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IgG4-related inflammatory orbital pseudotumors – a retrospective case series

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Abstract

Orbital diseases may be divided into congenital defects of the orbit, infectious and inflammatory diseases, orbital tumors (including malignant and benign tumors) and injuries. Idiopathic inflammatory syndromes are often encountered within the orbit and are usually classified as orbital pseudotumors. The etiology of pseudotumors of the vision organ is unknown. Infectious agents, autoimmune disorders and improper healing are taken into consideration in the pathogenesis of this disorder. Thanks to detailed studies conducted in recent years, a new disease syndrome was identified in 2001. It is known as IgG4-related disease, and its differentiation is based on the analysis of IgG4 levels in the affected tissues. Orbital locations of the disease were first reported in Japan as late as at the end of 2009. This finding triggered the European studies on this subject. To date, no such studies have been conducted in Poland. The starting study population consisted of 167 patients with isolated infiltrative tumor diseases within the orbital region treated at the Department of Otolaryngology, Head and Neck Surgery of the Medical College Jagiellonian University in Krakow. Detailed analysis and diagnostic screening for IgG4-related disease was performed in a total of 17 patients diagnosed with orbital pseudotumor.

Key words: *orbital diseases, pseudotumors, IgG4-related disease, idiopathic inflammation of the orbit.*

Introduction

Orbital diseases may be divided into congenital defects of the orbit, infectious and inflammatory diseases, injuries and tumors, including malignant and benign tumors. The diseases may either originate at orbital structures, or be due to continuous spread of the pathological process from adjacent tissues, or constitute distant metastases as well as symptoms of a systemic disease. The variety of tumors observed within the orbit is due to its complex development and structure [21].

Idiopathic inflammatory syndromes are often encountered within the orbit and are usually classified as orbital pseudotumors. Usually, inflammatory orbital pseudotumors are represented as non-granulomatous inflammatory processes in the orbit or the eyeball, with unknown local or systemic etiology. In most cases, the diagnosis is made on the basis of

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the interview, clinical presentation, response to steroid treatment and the results of laboratory investigations and biopsies. The clinical presentation of pseudotumors is very diverse and may resemble numerous other diseases, such as lymphoma, sarcoidosis, fibromatosis, or systemic connective tissue disorders [22]. Pseudotumors should exclude inflammations due to Wegener's granulomatosis, persistent foreign bodies, sclerosing hemangiomas, complications of injuries and inflammation of paranasal sinuses. Pseudotumors are the most common orbital disorder in adults after Graves' orbitopathy; their incidence is estimated at 4.7-6.3% of all orbital diseases [27]. Bilateral location of pseudotumors in adult patients may suggest the presence of a generalized disease such as generalized vasculitis or generalized lymphoid hyperplasia. Patients suffering from pseudotumors often complain of acute pain located within the orbit, limited mobility of the eyeball, eyeball protrusion and impaired acuity of vision. Conjunctival hyperemia, eyelid swelling and redness and excessive lacrimation are also common. Pseudotumors may affect various orbital structures, such as muscles, adipose tissue or lacrimal glands. The etiology of pseudotumors of the vision organ is unknown. Infectious agents, autoimmune disorders and improper healing are taken into consideration in the pathogenesis of this disorder. Macroscopically, orbital pseudotumors are most commonly solid, well-differentiated masses of yellow/gray or pink/gray color. Inflammatory pseudotumors are commonly multifocal and may cause inflammation of extraorbital muscles, lacrimal tracts, Tenon's capsule and cerebral meninges surrounding the optic nerve and the adjacent tissues [35].

Thanks to detailed studies conducted in recent years, a new disease syndrome was identified in 2001. It is known as IgG4-related disease, and its differentiation is based on the analysis of IgG4 levels in the affected tissues [39]. Orbital locations of the disease were first reported in Japan as late as at the end of 2009. This finding triggered the European studies on this subject. To date, no such studies have been conducted in Poland. It has been established that IgG4-related orbital disease is a recently defined inflammatory process that is characterized by 1) inflammatory infiltration of IgG4-producing plasma cells; 2) tendency to form tumorous lesions at different sites; 3) increased serum IgG4 levels, although this is not a required condition [22]. IgG4-related disease is considered to be a generalized process involving a wide spectrum of various diseases that may affect distant organs. Particular progress was made recently due to in-depth clinical and pathological studies of diseases suspected of being dependent on increased levels of IgG4-positive plasma cells [27]. This type of lesion has been observed in a variety of organs, such as pancreas, hepatobiliary duct, salivary glands, orbits, lymph nodes, retroperitoneal space, kidneys, lungs, skin, and aorta. It is difficult to estimate the incidence rate of IgG4-related diseases due to the relatively low awareness of the possibility of this disease among physicians. The most reliable data originating from Japan estimate the incidence rate of IgG4-related disease to be 0.28-1.08 cases per 100 000 individuals [30].

Clinical experiments on primary, isolated orbital tumors show that they remain difficult to diagnose and treat for physicians of different specialties; we decided to address this issue in light of the recent establishment of IgG4-related disease as a new nosocomial entity. Orbital IgG4-related disease is a recently reported issue that may prove important for elucidation of the etiology of idiopathic, lymphoplasmacytic or fibrotic disorders of various organs, including the orbits. The goal of this study is to facilitate the diagnostic procedures in the treatment of patients with non-neoplastic, primary, isolated tumors, excluding eyeball tumors, metastatic tumors and tumors infiltrating from adjacent tissues, including from the nose and paranasal sinuses. Detailed assessments were performed in a group of patients diagnosed with orbital pseudotumors in the clinical material of the Otorhinolaryngological Clinic of the Jagiellonian University Medical College over the last 11 years. The usefulness of immunohistochemical diagnostics in correct diagnosis of IgG4-related orbital disease was studied.

Material and methods

The study was undertaken to facilitate the diagnostics and treatment of patients with non-neoplastic, primary, isolated tumors, excluding eyeball tumors, metastatic tumors and tumors infiltrating from adjacent tissues, including from the nose and paranasal sinuses. Detailed, retrospective assessments were performed in a group of patients with isolated orbital diseases in the clinical material of the Otorhinolaryngological Clinic of the Jagiellonian

University Medical College in the years 2002-2012. All the experiments reported in this manuscript were conducted in accordance with the local ethics committee of Medical College Jagiellonian University, Krakow, Poland. The usefulness of immunohistochemical diagnostics in correct diagnosis of IgG4-related orbital disease was studied. The study was conducted in a group of patients qualified for radical procedures or biopsies (often without initial histopathological diagnosis). Patients with a history of previous surgery, radiation therapy and corticosteroid treatment in relation to the vision organ were excluded from the study. All specimens archived at the Chair of Pathomorphology of the Jagiellonian University Medical College in Krakow were subjected to histopathological examination. At the first stage, 17 cases of orbital pseudotumors were selected from histological specimens subjected to routine HE stain.

Immunohistochemical assays were carried out in a standard manner [31,32]. The assessment of eosinophils and neutrophils was carried out by means of HE staining, while quantitation of plasma cells was achieved by using murine monoclonal anti-CD138 antibodies (DakoCytomation, Denmark, 1 : 100, 30 min, citrate buffer). IgG levels were determined using rabbit polyclonal antibodies (DakoCytomation, Denmark, 1 : 800, 30 min proteinase K unmasking), while IgG4 levels were determined using rabbit monoclonal antibodies (Aabcam, 1 : 300, 30 min, citrate buffer). Visualization of the antigen-antibody complex was achieved using the Ultra Vision LP Value Detection System (LabVision Corp.) with 3,3'-diaminobenzidine (DAB) tetrahydrochloride (DAKO Corp.) chromogen kit. Cell nuclei were contrasted using Mayer's hematoxylin for 1 minute and then covered by cover glasses in Cytoseal XYL (Thermo SCIENTIFIC). Microscopic specimens were assessed using Olympus CX41 and Nikon Eclipse 50i microscopes.

In each case, guidelines [32] were followed by searching for three sites with the highest number of $IgG4^+$ plasma cells and assessing the number of these cells at these sites at 40x magnification. Next, total plasma cell counts and IgG-producing plasma cell counts were assessed in identical areas in samples assayed for IgG and CD138. Routinely stained specimens were assessed for fibrosis, other infiltrations within the lesion (infiltrations of acidophils and neutrophils as well as lymphoplasmacytic infiltration with or without formation of follicles) and vascular lesions manifested as wall thickening and lumen narrowing. All these lesions were assessed by semiquantitative methods (1+: small lesions; 2+: medium lesions; 3+: advanced lesions). Immunohistochemical assays using anti-IgG, anti-IgG4 and anti-CD138 antibodies were used to estimate the $IgG4^+/CD138^+$ and $IgG4^+/IgG^+$ ratios.

Results

Of the group of isolated orbital tumors, consisting of 167 patients, patients diagnosed with malignant tumors on the basis of postoperational histopathological assessment were excluded. A total of 116 remaining patients were included in the selected study group on the basis of postoperational histopathological assessment. Histopathological diagnoses included pseudotumor, vascular malformations, cavernous angioma, arterial angioma, dermoid cyst with inflammatory infiltration, mixed tumor of the lacrimal gland, inverted papilloma, neurinoma, neurofibroma, meningioma, and adipoma. Detailed analysis and diagnostic screening for IgG4-related disease was performed in a total of 17 patients diagnosed with orbital pseudotumor. The mean age at diagnosis was 49.65 years. The analysis of tumor locations in patients diagnosed with orbital pseudotumor revealed anteroequatorial location in 7 cases and retroequatorial location in 10 patients. Pseudotumors were located within the right orbit in 7 patients and within the left orbit in 9 patient. In one patient, pseudotumors were located in both orbits. A similar incidence of the tumor was observed in both genders (Fig. 1A); no significant differences were observed in relation to the affected orbit side (Fig. 1B).

A detailed analysis of histopathological lesions (Table I) in patients diagnosed with orbital pseudotumors revealed changes in the $IgG4^+/CD138^+$ and $IgG4^+/IgG^+$ ratios in patients subjected to immunohistochemical diagnostic screening for IgG4-related disease. Extensive vascular lesions with wall thickening and lumen narrowing were observed in all patients; the $IgG4^+/CD138^+$ ratio was higher than 10% in all cases. The mean $IgG4^+/CD138^+$ ratio was 32.4% (Fig. 2A). The results were obtained by calculating the $IgG4^+/IgG^+$ ratio, usually exceeding 40%, and more than 80% in 3 patients. The mean $IgG4^+/IgG^+$ ratio was 53.5% (Fig. 2B). Most histopathological

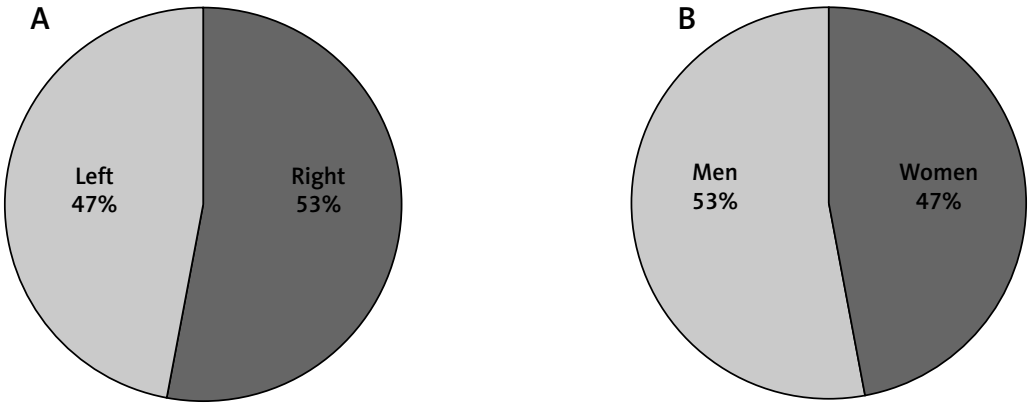

Fig. 1. A) Comparison of incidence of pseudotumors within the right or left orbit. **B)** Comparison of incidence of pseudotumors in females and males.

Table I. Detailed analysis of age, gender and tumor location in patients with histopathological diagnosis of orbital pseudotumor subjected to immunohistochemical screening for IgG4-related disease

Pseudotumor – IgG4⁺-related				
n	Sex	Age	IgG4⁺/CD138⁺	IgG4⁺/IgG⁺
1	F	41	> 20%	> 40%
2	F	44	> 40%	> 60%
3	F	67	> 20%	> 50%
4	M	52	> 30%	> 50%
5	M	17	> 20%	> 40%
6	M	18	> 20%	> 50%
7	M	54	> 40%	> 60%
8	F	75	> 10%	> 40%
9	M	41	> 80%	> 80%
10	F	40	> 50%	> 50%
11	M	62	> 10%	> 40%
12	F	32	> 20%	> 40%
13	F	79	> 10%	> 40%
14	F	50	> 40%	> 60%
15	M	55	> 80%	> 80%
16	M	66	> 20%	> 50%
17	M	51	> 40%	> 80%

F – female, M – male

specimens featured follicles and lacrimal gland tissue. Table I presents the lack of correlation between the IgG4⁺/CD138⁺ and IgG4⁺/IgG⁺ ratios depending on the age and gender of patients.

Table II presents a detailed analysis of histopathological lesions in patients with histopathological diagnosis of orbital pseudotumor subjected to immunohistochemical screening for IgG4-related disease. The following lesions were observed in histopathological examinations of operated patients: extensive fibrosis – mean grade of 2.67 (scale 0-3), numerous plasma cell infiltrations – 2.05 (scale 0-3), eosinophilic infiltrations of grade up to 1.5 (scale 0-3), i.e. as many as 20-25 cells in certain fields under large magnification (40x); in most cases only isolated neutrophils – 0.18 (scale 0-3), vascular lesions (wall thickening and stenosis of tiny vessels of different intensity) in all cases as well as inflammatory thrombotic lesions in 3 cases; the IgG4⁺/CD138⁺ ratio was always more than 10%, 32.3% on average, while the IgG4⁺/IgG⁺ was above 40% in all cases, and more than 80% in 3 patients (ca. 53.5% on average) (Table II). In all cases, fragments of lacrimal gland tissue and follicles were present in all histopathological specimens. Figure 3 presents a typical image of an inflammatory orbital pseudotumor. Profuse lymphoplasmacytic infiltration of fibrous tissue, and CD138⁺ plasma cells are visible. The IgG⁺ reaction seems to be present in a larger number of cells compared to the CD138⁺ reaction. However, it should be noted that IgG may also be produced by some of the B lymphocytes differentiating into plasma cells. What is interesting, nearly all immunohistochemistry-marked plasma cells (CD138⁺) are IgG4-positive.

Discussion

Reports of possible incidence of IgG4-related disease were published in late 2001. The first suspi-

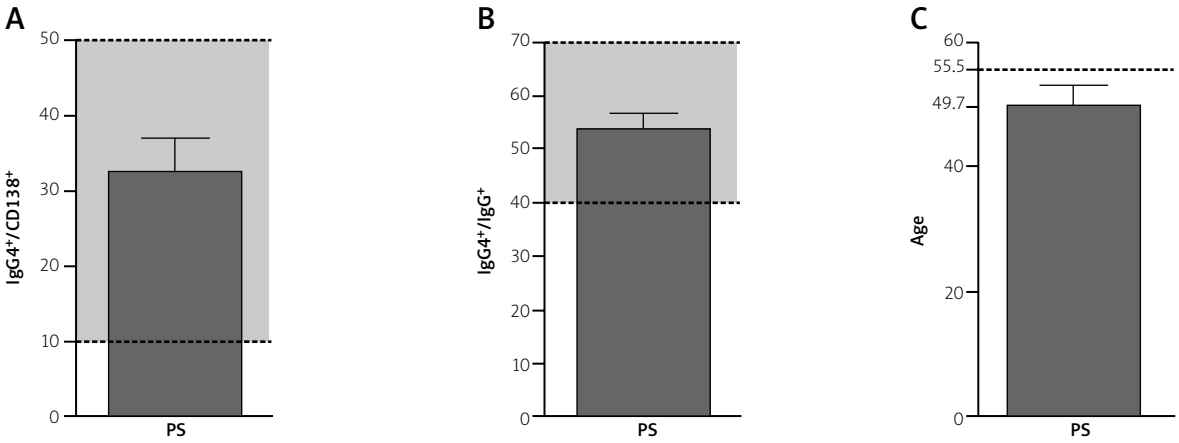

Fig. 2. Comparison of IgG4$^+$/CD138$^+$ ratio **(A)** and IgG4$^+$/IgG$^+$ ratio **(B)** in pseudotumors and average patient age **(C)**. In IgG4$^+$, the IgG4$^+$/CD138$^+$ ratio is 10-50 while the IgG4$^+$/IgG$^+$ ratio is 40-70.

Table II. Detailed analysis of histopathological lesions in patients with histopathological diagnosis of orbital pseudotumor subjected to immunohistochemical screening for IgG4-related disease

Pseudotumor – IGG4$^+$-related diseases						
n	FSS	Cell infiltration			Vascular changes	
		PLAS	NEUT	EOS	TVL	TBVW
1	+++	+++	–	++	++	+
2	+++	++	–	++	+++	++
3	+++	+++	–	+++	++	++
4	+++	+++	–	+++	++	+
5	++	+++	–	+	+	+
6	++	+++	–	+	+	+
7	+++	+++	+/–	++	+++	++
8	+++	+++	–	–	++	+
9	+++++	++	–	+	+++	+++
10	+++	+++/++	–	+++	++	++
11	+++	+++/++	–	+	++	+
12	++	+++/++	–	+	++	+/–
13	++	++	+/–	++	++	
14	+++	+/–	+/–	+/–	++	++
15	++	+++	+/–	+++	+	–
16	++	++	+/–	+	+	+
17	++	++	+/–	+	+	+

Scale: – none, +/– sparse, + low, ++ medium, +++ high, +++++ very high
FSS – fibrosis, PLAS – plasma cells, NEUT – neutrophils, EOS – eosinophils, TVL – thinning of the vascular lumen, TBVW – thickening of blood vessels walls

cions of orbital locations of the disease were reported in Japan as late as at the end of 2009. This finding triggered the European studies on this subject [4]. The basic consensus of the diagnostic criteria for IgG4-related diseases was established in 2010. IgG4-related orbital disease may also be diagnosed by the presence of criteria proposed by Umehara *et al.* [37]. Patients with suspected IgG4-related orbital disease may be assessed and diagnosed according to either of these two sets of diagnostic criteria [37]. In 2010, Zen and Nakanuma demonstrated that IgG4-related disease symptoms may have different anatomical locations despite the same levels of IgG4 in the studied tissues. This conclusion supports the

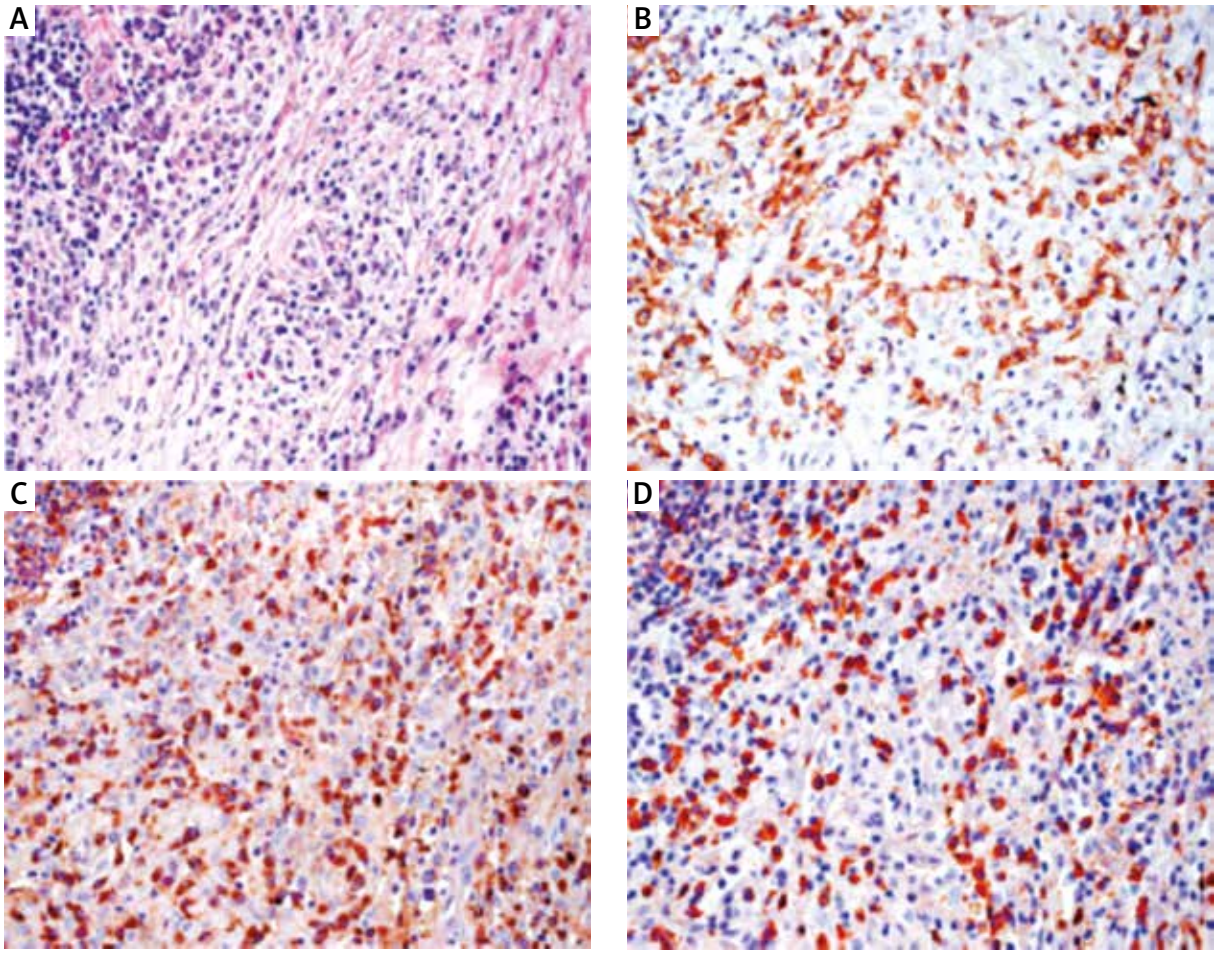

Fig. 3. Inflammatory orbital pseudotumor. **A)** Profuse lymphoplasmacytic infiltration of fibrous tissue. HE. 40x. **B)** Clear positive immunohistochemical reaction to CD138 marking the plasma cells. 40x. **C)** Clear positive immunohistochemical reaction to IgG-positive cells – the reaction appears to be present in a higher number of cells than the reaction to CD138. However, it should be noted that IgG may also be produced by some B lymphocytes differentiating into plasma cells. 40x. **D)** Nearly all immunohistochemistry-marked plasma cells (CD138+) are IgG4-positive. 40x.

IgG4 dependence of the disease [7,8]. IgG4-related orbital disease is a general term for the pathologies in the orbital region. Different orbital locations are possible. Most typically, the disease is diagnosed within the lacrimal gland (IgG4-related dacryoadenitis). This conclusion as drawn by other authors was also confirmed by the results of our study. The disease may also present as an IgG4-related orbital inflammatory pseudotumor or IgG4-related orbital myositis, which was also observed in the patients examined as part of this study.

To date, no such studies have been conducted in Poland. Examinations of such patients were analyzed both retrospectively and prospectively over the last 11 years to assess the possibility of IgG4-related orbital disease. The starting study population consisted of 167 patients with isolated infiltrative tumor diseases within the orbital region treated at the ORL Clinic of the Jagiellonian University Medical College in Krakow. Of all the studied and analyzed patients, a final group was selected to undergo diagnostic examinations for IgG4-related disease. The study group consisted of 17 patients with the diagnosis of pseudotumor lesions. According to the literature, the mean age for the established and probable cases of IgG4-related orbital disease is estimated at 55.5 years [2]. The value was similar in our study, being 49.6 years in the group of pseudotumor patients.

Orbital pseudotumors are idiopathic inflammatory processes occurring within the orbit and involving hypertrophy of fibrovascular tissue with low cellular polymorphism and lymphoplasmacytic infiltrations. Usually, orbital pseudotumors do not extend beyond the borders of the orbit, and their clinical course may be very diverse [21,22,25,40]. A total of 17 patients diagnosed with pseudotumors were selected from the population of non-malignant orbital lesion patients and subjected to diagnostic examinations for IgG4-related disease. The obtained results confirmed IgG4-related orbital disease. A high degree of fibrosis was observed in histopathological specimens, with numerous plasmacytic infiltrations containing numerous eosinophils, up to 25 cells per field. Only isolated neutrophils were observed in about 50% of cases. Vascular lesions (wall thickening and stenosis of tiny vessels of different intensity) were also observed in all cases; inflammatory thrombotic lesions were observed in three cases. Histopathological lesions observed in the study material were very similar to those described by other authors [2]. What is important, in all patients diagnosed with pseudotumors, the $IgG4^+/CD138^+$ ratio in orbital tissues was always more than 10%, and often as much as 40%. The $IgG4^+/IgG^+$ ratio was above 40% in all cases, and more than 80% in 3 patients. In all cases, fragments of lacrimal gland tissue and follicles were present in all histopathological specimens. As demonstrated by an increasing number of papers and confirmed by the results of this study, the tissue $IgG4^+/IgG^+$ ratio is the most important parameter for the diagnosed cases associated with $IgG4^+$ plasma cells, and its value should be higher than 40% [7,8,36,39]. Other criteria, such as obliterated venous pattern without the required inflammatory reaction or storiform fibrosis, are crucial for the diagnosis of IgG4-related disease [3,8,12,29,52,53]. In IgG4-related disease, the total number of IgG4-positive plasma cells must be elevated. It should be underlined that the study material was retrospective and has been analyzed several times.

Venous vessels are obliterated by profuse lymphoplasmacytic infiltration. Lymphocytes and plasma cells are present within both the vessel walls and the lumen. Partial obliteration of veins and inflammatory infiltration of the entire wall are also indicative of IgG4-related disease. Lacrimal gland tissue was predominant in specimens analyzed at the Krakow Clinic. Very high eosinophilic infiltration of up to 20 cells per field of view was a characteristic feature of the specimens. According to worldwide literature, IgG4-related orbital disease is rarely associated with lymphoplasmacytic infiltration and eosinophilic material-containing macrophages [9]. In this aspect of IgG4-related disease, our results are in contrast to these findings. On the other hand, we confirmed the presence of microvascular lesions, reported to occur rarely for IgG4-related disease by other authors [9,26]. The clinical presentation usually excludes definite diagnosis. Most commonly, patients present at the laryngologist's office with increasing orbital pain, impaired mobility of the eyeball and eyeball protrusion. In many cases, conjunctival edema and hyperemia, eyelid plethora and soft tissue edema were observed. Pain of the extraorbital muscle wall suggested a high likelihood of an orbital inflammatory syndrome, particularly myositis. Visual acuity was impaired in cases of optic nerve or posterior sclera involvement. Sometimes, systemic symptoms, such as leukocytosis and fever, might indicate inflammation, which was consistent with observations made by other authors [3,21,22,25,27,40].

Biopsy is not required in all cases, as the clinical and radiological presentation (including CT and MRI scans) may be sufficient to establish the diagnosis and start treatment. Other systemic disorders that accompany IgG4-related disease include autoimmune pancreatitis, retroperitoneal fibrosis, mediastinal fibrosis, sclerosing cholangitis, Sjögren's syndrome, xanthogranuloma, or inflammatory myofibroblastic tumor [4]. The diagnostics of IgG4-related disease involves the use of intravenous gallium-67, which is accumulated at inflammation sites and, as evidenced by numerous studies of IgG4-related diseases, is most commonly gathered within the lung tissue (hila) (77%) and the pancreas (76%). Gallium accumulation is also relatively common in salivary glands (54%), lacrimal glands (54%) and periaortal tissues (23%). Chronic inflammatory conditions that might obscure IgG4-related disease include: salivary tract inflammation, non-malignant oral lesions (e.g. cysts), gastrointestinal diseases (including Crohn's disease and intestinal diverticulitis), synovitis, some malignant tumors (squamous cell carcinoma, adenoid cystic carcinoma), and numerous inflammatory skin diseases.

Each of the examined patients was subjected to CT and/or MRI scans before the scheduled surgery. On this basis, the appropriate treatment method and

surgical approach were determined. Detailed radiological consultation was obtained, providing data to adopt a suitable treatment strategy. The entire management conducted at the Krakow Clinic of Otorhinolaryngology suggests that the group of pseudotumors is of a very diverse character. Pseudotumors may resemble numerous other diseases, such as lymphoma, sarcoidosis, fibromatosis, and systemic connective tissue disorders (e.g. lupus erythematosus and other granulomatous disorders), as was also reported in other studies [18,27,38].

The treatment and the outcomes in patients diagnosed with IgG4-related disease after one or more cycles of corticosteroids were different in female and male patients. IgG4-related orbital disease with the involvement of other organs may be considered a generalized disorder. The orbital location may coexist with an extraorbital location [24]. Most commonly, extraorbital location is associated with the involvement of parotid glands and lymph nodes [5,11,14,15,29,30].

Positron emission tomography is an imaging examination that markedly facilitates the diagnosis of a systemic IgG4-related disease, both in cases distant from the orbit and in clinically silent IgG4-related diseases [19]. Two such patients were identified in the study material, with generalized IgG4-related disease being confirmed by PET scans [9,24,35].

The consensus guidelines for histopathological diagnostics of IgG4-related orbital disease were published at an international symposium in 2011 [7,8]. It was determined that IgG4-related disease is characterized by different degrees of fibrosis and extensive lymphoplasmacytic infiltration of $IgG4^+$ cells [7,8,33]. Lymphoplasmacytic infiltrations are more extensive at early stages of the disease and consist of polyclonal T cells, $IgG4^+$ plasma cells and scattered eosinophils. Subsequent biopsies conducted in a case of IgG4-related inflammation of lacrimal ducts revealed increased fibrosis. The process has been proposed as the natural history of the disease which, when accumulated, in the fibrosis stage [5,10]. However, some diseases may originate from a primary sclerotic process. The histopathological image of IgG4-related orbital disease includes lymphoplasmacytic infiltration of various degree with predominant fibrosis or reactive lymphoid hyperplasia [14,15,26,29,36]. IgG4-related orbital disease may involve infiltrations of lymphoplasma cells, macrophages, as well as eosinophils [14,15]. The clinical material in this study was characterized by significant differences in the histopathological image compared to that presented by other authors. A characteristic trait in the histological presentation of IgG4-related disease is the presence of thromboangiitis obliterans, very rare in orbital IgG4-related disease [16,17,26]. The pathogenesis of the disease may include the immune response to an antigen within the upper segment of the respiratory/alimentary tract. Nosocomial entities currently identified as IgG4-related diseases include numerous disorders of heterogeneous clinical presentations, previously listed as separate and unrelated entities [13]. IgG4-related disease should be suspected on the basis of the presence of one of the accompanying symptoms, such as symmetrical swelling of lacrimal or salivary glands, autoimmune pancreatitis, inflammatory orbital pseudotumor, retroperitoneal fibrosis, lymphadenopathies, or Castleman's disease. The results presented in this study are in agreement with the conclusions of the panel of experts gathered in Boston in 2011 to present the "Consensus statement on the pathology of IgG4-related disease" [7,8]. The comprehensive diagnostic criteria proposed by Umehara *et al*. in 2012 provided a breakthrough in the establishment of IgG4-related orbital disease as a unique nosocomial entity; however, some details require further elucidation. The authors did not report on the size of the large magnification field to be used when counting IgG4-positive cells. IgG4-related orbital disease is a general term for pathologies in the orbital region. Different orbital locations are possible. Most typically, the disease is diagnosed within the lacrimal gland (IgG4-related dacryoadenitis); it may also present as an IgG4-related orbital inflammatory pseudotumor or IgG4-related orbital myositis. Serum IgG4 level is considered to be a less valuable diagnostic marker compared to the tissue IgG4 content and is usually elevated by 40% with biopsy-confirmed IgG4-related disease [28]. Recent results suggest that it is the ratio between serum IgG4 and IgG, rather than the levels themselves, that is important, as the serum levels themselves may be within the normal range. According to recent international studies [19,20] the serum $IgG4^+/IgG^+$ ratio of 5-10% may be a sensitive and specific marker indicative of early and single organ-limited development of an IgG4-related disease. Having analyzed the results of histopathological assays and serum IgG and IgG4 level tests, the researchers observed significantly elevated

serum IgG4 levels in only one case of bilateral orbital pseudotumor. The remaining results were within the normal laboratory range for IgG4 levels while being at the limit of the range in only 2 cases of orbital pseudotumors (single-sided). Despite the fact that the blood levels of IgG and IgG4 were normal, the analysis of the $IgG4^+/IgG^+$ ratio revealed a value of above 8%, indicative of possible development of an IgG4-related disease limited to a single organ, as suggested by Masaki et al. in their article published in 2012. Such results were observed in 3 of the diagnosed patients in whom pseudotumors were shown to be associated with elevated IgG4 levels in orbital tissues.

Idiopathic orbital inflammation poses a significant challenge to therapists and is characterized by a tendency to recur in more than 50% of cases [16,17]. The treatment is empirical in nature, as the pathophysiology of the disease has not been fully explained. Clinical treatment involves administration of corticosteroids. Physicians are often left with symptomatic treatment as the only option, including suppression of inflammation with corticosteroids. Identification of IgG4-related orbital diseases is important as lesions may be very sensitive to targeted biological treatment [13]. Unfortunately, no prospective clinical studies are available with regard to IgG4-related disease, with treatment methods being based on retrospective observations in relatively small patient groups. Before initiating treatment, it is important to establish the histopathological diagnosis and exclude possible malignancy [10]. Rituximab, a monoclonal anti-CD20 antibody, was used against B cells. Rapid reduction in blood IgG4 levels was observed in patients who received the drug [6]. Thus, modulation of B cell function led to a change in interactions between B cells and plasma cells, affording good therapeutic effects. Currently, a chemotherapeutic agent, bortezomib, is also in use.

To sum up, IgG4-related disease is most commonly manifested by a tumorous mass in the affected organ. Correct presurgical screening for IgG4-related disease may allow major orbital procedures to be avoided in some patients. Identification of typical histopathological lesions, particularly infiltrations of IgG4-positive plasma cells, remains the gold standard for establishing a correct diagnosis. Although an increased serum IgG level is neither sufficient nor necessary to diagnose IgG4-related disease, it may be helpful in the diagnostic process.

Disclosure

The authors report no conflict of interest.

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