Orbital IgG4-associated diseases

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Abstract
IgG4-related disease (IgG4-RD) is a distinct entity that frequently occurs in an ophthalmic location. IgG4-RD is not limited to the orbit, but may also involve other anatomical structures in and around the eye. Careful clinicoradiologic examination and the use of immunohistological examination are key diagnostic methods. Serum IgG4 levels are neither sensitive nor specific enough for the diagnosis of IgG4-RD and should not be relied upon solely. Careful evaluation of histologic and immunophenotypic features and clinical correlation are required to distinguish orbital IgG4-RD from other inflammatory lesions in the orbit. Glucocorticoids are the primary therapeutic choice for treatment of IgG4-RD. Azathioprine or Mofetil can be used as a second possibility. Rituximab can be effective in the patients with relapse IgG4-RD.

Keywords: IgG4, eye, inflammation, ophthalmology

Introduction
In 1892, Johan von Mikulicz-Radecki first described clinical manifestations in a case report of a 42-year-old farmer with symmetric bilateral lacrimal, parotid and submandibular gland enlargement associated with lymphocytic infiltration [1-3]. Since then, there have been additional cases of patients with the same clinical manifestation, labeled Mikulicz disease. The clinical symptoms of Sjögren disease are similar to Mikulicz and, in 1953, these similarities and the possibility of unifying these diseases were reviewed [4]. Yamamoto and colleagues detailed the pathological and clinical differences between Sjögren syndrome and Mikulicz disease [5].

In 2001, several studies revealed a connection between Mikulicz disease and high levels of IgG4, which significantly lowered after glucocorticoid therapy [1,2,6-9]. Based on these observations, Mikulicz disease is now classified as IgG4-related disease (IgG4-RD) [10]. Additional IgG4-RDs have been identified, based on systemic fibroinflammatory disease characterized by the presence of lesions with lymphoplasmacytic infiltrate with high levels of IgG4-positive plasma cells. In addition, a correlation between higher levels of IgG4 and good response to therapy with corticoids has been observed [2,6,9,11-18]. Hamano et al., [19,20] observed not only elevated levels of IgG4 in autoimmune pancreatitis, but also found characteristic histopathological manifestations accompanying retroperitoneal fibrosis. These observations formed the basis for recognition of multiorgan defect, which was later defined as IgG4-RD [6]. Unified classification and defined, precise diagnostic criteria of IgG4-RD appeared much later [21,22]. It is important to note that IgG4-RD is an idiopathic, multiorgan inflammatory state, possibly manifesting gas chronic, relapsing inflammation in virtually any organ [23]. For current concepts on ophthalmic IgG4-RD, see review by Mulay and Wick [24]. For background and pathology of IgG4-related ophthalmic disease, see review by McNab and McKelvie [25].

Review Diagnosis
The diagnosis of IgG4-RD uses a wide spectrum of diagnostic criteria and, in combination with organ-specific criteria, is based on evaluation of impaired organ (such as size increase, nodular lesions, and dysfunction). Additional criteria involve IgG4 levels above 1.35 mg/ml, histological findings of lymphoplasmacytic infiltrate, fibrosis, obliterating phlebitis, or eosinophil infiltrate. Vascular pathology is highly specific for IgG4-RD and helps to distinguished between IgG4-RD and similar diseases [2,7,8,21,22,26]; it is necessary to remember the limits of fine needle biopsy though, and to obtain an adequate...
tissue sample. An analysis of 64 cases of IgG4-RD showed significant pathological and clinical differences, and even suggested a new clinical entity [27].

Detection of low levels of IgG4 plays an important role in the differential diagnosis of orbital lymphoproliferative diseases [28]. Histologic features are not present in some clinical manifestations of IgG4-RD. However, in patients fulfilling organ-specific criteria for IgG4-RD, the diagnosis is definitive [22]. Specificity and sensitivity of diagnosis is improved with IgG4/IgG ratio levels higher than 0.08 [29,30]. Our own laboratory uses ratio levels higher than 0.1–0.12. In case of clinical manifestations with no possible histological verification, it is necessary to use the level of IgG4 (our group uses limit of 2.0 mg/ml). It is important to remember, however, that even this limit is not always unequivocal, as elevated levels of IgG4 can be found in several additional diseases such as autoimmune diseases, cancer, cystic fibrosis, interstitial pneumonitis, vasculitis, allergic problems, sarcoidosis, etc. [3,6,14,31]. An interesting study described topiramate-induced maculopathy in IgG4-RD [32], and interruption of treatment prevented risk of nonreversible loss of vision. Polyclonal increase of IgG4 levels as a result of common food and animal-derived allergens supports the idea of potential damage of regulatory mechanisms of immune system [33]. It is important to note that IgG4-RD can be diagnosed even without elevated levels of IgG4 [18,34]. Despite clear progress, dependable diagnostic criteria remain to be found [21,22]. Therefore, the search is still on for additional testing necessary to improve specificity and sensitivity. One of the most promising tests evaluates the level of plasmablasts in peripheral blood. Studies have shown this test to be independent of IgG4 levels [35], but with varying results in patients being treated [36]. Plasmablast counts (CD19+, CD20-, CD38+, CD27+ cells) can be an important diagnostic biomarker in IgG4-RD diagnosis. Another test under evaluation measures free light chains. However, their criteria remain to be found [36,37]. Making the use of this test rather questionable. Another possible clinical addition is an IgG4-RD index, which offers the possibility to further evaluate the conditions without the risk of overlooking possible diagnosis of multiorgan problems. In addition, this evaluation allows us to monitor the effects of treatment on clinical manifestation [30].

### Clinical observations

The discovery of systemic disease characterized by high levels of IgG4 and by significant changes of cellular substrate has resulted in changes of diagnostic and therapeutic management in several clinical domains. IgG4-RD can influence any cellular system in different organs. Eye problems are one of the main manifestations of this disease [12,17,38]. Table 1 summarizes the guidelines for diagnosis of IgG4-RD, Table 2 shows our current knowledge of clinical manifestations, occurring in different frequencies and often in connection with significant pathological and clinical differences, and even suggested a new clinical entity [27].

### Table 1. Guidelines for diagnosis of IgG4-RD (1,7,8,9,12,13,14,15,16,18,22,34,38,40).

| Clinical features highly suggestive of IgG4-RD |
|------------------------------------------------|
| - Symmetrical swelling of lacrimal, parotid, submandibular glands |
| - Autoimmune pancreatitis |
| - Inflammatory pseudotumor |
| - Suspicion of Castleman’s disease |
| - Interstitial nephritis |

| Laboratory data highly suggestive of IgG4-RD |
|---------------------------------------------|
| - Serum IgG4 > 1.7 g/L |
| - IgG4+ cells / IgG+ cells > 40% in biopsy |
| - Serum IgG4/IgG > 10% |
| - Blood plasmablasts |

| Clinical features suggestive of IgG4-RD |
|----------------------------------------|
| - Unilateral swelling of at least one lacrimal, parotid or submandibular gland |
| - Orbital pseudotumor |
| - Sclerosing cholangitis |
| - Prostatitis |
| - Interstitial pneumonitis |
| - Thyroiditis / hypofunction of thyroid |

| Laboratory data suggestive of IgG4-RD |
|---------------------------------------|
| - Hypogammaglobulinemia |
| - Immune complex |
| - Hypocomplementemia |

### Table 2. IgG4-ROD (Related Orbital Disease)-clinical involvement of other organs (1,7,8,11,12,15,18,28,34,38,40).

| Occular manifestation | Other clinical manifestation |
|-----------------------|-----------------------------|
| Prevalence |
| Dacryoadenitis | Autoimmune pancreatitis | 40% |
| Dacryoadenitis | Mikulicz’s disease | -- |
| Dacryoadenitis | Unilateral sclerosing sialadenitis | -- |
| Dacryoadenitis | Sjögren’s syndrome | -- |
| Dacryocystitis | Tubulointerstitial nephritis | 83% |
| Sialadenitis | Autoimmune pancreatitis | 17% |
| Sialadenitis | Arthralgia | 16% |
| Sialadenitis | Sick eye syndrome | 33% |
| Sialadenitis | Tubulointerstitial nephritis | -- |
| Idiopathic orbital inflammation | Lymphadenitis | -- |
| Idiopathic orbital inflammation | Dacryoadenitis | -- |
| Graves orbitopathy | Thyroiditis | -- |
| Graves orbitopathy | Lymphadenitis colli | -- |
| Nervus opticus atrophia | Submandibular lymphadenitis | -- |
| Nervus opticus swelling | Submandibular lymphadenitis | -- |

Note: In the groups of IgG4-ROD: lymphadenopathy occurs in 29%, autoimmune pancreatitis in 14%, gall bladder inflammation in 5%, thyreopathy in 5%, chronic rhinosinusitis in 1%.

impairment of other organs such as lungs, kidney, salivary glands, or thyroid gland [6,14-16,18]. Clinical manifestation in patients with suspected IgG4-RD can be accompanied by additional symptoms including ataxia, loss of weight,
abdominal pain, xerostomia, xerophthalmia, or lymphadenopathy [13]. Other studies have suggested that IgG4-related lymphadenopathy should be listed in the differential diagnosis of benign reactive lymph nodes, particularly when perifollicular granuloma and plasmacytosis coexist [39].

Orbital soft tissue and lacrimal glands are usually the first to show signs of IgG4-RD. It is well-established that IgG4 can be involved in more than one-third of idiopathic inflammation of orbital tissue. It has been shown that higher systemic manifestations of IgG4-RD can be observed in impaired adnexal involvement [11]. These can include changes in immunological and biochemical parameters. However, further development of new diagnostic steps allowing precise diagnosis is needed [38]. In addition, orbital soft tissue and periocular structures with intact lacrimal glands with clinical signs of proptosis can be affected. An international symposium (Boston, 2011) concluded that the combination of histopathological and immunohistochemical findings were significant in the diagnosis of IgG4-RD. However, the full correlation between clinical manifestations in individual patients needs to be taken into consideration [40]. When determining IgG4-RD, diagnostic biopsy should involve three major histopathologic manifestations: 1) dense lymphoplasmacytic infiltration with predominant T lymphocytes; 2) fibrotic signs arranged at least in storiform patterns; and 3) obliterating phlebitis. The IgG4-RD is defined by simultaneous occurrence of at least two of these characteristics. Other findings should also be taken into consideration such as phlebitis without obliteration, histiocytosis of sinuses, increased amount of eosinophils, or ratio of IgG4/IgG plasmatic cells above 40%. However, none of these can 100% guarantee that it is a case of IgG4-RD. The findings mentioned above can be also found in lymphoma, rheumatoid arthritis, and in histiocytosis of sinuses with massive lymphadenopathy (Rosai-Dorfman disease) [40]. We can assume these diseases to have close connections to IgG4-RD. However, our own experience has shown that it is better to postpone treatment until the final diagnosis is fully verified by laboratory and clinical results, as spontaneous regression of IgG4-RD has been known to occur.

The first choice in medications are glucocorticoids [40]. In literature, one can find significant differences in medical procedures, particularly between Japanese and American physicians. Japanese groups recommend starting daily doses of prednisone around 0.6-1 mg/kg for 2-4 weeks [1,8,14,17,21] followed by gradual lowering of the dose during the next 3-6 months based on clinical response to 5 mg/day and subsequent long-term treatment with 2.5-5 mg/day for next 3 years. Treatment recommended by the Mayo Clinic starts with 40 mg/day of prednisone for 30 days followed by gradual decrease of the dose by 5 mg for next 2 months and ending the treatment after 11-12 weeks [16].

Neither treatment stops relapses, which are rather common, particularly in cases of extrapancreatic forms of this disease. The main criteria for success of treatment with glucocorticoid is gradual decrease of plasmatic IgG4 levels, therefore followup evaluations of these levels in 3-month intervals is recommended, particularly during the first year of treatment.

Ebbos’s group described positive effects of azathioprine (75% effective), rituximab (67% effective), and methotrexate (50% effective) [13,14,15]. Some studies even found rituximab treatment to be 100% effective [13]. Other studies found similar effects for radiotherapy and for combination of prednisone and azathioprine [1]. Rituximab therapy leads to specific IgG4 reduction together with apparently very effective disease control, even in steroid refractory cases [36]. Radiotherapy can be recommended in patients with documented resistance to steroids or in patients where these drugs cannot be used (such as tuberculosis) [38]. Combination of steroids and mycophenolate is also used [40]. It is important to note, however, that long term medical effects of these drugs are currently not known, as the number of studies evaluating the patients for an extended period is very limited.

Conclusion

IgG4-associated disease remains an overlooked clinical challenge, and our knowledge slowly growing. Fifteen years after the first clear definition, we have seen improvements in diagnostics as well as expansion of adequate medical treatments. However, this rather new type of problem resulting from dysregulation of immune system needs to be evaluated and monitored in close cooperation of several medical sectors.

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

| Authors’ contributions         | MZ | JR | VV | IL |
|--------------------------------|----|----|----|----|
| Research concept and design    | ✓  | ✓  | -- | ✓  |
| Collection and/or assembly of data | ✓  | ✓  | ✓  | ✓  |
| Data analysis and interpretation | ✓  | ✓  | ✓  | ✓  |
| Writing the article            | ✓  | ✓  | ✓  | ✓  |
| Critical revision of the article | ✓  | ✓  | ✓  | ✓  |
| Final approval of article      | ✓  | ✓  | ✓  | ✓  |

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References
1. Kubota T and Moritani S. Orbital IgG4-Related Disease: Clinical Features and Diagnosis. *ISRN Rheumatol*. 2012; 2012:412896. | Article | PubMed Abstract | PubMed FullText
2. Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, Matsui S, Sumida T, Mimori T, Tanaka Y and Tsutoba K et al. A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details. *Mod Rheumatol*. 2012; 22:1-14. | Article | PubMed Abstract | PubMed FullText
3. Mikulicz J. Über eine eigenartige symmetrische Erkrankung der Thränena- und Mundspeicheldrüsen. In V. Czerny (ed), Beiträge zur Chirurgie. 1892; 610-630.
4. Lee S, Törbas A, McCann JD and Goldberg RA. Mikulicz’s disease: a new perspective and literature review. *Eur J Ophthalmol*. 2006; 16:199-203. | PubMed
5. Yamamoto M, Harada S, Ohara M, Suzuki C, Naishiro Y, Yamamoto H, Takahashi H and Imai K. Clinical and pathological differences between Mikulicz’s disease and Sjögren’s syndrome. *Rheumatology (Oxford)*. 2005; 44:227-34. | Article | PubMed Abstract | PubMed FullText
6. Lang D, Zwerina J and Pieringer H. IgG4-related disease: current challenges and future prospects. *Ther Clin Risk Manag*. 2016; 12:189-99. | Article | PubMed Abstract | PubMed FullText
7. Mikulová Š, Jilek D and Richter J. Nemoc asociovaná s IgG4. *Úvod, patogeneze, diagnostika 1. část.* Alergie. 2015; 1:16-24.
8. Mikulová Š, Jilek D and Richter J. Nemoc asociovaná s IgG4. Klinicky obraz, orgánová postižení a terapie 2 část. Alergie. 2015; 2:91-99.
9. Stone JH, Zen Y and Deshpande V. IgG4-related disease: features and treatment response in a French cohort: results of a multi-centre registry. *Medicine (Baltimore)*. 2012; 91:539-51. | Article | PubMed
10. Himi T, Takano K, Yamamoto M, Naishiro Y and Takahashi H. A novel concept of Mikulicz’s disease as IgG4-related disease. *Auris Nasus Larynx*. 2012; 39:9-17. | Article | PubMed Abstract | PubMed FullText
11. Aziz HA, Villa-Forte A, Plesec TP and Singh AD. Isolated Conjunctival Inflammation Suggestive of IgG4-Related Disease. *Ocul Oncol Pathol*. 2015; 2:51-3. | Article | PubMed Abstract | PubMed FullText
12. Carbone T, Azedo Montes R, Andrade B, Lanzieri P and Mocarzel L. Orbital Pseudotumor: Uncommon Initial Presentation of IgG4-Related Disease. *Case Rep Rheumatol*. 2015; 2015:324365. | Article | PubMed Abstract | PubMed FullText
13. Ebbo M, Daniel L, Pavic M, Seve P, Hamidou M, Andres E, Burtey S, Chiche L, Serratrice L, Longy-Boursier M, Riuward M, Haroche J, Goddeau B, Beucher AB, Berthelot JM and Papo T et al. IgG4-related systemic disease: features and treatment response in a French cohort: results of a multicenter registry. *Medicine (Baltimore)*. 2012; 91:49-56 | Article | PubMed
14. Ebbo M, Grados A, Bernt E, Vely F, Bourcrait J, Harle JR, Daniel L and Schleinitz N. Pathologies Associated with Serum IgG4 Elevation. *Int J Rheumatol*. 2012; 2012:602809. | Article | PubMed Abstract | PubMed FullText
15. Ghys C, Depiereux M, Ozalp E and Veilkeniers B. Cervical lymph nodes, thyroiditis and ophthalmopathy: the pleomorphic face of an immunoglobulin g4-related disease. *Eur Thyroid J*. 2014; 3:252-7. | Article | PubMed Abstract | PubMed FullText
16. Guma M and Firestein GS. IgG4-related diseases. *Best Pract Res Clin Rheumatol*. 2012; 26:425-38. | Article | PubMed
17. Kocabeyoglu S, Karadag O, Mocan MC, Erden A and Irkec M. Orbital Involvement and Ocular Surface Changes in IgG4-Related Systemic Disease. *Cornea*. 2016; 35:1449-1453. | Article | PubMed
18. Yu KH, Chan TM, Tsai PH, Chen CH and Chang PY. Diagnostic Performance of Serum IgG4 Levels in Patients With IgG4-Related Disease. *Medicine (Baltimore)*. 2015; 94:e1707. | Article | PubMed Abstract | PubMed FullText
19. Hamano H, Kawa S, Horiiuchi A, Unno H, Furuya N, Akamatsu T, Fukushima M, Nikaido T, Nakayama K, Usuda N and Kyosawa K. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med*. 2001; 344:732-8. | Article | PubMed
20. Hamano H, Kawa S, Ochi Y, Unno H, Shiba N, Wajiki M, Nakazawa K, Shimjmo H and Kyosawa K. Hydrenephrosis associated with retroperitoneal fibrosis and sclerosing pancreatitis. *Lancet*. 2002; 359:403-4. | Article | PubMed
21. Okazaki K and Umehara H. Are Classification Criteria for IgG4-RD Now Possible? The Concept of IgG4-Related Disease and Proposal of Comprehensive Diagnostic Criteria in Japan. *Int J Rheumatol*. 2012; 2012:357071. | Article | PubMed Abstract | PubMed FullText
22. Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, Matsui S, Yoshino T, Nakamura S, Kawa S, Hamano H, Kamisawa T, Shimosegawa T, Shimatsu A, Ito T, Notohara K, Sumida T, Tanaka Y, Mimori T, Chiba T, Mishima M, Hibi T, Tsutobuchi H, Inui K and Ohara H. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD). *2011. Mod Rheumatol*. 2012; 22:21-30. | Article | PubMed
23. Lee CS, Harocopos GJ, Kraus CL, Lee AV, Van Stavern GP, Couch SM and Rao PK. IgG4-associated orbital and ocular inflammation. *Ophthalmol Inflamm Infect*. 2015; 5:15. | Article | PubMed Abstract | PubMed FullText
24. Mulay K and Wick MR. Ophthalmic immunoglobulin G4-related disease IgG4-RD Current concepts. *Semin Diagn Pathol*. 2016; 33:148-55. | Article | PubMed Abstract | PubMed FullText
25. McNab AA and McKelvie P. IgG4-related ophthalmic disease. Part I: background and pathology. *Ophthal Plast Reconstr Surg*. 2015; 31:83-8. | Article | PubMed
26. Umehara H, Nakajima A, Nakamura T, Kawanami T, Tanaka M, Dong L and Kawano M. IgG4-related disease and its pathogenesis-cross-talk between innate and acquired immunity. *Int Immunol*. 2014; 26:835-95. | Article | PubMed Abstract | PubMed FullText | PubMed
27. Masaki Y, Dong L, Kurose N, Kitagawa Y, Morikawa Y, Nakada S, Sugiyama E, Matsui S and Orighuchi T et al. Proposal for a new clinical entity, IgG4-positive multorgan lymphoproliferative syndrome: analysis of 64 cases of IgG4-related disorders. *Ann Rheum Dis*. 2009; 68:1310-5. | Article | PubMed
28. Li J, Ma JM and Ge X. Role of IgG4 serology in identifying common orbital lymphoproliferative disorders. *Int J Ophthalmol*. 2016; 9:275-7. | Article | PubMed Abstract | PubMed FullText
29. Carruthers MN, Khosroshahi A, Augustin T, Deshpande V and Stone JH. The diagnostic utility of serum IgG4 concentrations in IgG4-related disease. *Ann Rheum Dis*. 2015; 74:14-8. | Article | PubMed
30. Carruthers MN, Stone JH, Deshpande V and Khosroshahi A. Development of an IgG4-RD Responder Index. *Int J Rheumatol*. 2012; 2012:259408. | Article | PubMed Abstract | PubMed FullText
31. Hao M, Liu M, Fan G, Yang X and Li J. Diagnostic Value of Serum IgG4 for IgG4-Related Disease: A PRISMA-compliant Systematic Review and Meta-analysis. *Medicine (Baltimore)*. 2016; 95:e3785. | Article | PubMed Abstract | PubMed FullText
32. DaCosta J and Younis S. Topiramate-induced maculopathy in IgG4-related disease. *Drug Healthc Patient Saf*. 2016; 8:59-63. | Article | PubMed Abstract | PubMed FullText | PubMed
33. Culver EL, Vermeulen E, Makuch M, van Leeuwen A, Sadler R, Cargill TE, Klenerman P, Aalberse RC, van Ham SM, Barnes E and Rispens T. Increased IgG4 responses to multiple food and animal antigens indicate a polyclonal expansion and differentiation of pre-existing B cells in IgG4-related disease. *Ann Rheum Dis*. 2015; 74:944-7. | Article | PubMed Abstract | PubMed FullText
34. Rajak SN, Eldredge TA, Rashid F and Brittain GP. IgG4-related orbital disease mass lesion. *Can J Ophthalmol*. 2016; 51:e70-2. | Article | PubMed
35. Zhang W, Luo J and Jiao J. Optic nerve involvement in immunoglobulin G4-related disease: A case report. *Exp Ther Med*. 2016; 12:111-114. | Article | PubMed Abstract | PubMed FullText
36. Carvajal Alegria G, Pochard P, Pers JO and Cornec D. Could abatacept directly target expanded plasmablasts in IgG4-related disease? *Ann Rheum Dis*. 2016; 75:e723. | Article | PubMed
37. Grados A, Ebbo M, Bourcrait J, Vely F, Aucouturier P, Rigolet A, Terrier
B, Saadoun D, Ghillani-Dalbin P, Costedoat-Chalumeau N, Harle JR and Schleinitz N. Serum Immunoglobulin Free Light Chain Assessment in IgG4-Related Disease. *Int J Rheumatol*. 2013; 2013:426759. | Article | PubMed Abstract | PubMed FullText

38. Lindfield D, Attfield K and McElvanney A. *Systemic immunoglobulin G4 (IgG4) disease and idiopathic orbital inflammation; removing ‘idiopathic’ from the nomenclature? Eye (Lond)*. 2012; 26:623-9. | Article | PubMed Abstract | PubMed FullText

39. Liang L, Zhou J and Chen L. Perifollicular granulomas with IgG plasmacytosis: A case report and review of literature. *World J Clin Cases*. 2015; 3:650-4. | Article | PubMed Abstract | PubMed FullText

40. Mejico LJ. *IgG4-related ophthalmic disease*. *Saudi J Ophthalmol*. 2015; 29:53-6. | Article | PubMed Abstract | PubMed FullText