent clinical findings (hypophysitis, pachymeningitis, lymphadenopathies) agreed with the final classification as IgG4-RPF according to ACR/EULAR criteria.

Although there were no significant differences between the subsets, half of IgG4-RPF patients had renal failure at diagnosis, 2 of them required renal replacement therapy and one of them was on the national transplant waiting list at the time when data were collected. We emphasize the early detection of this disease given the natural evolution to end organ damage. One of those patients had been diagnosed with tubulointerstitial nephritis according to biopsy at the onset (IgG4- related origin could not be established because she was treated in another hospital), but in most patients we could not determine if there is intrinsic IgG4- renal involvement beyond obstructive renal failure.

Erythrosedimentation rate (ESR) at the onset was higher among IgG4-RPF but there were not statistical differences whatsoever. We did not have protein reactive C (PCR) measurement in most patients. Despite the unspecific condition of ESR, inflammatory markers are elevated in IgG4-related periaortitis in contrast with other IgG4 phenotypes[11]. Nonetheless, inflammatory markers are elevated in IRF and do not help in differentiating idiopathic and IgG4- RD[12]. Although ESR and PCR levels may be high at the onset, these parameters should be interpreted carefully because they do not always express disease activity and relapses can occur when acute-phase reactants levels are normal[13]. We did not have serum IgG4 concentrations in most cases at the time of diagno-

sis, which may reflect lack of knowledge of this entity. In any case, increased serum level of IgG4 is less common in IgG4-RPF than in other IgG4 manifestations[10]. In our cohort, we highlight that we achieved a classification of IgG4-RPF even when serum IgG4 concentrations are normal or not measured, which is consistent with the robustness of the classification criteria[6].

Most patients in our series were diagnosed as IRF before 2010. By this time, the awareness of IgG4-RD was low and immunohistochemistry was not usually performed to rule out this diagnosis. There was an erratic management of IRF and most of them did not receive corticosteroids. Beyond medical treatment, this manifestation required invasive treatment, either endoscopic or surgical, in almost every patient in both groups. Advanced fibrosis led to irreversible anatomic changes requiring those interventions. Due to the biphasic nature of the IgG4-RD, early treatment before a total fibrotic phase may contribute to potential reversibility. In spite of this, subacute presentation tends to delay diagnosis anyway, and a challenge for future research is to elucidate the fibrotic phase of the disease and identify therapeutic targets.

One of the strengths of our study is that we use criteria that consider not only histopathological but also clinical, laboratory and imaging criteria. We agree with current evidence that none of these features taken in isolation are sufficient for either clinical diagnosis or accurate classification of patients. We were unable to find studies related to IgG4-RPF in Latin America, and comparisons cannot be established. As IgG4-RPF is frequent among FRI in our cohort, regional studies related to IgG4-RD are needed.

Regarding the limitations of our work, the number of patients included was rather low compared to worldwide reports, because it is an infrequent manifestation of a low-prevalence disease. Due to the retrospective nature of the study, systematic clinical or serologic data were not available. IgG4-RD was not ruled out in most patients with IRF at the time of diagnosis and they underwent irregular management with no statistically significant differences in terms of evolution. In the light of these results, every retroperitoneal fibrosis, especially circumferential around the infrarenal aorta or even iliac arteries, may be assessed following 2019 ACR/EULAR criteria to confirm IgG4-RD and start corticosteroid therapy. It is relevant to communicate these findings in order to get accurate and early diagnosis because IgG4-RPF may be responsive to prompt treatment.

In conclusion, over half of the patients in our IRF retrospective cohort met the criteria of IgG4-RPF. ACR/EULAR new criteria may be helpful in order to homogenize the identification of IgG4-RD. These findings may motivate further evaluation of this condition, increasing early recognition, accurate treatment and integral follow-up.

Conflict of interest: None to declare

References

1. Stone JH, Zen Y, Deshpande V. IgG4-related disease. *N Engl J Med* 2012; 366: 539-51.
2. Kamisawa T, Funata N, Hayashi Y, et al. A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol* 2003; 38: 982-4.
3. Shimizu Y, Yamamoto M, Naishiro Y, et al. Necessity of early intervention for IgG4-related disease--delayed treatment induces fibrosis progression. *Rheumatology* 2013; 52: 679-83.
4. Runowska M, Majewski D, Puszczewicz M. Retroperitoneal fibrosis - the state of the art. *Reumatologia* 2016; 54: 256-63.
5. van Bommel EFH, Jansen I, Hendriksz TR. Idiopathic retroperitoneal fibrosis. *Medicine* 2009; 88: 193-201.
6. Wallace ZS, Naden RP, Chari S, et al. The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-related disease. *Ann Rheum Dis* 2020; 79: 77-87.
7. Khosroshahi A, Carruthers MN, Stone JH, et al. Rethinking Ormond's disease: 'idiopathic' retroperitoneal fibrosis in the era of IgG4-related disease. *Medicine* 2013; 92: 82-91.
8. Lomborg N, Jakobsen M, Bode CS, Junker P. IgG4-related disease in patients with newly diagnosed idiopathic retroperitoneal fibrosis: a population-based Danish study. *Scand J Rheumatol* 2019; 48: 320-5.
9. Arora K, Rivera M, Ting DT, Deshpande V. The histological diagnosis of IgG4-related disease on small biopsies: challenges and pitfalls. *Histopathology* 2019; 74: 688-98.
10. Wallace ZS, Zhang Y, Perugino CA, Naden R, Choi HK, Stone JH. Clinical phenotypes of IgG4-related disease: an analysis of two international cross-sectional cohorts. *Ann Rheum Dis* 2019; 78: 406-12.
11. Akiyama M, Kaneko Y, Takeuchi T. Characteristics and prognosis of IgG4-related periaortitis/periarteritis: A systematic literature review. *Autoimmun Rev* 2019; 18: 102354.
12. Urban ML, Palmisano A, Nicastro M, Corradi D, Buzio C, Vaglio A. Idiopathic and secondary forms of retroperitoneal fibrosis: a diagnostic approach. *Rev Med Interne* 2015; 36: 15-21.
13. Vaglio A, Versari A, Fraternali A, Ferrozzi F, Salvarani C, Buzio C. (18)F-fluorodeoxyglucose positron emission tomography in the diagnosis and followup of idiopathic retroperitoneal fibrosis. *Arthritis Rheum* 2005; 53: 122-25.