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Eyelids oedema as a manifestation of IgG4-related disease: case report and literature review

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ABSTRACT

IgG4-related disease (IgG4-RD) is a condition of unknown etiology characterized by chronic inflammation leading to fibrosis of the affected organs and impairment of their functions. The variety of clinical manifestations makes its diagnosis a great challenge. This article presents a case study of a patient experiencing skin edema and subcutaneous tissue oedema of the eyelids as a manifestation of IgG4-RD. Treatment with glucocorticosteroids and immunosuppressive agents was administered, which led to a significant reduction in clinical manifestations and an improvement in the patient's quality of life.

Keywords: IgG4-related disease; IgG4-RD; autoimmune diseases; therapeutic approaches; rheumatology.

INTRODUCTION

IgG4-related disease (IgG4-RD) is a clinically diverse disorder characterized by several common features: tissue infiltration by IgG4-positive plasma cells, storiform fibrosis on histopathologic examination, and frequently, but not always, elevated serum concentrations of IgG4. The exact pathophysiology of this disease is still unknown. Genetic, environmental, and immunological factors, such as an abnormal immune response to an antigen or a deficit in the innate immune response, are taken into consideration [1]. Currently, it is proposed to distinguish 4 phenotypes of the disease: pancreato-hepatobiliary disease, retroperitoneal fibrosis with or without aortitis, head and neck-limited disease, and Mikulicz syndrome with systemic involvement. Here, we report a case of an IgG4-RD subtype limited to the head and neck in a 34-year-old woman, presenting as massive oedema of the subcutaneous tissue of the eyelids.

CASE REPORT

A 34-year-old patient was admitted to the Department of Internal Medicine, Rheumatology, Geriatrics, and Clinical Immunology due to recurrent sinusitis, cervical lymphadenopathy, and bilateral eyelid edema. Over the past 7 years, she had reported progressive swelling of the eyelids. She denied the presence of additional symptoms. Initially, the patient was treated at the Ophthalmology Clinic, where she received symptomatic treatment, including antihistamines and topical conjunctival glucocorticoids, which proved ineffective. Subsequently, surgical excision of the swollen eyelid tissue was performed. However, a rapid recurrence of eyelid edema was noted within a month postoperatively, coinciding with the onset of cervical lymphadenopathy.

Upon admission to the Rheumatology Clinic, physical examination revealed pronounced eyelid swelling (preventing full eye opening), subcutaneous swelling of the cheeks and forehead, as well as enlargement of the submandibular and anterior cervical lymph nodes. The patient was evaluated by an otolaryngologist and, based on a history of recurrent sinusitis, eyelid edema, subcutaneous tissue swelling of the forehead, and lymph node enlargement, was referred to our department with a suspicion of lymphoma.

Laboratory tests demonstrated an increased erythrocyte sedimentation rate (ESR) of 19 mm/h (0–12 mm/h) with a normal C-reactive protein (CRP) value and a significantly elevated serum IgG4 concentration of 4.41 g/dL (0.039–0.864 g/L) without an elevation in total IgG class. Other laboratory tests, including: matrix metalloproteinase 3 (MMP-3), antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), anti-endothelial cell antibodies (AECA), and C1q and C3d complement components, showed no abnormalities.

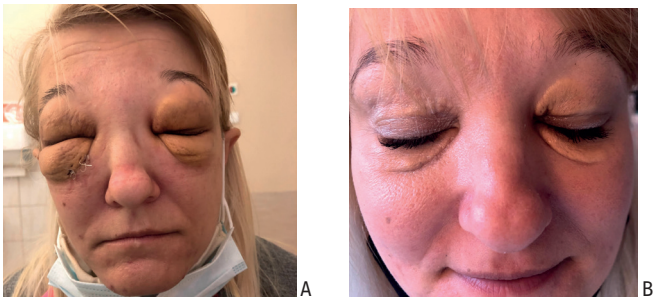
Magnetic resonance imaging (MRI) of the facial part of the cranium using fast spin echo (FSE), short tau inversion recovery (STIR), diffusion-weighted imaging (DWI), and liver acceleration volume acqusition (LAWA) sequences in T1- and T2-weighted scans revealed massive oedema of the subcutaneous tissue in the eyelids and forehead, as well as thickening of the mucosa in the maxillary, frontal, and nasal sinuses. Whole-body computed tomography (WBCT) showed numerous enlarged lymph nodes in the neck (submandibular, parotid, and cervical), up to 11 mm in diameter. Salivary gland ultrasonography revealed inhomogeneous submandibular salivary glands with hypoechoic areas. Scintigraphy of the salivary glands indicated poor tracer accumulation in the parotid and submandibular glands, suggesting impaired function. Other imaging tests, including gastroscopy, ultrasound of the heart

and abdominal cavity, and magnetic resonance cholangiopancreatography (MRCP) were normal.

Due to the presence of lymphadenopathy in the anterior cervical lymph nodes and suspicion of a hyperplastic condition, a lymph node biopsy was performed for histopathological evaluation, which excluded the diagnosis of lymphoma. Biopsy specimens from the swelling of the right eyelid were obtained. Histopathological analysis revealed a dense lymphoplasmacytic infiltrate and an increased density of IgG4-positive plasma cells within the tissue.

The entry criteria for IgG4-RD were met, as radiological findings revealed the involvement of characteristic organs, specifically both orbits. Following the completion of a comprehensive diagnostic evaluation, no criteria were identified that would exclude the diagnosis. The patient met the American College of Rheumatology (ACR) classification criteria for IgG4-RD, achieving a total score of 29 points (4 points for a dense lymphocytic infiltrate in the biopsy specimen, 11 points for a serum IgG4 concentration >5× the upper limit of normal, and 14 points for bilateral involvement of the periorbital tissues and lacrimal glands).

Treatment was initiated with intravenous methylprednisolone pulses at a dose of 500 mg daily for 3 days, followed by oral prednisone at a dose of 40 mg per day. Methylprednisolone pulses were continued for 6 months, with the dose of oral corticosteroids gradually tapered. Over a 6-month period, the patient received a cumulative corticosteroid dose equivalent to 14,000 mg of prednisone, resulting in disease remission, defined as the stabilization of eyelid and forehead subcutaneous tissue oedema and normalization of IgG4 serum concentration. At this stage of treatment, surgical intervention was performed on the right eyelid. To maintain remission, azathioprine was initiated at a dose of 50 mg twice daily (Fig. 1).



A B

FIGURE 1. Photographs: A – before treatment; B – after the full course of treatment and the surgical procedure

DISCUSSION

Diagnosis of IgG4-RD, due to its diverse clinical course, is a real challenge.

According to the latest epidemiological data from Japan, the prevalence of IgG4-RD is estimated to be 3 per 100,000 people. However, data from this study were mainly based on patients with type I autoimmune pancreatitis (AIP). Therefore, it should be assumed that the number of IgG4-RD cases is significantly underestimated [1]. The head and neck-limited subtype of the disease accounts for approx. 24% of diagnosed cases [2]. Unlike other known IgG4-RD phenotypes, which affect mainly middle-aged and elderly men (male-to-female ratio 4 : 1), the head and neck subtype may occur at a younger age with the same frequency in men and women [1].

Inflammatory infiltration of IgG4-RD cells in this phenotype may involve the eye socket, face and neck soft tissues, salivary glands, cervical lymph nodes, thyroid, nasopharyngeal cavity, cranial nerves, and meninges. Therefore, the clinical course may vary depending on organ involvement.

Given the severity of our patient's clinical presentation, characterized by significant eyelid oedema, a literature review of similar cases was conducted in PubMed using the following sets of keywords: "Eyelid oedema IgG4-RD", "Ophthalmic manifestation IgG4-RD", and "Orbital IgG4-RD". Only publications available in English were included in the analysis. Literature published up to September 2024 was selected. We applied 1 filter: "Case reports". A total of 127 works were identified. Forty-four studies described isolated involvement of the orbital region in the course of IgG4-RD. Six studies focused on the pediatric population under 18 years of age. The remaining 77 publications focused on patients with coexisting involvement of the orbit and other organs.

The most common ophthalmic manifestation of IgG4-RD is painless eyelid edema, which may present unilaterally or bilaterally and occurs in up to 77% of patients due to lacrimal gland and orbital fat involvement. Lacrimal gland involvement may also manifest as impaired tear secretion function. There have also been reports of oculomotor muscle infiltration, clinically manifested by ptosis, diplopia, and disturbed eye movements [3]. In the differential diagnosis of orbital pseudotumors and orbital inflammation, it is essential to consider conditions such as: orbital cellulitis, Tolosa–Hunt syndrome, lymphomas, sarcoidosis, granulomatosis with polyangiitis, intramuscular tumors, epithelial neoplasms, and metastatic lesions. Histopathological examination with IgG4 immunostaining is recommended in each case to ensure accurate diagnosis and minimize the risk of diagnostic errors [4].

A study conducted by Lai et al., involving 122 patients diagnosed with IgG4-RD with orbital involvement, revealed that up to 95% of these individuals demonstrated additional organ involvement, particularly within the head and neck regions, identified through comprehensive diagnostic imaging [5]. These findings underscore the importance of performing thorough imaging evaluations in patients presenting with clinically isolated forms of the disease to identify potential subclinical involvement of other organs.

Therefore, it is necessary to consider other clinical symptoms that may occur in this disease within the head and neck subtype. Neurological manifestations confined to this localization may include paralysis of cranial nerves, caused mainly by compression of the adjacent fibro-inflammatory infiltration. An example of central nervous system involvement is dura mater hypertrophy (pachymeningitis), manifested by recurrent headaches, visual disturbances in the form of reduced visual acuity or double vision, limb numbness, or convulsions [6, 7].

Upper respiratory symptoms, such as chronic sinusitis, blood-colored nasal discharge, and destruction of nasal cartilage – symptoms that rheumatologists associate mainly with granulomatosis with polyangiitis – may also be indicative of IgG4-RD [8]. In the described case, sinus involvement in the course of IgG4-RD cannot be ruled out, but material from the sinuses was not collected for histopathological examination.

Sialadenitis is the most common presentation of salivary gland involvement. Clinically, it presents as gland enlargement or localized pseudotumors. Submandibular glands are more frequently affected, but the parotid, sublingual, and labial salivary glands can also be involved. Currently, it is proposed that Kuttner's tumor, also known as chronic sclerosing sialadenitis, should be considered one of the manifestations of IgG4-RD [9]. In the described case, the atypical and abnormal appearance of the submandibular salivary glands on ultrasound examination may suggest changes in the course of IgG4-RD. Salivary gland involvement may be associated with enlargement of head and neck lymph nodes. In such cases, oncological vigilance should be maintained, and a malignant neoplasm should be included in the differential diagnosis.

The involvement of the skin and subcutaneous tissues of the face and neck accounts for less than 1% of diagnosed cases [9]. It most often manifests as a growing inflammatory tumor or swelling in different locations. The tumor size may gradually increase over months, potentially leading to the invasion of surrounding neuromuscular structures of the face. Unlike malignant neoplasms, patients present with fewer general symptoms, such as weakness, fever, or weight loss [10].

Regardless of the location of the affected organ within the head and neck region, maintaining a high level of diagnostic vigilance is essential, along with consideration of the exclusion criteria for IgG4-RD, as precisely defined in the 2019 ACR/European Alliance of Associations for Rheumatology (EULAR) classification criteria. These criteria encompass clinical, laboratory, and histopathological domains, as well as the exclusion of specific disease entities. Diagnostic efforts should prioritize the exclusion of malignant neoplasms that may exhibit clinical or radiological features resembling IgG4-RD or potentially coexist with this condition. The diagnosis poses significant challenges when exclusion criteria are identified in a patient. In cases where substantial clinical, radiological, or laboratory evidence supports the suspicion of IgG4-RD, histopathological evaluation of the affected organ should be considered to resolve diagnostic ambiguity, and the case should be reviewed by a multidisciplinary medical team to ensure a comprehensive diagnostic approach.

Increased concentrations of the IgG4 immunoglobulin subclass in blood serum are, so far, the most characteristic laboratory marker, occurring in 55–97% of patients with a diagnosed disease [11]. Its sensitivity in the diagnosis of IgG4-RD is estimated at 90% [12]. It shows a direct positive correlation with the number of involved organs. However, a normal IgG4 serum concentration does not exclude IgG4-RD. Patients with single-organ involvement may have normal serum IgG4 concentrations. In cases of clinical suspicion of IgG4-RD with normal serum IgG4 levels, it is advisable to determine the ratio of IgG4 to total IgG in serum. An increased IgG4/IgG ratio (>10%) improves diagnostic specificity [13]. According to conducted studies, elevation of IgG4 in serum has been observed in a broad spectrum of neoplastic, autoimmune, and infectious diseases. It should be remembered that immunosuppressive drugs such as corticosteroids, methotrexate, azathioprine, or anti-TNF agents can decrease IgG4 serum concentration [14].

The assessment and interpretation of widely available acute inflammation markers (CRP, ESR) remain controversial. In a study conducted by Yamada et al. in a group of 334 patients with IgG4-RD, only 27% had elevated CRP at the time of diagnosis. Most cases are associated with normal or slightly elevated CRP levels [13]. Our patient had a slightly elevated ESR and normal CRP, which confirmed this trend. The only subtype of IgG4-RD in which a significant increase in CRP and ESR was observed is retroperitoneal and aortic involvement. In this subtype of IgG4-RD, ESR and CRP concentrations significantly correlated with disease activity [14].

Peripheral blood eosinophilia and increased serum IgE levels occur in 30% of patients [15]. Antineutrophil cytoplasmic antibodies may be present in 40% of patients. In ELISA examinations, 20% of patients had antigen-specific antibodies, most often p-ANCA reacting mainly with myeloperoxidase (MPO). Their presence was most often found in patients with Mikulicz syndrome [16]. Antinuclear antibodies were positive in 15% of diagnosed cases in the absence of specific autoantibodies such as: dsDNA, SSA/Ro, and SSB/La [17].

Moreover, decreased serum C3 and C4 concentrations and polyclonal hypergammaglobulinemia were observed [18]. In our case, the patient did not have peripheral eosinophilia, reduced C3 and C4 levels, or hypergammaglobulinemia. Serological tests did not show the presence of ANCA or ANA.

The major histopathological features of IgG4-RD are a dense lymphoplasmacytic infiltrate rich in IgG4+ cells, fibrosis arranged in a storiform pattern, and obliterative phlebitis [18, 19]. In addition, phlebitis without obliteration of the lumen and eosinophil infiltration were described in specimens taken from patients with a confirmed diagnosis of IgG4-RD. It should be noted that the mentioned histopathological findings may be undetectable in cases of insufficient collection of biological material (e.g., fine-needle biopsy) [19].

Computed tomography and MRI supplement the diagnosis. They allow assessment of the location and extent of changes in the course of IgG4-RD, as well as monitoring of treatment effectiveness. However, in the head and neck-limited form of the disease, radiological features may not be characteristic and may resemble a proliferative process [20].

The management of the head and neck phenotype of IgG4-RD is consistent with the therapeutic approach employed for other phenotypes of the condition. The first-line drugs for inducing remission are glucocorticoids. In the described case, methylprednisolone infusions were administered due to significant deterioration in the patient's quality of life and the risk of local complications. In cases of a mild clinical course of the disease, oral corticosteroid treatment can be initiated.

Remission maintenance may consist of either a low dose of corticosteroids or disease-modifying anti-rheumatic drugs (DMARDs), such as azathioprine, methotrexate, or mycophenolate mofetil. It has not been specified which drug should be preferentially used. Rituximab is a promising strategy for patients who have not achieved remission with corticosteroids or who experience relapses after corticosteroid dose reduction [21, 22].

CONCLUSIONS

Due to the potential involvement of multiple organs in the course of the disease, including rare and atypical clinical presentations such as the case described, awareness of the symptoms, diagnosis, and treatment of IgG4-RD should be increased among physicians of all specialties. The number of newly diagnosed cases is expected to rise with effective interdisciplinary cooperation among physicians.

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