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Original Article

Comparison between Immunoglobulin G4-Related Eye Disease and Other Entities with Non-Immunoglobulin G4 Ocular Involvement

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Abstract

Objective: Distinguishing immunoglobulin G4 (IgG4)-related disease ocular involvement (IgG4-ROD) from other non-IgG4 pathologies in the orbit and eyeball is often complex. The objective was to compare clinical, analytical, imaging, and anatomopathological features of IgG4-ROD with other inflammatory and/or autoimmune ocular diseases (non-IgG4-ROD).

Methods: An observational, descriptive, and retrospective study included 18 patients diagnosed with IgG4-ROD according to Umehara's 2011 and/or 2020 comprehensive criteria, from 3 centers. Additionally, 12 patients with non-IgG4-ROD between 2014 and 2022 were selected, forming 2 groups. Data collection involved visualizing medical records. Demographic profile, clinical manifestations, analytical, histopathological, and radiological findings were analyzed using SPSS Statistics 19. Categorical variables were presented as frequencies and percentages, and continuous variables as means with standard deviation or median with interquartile range. Proportions were compared using the chi-square test, and means and medians were compared using T-tests and nonparametric tests. A confidence level of $\alpha = .05$ was selected.

Results: Thirty patients were analyzed: 18 with IgG4-ROD and 12 with non-IgG4-ROD. Among the latter, diagnoses included Histiocytosis (n = 4), Amyloidosis (n = 3), malignant secondary malignancy (n = 2), and other conditions (n = 3). Female sex predominated in IgG4-ROD (78% vs. 50%, $P = .12$). Mean age was 44 years, with no group difference ($P = .26$). Bilateral involvement was more common in non-IgG4 (92% vs. 72%, $P = .21$). Predominant symptoms in IgG4-ROD were proptosis, ocular pain, xerophthalmia, palpebral edema, and diplopia, while palpebral edema and ocular motility disturbance were more usual in other pathologies. Proptosis, xerophthalmia, and diplopia were significantly more frequent in IgG4-ROD ($P = .042$, $P = .021$, $P = .021$, respectively). Parotid involvement showed significant association in IgG4-ROD at 33% ($P = .031$). Statistically significant differences were observed in elevated serum IgG4 levels (67%, $P = .002$), IgG ($P = .037$), and IgG2 levels $\geq$ 5.3 g/L (56%, $P = .023$) in IgG4-ROD. There was also a significant difference between the association of eosinophilia and the non-IgG4 group (67% vs. 22%, $P = .034$), as did mean serum IgG value and the IgG4-ROD group ($P = .037$). Lacrimal gland involvement associated with IgG4-ROD ($P = .032$). Histopathologically, IgG4-ROD showed significant associations with lymphoplasmacytic infiltrate (100%, $P = .004$), storiform fibrosis (36%, $P = .05$), and presence of Eosinophils (64%, $P = .003$).

Conclusion: Immunoglobulin G4-related ophthalmic disease showed significant associations with xerophthalmia, proptosis, diplopia, and parotid involvement. Elevated serum IgG4, IgG, and IgG2 levels were also linked to this condition. Imaging studies revealed lacrimal gland involvement. Furthermore, lymphoplasmacytic infiltrate, storiform fibrosis, and eosinophil presence were significant in histopathological findings. Conversely, serum eosinophilia, bilateral involvement, and palpebral edema in imaging studies were statistically related to the non-IgG4 group.

Keywords: Immunoglobulin G4-related disease, IgG4-related ophthalmic disease, non-IgG4-ROD

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Introduction

immunoglobulin G4 (IgG4)-related disease (ER-IgG4) is a systemic fibroinflammatory condition defined by mass-forming lesions or pseudotumors that histologically present plentiful lymphoplasmacytic infiltrates marked by an abundance of IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis. [1,2]

Within the broad spectrum of manifestations of ER-IgG4 is IgG4-related ophthalmic disease (IgG4-ROD), thus naming the involvement of ocular adnexal tissues, such as the lacrimal gland, extraocular muscles (EOM), trigeminal nerve branches, eyelids, and orbital fat.[3]

The signs and symptoms outlined lack a high degree of specificity, which makes the process of diagnosis challenging. In order to arrive at the conclusion of an IgG4-ROD diagnosis, it is necessary to rule out a wide range of neoplastic and inflammatory conditions. Perseverance on the part of the physician and patient allows for accurate diagnosis and treatment.[4]

Among the wide variety of pathologies that can affect the orbit and its appendages, notable examples include Rosai–Dorfman disease (RDD), granulomatosis with polyangiitis, sarcoidosis, xanthogranulomatous disease, and thyroid orbitopathy. Given the range of potential differential diagnoses, it is vital to recognize the distinguishing characteristics between these conditions and IgG4-ROD ophthalmic disease in order to arrive at a timely and accurate diagnosis.

Patients with ocular involvement present a challenge even to the most skilled diagnosticians. A discerning clinician begins with a thorough patient history and focused clinical examination. Due to the variety of potential pathologies, including rare conditions, diagnostic challenges can arise. Ocular involvement is a common issue that is subjected to scrutiny, as it can pose a dilemma for even the most accomplished doctors. A diagnosis can uncover either a minor nuisance or a condition that poses a risk to ones vision or life.

Main Points

- Distinguishing ocular involvement in Immunoglobulin G4-related disease from other non-Immunoglobulin G4 pathologies in the orbit and eyeball
- Differential diagnosis with other non-Immunoglobulin G4 ocular diseases such as Rosai-Dorfman disease (RDD), granulomatosis with polyangiitis, sarcoidosis, xanthogranulomatous disease, and thyroid orbitopathy.
- Clinical, analytical, imaging, and anatomopathological signs aiding in the differential diagnosis among these pathologies.
- The behavior of serum Immunoglobulim G2 and ImmunoglobulinG4 in both groups.

Rheumatologists should be familiar with the signs, symptoms, and differential diagnosis of IgG4-ROD, and recognize the importance of laboratory tests, imaging, biopsy, and treatment.
To collate the clinical-analytical, imaging, and anatomopathological characteristics of IgG4-ROD with other inflammatory and/or autoimmune diseases with ocular involvement.

Materials and Methods

A retrospective, observational, and descriptive study was performed. Data collection was conducted by visualization of clinical histories. Two groups were formed. Eighteen patients with a diagnosis of IgG4-ROD were selected, according to compliance with the 2011 Umehara comprehensive criteria and/or its 2020 revision.[1,2] The group with ocular involvement of another cause was made up of 12 patients from Hospital JM Cullen, who presented adult xanthogranuloma associated with asthma, Erdheim–Chester disease (ECD), amyloidosis, multiple myeloma, malignant secondary affections, thyroid pphthalmopathy, sarcoidosis and granulomatous polyangiitis, which we have called NO-IgG4 ocular involvement, between the years 2014 to 2022.

Data concerning demographic profile, history of asthma, clinical manifestations, laboratory, histopathological, and radiological findings (CT and/or MR) were collected and analyzed.

Xerophthalmia was defined as those patients with a positive Schirmer's test and/or break up time.

The laboratory determinations evaluated responded to the initial diagnostic values, including hemogram, eosinophils, erythrocyte sedimentation rate, serum ANA levels, complementemia, IgE, IgG, and their subtypes. It was observed that patients presented a serum IgG4 value ≥2.8 g/L and IgG2 ≥5.3 g/L in both groups. Cut-off points: Eosinophilia (eosinophils > 500/µL), IgG4 ≥ 135 mg/dL, ANA (+ ≥1/160), Hypocomplementemia (C3 < 84 mg/dL and C4 <20 mg/dL) and in ESR the upper limit was calculated according to age and sex: age in years/ 2 for men and (age in years + 10)/2 for women) according to Miller et al.[5]

The anatomopathological specimens were not stained with elastin.

Informed Consent

Written informed consent was obtained from the patients who participated in this study. The privacy and protection policies for patient information have been respected.

The ethics and research committee of Hospital JM Cullen approved this work despite being a retrospective clinical research protocol (Approval Number: 0079; Date: September 29, 2023).

Statistical Analysis

The data were gathered and organized in an Excel database and Statistical Package for the Social Sciences (SPSS) version 19.0 (IBM SPSS Corp., Armonk, NY, USA) software was used for statistical analysis. Categorical variables were represented using frequencies and percentages, while for continuous variables, the presentation format depended on their distribution. If it was normal, these variables were reported as means with their standard deviation, and as median and interquartile range in the case of abnormality. Proportions were compared using the chi-square test, while means and medians were analyzed through the *t*-test and nonparametric tests. A confidence level of $\alpha = .05$ was selected.

Results

A combined total of 30 patients were analyzed, including 18 patients with IgG4-ROD and 12 patients with ocular involvement NO-IgG4, of which 4 patients presented diagnosis of Histiocytosis (3 with ECD and 1 with adult xanthogranuloma associated with asthma), 3 with Amyloidosis (1 also had multiple myeloma), 2 with secondary malignancy (lung and breast cancer respectively), 1 patient with thyroid ophthalmopathy, 1 with sarcoidosis, and 1 with granulomatous polyangiitis.

Female sex predominated in the IgG4-ROD group (78% vs. 50%, $P = .12$). The average age at presentation was 44 (±15.3) years old, with no difference between groups ($P = .26$).

Regarding orbital clinical manifestations, bilateral involvement predominated in the NO IgG4 group (92% vs. 72%, $P = .21$). Proptosis, ocular pain, xerophthalmia, palpebral edema, and diplopia were the predominant symptoms in IgG4-ROD, while palpebral edema and ocular motility disturbance (70% and 33%, respectively) were the predominant symptoms in the other pathologies.

Proptosis, xerophthalmia, and diplopia were significantly more frequent in the IgG4-ROD

Table 1. Ophthalmic Clinical Manifestations

	IgG4-ROD (n = 18)	NO-IgG4 (n = 12)	*P*
Bilateral	13/18 (72%)	11/12 (92%)	.21
Proptosis	13/18 (72%)	4/12 (33%)	.042 (*)
Eyelid edema	10/18 (50%)	7/12 (70%)	.59
Xerophthalmia	9/18 (50%)	1/12 (8%)	.021 (*)
Pain	9/18 (50%)	2/12 (17%)	.069
Visual acuity alteration	8/18 (44%)	3/12 (25%)	.24
Diplopia	9/18 (50%)	1/12 (8%)	.021 (*)
Motility disturbance	6/18 (33%)	4/12 (33%)	.66
Dacryoadenitis	5/18 (28%)	1/12 (8%)	.20
Ocular congestion	2/18 (11%)	2/12 (17%)	.53
Xanthelasmas	0/18	1/12 (8%)	.40
Raccoon eyes	0/18	2/12 (17%)	.15

*Proptosis, xerophthalmia, and diplopia were significantly more frequent in the IgG4-ROD group (*P* = .042; *P* = .021; *P* = .021 respectively).

group (*P* = .042; *P* = .021; *P* = .021 respectively) (Table 1).

Regarding extraophthalmic manifestations, parotid involvement presented a significant association in the IgG4-ROD group, being 33% (*P* = .031); pancreatic and hepatobiliary involvement also predominated in this group, corresponding to 22% and 17% respectively (*P* = .11 and *P* = .20), without being statistically significant. In contrast, renal involvement and adenopathies were more frequent in the NO-IgG4 group (17% in both cases, *P* = .53). (Table 2).

We compared laboratory tests between both groups, finding a significant difference in elevated serum IgG4 levels in the IgG4-ROD group (67%, *P* = .002). Serum IgE and serum ESR levels exhibited no significant variances between the groups; instead, statistical significance was found between the presence of eosinophilia and the NO-IgG4 group (67% vs. 22%, *P* = .034) and between the mean serum IgG value with the IgG4-ROD group (*P* = .037).

In patients with IgG4-ROD, serum IgG4 levels ≥2.8 g/L was found in 29% of cases (5/17 patients) in a non-statistically significant way (*P* = .116), while serum IgG2 value ≥5.3 g/L was found in 56% (9/16 patients) being statistically significant (*P* = .023) with respect to the NO IgG4 group. (Table 3).

Images were obtained from 16/18 (88.8%) patients with IgG4-ROD and from 10/12 (83.3%) of the NO-IgG4 group (12 patients had only CT, 4 had MR, and 10 had both).

Table 2. Extraophthalmic Manifestations

	IgG4-ROD (n = 18)	NO-IgG4 (n = 12)	*P*
Parotids	6/18 (33%)	0/12	.031 (*)
Pancreas	4/18 (22%)	0/12	.11
Hepato-biliary	3/18 (17%)	0/12	.20
Submaxillary	2/18 (11%)	0/12	.35
Kidney	2/18 (11%)	2/12 (17%)	.53
Pachymeningitis	1/18 (6%)	0/12	.60
Adenopathies	2/18 (11%)	2/12 (17%)	.53
Retroperitoneum	1/18 (6%)	1/12 (8%)	.65
Thyroid	1/18 (6%)	0/12	.60
Lung	1/18 (6%)	0/12	.60

*Regarding extraophthalmic manifestations, parotid involvement presented a significant association in the IgG4-ROD group, being 33% (*P* = .031).

It was observed that bilateral involvement and eyelid edema were higher in the NO-IgG4 group (n = 8), being statistically significant (*P* = .045; *P* = .05). On the contrary, lacrimal gland involvement was associated with EOR-IgG4 (n = 12, *P* = .032) (Table 4).

Anatomopathologic analysis of ophthalmic tissue was available in 11 of the IgG4-ROD patients, of which 9 were lacrimal gland and 2 were from extraocular muscles. It was compared with 10 samples from NO-IgG4 patients.

Histopathologically, a significant association was found in IgG4-ROD between lymphoplasmacytic infiltrate (100%, *P* = .004), storiform fibrosis (36%, *P* = .05) and the presence of eosinophils (64%, *P* = .003).

Lymphoplasmacytic infiltrate was the most frequent finding in both groups (100% in IgG4-ROD and 40% in NO-IgG4).

Immunohistochemistry for IgG4-positive plasma cells was performed in 9 of the 11 ocular samples in the IgG4-ROD group, showing an IgG4/IgG ratio ≥40% in 44.4% of the samples, with an IgG4+/HPF plasma cell count ≥10 in 7 of the biopsies.

Regarding Immunohistochemistry findings in the NO-IgG4 patients, presence of IgG4+ plasma cells was observed in one patient with ECD, in the patient with breast cancer, and in the patient with Thyroid Orbitopathy (Table 5).

Discussion

immunoglobulin G4-related ophthalmic disease is a relatively new entity that affects any ocular adnexal tissue, most frequently bilaterally, including the eyelids, the lacrimal gland and duct, extraocular muscles, orbital soft tissues, the orbital bones, cranial nerves, and sclera. It is characterized by a younger age of presentation and equal involvement between the sexes, compared to the involvement of other organs by IgG4-RD. Its diagnosis is based on clinical/radiological findings, such as frequent involvement of lacrimal glands, intra- and extraconal fat and involvement of the bellies of extraocular muscles, respecting tendon insertions6 and elevation of serum IgG4. Specific histologic characteristics comprise a dense lymphoplasmacytic infiltrate, a storiform pattern of fibrosis and obliterative phlebitis (the latter not being frequent in lacrimal gland involvement), and immunohistochemistry with IgG4-positive plasma cells. Less specifically, the presence of germinal centers and eosinophils can be observed.[1-3] The main

Table 3. Laboratory Findings

		IgG4-ROD	NO-IgG4	*P*
Serum IgG4	Greater than 135 mg/dL	12/18 (67%)	0/8	.002 (1*)
	Mean (SD) mg/dL	284.2 ± 347.7	73.76 ± 51.6	.006
	≥ 2.8 g/L	5/17 (29%)	0/8	.116
Serum IgG2	Mean (SD) mg/dL	1629.9 ± 1558.2	274.9 ± 187.0	.001
	≥ 5.3 g/L	9/16 (56%)	0/6	.023
Serum IgE (median)		8/14 (57%)	5/7 (71%)	.44
		179.1 (IC 102-555)	134 (IC 118-920)	.82
Serum IgG (mean)		3/13 (23%)	3/4 (75%)	.099
		1258.1 ± 383.2	832.0 ± 802.4	.037
VES >40		12/18 (67%)	4/7 (57%)	.49
Serum eosinophilia (2*)		4/18 (22%)	6/9 (67%)	.034
Hypocomplementemia		0/16	1/4 (25%)	.20
ANA +		2/18 (12.5%)	0/10	.40

1.significant difference in elevated serum IgG4 levels in the IgG4-ROD group (67%, *P* = .002). 2. instead a statistical significance was found between the presence of eosinophilia and the NO-IgG4 group (67% vs. 22%, *P* = .034) and between the mean serum IgG value with the IgG4-ROD group (*P* = .037).

Table 4. Ophthalmic Involvement by CT and/or MR Imaging (n = 26)

		IgG4-ROD	NO-IgG4 (n = 10)	*P*
Ocular involvement	Unilateral	8/16 (50%)	1/10 (10%)	.045 (*)
	Bilateral	8/16 (50%)	9/10 (90%)	
Lacrimal gland		12/16 (75%)	3/10 (30%)	.032 (*)
Lacrimal duct		0/16	0/10	-
Intra- and extraocular fat		8/16 (50%)	3/10 (30%)	.28
Extraocular muscles		5/16 (31%)	4/10 (40%)	.48
Extraocular muscles affected	Lateral rectus	3/16 (19%)	1/10 (10%)	.50
	Inferior rectus	3/16 (19%)	1/10 (10%)	.50
	Superior rectus	3/16 (19%)	0/10	.21
	Medial rectus	3/16 (19%)	2/10 (20%)	.66
	Oblique	0/16	0/10	-
EOM tendon insertion involvement		0/16	0/10	-
Paranasal sinus involvement	Ethmoidal	5/16 (31%)	3/10 (30%)	.65
	Maxilla	4/16 (25%)	3/10 (30%)	.56
	Frontal	1/16 (6%)	2/10 (20%)	.32
Orbital bone		2/16 (12%)	2/10 (20%)	.50
Eyelid edema		2/16 (12%)	5/10 (50%)	.05 (*)
Infraorbital N.		1/16 (6%)	0/10	.61
Sclera		1/16 (6%)	2/10 (20%)	.32
Conjunctiva		0/16	1/10	.38
Trigeminal nerve		0/16	0/10	-
Optic N.		0/16	1/10 (10%)	.38

*It was observed that bilateral involvement and eyelid edema were higher in the NO-IgG4 group (n = 8), being statistically significant (*P* = .045; *P* = .05). On the contrary, lacrimal gland involvement was associated with EOR-IgG4 (n = 12, *P* = .032).

associated extraophthalmic manifestation is the major salivary glands and lymph nodes.6[7-10]

The orbit and its appendages can be affected in a multiplicity of pathologies, which only sometimes present distinctive clinical features, being frequent the overlapping or superposition of the entities, which makes the timely diagnosis difficult. For this reason, it is very important to have a thorough knowledge of these manifestations, their frequency, usefulness, and correct interpretation of the appropriate complementary methods, whether imaging or anatomopathological.

Several significant inflammatory conditions are recognized for their involvement in orbital structures. These conditions encompass sarcoidosis and granulomatosis with polyangiitis, Rosai–Dorfman disease, to name but a few. Furthermore, a number of past cases of inflammation which involved the orbits have been previously classified as "idiopathic orbital inflammation" (IOI), frequently, without the benefit of a biopsy, or at the very least, lacking awareness of the recently described IgG4-RD.

In the present work, a comparison was made between the clinical-analytical, imaging, and anatomopathological features of IgG4-ROD and other non-IgG4 diseases with ocular involvement, including amyloidosis, non-Langerhans histiocytosis, thyroid ophthalmopathy, and metastatic malignant disease.

In our study, IgG4-ROD was significantly associated with clinical manifestations such as xerophthalmia, proptosis, diplopia, and parotid involvement; serum IgG4 and IgG elevation. In addition, a statistical relationship was observed between this group and the involvement of the lacrimal gland in imaging studies and with the presence of lymphoplasmacytic infiltrate, storiform fibrosis, and eosinophils in pathological anatomy, according to what has been described in the literature.

In our work, peripheral eosinophilia was present in 22% of patients with IgG4-ROD, finding a higher prevalence in non-IgG4-ROD patients. In contrast, tissue eosinophilia was a feature found exclusively in IgG4-ROD samples, accounting for 64% (*P* = .003). Bingxia Ming et al describe that around 20%-40% of patients with IgG4-RD present peripheral eosinophilia and 51-86% manifest as tissue eosinophilia, coinciding with our findings.[11] Being a non-specific parameter, eosinophilia in the non-IgG4-ROD group could correspond,

Table 5. Histopathological Findings

	IgG4-ROD (n = 11)	NO-IgG4 (n = 10)	*P*
Lymphoplasmacytic infiltrate	11/11 (100%)	4/10 (40%)	.004 (*)
Eosinophils	7/11 (64%)	0/10	.003 (*)
Storiform fibrosis	4/11 (36%)	0/10	.05 (*)
Germinal centers	4/11 (36%)	2/10 (20%)	.37
Non-storiform fibrosis	4/11 (36%)	2/10 (20%)	.37
Obliterative phlebitis	2/11 (18%)	0/10	.26
Non-obliterative phlebitis	0/11	0/10	–
Inmunohistochemistry			
IgG4+/IgG+ range ≥ 40%	4/9	0/8 E.C.D. < 40% Breast cancer 30%	
IgG4+/HPF ≥10 cells	7/9	0/8 E.C.D.: 9 cells Thyroid orbitopathy: 1 cell Breast cancer: 2 cells	

*Histopathologically, a significant association was found in IgG4-ROD between lymphoplasmacytic infiltrate (100%, *P* = .004), storiform fibrosis (36%, *P* = .05), and the presence of eosinophils (64%, *P* = .003).

in our study, to associated atopy as in the case of adult asthma associated with orbital xanthogranuloma, medication, malignancy, and concomitant infections, among others.

Importantly, serum IgG4 levels can fall within the normal range during the initial stages of IgG4-RD and may progressively rise in some patients. As a result, individuals suspected of having IgG4-RD should undergo repeated serum IgG4 level assessments to reach a conclusive diagnosis. The same author confirms that an increase in serum IgG4 levels is not exclusive to IgG4-RD. Before confirming a diagnosis of IgG4-RD in cases where serum IgG4 levels exceed 1.35 g/L, it is necessary to rule out several other pathological conditions, like recurrent infections, systemic autoimmune disorders, and conditions related to the pancreas and bile ducts. However, it is particularly crucial when IgG4-RD levels exceed two to three times the upper limit of the normal range.[12,13] Therefore, a serum IgG4 level of 2.8 g/L serves as a valuable marker for discriminating IgG4-RD from non-IgG4-RD diagnoses.[14] It also helps predict the likelihood of multiple-organ involvement and the risk of relapse in IgG4-RD. Although in our work, there were no statistically key differences between groups in serum IgG4 dosage ≥2.8 g/L, it is important to highlight that no patient in the NO IgG4 group reached this value, while 5/17 in the IgG4-ROD group exceeded it.

immunoglobulin G2, another member of the IgG family, holds promise as a potential avenue for exploration. It exhibits considerable increases in both serum IgG2 levels and tissue IgG2 plasma cell counts within orbital IgG4-RD, in contrast to non-IgG4 orbital inflammation (including idiopathic and autoimmune diseases—OID). This suggests that IgG2 might have a role in IgG4-RD. According to a retrospective study, serum and tissue IgG2 levels can effectively differentiate individuals with IgG4-RD from healthy controls. The study found that serum IgG2 levels with a cut-off of >5.3 g/L provided a sensitivity of 80% and specificity of 91.7% for orbital IgG4-RD, with an overall accuracy of 0.90.[15] Regarding this dosage, IgG2 levels were higher in 9/16 patients and were statistically significant with respect to IgG2 levels in the non-IgG4 group.

Orbital and adnexal amyloidosis is uncommon, representing only 4% of head and neck amyloidosis; it has varied presentations and may be the first sign of systemic involvement. In 60% of cases, the involvement is bilateral. The most frequently affected site is the conjunctiva (amyloid deposition weakens the vessels generating capillary fragility and consequent subconjunctival hemorrhage). The other reported sites of orbital and adnexal amyloidosis are the eyelids, extraocular muscles, lacrimal gland, lacrimal sac, and orbital fat. Clinically, it manifests as proptosis, displacement of the eyeball with limited motility and diplopia. At the cutaneous level, it is characterized by plaque-like lesions or waxy yellowish papules on eyelids and/or purpuric and ecchymotic lesions (in 16% of cases) like raccoon eye. Imaging studies show the involvement of the aforementioned structures with the characteristic that EOMs also usually have the tendon insertions respected as in EOR-IgG4, but unlike this pathology, in amyloidosis, the involvement may be nodular, irregular with a reticulated pattern or may have various degrees of fusiform enlargement with sharp edges and areas of calcifications. Histologically, it is characterized by presenting positive staining with Congo Red and apple green birefringence in polarized light microscopy, findings that allow its differentiation with IgG4-ROD.[16-18] Raccoon eye was present in 2 out of 3 patients with this entity, without statistical significance, but with clinical relevance that orients us to this pathology.

Ophthalmopathy is a common manifestation of autoimmune thyroid disease, being the primary reason for orbital inflammation in adults. It is predominantly female with a 5.5:1 ratio, more frequently between 30 and 50 years of age; the involvement is bilateral and most frequently symmetrical, although it can be asymmetrical.[19] It also manifests with red eye, eyelid edema, exophthalmos, diplopia, and visual acuity deficit. Imaging of thyroid orbitopathy includes the combination of involvement of the orbital fat and the belly of the inferior rectus muscle, followed by the medial rectus, respecting its tendinous insertions, with the particularity of preserving the lateral rectus until the end of the evolution of the disease. In contrast, detecting simultaneous enlargement of the lacrimal gland and lateral rectus muscle should prompt doctors to contemplate the possibility of IgG4-RD.[6,20] Histopathologic features include the infiltration of the extraocular muscles and orbital fat by lymphocytes, macrophages, plasma cells, and mast cells along with mucopolysaccharides. In turn, autoimmune thyroid disease and the presence of positive thyroid-stimulating immunoglobulin increase the probability of a diagnosis of thyroid orbitopathy, although it can occur in euthyroid as well as hyper- and hypothyroid patients.[17,21,22]

Orbital metastases constitute a minor yet progressively increasing portion of all orbital tumors. Various case studies and series report an incidence ranging from 1% to 13%.[17]

The uveal tract is the most frequent exophthalmic site for hematogenous spread of tumor metastases from other sites, related to the abundant blood flow within the choroidal tissue. Therefore, the choroid is the ocular tissue most commonly affected by metastatic involvement. Other less common ophthalmic sites of hematogenous metastases include the

orbit, eyelids, conjunctiva, retina, and vitreous humor.[23]

The thickness of the posterior wall is relevant in diagnostic guidance, as is the surface irregularity seen on optical coherence tomography described by Carol Shields et al as lumpy-bumpy surface images.[24,25]

Unilateral orbital disease is the usual oncologic presentation, while in IgG4-ROD involvement is frequently bilateral. Although the diagnosis of the primary tumor often precedes the finding of secondary involvement, in adults, metastases may precede the diagnosis in up to 30% of cases of breast, lung and melanoma carcinoma, with gastrointestinal, renal, thyroid, pancreatic and prostate tumors being less frequent. The symptoms described include pain, diplopia, proptosis, eyelid edema, palpebral ptosis. Imaging in MRI shows a lesion to be hypointense to fat in T1 and hyperintense in T2 (difference with orbital pseudotumor).[26]

Within the spectrum of non-Langerhans cell histiocytosis are the adult xanthogranulomatous orbital diseases (EXOA) characterized by xanthogranulomatous infiltration of the orbital and periorbital tissues, including Erdheim-Chester disease (EEC) and Adult Asthma Associated with Orbital Xanthogranuloma. They share histologic features such as the presence of foamy histiocytes and inflammatory infiltrate with Touton's giant cells and variable lymphoid infiltration. Although on immunohistochemistry IgG4+plasma cells are also present in IgG4-ROD, the occurrence of CD68 +, CD163 +, factor XIIIa +, and CD21 -, CD35 -, CD1a - and S100 - (it can rarely be +) is distinctive.[17,27,28]

Adult xanthogranuloma associated with asthma is characterized by affecting patients diagnosed with asthma in adulthood, bilateral xanthomatous eyelid involvement or orbital masses, indurated, non-ulcerated, yellowish-orange plaques, and its involvement may extend to orbital fat, EOM and lacrimal glands. Adult asthma associated with orbital xanthogranuloma lesions present association with chronic rhinosinusitis, nasal polyps, elevated serum IgE, lymphadenopathy, and infiltration of eosinophils in the periorbital tissue; these characteristics are shared with IgG4-ROD, being histology and immunohistochemistry fundamental for their differentiation.[27,29]

Erdheim–Chester disease most frequently affects elderly males, it can manifest from an indolent focal disease to multiorgan failure and can affect bone, retroperitoneum, periaorta, lung, central nervous system, as a space-occupying mass and skin. Orbital lesions in most cases are bilateral and intraconal, but they can be unilateral and extraconal. Clinically it manifests with exophthalmos and cutaneous xanthomas, yellowish periorbital lesions, but it can also affect optic nerve, lacrimal glands, EOM, and facial bones. Typical diagnostic features include bilateral cortical sclerosis in the metadiaphyseal region of long bones and histologically it presents with extensive interstitial fibrosis compared to other adult orbital xanthogranulomatous diseases.[30,31]

Sarcoidosis patients develop ocular involvement in 10%-50% of cases causing anterior and posterior uveitis, but only 10% affect the orbit, with the lacrimal gland being the most frequently involved structure, manifesting as pain, palpable mass, eyelid edema, proptosis, and less frequently ophthalmoplegia and loss of vision. Imaging studies show involvement of the lacrimal gland and enlargement of the optic nerve. The presence of snowball infiltrates and punch lesions in the ocular fundus may be diagnostic. Histologically, it differs from IgG4-RD by the presence of non-caseating granulomas not associated with vasculitis.[10,32,33,34,35]

In granulomatous polyangiitis, 28%-58% of cases affect the eye and manifest as episcleritis, scleritis, uveitis, peripheral ulcerative keratitis. Prevalent symptoms are epiphora, orbital mass, bilateral ocular pain, proptosis, erythema, and decreased ocular motility. It can affect the orbit either through localized involvement or by spreading from affected anatomical structures like the paranasal sinuses. Imaging findings include paranasal sinus involvement and bone destruction. Histologically, granulomatous inflammation, tissue necrosis, neutrophilic microabscesses, and vasculitis affecting arteries, capillaries, and veins are observed. IgG4+ plasma cells may also be present. In some cases, in orbital disease, these histologic findings may not be present, so it is necessary to associate the clinical manifestations with the laboratory results (ANCA +) to differentiate it from IgG4-RD.[10,32]

In conclusion, our study showed the variations in the characteristics of IgG4-ROD versus other pathologies with non-IgG4 orbital involvement.

immunoglobulin G4-related ophthalmic disease was significantly associated with clinical manifestations such as xerophthalmia, proptosis, diplopia, and parotid involvement; serum IgG4 and IgG elevation; lacrimal glandular involvement in imaging studies and a lymphoplasmacytic infiltrate, storiform fibrosis, and the presence of eosinophils in pathological anatomy. On the contrary, the presence of serum eosinophilia, bilateral involvement, and palpebral edema in imaging studies were statistically significantly related to the NO IgG4 group. Regarding serum IgG4 and IgG2 levels, although there were differences between both groups, a larger number of patients should be analyzed to see the real usefulness of these laboratory data.

The limitations of this study include its retrospective nature and the relatively small sample size, which might lead to the possibility of type 2 errors. However, it is essential to consider the low prevalence of these diseases.

Strengthening the study by focusing on a single basis for these diseases and conducting it in a single center could be a potential avenue for future research.

Ethics Committee Approval: This study was approved by the Ethics Committee of Hospital JM Cullen University (Approval No: 0079, Date: September 29, 2023).

Informed Consent: Informed consent was obtained from the patients who participated in this study.

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References

1. Umehara H, Okazaki K, Masaki Y, et al. *Comprehensive Diagnostic Criteria for IgG4-Related Disease (IgG4-RD)*; Mod Rheumatol Jpn Rheum Assoc 2011;22:21-30.
2. Umehara H, Okazaki K, Kawa S, et al. The 2020 revised comprehensive diagnostic (RCD) criteria for IgG4-RD. *Mod Rheumatol*. 2021;31(3):529-533. **[CrossRef]**

3. Goto H, Takahira M, Azumi A, Japanese Study Group for IgG4-Related Ophthalmic Disease. Diagnostic criteria for IgG4-related ophthalmic disease. *Jpn J Ophthalmol*. 2015;59(1):1-7. [CrossRef]
4. Sobel RK, Carter KD, Allen RC. Periorbital edema: a puzzle no more? *Curr Opin Ophthalmol*. 2012;23(5):405-414. [CrossRef]
5. Miller A, Green M, Robinson D. Simple rule for calculating normal erythrocyte sedimentation rate. *Br Med J (Clin Res Ed)*. 1983;286(6361):266. [CrossRef]
6. Tiegs-Heiden CA, Eckel LJ, Hunt CH, et al. Immunoglobulin G4–related disease of the orbit: imaging features in 27 patients. *AJNR Am J Neuroradiol*. 2014;35(7):1393-1397. [CrossRef]
7. Ebbo M, Patient M, Grados A, et al. Ophthalmic manifestations in IgG4-related disease: Clinical presentation and response to treatment in a French case-series. *Medicina (Baltimore)*. 2017;96(10):e6205. [CrossRef]
8. Zhao Z, Mou D, Wang Z, et al. Clinical features and relapse risks of IgG4- related ophthalmic disease: a single-center experience in China. *Arthritis Res Ther*. 2021;23(1):98. [CrossRef]
9. Gan L, Luo X, Fei Y, et al. Long-term outcomes of IgG4-related ophthalmic disease in a Chinese IgG4-related disease cohort. *Front Med (Lausanne)*. 2021;8:784520. [CrossRef]
10. Wallace ZS, Deshpande V, Stone JH. Ophthalmic manifestations of IgG4-related disease: single-center experience and literature review. *Semin Arthritis Rheum*. 2014;43(6):806-817. [CrossRef]
11. Ming B, Zhong J, Dong L. Role of eosinophilia in IgG4-related disease. *Clin Exp Rheumatol*. 2022;40(5):1038-1044. [CrossRef]
12. Ebbo M, Grados A, Bernit E, et al. Pathologies associated with serum IgG4 elevation. *Int J Rheumatol*. 2012;2012:602809. [CrossRef]
13. Carruthers MN, Khosroshahi A, Augustin T, Deshpande V, Stone JH. The diagnostic utility of serum IgG4 concentrations in IgG4-related disease. *Ann Rheum Dis*. 2015;74(1):14-18. [CrossRef]
14. Culver EL, Sadler R, Simpson D, et al. Elevated serum IgG4 levels in diagnosis, treatment response, organ involvement, and relapse in a prospective IgG4-related disease UK cohort. *Am J Gastroenterol*. 2016;111(5):733-743. [CrossRef]
15. Chan ASY, Mudhar H, Shen SY, et al. Serum IgG2 and tissue IgG2 plasma cell elevation in orbital IgG4-related disease (IgG4-RD): potential use in IgG4-RD assessment. *Br J Ophthalmol*. 2017;101(11):1576-1582. [CrossRef]
16. Correa Lemos M. y col. Amyloidosis of the orbit and adnexia. *Int J Ocul Oncol Oculoplasty*. 2018;4(2):105-109.
17. Sager L, Reibaldi A, Calvo R, et al. The eye: A diagnostic puzzle Descriptive observational study and review. *Revista Argentina de Reumatología* 2020;31(4):13-18.
18. Correa Lemos M, et al. Patients with orbitary and kidney commitment. Rare differential diagnoses. *Rev Argent Reumatolog* 2021;32(4): 13-18.
19. Fernández-Hermida RV, et al. Manifestaciones clínicas de la oftalmopatía tiroidea. *An Sis San Navar*. 2008;31(suppl).
20. Martin-Nares E, Amaya-Piña O, Delgado Hernández R, et al. Distinctive imaging features between IgG4-related ophthalmic disease and Graves' orbitopathy: a comparative study. *Arthritis Rheumatol*. 2019;71.
21. Martín-Nares E, Hernández-Molina G, Baenas DF, Paira S. IgG4-related disease mimickers and diagnostic pitfalls. *JCR J Clin Rheumatol*. 2022;28(2):e596-e604.
22. Shirley-Fung RV, et al. Thyroid Orbitopathy. *Reprinted from Australian Family Physician*. 2022;32(8):615-620.
23. Shah SU, Mashayekhi A, Shields CL, et al. Uveal metastasis from lung cáncer: clinic features, treatment, and outcome in 194 patients. *Ophthalmology*. 2014;121(1):352-357. [CrossRef]
24. Shields CL, Shields JA, Gross NE, Schwartz GP, Lally SE. Survey of 520 eyes with uveal metastases. *Ophthalmology*. 1997;104(8):1265-1276. [CrossRef]
25. Shields CL, Welch RJ, Malik K, et al. Uveal metastasis: clinical features and survival outcome of 2,214 tumors in 1,111 patients based on primary tumor origin. *Middle East Afr J Ophthalmol*. 2018;25(2):81-90. [CrossRef]
26. Vlachostergios PJ, Voutsadakis IA, Papandreou CN. Orbital metástasis of breast carcinoma. *Breast Cancer (Auckl)*. 2009;3:91-97. [CrossRef]
27. Green MB, Daly MK, Laver NMV, Lefebvre DR. Adult-onset asthma and periocular xanthogranuloma – A rare infiltrative disease of the orbit and eyelid. *Am J Ophthalmol Case Rep*. 2021;22:101043. [CrossRef]
28. Strehl y Col. numerous IgG4-positive plasma cells are ubiquitous in diverse localised non-specific chronic inflammatory conditions and need to be distinguished from IgG4-related systemic disorders. *J Clin Pathol*. 2011.
29. Gallo J, Piermattei N, Albertengo A, Stone JH, Paira S. A 26 years-old woman with asthma and bilateral ocular swelling. *Arthritis Care Res*. 2017;69(4):587-591. [CrossRef]
30. Roverano S, Gallo J, Ortiz A, Migliore N, Eletti M, Paira S. Erdheim-Chester disease: description of eight cases. *Clin Rheumatol*. 2016;35(6):1625-1629. [CrossRef]
31. Reibaldi A. y col. Enfermedad de Erdheim-Chester: serie de 19 casos y un diagnóstico diferencial de relevancia. *Rev Argent, Reumatolog*. 2020.
32. Lutt y col. *Orbital Inflamatory Disease*. Amsterdam: Elsevier; 2008.
33. Mochizuki M, Smith JR, Takase H, et al. Revised criteria of International Workshop on Ocular Sarcoidosis (IWOS) for the diagnosis of ocular sarcoidosis. *Br J Ophthalmol*. 2019;103(10):1418-1422. [CrossRef]
34. Wong AJ, Planck SR, Choi D, Harrington CA, Troxell ML, Houghton DC, et al. IgG4-immunostaining and its implications in orbital inflammatory disease. *PLoS One*. 2014;9(10): e109847.
35. Salvador O. JM y Col. enfermedad Xantogranunlomatosa orbitaria del adulto. Formas clínicas, evaluación y manejo. *Actas Dermo Sifiliogr*. 2017;108(5):400-406.