

Received: 2014.11.14

Accepted: 2014.12.23

Published: 2015.04.10

# Immunoglobulin G4-Related Disease (IgG4-RD) in the Orbit: Mucosa-Associated Lymphoid Tissue (MALT)-Type Lymphomas

Authors' Contribution:  
Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
Funds Collection G

ABCDEF G 1 **Krzysztof Oleś**  
ADEG 1 **Jacek Składzień**  
BC 2 **Wojciech Szczepański**  
BC 2 **Krzysztof Okoń**  
BCEF 1 **Joanna Leszczyńska**  
BCEF 1 **Emilia Bojanowska**  
BCE 3 **Krzysztof Bartuś**  
ABCDEF 4 **Joanna Mika**

1 Department of Otolaryngology, Medical College Jagiellonian University, Cracow, Poland  
2 Department of Pathomorphology, Medical College Jagiellonian University, Cracow, Poland  
3 Department of Cardiac and Vascular Surgery and Transplantology, Institute of Cardiology, Jagiellonian University Medical College, John Paul II Hospital, Cracow, Poland  
4 Department of Pain Pharmacology, Institute of Pharmacology, Cracow, Poland

**Corresponding Author:** Krzysztof Oleś, e-mail: olokrista@op.pl

**Source of support:** This research was supported by statutory funds of the Department of Otolaryngology of the Jagiellonian University, Cracow, Poland

**Background:** MALT lymphomas were classified for differential diagnostics of IgG4-dependent disease due to their exceptional predilection to intraorbital localization. Therefore, the goal of our studies was large retrospective analysis of patients diagnosed with MALT lymphomas within the orbital tissues, since no such studies have been conducted in Poland.


**Material/Methods:** 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 Cracow. The immunohistochemical assays using anti-IgG, anti-IgG4 and anti-CD138 antibodies were used to estimate the IgG4<sup>+</sup>/CD138<sup>+</sup> and IgG4<sup>+</sup>/IgG<sup>+</sup> ratios.

**Results:** Of all the studied and analyzed patients, a final group of 19 patients with orbital MALT lymphomas was selected to undergo diagnostic examinations for IgG4-related disease. Detailed analysis and diagnostic screening for IgG4-related disease was performed and results meeting the criteria of IgG4-dependent disease were obtained in 10 out of 19 patients with the diagnosis of MALT tumor established on the basis of immunohistochemical assays.

**Conclusions:** MALT lymphomas are the most common of all lymphomas occurring within orbital tissues. In this study, results consistent with the criteria of IgG4-related disease were obtained in approximately 50% patients with immunohistochemical diagnosis of orbital MALT lymphoma.

**MeSH Keywords:** **Immunoglobulin G • Lymphoma, B-Cell, Marginal Zone • Orbital Diseases • Orbital Neoplasms**

**Full-text PDF:** <http://www.medscimonit.com/abstract/index/idArt/893043>

 2905

 1

 6

 32



## Background

Orbital tissues are the most common locations of both malignant lymphomas and inflammatory diseases. Lymphomas often bilaterally involve lacrimal glands and conjunctiva, either simultaneously or after a time interval [1,2]. Extranodal marginal B-cell lymphoma involving the mucosa-associated lymphoid tissue (MALT) is the main pathological variant of malignant lymphoma formed within orbital tissues [1,2]. Prognoses are believed to be favorable if the tumor remains in the same location for a longer time [3]. MALT lymphoma is a separate clinical nosocomial entity of characteristic histopathological features. Tumors develop as a result of prolonged antigen stimulation that might be either of autoimmune nature or due to infection, e.g. with *Chlamydia psittaci*; it may also be accompanied by concomitant *Helicobacter pylori* infection in ca. 8% of cases [4]. MALT lymphomas are diagnosed worldwide in ca 7–8% of all non-Hodgkin's lymphoma patients worldwide. Several hypotheses have been proposed with regard to the etiology of MALT lymphomas. It is believed that there is a relationship between the tumor and the inflammation [5] because an IgG4-related disease may be a background for the development of lymphoma, particularly of MALT lymphoma within the orbital tissues [6–8]. In their recent study, Sato et al. [9] demonstrated the development of MALT lymphoma in orbital tissues on the background of chronic IgG4-dependent inflammation. Similarly, Yamamoto et al. [10] demonstrated the presence of tumors in 10.4% of patients with IgG4-related disease, i.e. ca. 3.5 times more frequently than in the overall population [10]. Marginal B-cell lymphomas producing IgG4 were described earlier [8]. This report suggests that not only the malignant tumor may occur in relation to an IgG4-related disease, but also IgG4 may be produced by cancer cells. Cheuk et al. [6] also described an IgG4-related ocular disease as a background for the development of a MALT lymphoma. The authors concluded that it was unclear whether the IgG4-related development of MALT lymphomas within the orbital tissues was due to the pre-existent IgG4-related disease or whether the observed pathology was a *de novo*-formed IgG4-positive MALT lymphoma. Also, other authors highlighted the difficulties in differential diagnostics between IgG4-related diseases with MALT lymphomas or other chronic inflammations. In addition, the relationship between secondary lymphomas and IgG4-related orbital diseases should be explained [11]. In the study by Go et al. [11], 14 cases of IgG4-related disease were studied, 9 of them being the MALT lymphomas, and 12 other cases consisting of other chronic inflammations of lacrimal glands and orbits. IgG4-related disease is very often associated with bilateral pathological lesions. There are no specific guidelines regarding the treatment of MALT lymphomas. The current international consensus diagnostic criteria for IgG4-related disease are as presented in Figure 1. Therapeutic options differ depending on tumor location. Therefore, diverse

<b>Consensus diagnostic criteria for IgG4-related disease</b>
Tumor or multiple tumors in different organs
In immunohistochemistry assays tissue IgG4 <sup>+</sup> /IgG <sup>+</sup> ratio > 40% total IgG4-positive plasma cells >10/fov
Histological presentation: Lymphoplasmacytic Infiltrations Fibrosis Vascular lesions
Elevated serum IgG4 levels ≥135 Mg/dl (+/-)

**Figure 1.** Current international consensus diagnostic criteria for IgG4-related disease.

treatment methods are being used. Orbital IgG4-related disease is a recently reported issue that may prove important for the elucidation of the etiology of idiopathic, lymphoplasmacytic or fibrotic disorders of the orbits. Within the head, neck, and brain, the symptoms of IgG4-related orbital disease include enlargement of salivary and lacrimal glands, inflammatory orbital and salivary gland pseudotumors, pituitary changes, dura mater thickening and Riedel's thyroiditis [12–15].

The objective of our study was to carry out a retrospective analysis of 167 patients diagnosed with MALT lymphomas in years 2002–2012, including histological and immunohistochemical differentiation of cases depending on the status of IgG4<sup>+</sup> plasma cells. In this study, MALT lymphomas were chosen for differential diagnostics of IgG4-related disease due to their exceptional predilection to orbital locations.

## Material and Methods

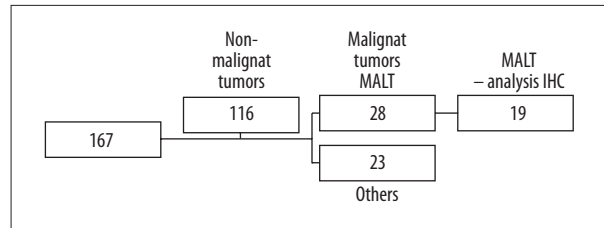
The study was taken up to facilitate the diagnostics and treatment of patients with non-neoplastic, primary, isolated tumors, excluding eyeball tumors, metastatic tumors and tumors infiltrating from the adjacent tissues, including from the nose and paranasal sinuses. Detailed, retrospective assessments 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 years 2002–2012.

All the experiments reported in this manuscript were conducted in accordance with the local ethics committee of Medical College Jagiellonian University, Cracow, 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 history of previous surgeries, radiation therapy

**Table 1.** Isolated orbital tumors within the orbital region treated at the Department Of Otolaryngology, Head and Neck Surgery of the Medical College Jagiellonian University in Cracow in years 2002–2012.

Isolated orbital tumors In years 2002–2012 – 167 patients	Women	Men
<b>Malignant tumors</b>		
Lymphoma malignum – MALT	15	13
Rhabdomyosarcoma embrionale	1	0
Neoplasma probabiliter epithelioma	1	1
Myeloid sarcoma	0	1
Carcinoma mucoepidermale	0	5
Carcinoma male differentiatum	3	1
Carcinoma glandulae lacrimalis	2	0
Carcinoma adenoides cysticum	0	3
Astrocytoma pilocytum	0	1
Adenocarcinoma	1	1
Solitary fibrous tumor	0	2
<b>Total</b>	<b>23</b>	<b>28</b>
<b>Non-malignant tumor</b>		
Pseudotumor	13	7
Malformtion vascular	6	2
Hemangioma cavernosum	19	7
Hemangioma capillare	1	1
Cyst dermoid	4	4
Tumor mixtus	6	8
Papilloma inversum	0	1
Schwannoma	4	2
Osteoma	1	1
Neurofibromatosis	2	2
Meningeoma	9	2
Lipoma	1	2
Lymphocyte/plasmacytoid infiltrations	11	0
<b>Total</b>	<b>77</b>	<b>39</b>

and corticosteroid treatment in relation to the vision organ were excluded from the study. A total of specimens archived at the Chair of Pathomorphology of the Jagiellonian University Medical College in Cracow were subjected to histopathological examination.

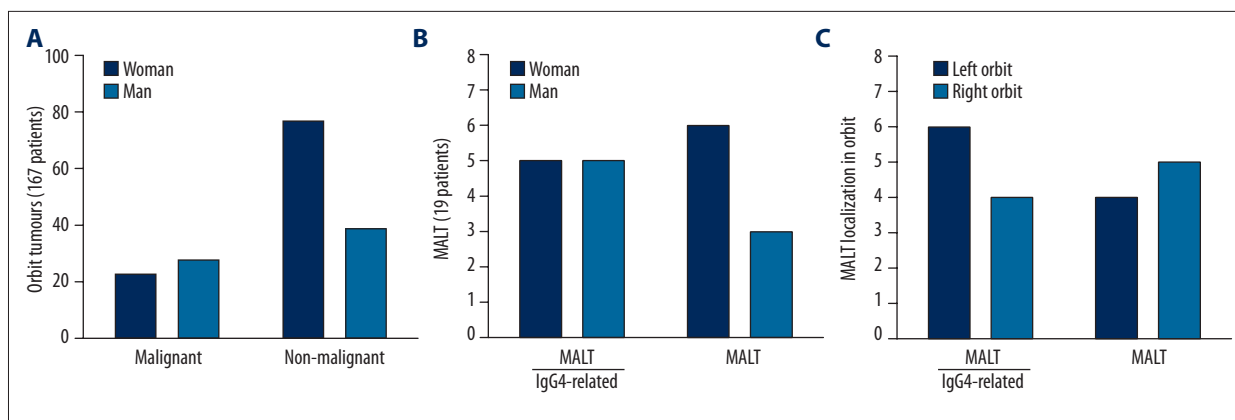


**Figure 2.** The group of isolated orbital tumors, consisting of 167 patients, patients with postoperational histopathological diagnoses of non- and malignant tumors. Out of the total of 19 MALT lymphomas were qualified for the immunohistochemical IgG4+ assay.

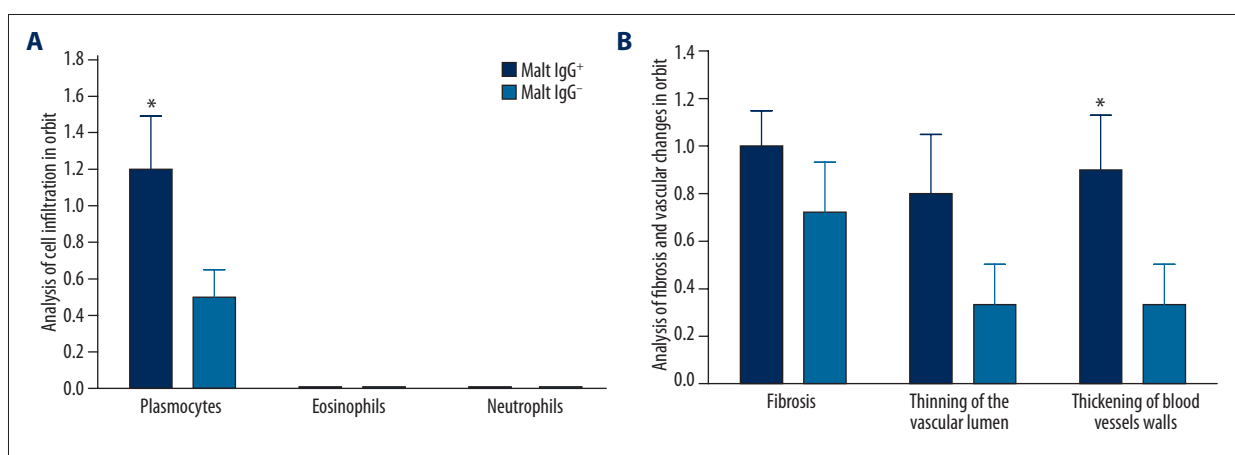
Of the group of isolated orbital tumors, consisting of 167 patients, patients with postoperational *histopathological diagnoses of malignant tumors, excluding non-Hodgkin's lymphoma, were excluded*. Histopathological analysis revealed 51 patients with malignant tumor of the orbit, and 116 patients with benign nodular and infiltrative tumor of the orbit (Table 1). Selected for further study a group of patients diagnosed with MALT lymphoma. Retrospective immunohistochemical studies to estimate the IgG4<sup>+</sup>/CD138<sup>+</sup> and IgG4<sup>+</sup>/IgG<sup>+</sup> ratios were feasible in 19 of 28 patients diagnosed with MALT lymphoma (Figure 2).

Immunohistochemical assays were carried out in a standard manner [16,17]. 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 (Dako Cytomation, Denmark, 1:100, 30 min., citrate buffer). IgG levels were determined using rabbit polyclonal antibodies (Dako Cytomation, 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 [16] were followed by searching for three sites with the highest number of IgG4<sup>+</sup> plasma cells and assessing the number of these cells at these sites at 40× 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 eosinophils 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.



**Figure 3.** An in-detail analysis of gender of all 167 patients undergoing surgeries for orbital tumors in years 2002–2012 (A) and of the 19 patients diagnosed with orbital MALT lymphoma subjected to immunohistochemical diagnostics for IgG4-related disease – analysis of gender (B) and tumor location (C).



**Figure 4.** An in-detail analysis of inflammatory infiltrations (A: plasma cells, neutrophils, eosinophils) and histopathology of tumors (B) diagnosed as IgG4<sup>+</sup> or IgG4<sup>-</sup> MALT lymphoma in patients subjected to immunohistochemical diagnostic examinations for IgG4-related disease (lesion scale: 0 – none, 0.5 – scarce, 1 – few; 2 – moderate number, 3 – abundant).

Immunohistochemical assays using anti-IgG, anti-IgG4 and anti-CD138 antibodies were used to estimate the IgG4<sup>+</sup>/CD138<sup>+</sup> and IgG4<sup>+</sup>/IgG<sup>+</sup> ratios. The criteria to qualify for IgG4 disease was based on consensus statement on the pathology of IgG4-related disease during the International Symposium on IgG4-related disease in Boston on 4–7 October 2011.

## Results

### Analysis of 167 patients undergoing surgery for orbital tumors in years 2002–2012

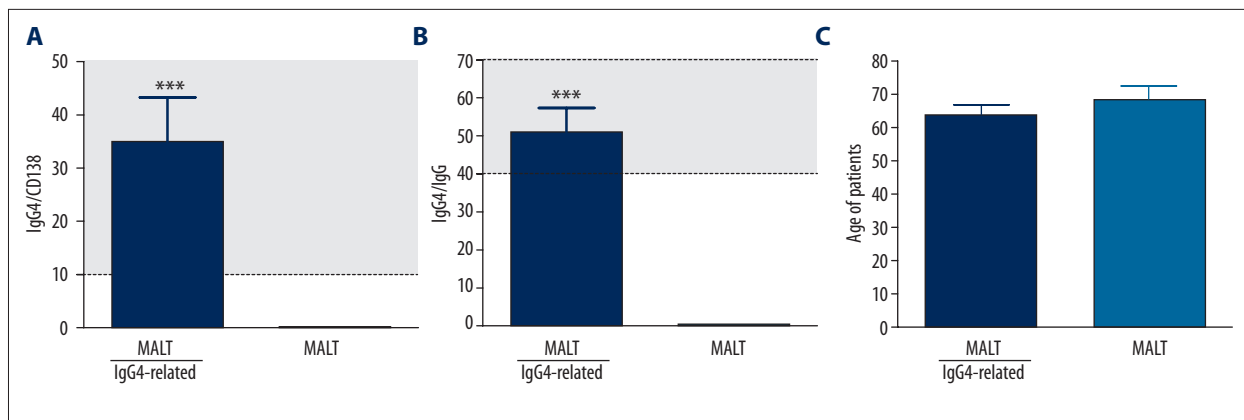
We have analyses of patients diagnosed with MALT lymphomas, performed with histological and immunohistochemical differentiation of cases depending on the assessed status of IgG4-positive plasma cells. A detailed analysis of the gender of all 167 patients undergoing surgery for orbital tumors in years

2002–2012 revealed that non-malignant lesions were predominant in women (66%) compared to men (34%) (Figure 3A). Of all the studied and analyzed patients, a final group of 19 patients with orbital MALT lymphomas was selected to undergo diagnostic examinations for IgG4-related disease. A similar incidence was observed in patients of both genders diagnosed with MALT IgG4<sup>+</sup> lymphomas, while a predominance of women was observed in the IgG4<sup>-</sup> group (Figure 3B). No significant differences were observed in relation to the affected orbit side (Figure 3C).

### In detail analysis of histopathological results obtained in patients diagnosed with malt lymphomas

#### A – Cellular infiltrations

Sparse plasma cell infiltrations (average of 1.2±0.29 in a 0-3 scale) and no neutrophil or eosinophil infiltrations were



**Figure 5.** In-detail analysis of the IgG4<sup>+</sup>/CD138<sup>+</sup> ratio (A); IgG4<sup>+</sup>/IgG<sup>+</sup> ratio (B); and age (C) in patients diagnosed with orbital MALT lymphoma and subjected to immunohistochemical diagnostic examinations for IgG4-related disease.

observed in the histopathological assessment of IgG4<sup>+</sup> MALT patients (Figure 4A). In patients diagnosed with MALT IgG4<sup>-</sup> lymphoma, no plasma cell infiltrations were detected in histopathological assessments of 3 patients, with small amounts of plasma cells being observed in the remaining 6 patients. The mean plasma cell infiltrations grading score in this group was  $0.5 \pm 0.15$  (in a 0–3 scale). No neutrophil or eosinophil infiltrations were detected in either of the specimens in this group. The statistical analysis revealed larger plasma cell infiltrations in patients diagnosed with MALT IgG4<sup>+</sup> lymphomas compared to patients with IgG4<sup>-</sup> lymphomas.

### B – Fibrosis

No lacrimal gland tissue was usually detected in histopathology specimens. Moderate fibrosis was observed in histopathology specimens; interstitial more often than marginal, with sparse or moderate plasma cell infiltrations and no eosinophil or neutrophil infiltrations. A low-degree fibrosis – mean grade of  $1.0 \pm 0.15$  (in a 0–3 scale) was observed in the histopathological assessments of specimens collected from IgG4<sup>+</sup> MALT lymphoma patients undergoing the surgery (Figure 4B); the change was not statistically significant compared to operated MALT IgG4<sup>-</sup> patients and amounted to  $0.72 \pm 0.21$ .

### C – Vascular lesions

Slight thickening of tiny blood vessels, as well as lumen stenosis, were observed in 11 out of 19 patients (Figure 4B). Mild to moderate vascular lesions were observed in histopathological examinations of 7 out of 10 IgG4<sup>+</sup> MALT lymphoma patients. Statistical analysis revealed the grade of tiny vessel wall thickening to be  $0.8 \pm 0.25$  and the grade of lumen stenosis to be  $0.90 \pm 0.23$  (in a 0–3 scale). In the operated IgG4<sup>-</sup> patients, slight tiny vessel wall thickening was found ( $0.33 \pm 0.17$ ) and lumen stenosis ( $0.33 \pm 0.17$ ) was observed in 3 out of 9 patients. The statistical analysis revealed larger vascular lesions

in patients diagnosed with MALT IgG4<sup>+</sup> lymphomas compared to patients with IgG4<sup>-</sup> lymphomas.

### The analysis of IgG4<sup>+</sup>/CD138<sup>+</sup> ratio, IgG4<sup>+</sup>/IgG<sup>+</sup> ratio and the age of patients with IgG4<sup>+</sup> and IgG4<sup>-</sup> MALT lymphomas

A significant increase in the ratio of IgG4-positive plasma cells to all CD138-positive plasma cells was observed (Figure 5A) in the histopathological assessments of 10 of the IgG4<sup>+</sup> MALT lymphoma patients (>10% in 3 patients, >20% in 1 patient, >30% in 2 patients, >40% in 2 patients, >60% in 1 patient and >95% in 1 patient); the mean value was  $35 \pm 8.3$ ; in two MALT IgG4<sup>-</sup> lymphoma patients, the value was  $0 \pm 0$ .

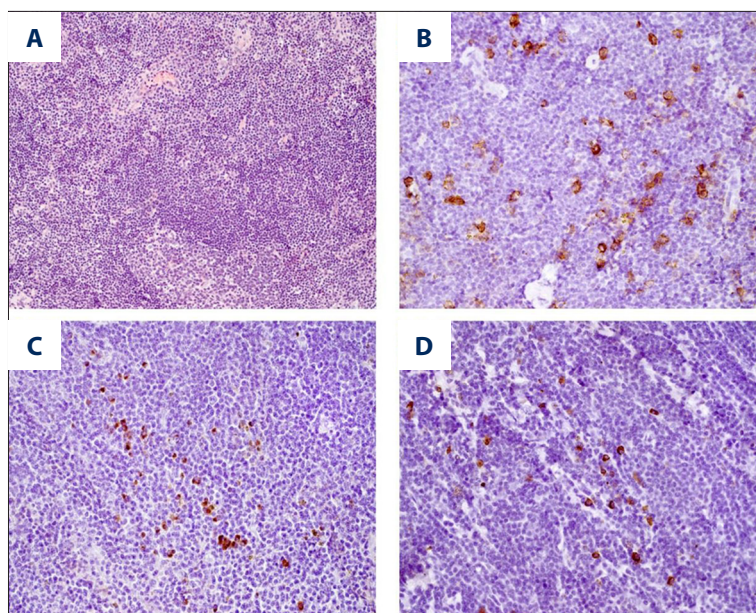
IgG4<sup>+</sup>/IgG<sup>+</sup> ratio of above 40% was observed in 10 MALT IgG4<sup>+</sup> patients undergoing surgery (>40% in 7 patients >50% in 1 patient, >80% in 1 patient, >95% in 1 patient) (Figure 5B). Value in this group of patients was  $51 \pm 6.3$ %. A lacrimal gland tissue fragment was detected in a single case; otherwise, no lacrimal gland tissue was identified in all histopathology specimens. The IgG4<sup>+</sup>/IgG<sup>+</sup> ratio in the histological assessment of MALT IgG4<sup>-</sup> patients undergoing surgery was  $0 \pm 0$ ; no lacrimal gland tissue was observed in histopathology specimens (Figure 5B). The example of immunohistochemical staining of MALT lymphoma is present on Figure 6.

A similar incidence of IgG4<sup>+</sup> and IgG4<sup>-</sup> MALT lymphomas was observed regardless of patients' age. The mean age in the MALT IgG4<sup>+</sup> group was  $64 \pm 2.8$ , while the mean age in the MALT IgG4<sup>-</sup> group was  $69 \pm 3.5$  (Figure 5C).

## Discussion

Cases of MALT lymphomas were included in the study group on the basis of literature reports stating a significant percentage of IgG4<sup>+</sup> plasma cell infiltrations being detected in this





**Figure 6.** MALT lymphoma tissue visible in the specimen. Disintegrating follicle visible in the lower part of the picture. HE. 20× (A); Immunohistochemical reaction to CD138 (plasma cells) in the reported case. HE. 40× (B); Immunohistochemical reaction to IgG-producing lymphoplasmatic cells. 40× (C). Immunohistochemical reaction to IgG4-producing plasma cells. 40× (D).

disorder. None of the currently available reports in the worldwide literature presents any explicitly documented features of IgG4<sup>+</sup> plasma cell infiltrations that might be accepted as diagnostic criteria for malignancy [18]. The presence of these infiltrations is certain; however, it is currently believed that they may only mask the neoplastic process as some IgG4-producing cells were identified to be cancer cells [9]. In the study material, results consistent with the criteria of IgG4-related disease were obtained in 10 out of 19 patients with immunohistochemical diagnosis or orbital MALT lymphoma. To date, with the exception of two reported cases of MALT lymphomas due to IgG4-dependent pseudotumors and one persistent MALT lymphoma in one of the orbits following radiation lymphoma treatment, no cases of patients diagnosed with MALT lymphoma subjected to immunohistochemical diagnostic examinations for IgG4-related disease were identified in international literature.

Moderate fibrosis was observed in histopathology specimens; interstitial more often than marginal, with sparse or moderate plasma cell infiltrations and no eosinophil or neutrophil infiltrations. Vascular lesions (wall thickening and lumen stenosis) were observed in about 11 cases; however, these were of rather mild intensity. No IgG4<sup>+</sup> plasma cells were detected in 9 MALT lymphoma patients; however, the IgG4<sup>+</sup>/CD138<sup>+</sup> ratio in orbital tissues was higher than 35% in as many as 10 cases. In the group of IgG4<sup>+</sup> MALT lymphoma patients, the IgG4<sup>+</sup>/IgG<sup>+</sup> ratio in orbital tissues was above 40% in all cases, up to more than 80% in 2 patients. The tissue IgG4<sup>+</sup>/IgG<sup>+</sup> ratio is the most crucial parameter for the diagnosed cases; its value should not exceed 40% [18–21]. The total count of IgG4-positive plasma cells must be elevated for the disease to be IgG4-related. Venous blurring with no inflammatory reaction is not sufficient to confirm the diagnosis of an IgG4-related

disease [16–19,22–24]. The results of these studies appear to be particularly interesting as the literature reports contain only isolated cases of IgG4<sup>+</sup> plasma cells being present in MALT lymphomas [25]. Our results confirm the results of these two studies mentioned in the consensus statement [26], but our material is significantly larger and seems to be more reliable. To date, only 21 non-Hodgkin's lymphoma cases originating from orbital tissues and meeting current requirements and criteria of being associated with the IgG4-related disease were described in worldwide literature [6,9,27]. MALT lymphoma is the most common lymphoma originating from orbital tissues and accompanying the IgG4-related disease [28].

When assessing the obtained results, one may arrive at the conclusion that these important findings should convince other researchers to pursue detailed analysis of the morphology, phenotype and genetic profile of the lymphoma types in the context of data obtained from patients with IgG4-related orbital disease [9].

MALT lymphomas were chosen for differential diagnostics of IgG4-related disease due to their exceptional predilection to orbital locations. In 2008 Cheuk et al. [6] demonstrated that diseases associated with the presence of IgG4<sup>+</sup> plasma cells in orbital tissues increase the risk of future development of MALT lymphomas. In addition, the decision of selecting MALT lymphomas was influenced by two literature reports [9,25] stating a possibility of lymphomas developing from underlying IgG4-related orbital diseases. In 2012, a report was published by Takahira et al. [29], in which no evidence to the possible transformation of IgG4-dependent disease into a malignant lymphoma was found in either of 22 cases of MALT lymphomas and 16 cases of orbital IgG4-related disease.

The number of plasma cells in MALT lymphomas is quite sparse, yet a high percentage of IgG<sup>+</sup> lymphocytes are characteristically significant in many cases [11]. Moderate fibrosis with sparse plasma cell infiltrations was confirmed and a significant difference was demonstrated with regard to the very high relative presence of IgG4<sup>+</sup> cells as compared to other cells as described in international reports. The IgG4<sup>+</sup>/CD138<sup>+</sup> ratio was above 10%, in all cases, often exceeding 30% and up to more than 90% in one case 90%. The IgG4<sup>+</sup>/IgG<sup>+</sup> ratio was above 40% in all cases, up to more than 80% in 2 patients.

IgG4-related disease preceding the diagnosis of dura matter lymphoma was also reported [30,31]. In one patient, IgG4-related disease within the left orbit was preceded by an IgG4-expressing MALT lymphoma. In addition, IgG4-dependent disease was confirmed in both orbits following radiation therapy for MALT lymphoma. At the time, no expression of IgG4 was observed in the lymphoma cells within the right orbit while being detected in the left orbit. In other words, the lymphoma of the right orbit contained no IgG4-producing cells while the lymphoma of the left orbit contained plasma cells that produced IgG4. The IgG4-expressing plasma cells within the right orbit might have as well been cancer cells [8,25,29]. One possible explanation is that IgG4-producing plasma cells constituted basis for the development of MALT lymphoma and that these non-cancer plasma cells expressing IgG4 survived radiation therapy to contribute to the development of IgG4-related disease due to their subsequent growth [32].

Patients may suffer from subclinical (smoldering) IgG4-related disease for significant periods of many months, and even years. In relation to IgG4-related MALT lymphomas, if any, the IgG4-related disease may underlie the development of lymphoma.

## References:

1. Matsuo T, Ichimura K, Okada H et al: Clonal analysis of bilateral, recurrent, or systemically multifocal ocular adnexal lymphoma. *J Clin Exp Hematop*, 2010; 50: 27–38
2. Matsuo T, Ichimura K, Sato Y et al: Immunoglobulin G4 (IgG4)-positive or -negative ocular adnexal benign lymphoid lesions in relation to systemic involvement. *J Clin Exp Hematop*, 2010; 50: 129–42
3. Isaacson PG, Du MQ: MALT lymphoma: from morphology to molecules. *Nat Rev Cancer*, 2004; 4: 644–53
4. Zucca E, Conconi A, Pedrinis E et al: International Extranodal Lymphoma Study Group. Non-gastric marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. *International Extranodal Lymphoma Study Group. Blood*, 2003; 101(7): 2489–95
5. Sagaert X, Van Cutsem E, De Hertogh G et al: Gastric MALT lymphoma: a model of chronic inflammation-induced tumor development. *Nat Rev Gastroenterol Hepatol*, 2010; 7: 336–46
6. Cheuk W, Yuen HK, Chan AC et al: Ocular adnexal lymphoma associated with IgG4 chronic sclerosing dacryoadenitis: a previously undescribed complication of IgG4-related sclerosing disease. *Am J Surg Pathol*, 2008; 32(8): 1159–67
7. Kubota T, Moritani S, Katayama M, Terasaki H: Ocular adnexal IgG4-related lymphoplasmacytic infiltrative disorder. *Arch Ophthalmol*, 2010; 128: 577–84
8. Sato Y, Notohara K, Kojima M et al: IgG4-related disease: historical overview and pathology of hematological disorders. *Pathol Int*, 2010; 60: 247–58
9. Sato Y, Ohshima K, Takata K et al: Ocular adnexal IgG4-producing mucosa-associated lymphoid tissue lymphoma mimicking IgG4-related disease. *J Clin Exp Hematop*, 2012; 52(1): 51–55
10. Yamamoto M, Takahashi H, Tabeya T et al: Risk of malignancies in IgG4-related disease. *Mod Rheumatol*, 2012; 22(3): 414–18
11. Go H, Kim JE, Kim YA et al: Ocular adnexal IgG4-related disease: comparative analysis with mucosa-associated lymphoid tissue lymphoma and other chronic inflammatory conditions. *Histopathology*, 2012; 60(2): 296–312
12. Chan SK, Cheuk W, Chan KT, Chan JK: IgG4-related sclerosing pachymeningitis: a previously unrecognized form of central nervous system involvement in IgG4-related sclerosing disease. *Am J Surg Pathol*, 2009; 33: 1249–52
13. Kosakai A, Ito D, Yamada S et al: A case of definite IgG4-related pachymeningitis. *Neurology*, 2010; 75(15): 1390–92
14. Shimatsu A, Oki Y, Fujisawa I, Sano T: Pituitary and stalk lesions (infundibulohypophysitis) associated with immunoglobulin G4-related systemic disease: an emerging clinical entity. *Endocr J*, 2009; 56: 1033–41
15. Sogabe Y, Miyatani K, Goto R et al: Pathological findings of infraorbital nerve enlargement in IgG4-related ophthalmic disease. *Jpn J Ophthalmol*, 2012; 56(5): 511–14

PET/CT scans may help in detecting both lymphomas [1] and orbital IgG4-related diseases [2], while not allowing differentiation between the two. Clinical symptoms and imaging scan results suggesting recurrent MALT lymphoma may not always indicate the tumor recurrence. Therefore, proper treatment should always be preceded by histopathological assessment of biopsy specimens. Resection, radiation therapy, chemotherapy and immunotherapy proved efficient in the treatment of MALT lymphomas. Efficacy of mycophenolate mofetil in the treatment of refractory IgG4-dependent disease and MALT lymphoma was demonstrated. Combination treatment methods are often used.

## Conclusions

MALT lymphomas are the most common of all lymphomas occurring within orbital tissues. A relationship between chronic inflammation and neoplastic transformation has been established. Therefore, transformation of IgG4-related orbital disease into MALT lymphoma is highly probable. In this study, results consistent with the criteria of IgG4-related disease were obtained in 10 out of 19 patients with immunohistochemical diagnosis of orbital MALT lymphoma. When assessing the obtained results, one may arrive at the conclusion that these important findings should convince other researchers to pursue detailed analysis of the morphology, phenotype and genetic profile of the lymphoma types being discussed here, including the comparison of the incidence of common features with IgG4-related orbital disease.

## Statement

The authors have no financial interest.

16. Shrestha B, Sekiguchi H, Colby TV et al: Distinctive pulmonary histopathology with increased IgG4-positive plasma cells in patients with autoimmune pancreatitis: report of 6 and 12. cases with similar histopathology. *Am J Surg Pathol*, 2009; 33(10): 1450–62
17. Sato Y, Kojima M, Takata K et al: Systemic IgG4-related lymphadenopathy: a clinical and pathologic comparison to multicentric Castleman's disease. *Mod Pathol*, 2009; 22(4): 589–99
18. Deshpande V, Zen Y, Chan JK, Yi EE et al: Consensus statement on the pathology of IgG4-related disease. *Mod Pathol*, 2012; 25(9): 1181–92
19. Deshpande V: The pathology of IgG4-related disease: critical issues and challenges. *Semin Diagn Pathol*, 2012; 29(4): 191–96
20. Strehl JD, Hartmann A, Agaimy A: Numerous IgG4-positive plasma cells are ubiquitous in diverse localised non-specific chronic inflammatory conditions and need to be distinguished from IgG4-related systemic disorders. *J Clin Pathol*, 2011; 64: 237–43
21. Umehara H, Okazaki K, Masaki Y et al: Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD). *Mod Rheumatol*, 2012; 22(1): 21–30
22. Deshpande V, Sainani NI, Chung RT et al: IgG4-associated cholangitis: a comparative histological and immunophenotypic study with primary sclerosing cholangitis on liver biopsy material. *Mod Pathol*, 2009; 22(10): 1287–95
23. Zen Y, Nakanuma Y: IgG4-related disease: a cross-sectional study of 114 cases. *Am J Surg Pathol*, 2010; 34(12): 1812–19
24. Khosroshahi A, Stone JH: A clinical overview of IgG4-related systemic disease. *Curr Opin Rheumatol*, 2011; 23(1): 57–66
25. Matsuo T, Ichimura K, Yoshino T: Local recurrence as immunoglobulin G4 (IgG4)-related disease 10 years after radiotherapy to ocular adnexal extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. *J Clin Exp Hematop*, 2011; 51(2): 125–33
26. Andrew N, Kearney D, Selva D: IgG4-related orbital disease: a meta-analysis and review. *Acta Ophthalmol*, 2012; 11: 1–7
27. Karamchandani JR, Younes SF, Warnke RA, Natkunam Y: IgG4-related systemic sclerosing disease of the ocular adnexa: a potential mimic of ocular lymphoma. *Am J Clin Pathol*, 2012; 137(5): 699–711
28. McKelvie PA: Ocular adnexal lymphomas: a review. *Adv Anat Pathol*, 2010; 17(4): 251–61
29. Takahira M, Ozawa Y, Kawano M et al: Clinical Aspects of IgG4-Related Orbital Inflammation in a Case Series of Ocular Adnexal Lymphoproliferative Disorders. *Int J Rheumatol*, 2012; 2012: 635473
30. Hejazi N: Intraorbital lymphomas: neurosurgical experiences and management strategies. *Neurosurg Rev*, 2006; 29(2): 123–29
31. Venkataraman G, Rizzo KA, Chavez JJ et al: Marginal zone lymphomas involving meningeal dura: possible link to IgG4-related diseases. *Mod Pathol*, 2011; 24(3): 355–66
32. Masaki Y, Dong L, Kurose N et al: Proposal for a new clinical entity, IgG4-positive multiorgan lymphoproliferative syndrome: analysis of 64 cases of IgG4-related disorders. *Ann Rheum Dis*, 2009; 68(8): 1310–15