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ORIGINAL ARTICLE

Clinical manifestation of malignant lymphomas of the head and neck region

Katarzyna Bojanowska-Poźniak[1], Monika Nurkowska[1], Marian Danilewicz[2], Wioletta Pietruszewska[1]

[1]Otolaryngology and Oncolaryngology Clinic of the Medical University of Lodz, Head of the Clinic prof.Wioleta Pietruszewska Phd, MD
[2]Department of Pathomorphology, Medical University of Lodz; Head of the Clinic prof. Marian Danilewicz Phd, MD

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ABSTRACT:

Introduction: Malignant lymphoma (ML) is a neoplasm caused by clonal expansion of undifferentiated B, T and NK-lymphoid cells. WHO classification divides lymphomas into two main types, i.e. Hodgkin lymphoma (HL), and non-Hodgkin lymphoma (NHL), with numerous subtypes. The majority of MLs are localized in lymph nodes, but extranodal locations are also possible. MLs represent approximately 3-5% of all malignant neoplasms in Poland, but their incidence has been increasing in recent years, especially in young patients. The objective of the study was to evaluate clinical manifestations and diagnostic process in patients with malignant lymphomas of the head and neck region as diagnosed in the Department of Otorhinolaryngology of the Medical University of Lodz in years 2013-2017. Material and method: 30 patients diagnosed with malignant lymphomas of the head and neck region at the Department of Otorhinolaryngology of the Medical University of Lodz in 2013-2017. Results: The study group consisted of 8 cases of nodal lymphomas and 22 cases of extranodal lymphomas. In 29 cases B-cell lymphomas were diagnosed. The most common symptoms included lymphadenopathy or neck tumor. Other symptoms were associated with the location of tumors in particular body organs. The diagnosis was based on histopathological examination of biopsy (needle or surgical) samples. Conclusion: Malignant lymphomas should be taken into account during differential diagnosis of the tumor or lymphadenopathy of the neck. The diagnosis is difficult because of the nonspecificity of symptoms and the need for interdisciplinary cooperation of many specialists.

KEYWORDS: malignant lymphoma, head and neck neoplasm, extranodal lymphoma

INTRODUCTION

Malignant lymphoma (ML) is a neoplasm caused by clonal expansion of undifferentiated B, T and NK-lymphoid cells (Picard 2015, Cooper 2009, Hoffman 1998). In Poland, lymphomas are the sixth most common malignancy, and their incidence has recently been increasing by 3-4% each year. Lymphomas are slightly more prevalent in male patients, with two peaks of morbidity between 20 and 30, and between 60 and 70 years of age (www.onkologia.org.pl, www.cancerresearchuk.org, Walewski 2011, Warzocha 2011). The etiology of lymphomas has not been fully elucidated, and risk factors include immunodeficiency, autoimmune diseases, viral and bacterial infections (including HIV, HTLV-1, EBV, HCV, HBV, and others), and environmental factors (Niemczyk 2015, Szczeklik 2011).

Neoplasms of the hematopoietic and lymphatic system are classified according to a system published by WHO in 2008 and developed on the basis of the Revised European–American Classification of Lymphoid Neoplasms (REAL). Lymphomas are still classified into Hodgkin lymphomas (HL) and Non-Hodgkin lymphomas (NHL). The WHO classification identifies more than 30 types of lymphomas, with the main classification criterion consisting in the tumor originating from B cells (86%), T cells (12%), or natural killer (NK) cells (2%) (Walewski 2011, Swerdlow 2008, Niemczyk 2015) (Table 1). Lymphomas are staged according to the four-point Ann Arbor staging system (Walewski 2011).

Clinical symptoms are diverse and depend on location, histological type, and stage of the tumor (Picard 2015) . The first symptom usually consists in non-painful, slowly enlarging lymph nodes, often accumulating into clusters (Niemczyk 2015). Symptoms of extranodal lymphomas depend on the location of the tumor. Local symptoms may be accompanied by general complaints such as pyrexia, weight loss, night sweats. Patients with Hodgkin lymphomas may also experience fatigue, pruritus and pain of affected lymph nodes after alcohol consumption (Herd 2012).

Malignant lymphomas are the third most common type of head and neck cancers (Piccard 2015, Cooper 2009). About

2/3 of lymphomas in that region manifest as localized tumorous lesions or as part of generalized lymphadenopathy. The remaining cases are extranodal lymphomas, sometimes even originating from organs that do not house lymphoid tissue at all (Marszałek 2006, Zucca 2015).

The objective of the study was to evaluate clinical manifestations and diagnostic process in patients with malignant lymphomas of the head and neck region as diagnosed in the Department of Otorhinolaryngology of the Medical University of Lodz in years 2013-2015.

MATERIAL AND METHOD

Thirty patients (18 male and 12 female) with malignant lymphomas diagnosed at the Department of Otorhinolaryngology of the Medical University of Lodz in years 2013-2017

RESULTS

The study group comprised of a total of 30 patients consisted of 8 (27%) cases of nodal lymphomas and 22 (73%) cases of extranodal lymphomas (originating from nasopharynx, base of the tongue, palatine tonsil, nose and paranasal sinuses, submandibular salivary gland, middle ear, and larynx – Table 1). B-cell lymphomas were diagnosed most commonly in histopathological examination and immunohistochemical assays (29 cases, 97%). Only in 1 case (3%), histopathological examination led to the diagnosis of T-cell lymphoma (Fig. 1).

Patients reported to the Department for cervical lymphadenopathy or neck tumors – 14 patients (47%). In 8 patients with nodal lymphoma, that was the only significant deviation from normal presentation in laryngological examination. Lymph node enlargement or neck tumors were also encountered in 2 cases of lymphomas located within the palatine tonsil, 2 cases of lymphomas located within the lingual tonsil, 2 cases of lymphomas located within the nasopharynx, and 1 case of lymphoma located within the submandibular salivary gland. Other symptoms were associated with extranodal location of lymphomas. Impaired nasal patency, rhinorrhea, and disturbed sense were experienced by patients with lesions located within the nose, paranasal sinuses, or nasopharynx. In one of those patients, the symptoms were suggestive of exacerbation of chronic sinusitis with orbital complication and loss of vision within the right eye along with significant deterioration of vision within the left eye. The feeling of pharyngeal obstruction and asymmetry of palatine and lingual tonsils were reported by patients with lymphomas located within the base of the tongue, palatine tonsil, and larynx. Shortness of breath, worsening over several weeks, was the leading symptom in a patient with laryngeal lymphoma. The same patient was also the only patient reporting general symptoms such as body weight loss and night sweats. On the other hand, one patient was initially diagnosed with chronic otitis media complicated with facial nerve palsy; the problem was finally diagnosed as B-cell lymphoma located within the middle ear (Table 2).

The diagnoses of lymphoma were also made on the basis of histopathological examinations and immunohistochemical assays of biopsy specimens. In 3 patients with nodal lymphomas, unambiguous diagnosis was made following thin needle aspiration biopsy while 5 other patients were diagnosed following surgical biopsy of lymph nodes. Extracellular postoperative specimens were used as the basis for the diagnosis in 8 patients with lymphomas located within the palatine tonsils (5

Tab. I. Location of malignant lymphomas in patients diagnosed at the Department of Otorhinolaryngology of the Medical University of Lodz in years 2013-2017

LOCATION	NUMBER OF PATIENTS
neck	8
nasopharynx	7
palatine tonsil	5
base of the tongue	4
nose and paranasal sinuses	3
submandibular salivary gland	1
larynx	1
middle ear	1

Tab. II. Symptoms of malignant lymphomas in patients diagnosed at the Department of Otorhinolaryngology of the Medical University of Lodz in years 2013-2017

SYMPTOM	NUMBER OF PATIENTS
Cervical lymphadenopathy	14
Impaired nasal patency	8
Feeling of pharyngeal obstruction	8
Asymmetry of palatine and lingual tonsils	9
Discharge in nasal cavities	4
Orbital symptoms	1
Shortness of breath	1
Impaired sense of smell	1
Discharge from the ear, hearing loss accompanied by facial nerve palsy	1
General symptoms	1

patients – tonsillectomy), submandibular salivary gland (1 patient – radical resection of the salivary gland), and paranasal sinuses (2 patients – endoscopic surgery of nose and paranasal sinuses). Histopathological examination of specimens was used as the basis for the diagnosis in the remaining 14 patients with lymphomas localized within the base of the tongue, nasal cavity, nasopharynx, and larynx.

DISCUSSION

Due to the increase in their incidence in recent years, malignant lymphomas became one of the most common malignancies, particularly in young patients. Thus, they are an important area of interest for oncologists. Along with the increase in the overall incidence of lymphomas, they are more and more frequently identified within the head and neck region (www.onkologia.org.pl, Walewski 2011, Warzocha 2011, www.cancerresearchuk.org).

Similarly to ratios observed in other locations, nodal lymphomas of the head and neck region constitute about 2/3 of all cases while the remaining 1/3 of cases are extranodal lymphomas, sometimes even located within organs that house no lymphoid tissue at all (Marszałek 2006, Zucca 2015). In our study group, however, nodal lymphomas comprised as little as 22% of all cases. Most extranodal lymphomas were located in organs housing some lymphoid tissue. Location within organs that housed no lymphoid tissue at all (nose and paranasal sinuses, submandibular salivary gland, larynx) was observed in 5 patients. The most common extranodal location of non-Hodgkin lymphomas was the lymphoid tissue within the Waldeyer's ring. These tumors are characterized by particular preference for palatotonsillar and nasopharyngeal locations (Niemczyk 2015, Maeshima 2015). On the other hand, locations within nasal cavities and paranasal sinuses are rare and account for 5-8% of all extranodal lymphomas of the head and neck region (Shawabkeh 2016). In our study material, we observed similar incidence of lymphomas within the nasopharynx, palatine tonsils, and base of the tongue (5, 5, and 4 cases, respectively). Laryngeal lymphomas are very rare and account for less than 1% of all laryngeal malignancies (Zhu 2016, Zapparoli 2014). B-cell lymphomas constituted a vast majority of cases within our study group (96.3%), in line with other literature data (Niemczyk 2015). The authors suggest that non-Hodgkin lymphomas (NHL) constitute the majority of all tumors of this type. Notably, head and neck location is the second most common location of extranodal NHLs after the gastrointestinal tract (Vega 2005). Hodgkin lymphomas are less common than NHLs; however, it is one of the most common malignancies occurring in young adults (www.onkologia.org.pl, Marszałek

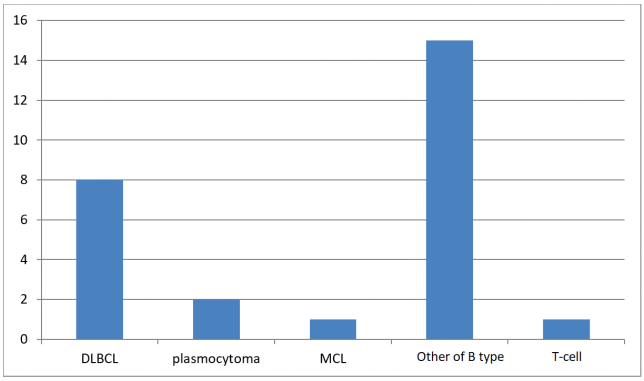

Fig. 1. Histopathological classification of lymphomas in patients diagnosed at the Department of Otorhinolaryngology of the Medical University of Lodz in years 2013-2017

2006). In the head and neck region, NHL usually manifests as non-painful cervical lymphadenopathy; extranodal locations are very rare (1-5%) (Zapater 2010, Herd 2012).

As mentioned before, the symptoms of malignant lymphomas depend on their type, stage, and location. In our study group, the most common symptom was cervical lymphadenopathy or neck tumor (52% of patients) which accompanied the nodal tumors as well as some extranodal tumors located within the palatine tonsil, lingual tonsil, nasopharynx, and submandibular salivary gland. Other symptoms were also associated with the involvement of a particular organ by the extranodal form of the neoplasm and suggestive of a tumor of that particular organ. Diagnosis of lymphoma was possible only after histopathological examination. Most common symptoms of lymphomas within the mouth and the oropharynx include asymmetry of palatine tonsils, submucosal mass within the base of the tongue or, less commonly, mucosal ulceration. Sometimes, the tumor growth may be asymptomatic over a long period (Niemczyk 2015). Symptoms of lymphoma located within the nasal cavities and paranasal sinuses, such as impaired nasal patency, are nonspecific and usually suggestive of chronic inflammation. An example may be provided by a patient previously treated for exacerbation of sinusitis with orbital complications and finally diagnosed with T-cell lymphoma (Fig. …). Symptoms of nasopharyngeal lymphomas include impaired patency of nasal cavities, nasal bleeding, and the feeling of "ear plugging" (Niemczyk 2015, Brnes 2005, Shawabkeh 2016, Vähämurto 2016). Regardless of their location, aggressive lymphomas such as DLBCL or Burkitt's lymphoma are characterized by extensive symptoms and rapid growth; therefore, the time between the onset of the process and diagnosis may often be short. On the other hand, indolent lymphomas such as plasmocytoma or MALT lymphoma, are characterized by latent onset, slow growth, chronic symptoms, and longer times until diagnosis

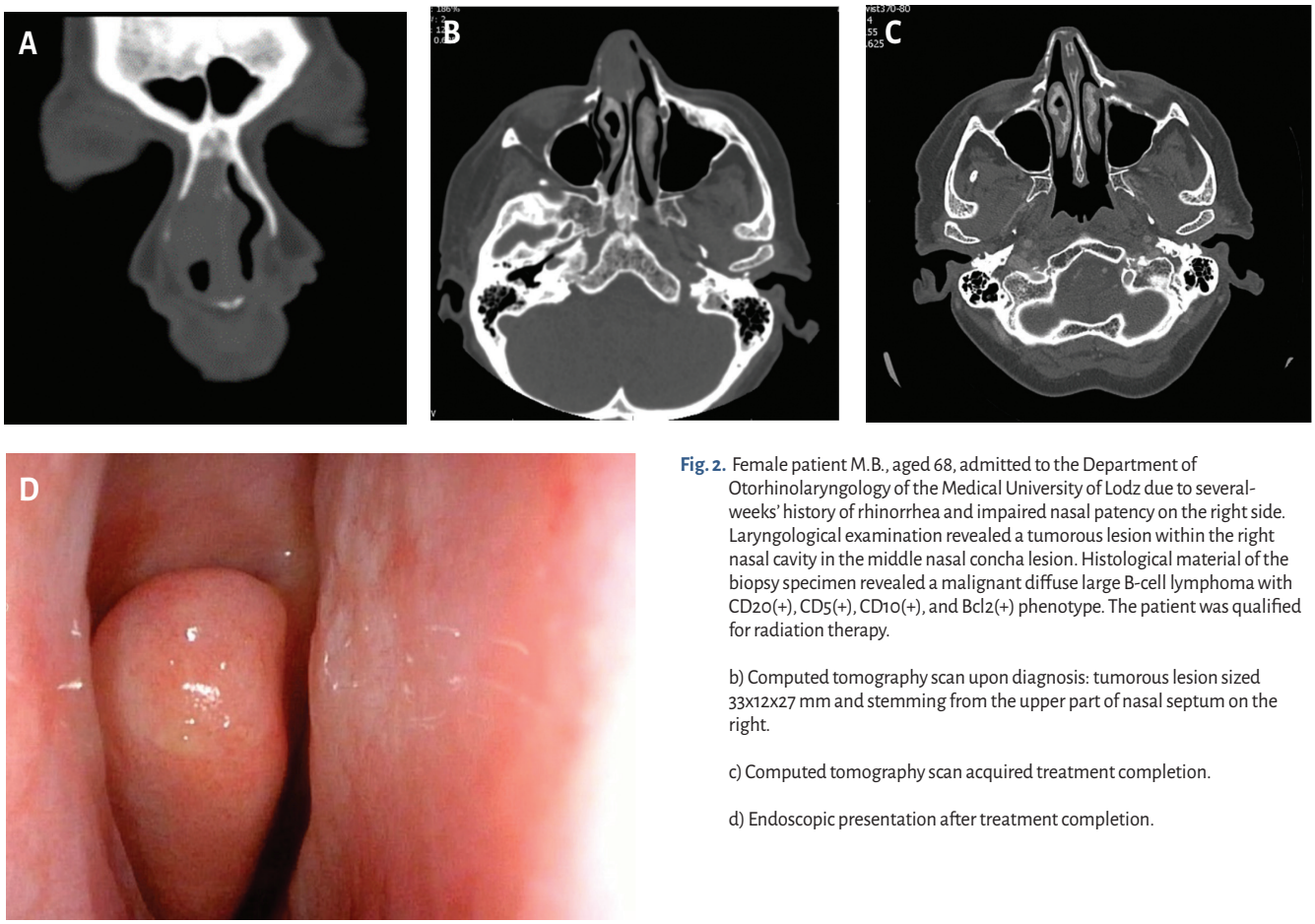

Fig. 2. Female patient M.B., aged 68, admitted to the Department of Otorhinolaryngology of the Medical University of Lodz due to several-weeks' history of rhinorrhea and impaired nasal patency on the right side. Laryngological examination revealed a tumorous lesion within the right nasal cavity in the middle nasal concha lesion. Histological material of the biopsy specimen revealed a malignant diffuse large B-cell lymphoma with CD20(+), CD5(+), CD10(+), and Bcl2(+) phenotype. The patient was qualified for radiation therapy.

b) Computed tomography scan upon diagnosis: tumorous lesion sized 33x12x27 mm and stemming from the upper part of nasal septum on the right.

c) Computed tomography scan acquired treatment completion.

d) Endoscopic presentation after treatment completion.

(Picard 2015). According to literature data, generalized symptoms occur in about 30% of patients and are usually associated with higher stage of the disease. In our study group, however, general symptoms including body weight loss and night sweats were reported by only one patient with laryngeal lymphoma.

The diagnostics of head and neck lymphomas is based on careful laryngological examination complete with endoscopic examination; the latter is particularly useful in the assessment of poorly accessible anatomical structures (Fig. 4). In cases of extranodal lymphomas, histopathological examination is performed on postoperative material or tumor specimens. Thin-needle aspiration biopsy (TNAB) is the first biopsy procedure performed in patients with cervical lymphadenopathy. However, TNAB is of limited value in the diagnostics of lymphomas as it is usually insufficient for determination of the type of the disorder (Mizera-Nyczak 2006). Therefore, it is recommended to collect the entire node and capsule and extend histopathological diagnostics so that it includes immunohistochemical assays. Firstly, screening for cytokeratins (CK), i.e. epithelial cell markers, and leukocyte common antigen (LCA) is performed so as to differentiate the origin of cancer cells. Subsequent immunohistochemical assays facilitate the assessment of expression of cellular antigens, particularly clusters of differentiation (CD). CDs correspond to individual subtypes of lymphocytes/leukocytes and their levels of functional maturity, thus facilitating determination whether the neoplasm originates from B, T, or NK cell lines. The diagnostic process is complete with the assessment of expression of antigen Ki-67 (mitotic index marker), and sometimes also of the expression of protein products of genes such as bcl-2, bcl-6, p53, or Rb, which act as markers of the activity of cellular cycle inhibitors (Marszałek 2006, Mizera-Nyczak 2006).

In the study, group, histopathological diagnosis of malignant lymphoma and basic determination of its type was achieved by using a panel of markers including CK, LCA, CD, and Ki67. Vast majority of the study group consisted of patients with type B lymphomas – 22 cases, 95.7%). According to literature data, type B lymphomas constitute a great majority (>60%) of

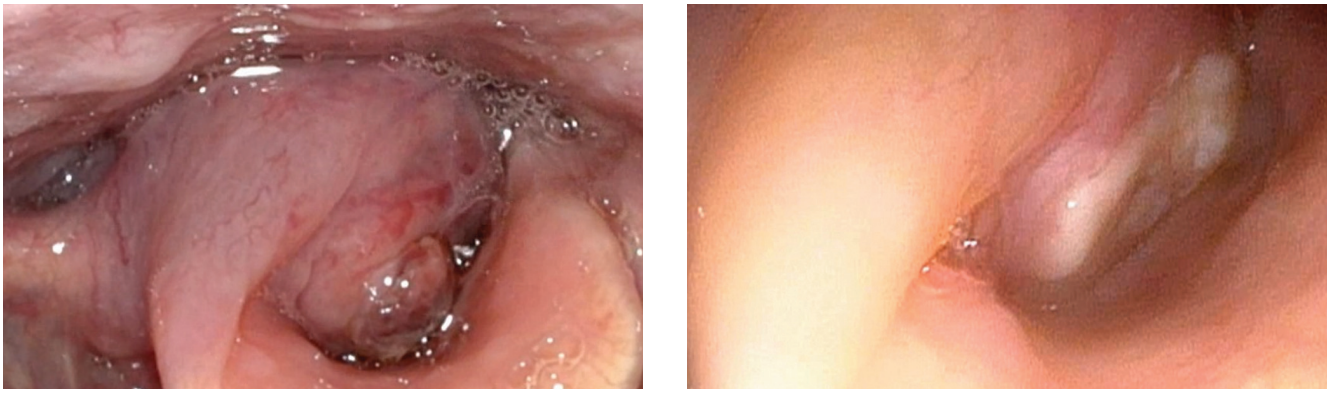

Fig. 3. Male patient R.B., aged 58, admitted in the emergency setting to the Department of Otorhinolaryngology of the Medical University of Lodz due to 3-weeks' history of hoarseness, shortness of breath and difficulty swallowing. The patient reported body weight loss as well as night sweats experienced for one month. Tracheostomy and direct laryngoscopy were performed in the emergency setting and included the collection of specimens of the laryngeal tumor. Histopathological examination revealed a malignant lymphoma of the following immunohistochemical profile: Ki67 80%, LCA (+), CK AE1/AE3 (–), TTF (–), CD56 (–). The patient was referred for further diagnostics and treatment to the Oncology Center in Łódź.

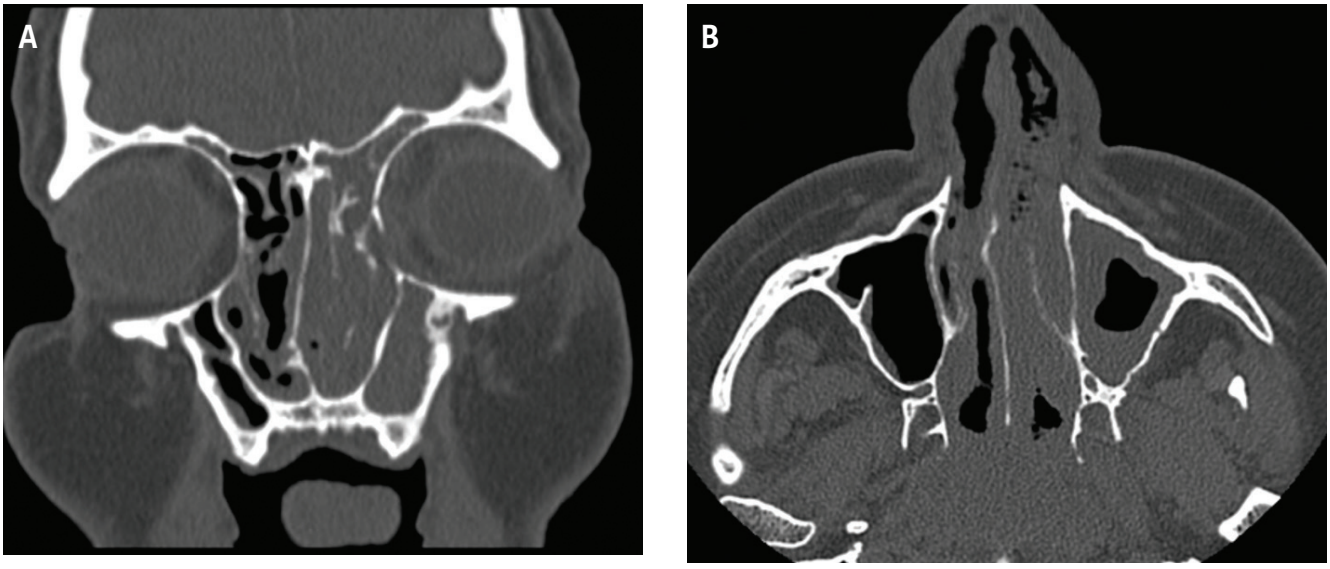

Fig. 4. Male patient M.W., aged 50, admitted to the Department of Otorhinolaryngology of the Medical University of Lodz after 3 weeks of conservative treatment of chronic sinusitis and left eye uveitis. Endoscopic surgery of the nose and paranasal sinuses was performed; chronic inflammatory lesions were confirmed in histopathological examination of postoperative specimens. One month later, the patient was readmitted due to left-sided cranial and facial pain, loss of vision in the right eye, and swelling of left eyelids, with drying mucopurulent discharge and necrotic tissue within the nose. Resurgery of paranasal sinuses was performed. Dye to the worsening disturbance of vision within the left eye, numerous consultations led to the suspicion of Wegener's granulomatosis. Solumedrol, prednisone, and cyclophosphamide were included to achieve slight improvement in local condition. Histopathological examination of the postoperative material revealed Ki67>50%, CD20 (+), CD3 (+), bcl2 (+), and abnormal T-to-B-cell ratio. The clinical presentation was indicative of T-cell lymphoma.
a) Computed tomography scan upon admission to the Department – shading of all paranasal sinuses on the left.
b) bo Computed tomography scan upon recurrence of complaints – shading of all paranasal sinuses on the left visible again.

oropharyngeal tumors (Brnes 2005). In cases of tumors located within the nose, paranasal sinuses, or nasopharynx, type B lymphomas are predominant in Caucasian population, while T/NK-cell based lymphomas are predominant in Asian and South American countries (60-80% of patients), occurring mainly within the nasal cavities (Brnes 2005, Lombard 2015). Despite the fact that the etiology of this cancer is unknown, its relationship with Epstein-Barr virus (EBV) infection has been raised, as the infection is confirmed in as many as 90-100% of T/NK-cell based lymphomas (Brnes 2005, Katsuyuki 2008). The only case of a T-cell based lymphoma in our study group was located within the patient's nose and paranasal sinuses.

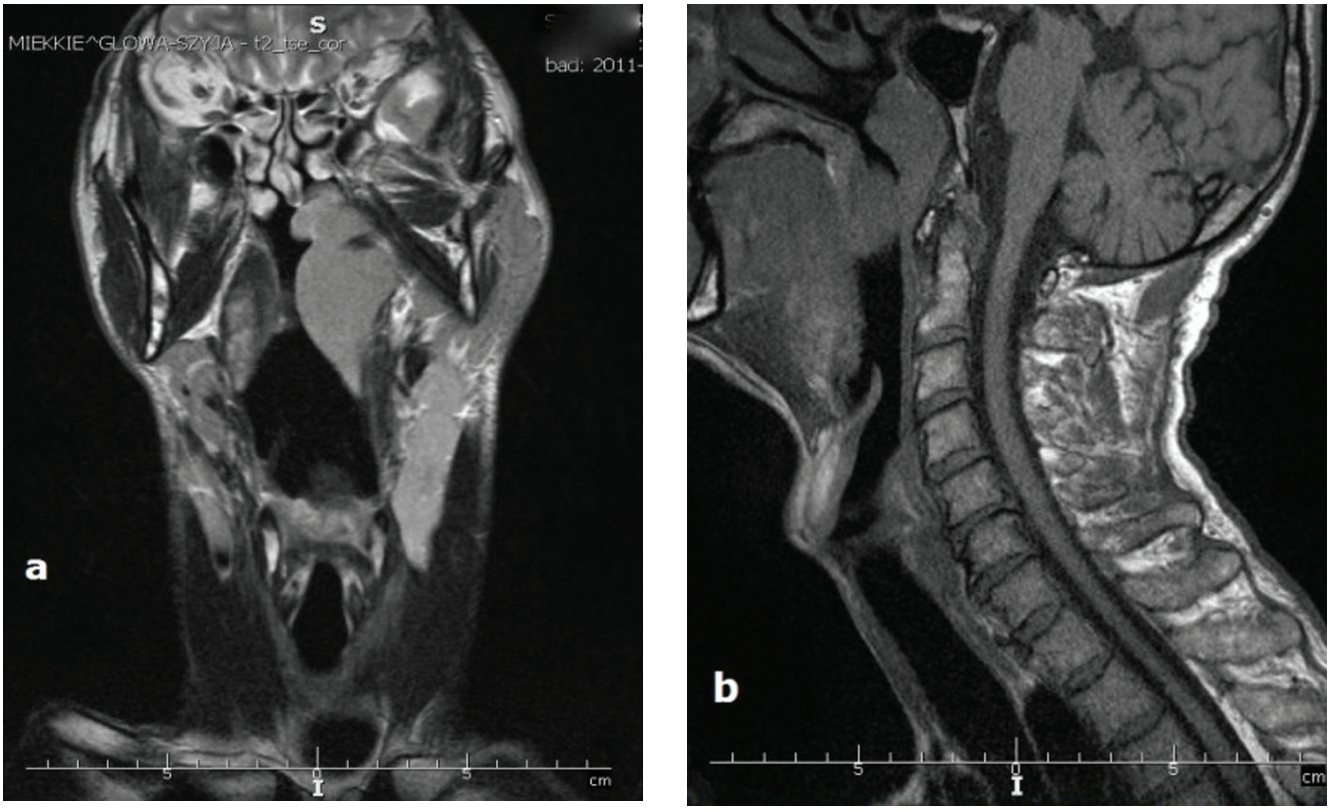

Fig. 5. Male patient S.E., aged 56, admitted to the Department of Otorhinolaryngology of the Medical University of Lodz due to several weeks' history of impairment of nasal patency, loss of hearing within the left eye and pharyngeal obstruction including enlarged cervical lymph nodes on the left. Endoscopic examination revealed a tumorous lesion within the nasopharynx. Histopathological examination of a tumor specimen revealed the diagnosis of mantle cell lymphoma (MCL, a subtype of B-cell lymphoma) with CD30(+), CD5(+), bcl2(+), bcl2(–), CD30(–), Ki67 80% phenotype. The patient was referred for further diagnostics and treatment to the Oncology Center in Lodz.

All patients in the study group were referred to the Oncology Center in Lodz for further diagnostics and treatment. Accurate staging of the disease is required for the optimum choice of lymphoma treatment. Despite the fact that CT scans are performed most frequently, fluorodeoxyglucose F^{18} positron emission tomography coupled with computed tomography (PET-CT) is the recommended method of choice for diagnostics as well as for subsequent monitoring of the course of the disease and the treatment. Magnetic resonance imaging is the method of choice for orbital lymphomas or suspected central nervous system involvement (Cheson 2014). Patients are qualified for treatment on the basis of the diagnosis of a particular type of lymphoma, tumor stage determined according to the Ann Arbor staging system, and the assessment of prognostic factors comprising the International Prognostic Index (IPI) (Prochorec-Sobieszek 2013). The treatment of lymphomas is based on various chemo- and radiotherapy regimens developed for particular types of the disease. The highest percentage of curative outcomes is achieved for Hodgkin lymphomas while T-cell lymphomas are associated with the worst prognoses (Niemczyk 2015).

Other head and neck cancers and, less often, non-cancer diseases should be taken into account in differential diagnostics of head and neck lymphomas. Differential diagnostics of oropharyngeal lymphomas should take into account potential infectious mononucleosis, benign lymphoid hyperplasia, and myeloid sarcoma (a rare, extramedullary manifestation of acute myeloid leukemia, myelodysplastic syndrome, or blast crisis in the course of chronic myeloproliferative diseases) (Brnes 2005). Symptoms of nasal and sinusal lymphomas usually mimic a chronic inflammatory process, and therefore this process should be taken into account, along with other cancer diseases, at the early stage of the differential diagnostic process. Before they are properly diagnosed, most patients are treated with topical and systemic antibiotics or steroids (Steele 2016). Differential diagnostics of nasopharyngeal lymphomas should take into account nasopharyngeal carcinoma (characterized by CK(+) and CD20(–) expression), other malignant tumors (CD56(+), CD3(+), EBER(+)), infectious mononucleosis, or herpes simplex infection (CD4(+), CD5(+), EBER(–)) (Brnes 2005).

In summary, it must be noted that the increasing overall incidence of malignant lymphomas translates into the increased incidence of head and neck lymphomas. However, diagnosis of head and neck lymphomas may still be difficult due to the non-specificity of symptoms, absence of lymphadenopathy or location in organs that house no lymphoid tissue at all, as well as to the need of including immunohistochemical assay panels in the diagnostic process. The diagnostic process should be conducted at specialized sites as it requires interdisciplinary approach and collaboration of specialists in numerous areas such as otorhinolaryngology, hematology, oncology, and pathomorphology.

Magnetic resonance imaging visualized a homogeneous, solid, contrast-enhanced mass within the nasopharynx. The mass was asymmetrical, thicker on the left side, protruding into the pharynx as a 35x80 mm tumor along with bilaterally enlarged lymph nodes, accumulating into clusters sized up to 40x35 mm on the left.

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Corresponding author: Katarzyna Bojanowska-Pozniak; Department of Otorhinolaryngology, Medical University of Lodz, Poland;
E-mail: pozniakk@interia.pl

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