OPHTHALMIC MANIFESTATIONS OF IgG4-RELATED DISEASE

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INTRODUCTION

IgG4-related disease (IgG4-RD) was identified as a distinct systemic disease only a decade ago and recognition of this condition has grown quickly in recent years[1] (Figure 1).

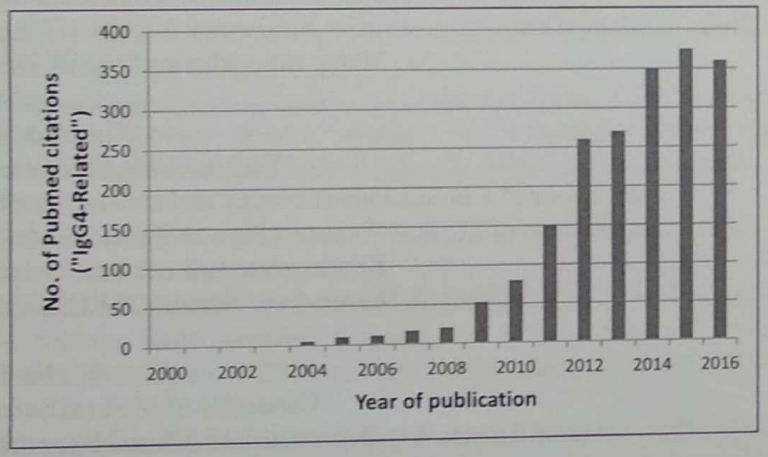

Figure 1. The yearly number of PubMed citations since 2000 containing the search term "IgG4-related"[2]

IgG4-RD is an immune-mediated fibro-inflammatory condition that is characterized by enlargement of tissues or organs, abundant IgG4+ plasma cell infiltration in damaged organs, and elevated serum IgG4 levels[3]. Various single-organ manifestations of IgG4-RD have already been established in the 19th century, when histopathological tissue examination emerged. Those eponymous syndromes, such as Mikulicz's disease, Riedel's thyroiditis, Morbus Ormond, or Küttner's tumor, were believed to be rare, isolated disease entities. The first step toward the discovery of IgG4-RD was the description of an autoimmune mediated, steroid responsive form of pancreatitis, today known as type 1 autoimmune pancreatitis (AIP) in 1995. Subsequently, in 2001, Hamano et al. reported an elevation of serum IgG4 levels in patients with AIP and described also the characteristic histopathological pattern in concomitant retroperitoneal fibrosis, thus paving the way for the recognition of the truly multiorgan nature of IgG4-RD[4]. In 2012, a unified nomenclature of IgG4-RD was published, abandoning all other synonymous names for IgG4-RD and its organ manifestations. In the same year, comprehensive diagnostic criteria and international consensus recommendations on the management and treatment of IgG4-RD were proposed[5]. In 2018 at the annual meeting of American College of Rheumatology and European League Against Rheumatism (ACR/EULAR) in Chicago the draft of classification criteria for IgG4-RD was presented[6].

1. Epidemiology, etiopathogenesis and pathomorphology of IgG4-RD

IgG4-RD is considered a rare disease, but its true epidemiology has not yet been fully clarified. The available epidemiologic data are mainly derived from Japanese cohorts[7]: Uchida et al. estimated the annual incidence of IgG4-RD at 0.28-1.08/100,000. IgG4-RD usually affects individuals of middle to upper age, with an onset at 50-70 years 4. Men are affected more often than women, particularly with pancreatobiliary involvement, where the gender ratio is 3:1. Gender differences are less pronounced among patients with salivary gland involvement[8].

The etiology of IgG4-RD remains obscure, and it is easier to describe the inflammatory response in affected patients than to identify definitive causative mechanisms. Evidence suggests that the disease is associated with both T helper 2 (Th2) and regulatory T-cell (Treg) immune responses. Th2 responses are linked to the development of allergies and bronchial

[1] Carruthers M.N., et al. The diagnostic utility of serum IgG4 concentrations in IgG4-related disease. Annals of the Rheumatic Diseases 2015. Vol 74. P. 14–18.

[2] Weindorf S.C., Frederiksen J.K. IgG4-Related Disease: A Reminder for Practicing Pathologists. Arch Pathol Lab Med. 2017. Vol 141. P. 1476–1483.

[3] Chen Y., et al. Types of Organ Involvement in Patients with Immunoglobulin G4-related Disease. Chin Med J (Engl) 2016. Vol 129. № 13. P. 1525–1532.

[4] Lang D., Zwerina J., Pieringer H. IgG4-related disease: current challenges and future prospects. Ther Clin Risk Manag 2016. Vol 12. P. 189–199.

[5] Umehara H., et al. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. Mod Rheumatol 2012. Vol 22. №1. P. 21–30.
Khosroshahi A.M., Wallace Z.C., Crowe J.L. International Consensus Guidance Statement on the Management and Treatment of IgG4-Related Disease. *Arthritis Rheumatol* 2015. Vol 67. №7. P. 1688–1699.

[6] Stone J.H. Oral presentation at the annual meeting of the American College of Rheumatology (24 October 2018, Chicago).

[7] Uchida K., et al. Prevalence of IgG4-Related Disease in Japan Based on Nationwide Survey in 2009. International journal of rheumatology 2012; 358371.

[8] Vikse J., Haland S., Norheim K.B. IgG4-related disease. *Tidsskr Nor Legeforen*. 2017. Vol. 137. P. 1–8.

asthma, conditions that are more prevalent in patients with IgG4-RD. They are characterized by CD4+ T-cells secreting the cytokines interleukin-4 (IL-4), IL-5, and IL-13, and they promote class switching to IgG4, increased IgE synthesis, and eosinophilia. Treg, in contrast, secrete cytokines such as IL-10 and transforming growth factor β (TGF-β). Repeated cycles of antigenic stimulation and cytokine secretion then produce the histopathologic findings of tissue fibrosis and a lymphoplasmacytic infiltrate rich in IgG4+ plasma cells. However, direct evidence that Th2-associated cytokines truly drive the inflammation in IgG4-RD is still lacking, and no convincing environmental trigger (infectious or otherwise) or autoantigen has been identified. Other possible predisposing conditions or contributors to IgG4-RD pathogenesis include specific human leukocyte antigen (HLA) alleles and single-nucleotide polymorphisms within some non-HLA genes.

Also puzzling is the precise role of IgG4 in the disease. IgG4 is the least common IgG subtype, comprising less than 5% of total IgG, and is generally considered to be a non-inflammatory immunoglobulin due to its limited ability to fix complement and bind activating Fc receptors. In addition, owing to unstable inter-heavy chain disulfide bonds, IgG4 can exchange its Fab arms with other IgG4 molecules, rendering it functionally monovalent2. The molecule of IgG4 is thought to play an important role in immune mediated conditions such as pemphigus vulgaris, idiopathic membranous glomerulonephritis and thrombotic thrombocytopenic purpura[9]. Nevertheless, 20-40% of the patients with IgG4-RD may have the IgG4 value in the normal ranges. On the other hand, the increased amount of IgG4 can be observed in different diseases: the primary Sjögren syndrome (7%), lupus erythematosus (10%), and rheumatoid arthritis, cancers and also in the healthy population (2%)[10].

The critical histopathological features of IgG4-RD are a dense lymphoplasmacytic infiltrate, a storiform pattern of fibrosis, and obliterative phlebitis. Other histopathological features are phlebitis without obliteration of the lumen and increased numbers of eosinophils. IgG4 immunostaining is an essential test for the pathological diagnosis of IgG4-RD[11].

[9] Sedhom R., Sedhom D., Strair R. IgG4-related disease: A mini-review. J Rare Dis Res Treat 2017. Vol 2. № 2. P. 18–23.

[10] Sebastian A., et al. The variety of clinical presentations in IgG4-related disease in Rheumatology. *Rheumatol Int*. 2017. Vol 36. P. 1–7.

[11] Deshpande V., et al. Consensus statement on the pathology of IgG4-related disease. *Modern Pathology*. 2012. Vol 25. P. 1181–1192.

2. Nomenclature and clinical manifestations of IgG4-RD

The clinical presentation is variable, as this disease may affect nearly every organ (Table 1). According to Chen Y. et al., involvement of lymph nodes was present in 56,5% of patients, submandibular salivary glands – 51%, pancreas – 38,5%, lungs – 32%, paranasal sinuses – 21,5%, kidneys – 10%. The variable organ dysfunction reflects the clinical presentation.

Table 1

Preferred nomenclature for individual organ manifestations of IgG4-RD[12]

Organ system/tissue	Preferred name
Pancreas	Type 1 autoimmune pancreatitis (IgG4-related pancreatitis)
Eye	IgG4-related ophthalmic disease is the general term for the periocular manifestations of this disease
Lacrimal glands	IgG4-related dacryoadenitis
Orbital soft tissue (orbital inflammatory pseudotumor)	IgG4-related orbital inflammation (or IgG4-related orbital inflammatory pseudotumor)
Extraocular muscle disease	IgG4-related orbital myositis
Orbit with involvement of multiple anatomic structures	IgG4-related panorbital inflammation (includes lacrimal gland disease, extraocular muscle involvement, and other potential intraorbital complications)
Salivary glands (parotid and submandibular glands)	IgG4-related sialadenitis or, more specifically, IgG4-related parotitis or IgG4-related submandibular gland disease
Pachymeninges	IgG4-related pachymeningitis
Hypophysis	IgG4-related hypophysitis
Thyroid (Riedel's thyroiditis)	IgG4-related thyroiditis
Aorta	IgG4-related aortitis/periaortitis
Arteries	IgG4-related periarteritis
Mediastinum	IgG4-related mediastinitis
Retroperitoneum	IgG4-related retroperitoneal fibrosis

[12] Stone J.H., et al. Recommendations for the nomenclature of IgG4-related disease and its individual organ system manifestations. *Arthritis Rheum*. 2012. Vol 64. № 10. P. 3061–3067.

Mesentery	IgG4-related mesenteritis
Skin	IgG4-related skin disease
Lymph node	IgG4-related lymphadenopathy
Bile ducts	IgG4-related sclerosing cholangitis
Gallbladder	IgG4-related cholecystitis
Liver	IgG4-related hepatopathy (refers to liver involvement that is distinct from biliary tract involvement)
Lung	IgG4-related lung disease
Pleura	IgG4-related pleuritis
Pericardium	IgG4-related pericarditis
Kidney	IgG4-related kidney disease. The specific renal complications should be termed tubulointerstitial nephritis secondary to IgG4-RD and membranous glomerulonephritis secondary to IgG4-RD. Involvement of the renal pelvis should be termed IgG4-related renal pyelitis
Breast	IgG4-related mastitis
Prostate	IgG4-related prostatitis

The presentation of IgG4-RD is typically subacute. Symptoms may wax and wane with spontaneous improvement, with years of disease inactivity9. Patients may be asymptomatic and only incidentally diagnosed at the physical examination or imaging10. The most common clinical manifestation is the development of a mass lesion that produces site-specific symptoms and raises suspicion for malignancy. The effects range from simple swelling of the affected organs (salivary and lacrimal glands, lymph nodes) to obstruction (pancreaticobiliary, ureteral), organ dysfunction (pituitary insufficiency secondary to hypophysitis, kidney disease), and even medical emergency (aortic dissection, pachymeningitis, pancreatitis). Apart from the mass effects, a small number of patients may experience constitutional symptoms such as fever and weight loss2. The most common symptoms are presented in table 2.

Table 2

Main clinical manifestations in patients with IgG4-RD

Clinical manifestations	Proportion of patients (%)
Submandibular gland swelling	51,0%
Lacrimal gland swelling	42,0%
Superficial lymph node enlargement	37,0%
Abdominal pain	35,0%
Parotid gland swelling	24,0%
Nasal congestion	21,5%
Jaundice	14,0%
Pruritus	13,5%
Cough	13,5%
Low back pain	13,5%
Dysuresia	13,0%
Dry mouth and/or dry eye	12,5%
Nausea and/or vomiting	12,0%
Fever	9,0%
Edema	8,5%
Exophthalmos	5,5%
Arthralgia	4,0%
Thyroid enlargement	2,5%
History of allergy	59,0%
Asymptomatic	1,0%

Chen et al. analyzed the types of organ involvement in IgG4-RD. The majority of patients with only one type of organ involved suffered from Mikulicz's disease (MD), and accounted for up to 13,0% of patients, followed by retroperitoneal/mediastinal fibrosis (7,5%), and pancreatic-hepatobiliary-splenic system involvement (7,0%). Meanwhile, patients who had only lung or kidney involvement were rare. Among patients with two types of involved organs, MD combined with another organ type was more frequent (26,5%), and of these, the respiratory system was most commonly involved (16,5%), followed by the pancreatic-hepatobiliary-splenic system (7,0%). In addition, a combination of MD with two other types of involved organs represented 14,0% of cases. However, patients with three types of involved organs without MD accounted for only 1,5% of cases. Moreover, the constituent ratio of patients with multi-type (≥3)

organ involvement was 12,0%, and most of these patients also suffered from MD. Scientists thus evaluated the level of confidence for IgG4-RD indication as strong, moderate, or weak according to the proportion of these types of organ involvement3 (Table 3).

Table 3

Confidence level for IgG4-RD indication according to type of organ involved

Types of organ involved	Confidence for indication of IgG4-RD
Only one type of involved organ	
Salivary glands/lacrimal glands (MD)	Strong
Hepatobiliary-pancreatic-splenic	Moderate
Retroperitoneal/mediastinal fibrosis	Moderate
Regional or systemic lymphadenopathy	Weak
Respiratory system (sinus/lung parenchyma/airway/pleura)	Weak
Urinary system (kidney/ureter/bladder/prostate)	Weak
Two types of involved organs	
MD + respiratory system	Strong
MD + pancreatic-hepatobiliary-splenic	Strong
MD + one other type of organ	Moderate
Retroperitoneal/mediastinal fibrosis + pancreatic-hepatobiliary-splenic	Moderate
Two other types of organs	Weak
Three types of involved organs	
MD + pancreatic-hepatobiliary-splenic + respiratory system	Strong
MD + pancreatic-hepatobiliary-splenic + retroperitoneal/mediastinal fibrosis	Strong
MD + pancreatic-hepatobiliary-splenic + urinary	Moderate
MD + two other organ types involved	Moderate
Three other organ types involved	Weak
Multi-type organ involvement	
MD + greater than or equal to three types of organs involved	Strong
Other multi-type organ involvement	Moderate

3. Ophthalmic manifestations in IgG4-RD

Orbital involvement occurs in 4-34% of patients and can often be the first manifestation of the disease. The most common localization is the lacrimal glands, although eyelids, extraocular muscles (EOM), orbital soft tissue, optic and/or trigeminal nerve, bony orbit, nasolacrimal ducts may also be involved. Affection of conjunctiva is considered casuistic. Typical clinical manifestations include painless uni– or bilateral periorbital swelling and exophthalmos with/without diplopia. Visual acuity is usually not impaired, although cases of vision loss due to optic nerve compression have been reported. Affection of EOM may lead to the impairment of their function. Extra-ophthalmic manifestations were reported in 78,9% of cases. In particular, a symmetric lesion of the lacrimal and salivary glands is called Mikulicz's disease[13].

Tiegs-Heiden C.A. et al. retrospectively analyzed the spectrum of periorbital involvement in IgG4-RD of the orbit and revealed that EOM were enlarged in 89% of patients, 88% bilaterally. In 71% of affected orbits, the lateral rectus was the most enlarged muscle. In 96% of patients, the tendons of the extraocular muscles were spared. 70% of patients had lacrimal gland enlargement, 44% – an infiltrative process within the orbital fat, 30% – infraorbital nerve enlargement, 89% – sinus disease (paranasal sinus mucosal thickening). According to these characteristics, a diagnostic algorithm for patients with proptosis and/or periorbital swelling was developed: in case of lacrimal gland and EOM involvement (especially when the lateral rectus is the most enlarged), with sparing of tendons, which is accompanied by paranasal sinus mucosal thickening, IgG4-RD should be a leading differential consideration[14] (Figure 2).

[13] Ebbo M., et al. Ophthalmic manifestations in IgG4-related disease: Clinical presentation and response to treatment in a French case-series. Kers J ed Medicine 2017. Vol 96. № 10: e6205.

[14] Tiegs-Heiden C.A., et al. Immunoglobulin G4–Related Disease of the Orbit: Imaging Features in 27 Patients. *Am J of Neuroradiol* 2014. Vol 35. № 7. P. 1393–1397.

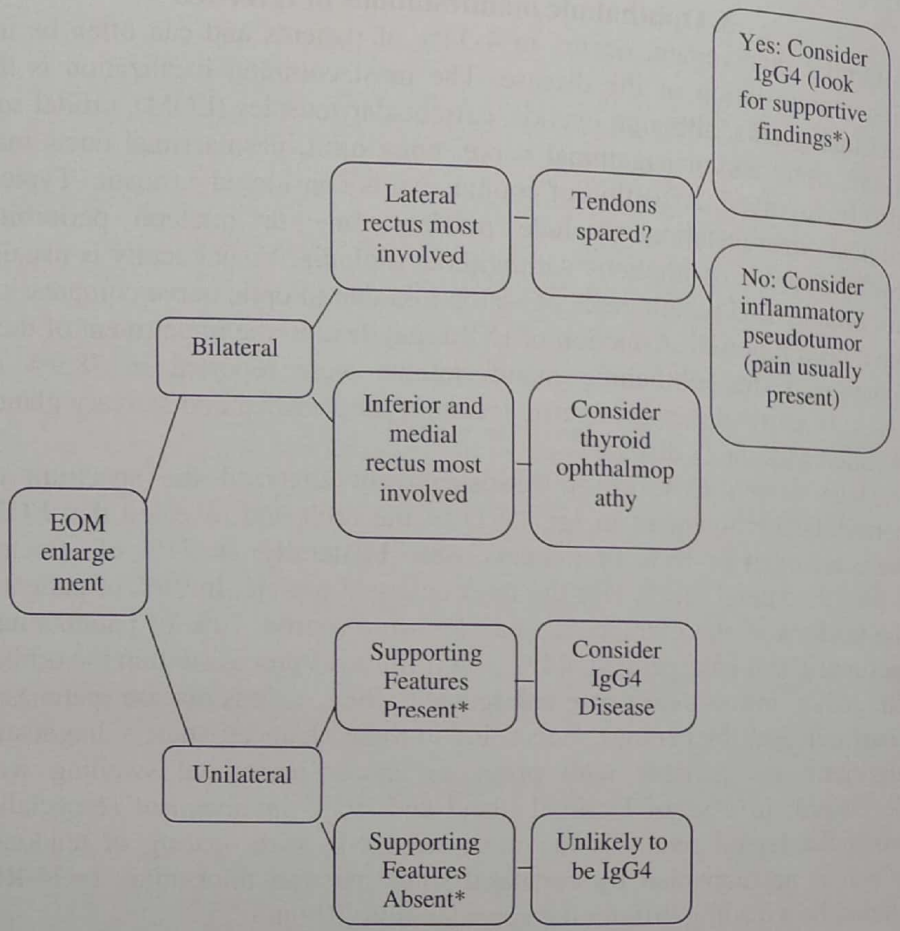

Fig. 2. Decision tree for the differential diagnosis of EOM enlargement

**Supporting features: lacrimal gland involvement, sinus disease, infraorbital nerve enlargement, and/or an infiltrative process in the orbital fat*

IgG4-related ophthalmic disease requires a thorough differential diagnosis, since a significant number of rare diseases may occur with orbit involvement. According to Vasilyev V. et al., the reason of ophthalmic manifestations in 35% of patients is IgG4-RD, 29% – granulomatous

diseases, 17,5% – non-Hodgkin's lymphomas[15] (Table 4). The differential diagnosis of Mikulicz's disease (MD) from Sjogren's syndrome (SS) is also important. There are considerable differences between MD and typical SS: 1) MD occurs in both men and women whereas SS occurs mainly in women, 2) significant enlargement of the lacrimal and salivary glands but relatively mild xerostomia and xerophthalmia, 3) a good response to glucocorticoid therapy, 4) raised levels of serum IgG4 and IgE, significantly lower incidences of rheumatoid factor, antinuclear antibody, anti-SS-A/Ro and anti-SS-B/La antibody, 6) often associated with autoimmune pancreatitis, 7) lymphocytic follicle formation in tissue[16].

Table 4

Spectrum of the diseases with orbital involvement in rheumatologic practice

	N, pts	N, %		N, pts	N, %
Non-neoplastic conditions	**108**	**78.5**	**Hematologic conditions**	**30**	**21,5**
–IgG4-RD	48	35.0	– Non-Hodgkin lymphomas	20	14,5
–Granulematous lesions (sarcoidosis, granulematosis with polyangiitis, necrosing sarcoidal granulematosis)	41	29	– Erdheim-Chester disease	1	0,7
–Autoimmune dacryoadenitis (non-differentiated)	7	5	– AL-amyloidosis	3	2,1
–Idiopathic orbital inflammation	7	5	– NK/T-cell nasal lymphoma	1	0,7
–Endocrine ophthalmopathy	2	1.4	– Histiocytosis	4	2,9
–Cogan's syndrome	1	0.7	– Calcifying aponeurotic fibroma	1	0,7
–Relapsing polychondritis	1	0.7			

[15] Vasilyev V., et al. Spectrum of the diseases with orbital involvement in rheumatology: single-center study. *Ann Rheum Dis.* 2017. Vol 76. P. 424–425.

[16] Masaki Y., et al. Proposal for a new clinical entity, IgG4-positive multiorgan lymphoproliferative syndrome: analisys of 64 cases of IgG4-related disorders. Ann Rheum Dis 2009. Vol 68. P. 1310–1315.

4. Diagnosis and treatment of IgG4-RD

There is no standard laboratory parameter that would explicitly mark the presence of IgG4-RD. C-reactive protein may be elevated, and low complement levels, especially in patients with IgG4-related kidney disease, have been frequently reported. Also, peripheral eosinophilia and elevated serum IgE are often present among patients with IgG4-RD. Antinuclear antibodie and rheumatoid factor have been found in a relatively large percentage of patients, but usually at low serum titers. Altogether, the diagnostic value of these findings is only limited and does not allow to draw any conclusions on the localization and extent of IgG4-RD.

As IgG4-RD frequently presents itself with organ enlargement and tumefactive lesions, imaging is obviously essential as malignancy is usually the main differential diagnosis. As a result, a majority of patients will have computed tomography or magnetic resonance imaging scans probably before IgG4-RD is even thought of. Generally, imaging techniques are certainly useful differential diagnosis and useful in judging the extent of disease, but they do not provide signs specific of IgG4-RD. 18F-fluorodeoxyglucose positron emission tomography (FDG PET)/CT may be an effective diagnostic utility in IgG4-RD as it can highlight active inflammatory lesions and thus enables estimating the extent of disease. Furthermore, FDG PET/CT is a useful tool for staging and monitoring of disease activity, for assessing response to treatment, and also for guiding biopsies.

In 2012, Japanese investigators proposed comprehensive diagnostic criteria for IgG4-RD, according to which diagnosis should be based on three pillars (Table 5).

Table 5

Comprehensive clinical diagnostic criteria for IgG4-RD

Examination	Characteristic features	Diagnosis IgG4-RD
Clinical (1)	Diffuse/localized swelling or masses in single or multiple organs	Definite: 1 + 2 + 3
Hematological (2)	Elevated serum IgG4 concentrations (>135 mg/dl)	Probable: 1 + 3
Histopathologic (3)	Marked lymphocyte and plasmacyte infiltration and fibrosis. Infiltration of IgG4+ plasma cells: ratio of IgG4+/IgG+ cells >40% and >10 IgG4+ plasma cells/HPF	Possible: 1 + 2

At the annual meeting in Chicago (2018) ACR/EULAR panel has written the first-ever classification criteria for IgG4-RD, and the draft version of the criteria identified the disorder with 99,2% specificity and 85,5% sensitivity when compared with expert case opinions. The first step in classifying a patient with IgG4-RD is to identify involvement of at least one organ from the list the panel compiled of 10 organs where involvement typifies the disease: pancreas, bile ducts, orbits, lacrimal glands, major salivary glands, retroperitoneum, kidney, aorta, pachymeninges, and thyroid gland (Riedel's thyroiditis, but not Hashimoto's disease). Patients who do not have disease involvement in at least one of these organs don't qualify as having IgG4-RD. The next step is to rule out patients who have at least one exclusion criterion from a list of 21 exclusions the panel cited, divided into four categories based on the test that finds each exclusion: clinical examination, serology, radiology, or pathology (Table 6). The last step is to identify enough individual classification hallmarks in the patient so that collectively they definitively identify IgG4-RD (Table 7). The writing panel endorsed seven inclusion-criteria domains that each contain at least two different disease manifestations that confer points if fulfilled. To qualify for IgG4-RD classification, a patient needs to have enough manifestations to tally at least 19 points.

Table 6

Exclusion criteria for IgG4-RD

Clinical exclusions	Fever
	Unresponsive to steroids
	Leukopenia and thrombocytopenia
	Peripheral eosinophilia (>3000 per mm^3)
Serological exclusions	PR3 or MPO-ANCA positive
	Anti-Ro or La positive
	Extractable nuclear antibody positive (anti-dsDNA, anti-RNP, anti-Sm antibodies)
	Cryoglobulins
	Other disease-specific antibodies
Radiology exclusions	Rapid radiographic progression
	Large bone abnormality (such as Erdheim-Chester disease)
	Splenomegaly
	Concern regarding infection, malignancy, or both
Pathology exclusions	Primarily granulomatous inflammation
	Necrotizing vasculitis

	Malignant infiltrate
	Prominent histiocytic infiltrate
	Prominent neutrophilic infiltrate
	Multicentric Castleman's pathology
	Prominent necrosis
	Inflammatory pseudotumor pathology

Table 7

IgG4-RD inclusion domains and point assignments

Domains		Points
IgG4 level	Normal	0
	Above normal and less than 2× upper limit of normal	3,7
	2× to 5× ULN	6,1
	Above 5× ULN	10,8
Histology and immunostaining	Uninformative biopsy	0
	Dense lymphoplasmacytic infiltrate (DLI)	3,7
	DLI plus obliterative phlebitis	6,1
	DLI plus storiform fibrosis	13,3
Lacrimal and major salivary gland enlargement	One set of glands involved	5,9
	Two or more sets of glands involved	13,8
Chest and thoracic aorta	Peribronchovascular and septal thickening	3,8
	Paravertebral band-like soft tissue in the thorax	9,8
Pancreas and biliary tree	Diffuse pancreas enlargement (loss of lobulations)	8,0 10,5
	Diffuse pancreas enlargement and capsule-like rim with decreased enhancement	18,7
	Pancreas and biliary tree involvement	
Kidney	Hypocomplementemia	5,8
	Renal pelvis thickening or soft tissue or both	8,1
Retroperitoneum	Diffuse thickening of the abdominal aortic wall	4,1
	Circumferential or anterolateral soft tissue around the infrarenal aorta or iliac arteries	7,8

Note: A patient must tally at least 19.0 points to receive IgG4-RD classification

Untreated IgG4-RD in vital organs such as pancreas and kidney can – even if asymptomatic – lead to irreversible organ damage within only months and therefore requires immediate treatment. Still, spontaneous remissions have repeatedly been reported, and disease progression in untreated patients can be absent for a long period of time. Thus, watchful waiting with close follow-up examinations may be an option to be considered in certain patients with no or only mild symptoms, without signs of organ dysfunction and with IgG4-RD in locations not likely to cause major complications.

Glucocorticoids (GC) have been considered the first-line therapy in IgG4-RD ever since the first description of AIP in 1995, when prompt response to GC treatment was reported as a characteristic finding. According to the recently published consensus statement on the treatment of IgG4-RD, the vast majority of IgG4-RD experts still regard GC as the first-line therapy for active, untreated disease. Remission induction is commonly initialized with 30-40 mg/day prednisone or a weight-adjusted dose at 0,6 mg/kg/day, which can be varied according to disease activity and urgency. Response to GC therapy is usually seen within days or weeks, and remission can be achieved within months in the majority of patients. Slow tapering of the GC dose should begin 2-4 weeks after induction of therapy and last for 3-6 months, whereas various regimes have been suggested. Whether long-term maintenance therapy with low-dose GC (2,5-5 mg/day prednisolone) for up to 3 years is indicated, as suggested by Japanese guidelines for AIP, is still object to discussion. Patients with multiorgan disease, especially with localization in vital organs and with a history of relapses, will probably benefit from long-term maintenance therapy. Expert opinions are divided on the question, if steroid-sparing agents such as azathioprine, methotrexate, or mycophenolate-mofetil should be used in induction and maintenance therapy besides GC. Recently, the introduction of B-cell depletion with rituximab (RTX) has brought a new impetus into the treatment of IgG4-RD. RTX therapy leads to specific IgG4 reductions together with apparently very effective disease control, even in steroid refractory cases. Still, although recently reported results are promising, relapses also happen under RTX. Besides, there is still no consensus regarding dosage and frequency of RTX application, so that the efficacy of RTX in IgG4-RD cannot be ultimately judged yet.

5. Case report

24-year-old female presented on 03 Feb, 2011, with submandibular swelling for the previous few months. On maxillofacial CT with IV contrast: symmetric enlargement of lacrimal and major salivary glands (particularly left submandibular) with homogeneously enhancing; pan sinus opacification and severe mucosal thickening; other tissues are unremarkable. Complete blood count (CBC) and urinalysis – within normal limits. Antibodies to dsDNA, Ro(SS-A), La(SS-B), Scl-70 – negative. Final diagnosis was not established. The part of left submandibular gland was removed (histologically – nonspecific hyperplasia), but after a few months the swelling of the same area reappeared. After some time ophthalmic manifestations (periorbital swelling and exophthalmos) developed, cervical lymphadenopathy and parotid swelling appeared. In Jan 2012 excisional biopsy was performed: 1) left submandibular gland: features of chronic sclerosing sialadenitis. Immunohistochemistry results: IgG4 positive plasma cells >75/HPF, the IgG4/IgG ratio 80%. 2) parotid gland: features of lymphocytic sialadenitis. 3) posterior cervical lymph node: features of reactive follicular hyperplasia. Probable diagnosis of IgG4-RD was made based on clinical and histopathological findings (ratio IgG4+/IgG4 >40% and >10 IgG4+ plasma cells/HPF) according to diagnostic criteria of Umehara H. et al5. Treatment with GC was started. But the patient avoided the permanent use of GC, she occasionally took prednisolone for 5-7 days in various doses (40, 20, 10, 5 mg) trying to find the minimal "effective dose". Indeed, periorbital edema significantly decreased by the 2-3rd day, but after the discontinuation of GC it reappeared nearly after 2 weeks, often even more significant than before (Figure 3).

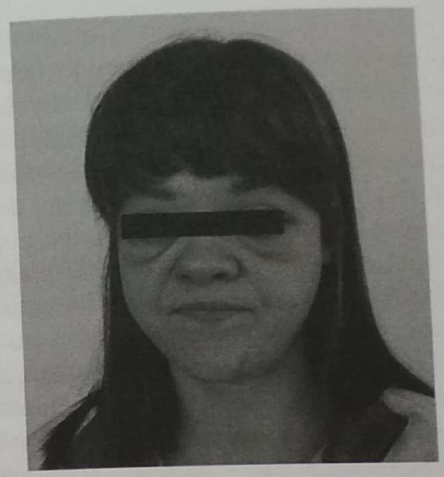

Fig. 3. Periorbital swelling in patient with IgG4-RD

Due to the persistence of symptoms, insufficient effect of episodic GC administration, as well as addition of dyspnea, the patient applied for a re-examination. On chest CT (Apr 2016): scattered ground glass opacities; interstitial thickening in the perihilar regions; enlarged paratracheal and axillary lymph nodes. Immunological blood test: IgG4 >300 mg/dL (normal 4-86 mg/dL). CBC: neutrophilic leukocytosis ($12.2x10^9/l$). Maxillofacial CT with IV contrast (Oct 2016): emerging of diffuse enlargement of the EOM most severely affecting the lateral rectus muscle, with sparing of tendons; progression of the enlargement of major salivary and lacrimal glands; features of chronic sinusitis remain unchanged. Given the progression of the disease, the patient was recommended therapy with GC and methotrexate. But the patient refused to take methotrexate because she planned pregnancy. Therefore, she was prescribed prednisolone 40 mg/day with a slow dose reduction in 2-4 weeks according to International consensus guidance statement on the management of IgG4-RD[17]. Maintenance therapy with prednisolone 5 mg/day was recommended for 1-3 years. In the future, depending on the possibility of achieving remission and reducing the dose of GC, it is planned to consider the possibility of treatment with rituximab.

[17] Khosroshahi A.M., Wallace Z.C., Crowe J.L. International Consensus Guidance Statement on the Management and Treatment of IgG4-Related Disease. Arthritis Rheumatol 2015. Vol 67. № 7. P. 1688-1699.

CONCLUSIONS

IgG4-RD is a newly recognized systemic autoimmune disorder characterized by elevated serum IgG4 levels and tumorlike fibroinflammatory masses with distinctive histopathologic features that almost always include infiltrates of IgG4+ plasma cells. The incidence of IgG4-RD across all organ systems is difficult to determine, since the disease has only recently been described and global population-based data are lacking. The clinical features of IgG4-RD manifest as single or multiple organ swellings or masses that occur in various sites, including lacrimal glands, salivary glands, pancreas, bile ducts, retroperitoneal tissues, lung, kidney, prostate, pituitary gland, thyroid, and uterus. Patients may be asymptomatic and only incidentally diagnosed at the physical examination or imaging. The diagnosis of IgG4-RD relies heavily on the histopathologic characteristics of biopsy specimens, including a lymphoplasmacytic infiltrate enriched with IgG4+ plasma cells, storiform fibrosis, obilterative phlebitis, and a mild to moderate tissue eosinophilia. Early treatment is crucial for avoiding progressive fibrosis and irreversible loss of organ function. The first-line choice for treatment for IgG4-RD is high-dose peroral prednisolone (0,6 mg/kg) for 2-4 weeks, followed by gradual tapering to a maintenance dose of 2,5 to 5 mg daily. The duration of maintenance treatment has not been defined. Most patients have a prompt clinical response to GC, but recurrence in connection with tapering or cessation is frequently seen.

Our case report demonstrates typical involvement of periorbital tissues in IgG4-RD: IgG4-related sialadenitis, dacryocystitis, orbital myositis. Not only the results of immunohistochemistry and elevated serum IgG4 levels were essential for diagnosis, but also such characteristic signs of IgG4-related ophthalmic disease: involvement of lacrimal glands and lateral rectus muscles with sparing of their tendons, accompanied by mucosal thickening of paranasal sinuses. In addition, the described case report illustrates a quick but unstable response to GC therapy and confirms the need for their long-term administration.

SUMMARY

The article is devoted to study of the ophthalmic manifestations in patients with IgG4-RD. We report a case of IgG4-related ophthalmic disease in a patient with periorbital and submandibular swelling associated with lymphadenopathy and dyspnea. Maxillofacial CT revealed enlargement of lacrimal and major salivary glands, mucosal thickening of paranasal sinuses, and involvement of extraocular muscles most severely affecting the lateral rectus muscle, with sparing of tendons. Diagnosis was confirmed by immunohistochemistry and elevated serum IgG4 levels. Treatment with glucocorticoids was recommended.

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