Chłoniaki pierścienia chłonnego Waldeyera
Lymphomas of Waldeyer’s ring

ABSTRACT
The problem of Waldeyer’s ring lymphomas was presented in this paper. The pathogenesis, clinical manifestation, diagnostic procedures were presented in details. Currant treatment strategies included bone marrow and stem cells transplantation were discussed. Selected kinds of lymphomas either non-Hodgkin and Hodgkin, involving Waldeyer’s ring elements were widely presented.

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INTRODUCTION
The term Waldeyer’s ring (WR) is used to encompass the lymphoid tissues of the faunal tonsils, nasopharynx, base of tongue, and oropharynx and, as defined by others, is an extranodal but not an extralymphatic site. Waldeyer’s ring may be involved by a variety of neoplasms, and carcinomas most often metastatic from nearby head and neck sites.

Lymphomas are a heterogeneous group of lymphoproliferative malignancies, originating from lymphocytes or their derivatives, with differing patterns of behavior and responses to treatment. Lymphomas usually originates in the lymphoid tissues and can spread to other organs.

The current World Health Organization (WHO) classification divides lymphoid malignancies largely into T-cell and B-cell neoplasm (both constituting non-Hodgkin lymphoma, NHL), and Hodgkin’s disease. The division of lymphomas according WHO 2008 classification is presented below.
PATHOGENESIS OF LYMPHOMAS

Malignances affecting B cell lineage comprise the vast majority of human lymphomas. There are at least 15 different types of B cell lymphomas (BCLs), differing in clinical behavior, biological phenotype, pathogenesis, and response to treatment. Irrespective of their type, however, most BCLs share two features: chromosomal translocations that involve an immunoglobuline gene and one or another proto-oncogene, and expression of a B cell antigen receptor (BCR) [1]. Chromosomal translocation have long been considered crucial to the pathogenesis of the tumors. The human BCL6 gene on chromosome 3 band q27, which encodes a transcriptional repressor, is implicated in the pathogenesis of human lymphomas, especially the diffuse large B-cell type (DLBCL) [2, 3]. BCL-6 is a transcriptional repressor that is required for mature B cells to differentiate into germinal center B cells during an immune response. Normal germinal center B cells express BCL-6 at high levels but BCL-6 expression is silenced during plasmatic differentiation. BCL-6 is deregulated by chromosomal translocations in roughly 20% of DLBCLs, but the high expression of BCL-6 in DLBCLs is not accounted for by these translocations. Rather, BCL-6 is expressed in DLBCLs along with a host of other germinal center B cell restricted genes because these DLBCLs are derived from normal germinal center B cells and retain much of their biology [4]. In keeping with these notions, DLBCLs have ongoing somatic hypermutation of their immunoglobulin genes, a characteristic feature of normal germinal center B cells. To elucidate the mechanism by which BCL-6 regulates germinal center B cell differentiation, gene expression profiling was used to identify the target genes of BCL-6 expression. One group of BCL-6 target genes are genes that are induced when B cells are activated through the antigen receptor, including cyclin D2, CD69, CD44, and MIP-1 alfa [5]. By blocking expression of B cell activation genes, BCL-6 may guide an antigen-stimulated B cell towards germinal center differentiation and away from the alternate fate of rapid plasmacytic differentiation. Another important BCL-6 target gene is p27kip1, which encodes a negative regulator of cell cycle progression. By repressing p27kip1, BCL-6 may contribute to the extraordinarily high proliferation rate of germinal center B cells [6, 7]. Particularly illuminating BCL-6 target gene is Blimp-1, which encodes a transcriptional repressor that is required for plasma cell differentiation. BCL-6 binds to a motif in intron 5 of the Blimp-1 gene that is conserved between the human and mouse genes. Since BCL-6 is bound to the site in vivo, as judged by chromatin immunoprecipitation, Blimp-1 appears to be a direct target of BCL-6 repression. Presently, are also increasing evidence that signaling from BCR may be a coconspirator in lymphomas pathogenesis [8].

RISK FACTORS OF LYMPHOMAS DEVELOPING

Numerous risk factors may be responsible for DNA damage within the body’s lymphocytes. One of them, such as age and genetics, are non-modifiable (beyond our control). Other factors, such as environmental or lifestyle-related variables are modifiable (can be changed).

The risk factors now believed to have strongest associations with lymphoma include the following:

— the rate of NHL increase exponentially with age between 20 and 79 years. The rate of HL is highest in two age groups: young adults (aged 15–40) and older adults (age 55 and more);
— sex: in generally, both HL and NHL affect men more often than woman [9];
— infections: the risk for developing NHL is increased in people who have been exposed to:
  - human T-lymphotropic virus type 1 (HTLV-1),
• Epstein-Barr (EBV) virus,
• human immunodeficiency virus (HIV),
• human herpes virus,
• malaria, especially in areas of Africa, where Burkitt's lymphoma is common,
• *Helicobacter pylori*, this bacterial infection can cause lymphomas of the stomach;

— medical conditions:
• autoimmune diseases (e.g. rheumatoid arthritis, systemic lupus erythematosus, Sjogren’s syndrome),
• inherited immune deficiency syndromes (e.g. *ataxia telangiectasia*),
• organ transplants that require the use of immunosuppressant drugs;

— chemicals: exposure to chemicals also increase the risk for NHL. They include the following:
• benzene and certain other solvents,
• herbicides,
• pesticides,
• medications — e.g. antiepileptic medicine — phenytoin;

— genetics: rates of lymphoma and leukemia (e.g. chronic lymphocytic leukemia, CLL) are especially high in some Jewish population, whereas Asian population rarely develop CLL [10].

### Cancer therapy

Patients who have received chemotherapy and/or radiotherapy for previous cancers have an increased risk for developing NHL or secondary leukemia [10, 11].

On the other hand, allergic and atopic conditions and their correlates such as early birth order, appear to be associated with a decreased risk of NHL developing [12].

### Clinical Manifestation

Malignant lymphoma is primarily a disorder of the lymph nodes; however they may arise from extranodal sites, and there appears to be an increasing incidence of such lymphomas during the past few decades. Extranodal presentation concern 24% to 48% of all non-Hodgkin lymphomas (NHL), constituting the second most frequent type of extranodal malignant lymphomas. Approximately 10% of patients with NHL present extranodal disease in the head and neck region [13]. Furthermore, more than half of these head and neck lymphomas occur in the Waldeyer’s ring, and 40% to 50% of these arise from the tonsil. In published studies, approximately 90% of all lymphomas involving WR are types of NHL. In 3–10% of patients with non-Hodgkin’s lymphoma involvement of WR (primary or secondary in patient with disseminated disease) is found. Characteristically, these lymphomas arise in elderly men in the age group 50–60 years, and present as a tonsillar swelling, cervical adenopathy, dysphagia, odynophagia, or with a sore throat [14].

All varieties of non-Hodgkin’s lymphomas are seen in WR, but up to 85% of such lymphomas are diffuse, and most diffuse lymphomas are of the B-cell origin and the most common histological type is DLBCL according to the WHO classifications. As far as other types of NHLs, extranodal natural killer/T-cell lymphoma of nasal type and a lesser number of other types, including extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue, mantle cell lymphoma, and peripheral T-cell lymphoma are observed [15].

### Diagnostics of Waldeyer’s ring lymphoma

In the past 10 years, fine needle aspiration (FNA) cytology has become accepted as a means diagnosis and typing common forms of lymphoma, particularly small lymphocytic lymphoma, follicular lymphoma, and large B cell lymphoma [16]. The usefulness of FNA cytology in the diagnosis of these lymphomas is reliant on immunoflow cytometry (IFC) and cell block immunohistochemistry (IHC). It is also reliant on the pathologist making “near patient” provisional assessment of the nature of the specimen and then collecting appropria-
te specimens. Standard panels of lymphomas characteristic antibodies are evolved with the acquisition of a flow cytometer [17]. In some cases, more specialized panel to investigate a specific diagnosis. The number of used is sometimes restricted by the scarcity of cells.

For some cases cell blocks for immunohistochemistry are collected, usually when FNA is not diagnostic, showing overtly malignant cytology [18]. In the cases of B-cell lymphomas, B-cell markers CD 19+, CD 20+ are assessed and proportion light and heavy chains anti-kappa and anti-lambda, showing light chain restriction. In the cases of Burkitt lymphoma, Burkitt-like B-cell lymphoma CD 10 and CD 77, showing 8q24c-myc breakpoint gene rearrangement are strongly expressed [18]. A “small cell” lymphoma with an immunophenotype of CD 5+, CD 19+, and CD 23 — strongly suggests a mantle cell lymphoma.

HIGH-GRADE B-CELL LYMPHOMAS

Diffuse large B-cell lymphoma

These are lymphomas composed of patternless sheets of large, transformed lymphoid cells with variable cytoplasmic content and enlarged, vesicular nuclei containing dispersed (activated) chromatin that allows one-to-several nucleoli to become visible in each nucleus [19]. This turns out to be the largest group of lymphomas involving Waldeyer’s ring, quoted figures in large series being: 57% “centroblastic” (i.e. morphologically resembling the B-blasts of the germinal centre) of 79 cases, 66% of 77 cases and 75% of 65 cases (SGH/TTSH/CGH, 1992–1996) [20].

Gene expression profiling studies revealed that that DLBCL is comprised of at least two molecularly and clinically distinct diseases. One subgroup of DLBCL, termed germinal center B cell-like (GCB) DLBCL, expresses genes that are hallmarks of normal germinal center B cells. By contrast, another DLBCL subgroup, termed activated B-cell-like (ABC) DLBCL, lacks expression of germin center B cell-restricted genes and instead expresses genes that are induced during mitogenic stimulation of blood B cells. These two subgroups of DLBCL differ in the expression of thousands genes, and in this respect they are as different as acute myelogenous leukemia and acute lymphoblastic leukemia. More recently, a third subgroup of DLBCL has been defined by gene expression profiling, termed primary mediastinal B cell lymphoma (PMBL). These three DLBCL subgroups should be considered separate disease entities since they arise from B cells at different stages of differentiation, utilize different oncogenic pathways, and have distinct clinical behavior [21]. These DLBCL subgroups also differ in their care rate following anthracycline-based multiagent chemotherapy. Patients with ABC DLBC, GCB DLBC and PMBL have five-year survival rates of 31%, 59% and 64% respectively. Relatively few relapses occur beyond five years, so these survival rates roughly reflect the probability that patients in each DLBCL subgroup will be cured by chemotherapy [22].

Peripheral T/NK (natural killer)-cell lymphomas

As a rule, these are also rare in Waldeyer’s ring. Only 4 (6%) of the 65 cases from SGH, TTSH and CGH seen from 1992 to 1996 were of T-cell phenotype. Separate data accumulated from 1991 to 1999 came from NUH. Of 26 Waldeyer’s ring lymphomas, only 5 (19%) were of T-cell phenotype, resulting in B:T-cell lymphoma ratio of 4.2.

Although NHLs of the Waldeyer’s ring are mainly of the diffuse large B-cell type, WR is the most common site of nasal-type NK/T-cell lymphoma in the upper aerodigestive tract [22].

For the WR-NKTL cases, the nasopharynx (57%) is the most frequently involved, followed by the tonsil (38%). In contrast, in all patients with NHL of Waldeyer’s ring, the tonsil was the most frequently involved site, accounting for 50% to 80% of all primary lesions [23].
Extranodal NK/T-cell lymphoma, nasal type, recently was recognized as a distinct entity of malignant lymphoma. Because this type of lymphoma often shows an angiocentric and angiodestructive growth pattern, together with a broad cytoligic spectrum of atypical cells and a zonal necrosis, it was categorized as angiocentric lymphoma in the revised European-American lymphoma classification. These lymphomas are uncommon in the U.S. and Europe, but they are prevalent in East Asia and in certain parts of Central and South America [22].

Patients with WR-NKTL showed better response to radiotherapy than chemotherapy. Recently, radiotherapy as primary treatment for early-stage nasal NK/T-cell lymphoma has been validated in many large retrospective studies. Primary radiotherapy results in a better outcome compared with chemotherapy alone or initial chemotherapy, and the addition of chemotherapy to radiotherapy does not further improve survival rates for stage I and II diseases [21].

Extranodal marginal zone lymphoma of MALT

MALT lymphomas were first by Issacson and Wright in 1983 in a small series of patients with low grade B cell gastrointestinal lymphomas. Although MALT lymphomas — extranodal lymphomas arising from MALT — occur most frequently in the stomach, they have also been described at various non-gastrointestinal sites. In Waldeyer’s ring, these lymphomas constitute only a minority of cases, the percentages derived from various large series being 3.6% of 329 cases, 1.3% of 79 cases and 0% of 65 cases (SGH/TTSH/CGH, 1992–1996) [22]. MALT lymphomas are characterized by neoplastic marginal cells which display a variable combination of colonization of reactive germinal centers, plasma differentiation, and destructive epithelial infiltration forming lymphoepithelial lesions [24]. Immunohistochemical examination often shows the characteristic B cell lymphoma with monoclonal expansion by monotypic cytoplasmic immunoglobulin. This low-grade malignancy has a tendency to remain localized to the primary site and to respond favorably to local treatment such as surgery and/or radiotherapy. The outcome and prognosis for MALT lymphomas are more favorable than for other extranodal lymphomas reported in the literature [23].

Mantle cell lymphoma

Mantle cell lymphoma (MCL) is a non-Hodgkin’s lymphoma which has a marked male predomiance that typically is nodal-based but can involve extranodal sites. Among the more common extranodal sites of involvement are the tonsils, large intestine, stomach, upper aero digestive tract. This again, is rare entity in Waldeyer’s ring, quotable percentages being: 11% “ centrocytic” of 79 cases, 4% of 77 cases and 3% of 65 cases (SGH/TTSH/CGH, 1992–1996) [24].

Typically, mantle cell lymphoma has rather characteristic nuclear features, including monotonous nuclei with finely stippled chromatin. However, there are variants with an atypical appearance and immunophenotype. To make a definite diagnosis one usually needs to demonstrate nuclear overexpression of cyclin D1 on immunohistochemistry.

One of the outcomes of the recent change in lymphoma classification is that mantle cell lymphoma under the current WHO classification has been found to correspond largely to what used to be called “centrocytic lymphoma” in the preceding Kiel classification [23].

Low-grade follicular lymphoma

Follicular lymphoma (FL) is a prototype of indolent lymphoma, a slowly growing lymphoma arising from follicular center B cells with a scarce tendency to invade to non-lymphoid tissues and a protracted clinical course. In physiological conditions, the stable formation of germinal centers requires the presence of
functionally specialized T cells, dendritic and stromal cell subpopulations. FL is recognized as a disease of functional B cells in which T-cell co-stimulation is essential for the maintenance and ongoing development of B-cell secondary follicles. 15% of patients with FL have objective tumor regression in the absence of any antitumoral therapy. On the other hand, tumor transformation and development of unresponsiveness to standard chemotherapy or immunochemotherapy regimens in the course of FL represent the main causes of death in patients with this lymphoma. Follicular lymphomas occur commonly in the lymph nodes, and duodenum. FL is reported to be rare. Quoted figures for the frequency of follicular lymphoma in Waldeyer’s ring lymphoma series are: 6% of 79 cases 6% of 77 cases and 9% of 65 cases (SGH/TSSH/CGH, 1992–1996) [25].

Burkitt’s lymphoma
Burkitt’s lymphoma, an aggressive form of non-Hodgkin’s B-cell lymphoma is usually diagnosed in children and young adults, and to a lesser extent in middle-aged adults. Endemic, sporadic (non-endemic) and immunodeficient variants have been recognized. They are recognized as small non-cleaved cell lymphomas displaying a starry sky appearance due to the high rate of proliferation and spontaneous cell death. Chromosomal translocation involving the Myc oncogene are to believed to highlight the hallmark of the disease [26]. Endemic variant is found in equatorial Africa, as associated with Epstein-Barr virus (EBV) infection, as well as frequent concomitant malaria infection. The sporadic form tends to present in the lymphoid tissues of the gut, often presenting as masses in the Waldeyer’s ring or terminal ileum, or even massive abdominal involvement. This form of Burkitt’s lymphoma involve WR in 3% to 5% of cases. Bone marrow involvement is commonly seen in progressive disease.

EBV involvement is reported in around 15–30% of cases. The immunodeficient form is often associated with HIV infection, and may also be seen in post-transplant patients who are chronically immunosuppressed [25].

However, it is important to recognize as an oncologic emergency, being a highly aggressive lymphoma characterized primarily by activation of the c-myc oncogene that drives its cell proliferation fraction to virtually 100%, thereby rendering it also highly chemosensitive and prone to the tumor lysis syndrome.

Hodgkin lymphoma
Hodgkin lymphoma (HL) represents approximately 4% of all lymphomas of the head and neck, and most of these neoplasms involve lymph nodes, most frequently in the cervical regions. Extranodal involvement by HL, including Waldeyer’s ring, is rare. Among this group, HL involving Waldeyer’s ring, which encompasses the lymphoid tissues of the tonsils, nasopharynx, base of the tongue, and oropharynx wall, is even more rare. For example, Todd and Michaels reported a frequency of 1% for involvement of the nasopharynx and 1.5% for tonsil and oropharynx [26].

Similarly, Kaplan and colleagues reported that 5 (1.8%) of 285 consecutive patients with HL had involvement of Waldeyer’s ring. As a result, most previously published series of HL involving Waldeyer’s ring have been small groups of patients or case reports.

However, the incidence of extranodal HL is increasing due to the emergence of the acquired immunodeficiency syndrome. EBV has been implicated in the etiopathogenesis of HL and EBV-LPM has transforming and oncogenic properties. Both HL and Infectious Mononucleosis are EBV-related and likely to be endpoints of distinct pathogenic pathway [26].

TREATMENT MANAGEMENT
The treatment in the individual lymphoma subtypes is largely dictated by the previous broad categorization into low- and high-grade lymphomas, as well as the sites of involvement. At the end of the scale, patients pre-
senting with low-grade lymphomas who are asymptomatic may simply be followed without treatment until symptoms develop or transformation occurs [27].

At the other end of the scale, patients presenting with high-grade disease may be successfully treated with multi-agent chemotherapy with most attaining a remission and up to 50% of patients achieving long-term disease-free survival. Generally, treatment policies for Waldeyer’s ring lymphomas have included RT with or without CTh for limited stage disease and aggressive CTh with or without RT for advanced stage disease [26]. The general guidelines recommend radiotherapy for localized lymphomas, cyclophosphamide, vincristin and prednisone chemotherapy or chlorambucil for stage III–IV indolent NHL, cyclophosphamide, hydroxydaunomycin, vincristin and prednisone chemotherapy for stage II–IV aggressive and very aggressive NHL, followed by radiotherapy for bulky tumors or persistent lesions. Chemotherapy schemes were divided into two groups: one with an anthracycline and other without (mitoxantrone-based chemotherapy was not considered among the anthracyclines). No specific recommendations were made for the treatment of patients with WR NHL [26].

Radiotherapy has a role in low- and intermediate-grade NHL but is usually inappropriate for treatment of high-grade lymphomas which are frequently widely disseminated tumors. Many studies revealed that patients receiving an RT dose of > or = 45 Gy had statistical significant improvement in CR (complete response), DSF (disease-free survival) and OS (overall survival) rates over those treated with a lower doses [27].

In the past decade, overall survival improvements have been observed in the two most common lymphoma histologies: diffuse large B cell lymphoma and follicular lymphoma. The monoclonal antibody rituximab has significantly contributed to these improvement therapeutic outcomes. Rituximab is a monoclonal antibody targeting the CD20 molecule on B lymphocytes. The initial indication was for the treatment of patients with relapsed or refractory, low-grade or follicular, CD20 positive, B-cell, non-Hodgkin lymphoma (NHL) [28]. Subsequent indications have expanded to include first-line treatment of follicular, CD20 positive, B-cell NHL in combination with cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy; treatment of low-grade, CD20 positive, B-cell NHL in patients with stable disease or who achieved a partial or complete response following first-line treatment with CVP chemotherapy; and for the first line treatment of diffuse large B-cell, CD20-positive, NHL in combination with cyclophosphamide, doxorubicin, vincristin, and prednisone (CHOP) or other antracycline-based chemotherapy regimens. Subsequent antibodies to reach the market for lymphoma chemo-immunotherapy include the radionabeled anti-CD20 antibodies iodine-131-tositumomab and ibritumomab tiuxetan — each indicate for the treatment of relapsed or refractory low grade or follicular lymphoma, including transformed lymphoma and rituximab-refractory lymphoma. However, once relapse occurs, particularly if remission is short, further response to salvage chemotherapy is difficult to sustain [28].

Patients who relapse after achieving complete remission (CR) or never achieve CR of non-Hodgkin lymphoma can rarely be cured with further chemotherapy. However, high-dose chemoradiotherapy with autologous bone marrow or peripheral blood stem-cell transplantation is curative in some patients and is superior to conventional chemotherapy [29]. Chemosensitivity of the lymphoma is one of the most important predictors of outcome with autologous transplantation. Intensification of conditioning regimens has not resulted in an increase in disease-free survival but is associated with an increase in transplantation-related deaths. The success of high-dose chemoradiotherapy and stem-cell
transplantation for patients with advanced hematologic malignancies is limited primarily by a high incidence of relapse. The cytoreductive regimen used very often consisted of high-dose cyclophosphamide, etopside, and total body irradiation [29].

Authors have reported 5-year survival rates of 60% to 80% for patients with early stage disease. Qin et al reported a 5 year OS of 84% for stage I–II tonsil NHL, whereas Gao et al reported an OS of 65% for these patients. Large size of the tumor, poor performance status, presence of systemic symptoms and a higher Ann Arbor stage were indicative of a poor prognosis.

**DIFFERENTIAL DIAGNOSIS**

Waldeyer’s ring lymphomas should be differentiated with other malignances especially squamous cell carcinoma, tonsillar hypertrophy, tonsillar swelling, sore through, painful swallowing accompanied with autoimmunological diseases like rheumatoid arthritis, Sjogren syndrome or systemic lupus erythematosus. They should be also considered in patients with immunological deficiencies either acquired (HIV/AIDS infection) or congenital syndromes (e.i. ataxia — teleangiectasia) [30].

**CONCLUSIONS**

Lymphomas affecting Waldeyer’s ring should be taken under consideration in all cases of tonsillar hypertrophy, especially one-sided, asymmetric hypertrophy especially in group of young adults and adults over 40 years old. Clinical symptoms mentioned above should also rise suspicious in the direction of lymphomas in these groups of patients.

**REFERENCES**