IgG4 RELATED DISEASE WITH ORBITAL MANIFESTATION

Edita Dervišević*[1], Almir Dervišević[2], Nejira Ibrišević[1]

*Corresponding author

Dr. Edita Dervišević
Malta 9
71000 Sarajevo
Bosnia and Herzegovina
Phone: +38761925750
E- mail: emaedita@gmail.com

[1] Eye Clinic of the Clinical Center of University of Sarajevo, Sarajevo, Bosnia and Herzegovina

[2] Department for Head and Neck Surgery of the Clinical Center of University of Sarajevo, Sarajevo, Bosnia and Herzegovina

ABSTRACT

IgG4 (Immunoglobulin G4) is an immune-mediated fibro-inflammatory process affecting various organs, predominantly salivary and lacrimal glands, pancreas and liver. It can also be manifested as tubule-interstitial nephritis, periaortitis and dacryoadenitis. It represents newly recognized disease, with increasing incidence, probably due to improvement in its awareness.

In this paper, we present an interesting case of IgG4 related disease with orbital manifestation in terms of severe protrusion of both eye balls and the pathway and challenges in diagnose and treatment as well. To the best of our knowledge, this is the first published and described case of this type IgG4 related disease with exophthalmus in Bosnia and Herzegovina.

Keywords: IgG4, severe protrusion of eye balls, diagnose, treatment.

Introduction

IgG4 related disease is a systemic immune-mediated fibro inflammatory condition affecting several organ systems. It can affect almost any organ in human body, but it is predominant for pancreas, biliary system, salivary and lacrimal glands. Idiopathic fibrosis disorders like Mikulicz disease, Riedel's thyroiditis, Morbus Ormond, sclerosing mesenteritis were considered as rare, isolated disease entities. Today, it is known that they are part of IgG4-RD spectrum. IgG4-RD is easily misdiagnosed due to the lack of the clinicians' experiences and because of the lack of reliable biomarkers.

It is only little known about epidemiology of IgG4-RD. Available data is mainly derived from Japan's cohorts and they estimated the annual incidence of IgG4-RD at 0.28–1.08/100,000 [1]. No data is available for our country.

Clinical presentation

Disease affects nearly any organ except synovial tissue. Patients are usually presented with subacute formation of a mass lesion on an organ. The disease itself does not cause constitutional symptoms or pain. Lymphoproliferative disorders are one of the big mimickers of IgG4-RD.

Diagnosis

Diagnosis of IgG4-RD requires detailed clinical history and physical examination, with lab testing, imaging. Histopathological examination remains the most accurate and the most important method to diagnose IgG4-RD, especially in tumefactive lesions where malignancy must be excluded.

No standard laboratory parameter that would precisely mark the presence of IgG4-RD has been found. It has been found that elevated serum IgG4 levels are neither necessary nor sufficient for the diagnosis. Most common laboratory findings associated with IgG4-RD are: IgG4 level > 135, elevated IgG4: IgG ratio >10%, peripheral eosinophils, normal CRP, normal ESR, ANA low titer positive, elevated IgE levels, hypo-complementemia, increased number of circulating plasma blasts by flow cytometry, qPCR of IgG4/IgG RNA [2]. The typical histologic abnormalities are a dense lympho-plasmatic infiltrate, storiform fibrosis, and obliterate phlebitis [3].

Radiologic imaging plays an important role in diagnosing of IgG4-RD. CT or MR demonstrate infiltration and enlargement of involved organs.

Treatment

A phase 2 trial on 44 patients with IgG4-RD from Japan showed an overall response rate of 93% and complete response rate of 66% with steroids used as the first-line therapy [4]. They used prednisone 0.6 mg/kg/day initially with a gradual decrease of 5 mg every 2 weeks [4].

Disease-modifying anti-rheumatic drugs are not very effective for induction of remission but may have a role in maintaining remission for some patients [5].

Rituximab has shown promise in treating patients with IgG4-RD in multiple case series. One of them showed high effectivity of Rituximab for IgG4-RD, with a response rate of 97% in one prospective trial [6].

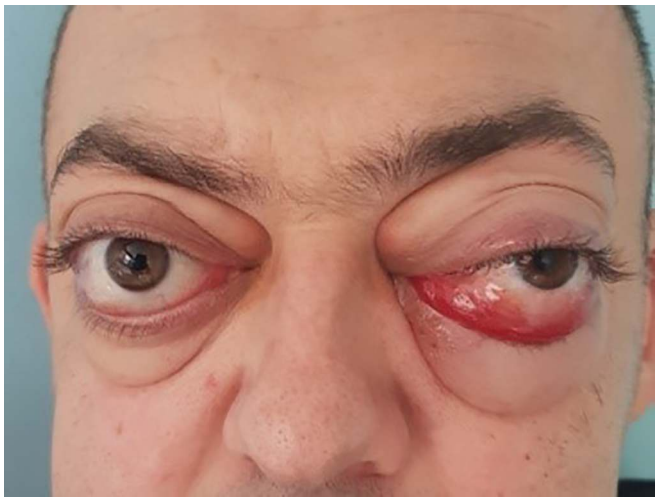
RTX therapy leads to specific IgG4 reductions together with apparently very effective disease control, even in steroid refractory cases [6]. RTX seems to be a very specific agent interfering with the immunological processes underlying IgG4-RD, though it has not yet been fully elucidated. [7]. Although recently reported results are promising, relapses also happen under RTX. [8].

Case presentation

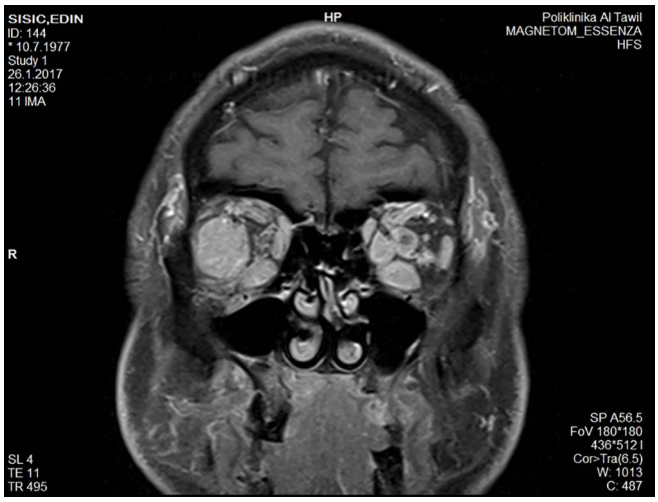
A 42 old male with severe case of bilateral proptosis has been admitted to Eye Clinic of the Clinical Center of University of Sarajevo, 2 years after no success in finding the correct diagnose. Due to non-measuring and extreme proptosis he was mistaken for thyroid disease Bazedov. But his hormonal status was in referent range. All other results were as follows.

Patient neglected pain.

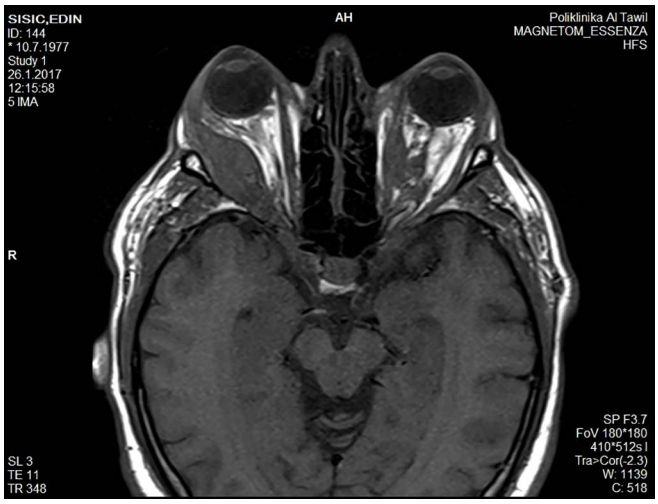
Visual acquits of the right eye was 1.0 without correction, and for the left eye was 0.02 without correction. Intraocular pressure was 18 mmHg for right eye and 9 mmHg for left eye.



Picture 1.
Bilateral proptosis, after 2 years of an adequate treatment



Picture 2.
Enlargement of the extraocular muscles



Picture 3.
Enlargement of the extraocular muscles

Slit lamp examination:

Right eye: lids - edematous, eye ball - in protrusion, extraocular movements - full, with no restrictions; conjunctiva - normal, cornea - clear, anterior chamber - deep and quiet, iris - normal, lens-clear, vitreous - clear. Fundus: optic nerve head, macula, blood vessels and periphery were normal.

Slit lamp of left eye: lids - edematous, eye ball was in severe protrusion, extraocular movements - incomplete ophthalmoplegia; conjunctiva – chemosis, cornea - clear, anterior chamber - deep and quiet, iris - normal, lens - clear, vitreous - clear. Fundus: optic nerve head was pale; macula, blood vessels and periphery were normal.

Neurologic visual field shows quite enhanced loss of sensibility in visual field of the left eye and depression of the Bebie curve.

His lab test showed: SE: 7, CRP: 8.0 mg/L. Complete blood count with differential was in referent range. Liver enzymes, urea, creatinine, total bilirubin, glucose level, TP, ALB were in referent range. Total globulins were 36, IgG2 and IgG3: in referent range but IgG4 was 10.2 g/l. ANA IFT was negative, ds DNA also negative. C1Q IgG: 4.75; IgG: 14.9 g/l. C3c, C4, IgE were in referent range.

T3, T4 were in referent range, TSH was slightly elevated 4.43 uIU/ml (0.27-4.20), AST: 14 U/L, (17-59), Urea 8.4 mmol/l (2.0-7.8)

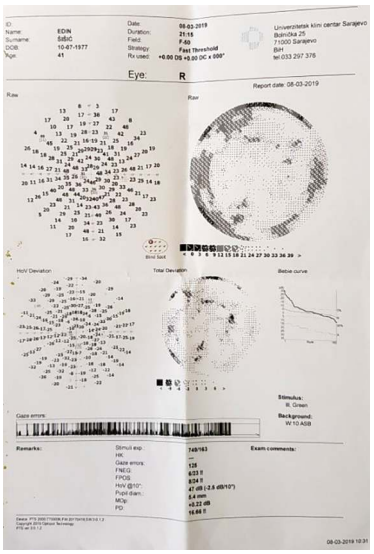
Results of flow citomery: in sample of peripheral blood there were found 1.4% plasma cells CD 38+CD20-CD19dimCD27.

He had hiatus hernia and few gastric mucosal erosion.

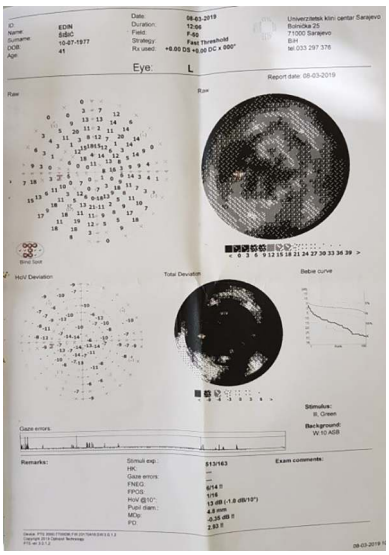
Neck ultrasound showed enlarged neck lymph nodes, submdibular lymph node was 11x2.5 mm with no palpable peripheral lymphadenopathy. Ultrasound of abdomen and thyroid gland were in physiological limits.

MR of orbits showed enlargement of extraocular muscles, probably idiopathic orbital inflammation, orbital pseudo tumor, Tolosa Hunt syndrome or lymphoma.

Biopsy of extraocular muscle was performed. It showed part of striated muscle tissue and loose connective tissue with small spindle cells and their hyperchromatic nuclei, ecstatic vascular spaces sporadically surrounded with lymphocytic infiltration. Tumorous cells hasn't been found.



Picture 4.
Neurologic visual field of right eye



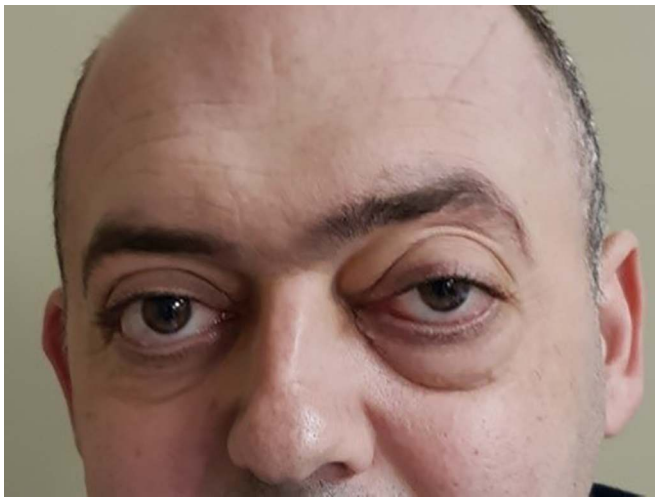
Picture 5.
Neurologic visual field of left eye

Treatment

Solumedrol was given by the scheme: 60 mg/day intravenous during the hospitalization; then 48 mg/day for a month. Afterwards, weekly decrease by 4 mg was done.

Rheumatologist gave azathioprin- immunosuppressive antimetabolite.

Patient underwent immunosuppressive antimetabolite therapy after being on corticosteroid therapy for few months with regular rheumatologist and ophthalmologist checkups.



Picture 6. Same patient, after diagnosing IgG4 related disease and starting adequate therapy

References

1. Uchida K, Masamune A, Shimosegawa T, Okazaki K. Prevalence of IgG4-related disease in Japan based on Nationwide Survey in 2009. Int J Rheumatol. 2012;2012:358371.
2. Abraham M, Khosroshahi A. Diagnostic and treatment workup for IgG4-related disease. Expert Rev Clin Immunol. 2017;13(9):867–875.
3. Sedhom R, Sedhom D, Strair R. IgG-4 related disease: A mini-review. J Rare Dis Res Treat. (2017) 2(2): 18-23
4. Yasufumi Masaki, Shoko Matsui, Takako Saeki et al. A multicenter phase II prospective clinical trial of glucocorticoid for patients with untreated IgG4-related disease, Modern Rheumatology, 27:5, 849-854.
5. Hart PA, Topazian MD, Witzig TE, et al Treatment of relapsing autoimmune pancreatitis with immunomodulators and rituximab: the Mayo Clinic experience. Gut 2013;62:1607-1615.
6. Carruthers MN, Topazian MD, Khosroshahi A, et al. Rituximab for IgG4-related disease: a prospective, open-label trial. Annals of the Rheumatic Diseases 2015;74:1171-1177.
7. Lang D, Zwerina J, Pieringer H. IgG4-related disease: current challenges and future prospects. Ther Clin Risk Manag. 2016;12:189–199.
8. Murakami J, Matsui S, Ishizawa S, et al. Recurrence of IgG4-related disease following treatment with rituximab. Modern rheumatology 2013 Nov;23(6):1226-30