Main Topic:
Lymphomas in South East Europe

May 27-29, 2013 Skopje,
Republic of Macedonia

In collaboration with International Non-Hodgkin Lymphoma Study Group
Under the auspice of the
Ministry of Health of R. Macedonia and
University “Ss Cyril and Methodius” Faculty of Medicine

Proceedings & Abstracts
PROCEEDINGS AND ABSTRACTS
of the 1st Macedonian Inter-Congress Meeting
with International Participation

May 27-29, 2013
Skopje, Republic of Macedonia
Disclaimer

The abstract book has been produced using authors-supplied texts. Editing has been restricted to some corrections of spelling and style where appropriate. No responsibility is assumed for any claims, instructions or methods contained in the abstracts.
COMMITTEES AND ORGANIZERS

Executive Committee of the Macedonian Association of Pathology

President: Neli Basheska
Secretary: Gordana Petrushevska
Members: Vesna Janevska
Slavica Kostadinova-Kunovska
Blagica Dukova

Local Organizing Committee

President: Gordana Petrushevska
Members: Neli Basheska
Vesna Janevska
Secretary: Rubens Jovanovik
Technical Secretaries: Blagica Dukova
Magdalena Bogdanovska-Todorovska
Ivan Domazetovski

International Organizing Committee

President: Hans Konrad Muller-Hermelink (Germany)
Members: Snjezana Dotlic (Croatia)
Bogdan Fetica (Romania)
Dobrea Camelia (Romania)
Laszlo Pajor (Hungary)
Tatjana Terzic (Serbia)
Maja Perunicic-Jovanovic (Serbia)
Gorana Gasljevic (Slovenia)
Metka Volavsek (Slovenia)
Margarita Guenova (Bulgaria)

Scientific Committee

President: Hans Konrad Muller-Hermelink (Germany)
Members: Dennis Weisenburger (USA)
Jacques Diebold (France)
Bharat Nathwani (USA)
Kenneth Maclellan (United Kingdom)
Stefan Dojcinov (United Kingdom)
Snjezana Dotlic (Croatia)
Bogdan Fetica (Romania)
Dobrea Camelia (Romania)
Igor Aurer (Croatia)
Laszlo Pajor (Hungary)
Gordana Petrushevska (Macedonia)

27-29 May, 2013
Skopje, Macedonia
CONTENTS

TOPIC LECTURES

TL-01. Malignant lymphomas around the world with special regard on lymphomas in South-East Europe
Weisenburger D........................................................................................................................................ 11

TL-02. Peripheral T-cell lymphomas
Muller-Hermelink H. K.......................................................................................................................... 11

INVITED LECTURES

SYMPOSIUM ON EXTRANODAL LYMPHOMAS
L-01. Splenic lymphomas
Diebold J.................................................................................................................................................. 12

L-02. Cutaneous lymphomas: a modern view based on histopathology and clinical manifestation
Kempf W.................................................................................................................................................. 12

SYMPOSIUM ON PLASMA CELL DISORDERS AND SECRETORY LARGE CELL LYMPHOMA
L-03. IgG4 sclerotic disease and related lymphoproliferations
Muller-Hermelink H. K................................................. 14

L-04. Follicular lymphomas
Nathwani B........................................................................................................................................... 14

SYMPOSIUM ON SMALL CELL LYMPHOMAS AND PTCL
L-05. An update on EBV associated lymphoproliferations
Dojcinov S................................................................................................................................................ 15

L-06. Bone marrow diagnosis of malignant lymphomas and plasma cell disorders
Pajor L........................................................................................................................................................ 16

SYMPOSIUM ON GRAY ZONE LYMPHOMAS
L-07. The borderline of Hodgkin’s lymphoma
Maclennan K........................................................................................................................................... 18

WORKSHOP ON EXTRANODAL LYMPHOMAS AND EXTRANODAL LOCALIZATION OF LYMPHOMAS
L-08. Extranodal lymphomas - an update
Dotlic S.................................................................................................................................................... 19

L-09. Extranodal lymphomas and extranodal localizations of nodal lymphomas - clinicians perspective
Aurer I....................................................................................................................................................... 21

L-10. First line treatment of diffuse large B-cell lymphoma
Basic-Kinda S........................................................................................................................................ 22
WORKSHOP ON PLASMA CELL DISORDERS, SECRETORY LARGE CELL LYMPHOMAS AND PITFALLS AND DIFFICULT CASES

L-11. Histological and immunohistochemical study of malignant lymphomas in Macedonia - Study of 222 cases

L-12. Plasma cell disorders and secretory large cell lymphoma
Jovanovik R. ............................................................................................................. 26

L-13. Diffuse large cell lymphoma - advance in the diagnosis and treatment in last decades in Macedonia
Stojanovik A. ........................................................................................................ 26

Case 1: Testicular plasmacytoma
Domazetovski I., Dukovski D., Petrushevska G. .......................................................... 28

Case 2: Diffuse large B-cell lymphoma, immunoblastic variant with plasmablastic differentiation
Bogdanovska-Todorovska M., Petrushevska G., Popova-Simjanovska M. .................. 29

Case 3: Osseal diffuse large B-cell lymphoma with plasmablastic differentiation
Dukovski D., Dukova B., Petrushevska G. ................................................................. 30

Case 4: Diffuse large B cell lymphoma - small cell plasmacytoid type
Kostadinova-Kunovska S., Trajkova S., Petrushevska G. ........................................... 30

Case 5: Lymphoplasmacytic lymphoma
Popova-Simjanovska M., Jovanovik R., Petrushevska G. ........................................... 31

L-14. Pitfalls and difficult cases
Petrushevska G., Trajkova S., Ivkovski Lj., Muller-Hermelink H. K., Weisenburger D. ... 32
Epithelioid angiosarcoma mimicry (Case Ma-128) ...................................................... 32
Thymoma B1 and its differential diagnosis (Case Ma-130) ........................................... 33
Atypical lymphoid hyperplasia (Case Ma-125) .......................................................... 34
Unclassifiable case, probably peripheral T Cell lymphoma of cerebellum
Janevska V., Petrushevska G., Filipche V., Jovanovik R., Ognenoska-Jankovska B. ...... 35

WORKSHOP ON SMALL CELL LYMPHOMAS AND PTCL
L-15. Indolent B-cell lymphomas and mantle cell lymphoma in Romanian lymphoma series
Fetica B. .................................................................................................................. 36

SATELLITE SYMPOSIUM LECTURES

HOFFMAN-LA ROCHE SATELLITE SYMPOSIUM
SS-01. Diagnostic algorithm of malignant lymphomas, classification and pathohistological characteristics
Petrushevska G. ........................................................................................................ 37

SS-02. MabThera treatment of NHL and CLL
Georgievski B. ........................................................................................................ 37
NOVARTIS ONCOLOGY SATELLITE SYMPOSIUM

SS-03. The evolution in CML continues...
Karanfilski O................................................................................................................................. 37

PROFFERED PAPERS

PP-01. Distribution of lymphoid neoplasms in Serbia
Perunicic-Jovanovic M., Cemerikic-Martinovic V., Terzic T., Krstic M., Mihailovic D., Stojnev S., Nikin Z., Jakovic Lj........................................................................................................ 38

PP-02. Descriptive epidemiology of lymphomas: What is going on in Slovenia in the last few years
Gasljevic G., Zadnik V., Gacic B., Gjidera M., Grcar-Kuzmanov B., Volavsek M............. 38

PP-03. Bone marrow involvement in non-Hodgkin lymphoma
Terzic T........................................................................................................................................... 40

PP-04. Splenectomy for hematological disorders
Jankulovski N....................................................................................................................................... 40

PP-05. Primary gastric diffuse large B-cell lymphoma
Antic D., Jelicic J., Djurasinovic V., Vukovic V., Milic N., Todorovic M., Bila J., Andjelic B., Perunicic-Jovanovic M., Jakovic Lj., Mihaljevic B.......................................................... 40

PP-06. Prediction value of the immunohistochemical GCB/NON GCB classification and outcome of diffuse large B-cell lymphoma patients treated with R-CHOP regimen-single centre experience
Trajkova S., Panovska-Stavridis I., Stojanovik A., Perushevksa G., Ivanovski M., Dukovski D., Popova-Simjanovska M., Chadiievski L., Chevreska L......................................................... 41

PP-07. The prognostic significance of bcl-2, tumor associated macrophages and total lymph node involvement by neoplastic and inflammatory cells in advanced stage classical Hodgkin’s lymphoma
Jakovic Lj., Mihaljevic B., Perunicic-Jovanovic M., Bogdanovic A., Andjelic B., Bumbasirevic V............................................................................................................................... 42

POSTER PRESENTATIONS

P-01. Acute renal failure in a patient with diffuse large B-cell lymphoma

P-02. Biological differentiation of diffuse large B-cell lymphoma patients associated with bulky disease and advanced stage using immunohistochemistry

P-03. Using immunohistochemistry for biological characterization of nodal versus extranodal presentation of diffuse large B-cell lymphoma patients

27-29 May, 2013
Skopje, Macedonia
**P-04.** Rituximab maintenance therapy in diffuse large B-cell lymphoma: single center experience

*Popova-Simjanovska M., Chevreska L., Trajkova S., Dukovski D., Ivanovski M., Stankovik S., Panovska-Stavridis I.*

**P-05.** AIDS and non-Hodgkin’s lymphoma

*Durbaku A., Ivanaj A., Kokciu M., Nina H.*

**P-06.** Kikuchi disease presenting as axillary lymphadenopathy - case report

*Kubelka-Sabit K., Jashar Dz., Filipovski V., Jovanovik R., Petrushevska G.*

**P-07.** Diffuse large B-cell lymphoma diagnosed in a minor salivary gland biopsy - case report

*Benedetti A., Popovski V., Monevska D., Kirkov A., Panchevski G., Bozhovic S., Iliev A.*

**AUTHOR’S INDEX**
TOPIC LECTURES

TL-01
Malignant lymphomas around the world with special regard to lymphomas in South-East Europe

Weisenburger D.
City of Hope National Medical Center, Department of Pathology, Duarte, CA USA

The relative frequencies of non-Hodgkin lymphoma (NHL) subtypes differ by geographic region around the world, but no systematic comparative study of NHL subtypes by geographic region has ever been done. In 1995, the International Non-Hodgkin Lymphoma Classification Project was initiated and five expert hematopathologists have reviewed over 4,500 NHL cases from 24 countries. Marked differences in the relative frequencies of the various NHL subtypes have been noted including a high frequency of low-grade B-cell NHL, such as follicular lymphoma, in North America (NA) and Europe (EU), and a high frequency of high-grade NHL, such as diffuse large B-cell lymphoma (DLBCL) and the T/NK-cell lymphomas, in developing countries. In South-East Europe (S.E.EU), patients with NHL were significantly younger (median age, 59 yrs.) compared to NA (65 yrs.). Like other developing regions, S.E.EU had a lower frequency of low-grade B-cell NHL (47%) compared to NA (56%), and a higher frequency of high-grade B-cell NHL (44.4% vs. 34.6%), whereas T/NK-cell NHL was similar (8.9% vs. 9.5%). Follicular lymphoma was low in Romania (12%) and Macedonia (13%), and intermediate in Croatia (20%) compared to NA (32%). DLBCL was high in Croatia (39%), Macedonia (41%), and Romania (44%) compared to NA (29%). Recent studies have shown that follicular lymphoma appears to increase as countries become more westernized. Therefore, epidemiologic and molecular biologic studies of etiologic risk factors and host response factors are needed to better understand these differences and elucidate complex etiologies.

TL-02
Peripheral T-cell lymphomas

Muller-Hermelink H. K.
Medical Faculty, University of Wurzburg, Wurzburg, Germany
INVITED LECTURES

SYMPOSIUM ON EXTRANODAL LYMPHOMAS

L-01
Splenic lymphomas
Diebold J.
Hospital Hotel de Diue, Medical Faculty, University of Paris, Paris, France

L-02
Cutaneous lymphomas: a modern view based on histopathology and clinical manifestation
Kempf W.
Department of Dermatology, University Hospital Zurich, Zurich, Switzerland

Cutaneous lymphomas represent a unique group of lymphomas and are the second most frequent extranodal lymphomas. Primary cutaneous T-cell lymphomas (CTCL) represent the majority of cutaneous lymphomas and are a spectrum of diseases with a wide variety of clinical, histological and phenotypic features as well as diverse biological behavior. Mycosis fungoides (MF) is the most common form of CTCL. MF is clinically characterized by patches and plaques and histologically by epidermotropic infiltrates of atypical lymphocytes. MF displays a broad spectrum of clinical and histological variants. The unilesional form exhibits an excellent prognosis, whereas the folliculotropic, and the granulomatous variant are associated with an impaired prognosis.

CD30+ lymphoproliferative disorders of the skin (CD30+ LPD) comprise lymphomatoid papulosis (LyP) and anaplastic large-cell lymphoma (ALCL) which share the expression of CD30 antigen as a common phenotypic hallmark, but differ in regard to their clinical and histological features as well as their biological behavior. Traditionally, three patterns of LYP (type A-C) have been delineated. Recently, two new LyP variants have been identified including the epidermotropic CD8+ variant (LyP type D) and the angioinvasive variant (LyP type E), which histologically simulates aggressive lymphomas and therefore may be diagnostically challenging.

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) accounts for 1% of all CL and is by definition restricted to cases expressing a T-cell receptor (TCR) alpha/beta phenotype. Histologically, lobular infiltrates of small to medium-sized lymphoid cells with pleomorphic nuclei are found. Phenotypically, SPTCL expresses CD8, cytotoxic proteins and by definition betaF1 (TCR alpha/beta chain). The disease exhibits a good prognosis with a 5-year survival rate of 80%. In contrast, tumor cells in subcutaneous lymphoma with a gamma/delta phenotype express CD56, TCR gamma/delta (TCR delta-1+), but usually are negative for CD4 and CD8. In contrast to the TCR alpha/beta-positive SPTCL, the gamma/delta positive has an unfavorable prognosis. Cases displaying a TCR gamma/delta phenotype were therefore excluded from SPTCL and classified as part of primary cutaneous gamma/delta T-cell lymphoma. All cases, which do not belong to MF, SS, CD30+ LPD,
SPTCL and extranodal NK/T-cell lymphoma, are assigned to the group of peripheral T-cell lymphoma, unspecified (PTL NOS) according to the WHO-EORTC and the WHO classifications. This still poorly characterized CTCL forms most often presents with rapidly evolving multiple nodules without preceding patches and plaques as in MF. By definition, CD30 expression is absent or limited to only a minority of tumor cells.

Cutaneous gamma/delta lymphomas and primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphomas (CD8+ AETCL) represent subtypes of PTL associated with a poor prognosis and a median survival time of less than three years. In contrast, primary cutaneous CD4+ small/medium T-cell lymphoma (CD4+ SMTL) is a provisional entity within the group of PTL, which is associated with a favorable prognosis, especially when clinically manifesting with a solitary nodule. The lymphoid cells in CD4+ SMTL express markers of follicular helper T-cells (PD-1, CXCL-13, bcl-6). There is an increasing spectrum of CTCL with expression of CD8 by tumor cells including CD8+ MF, CD8+ forms of cutaneous CD30+ LPD as outlined above and CD8+ small/medium-sized lymphoproliferations, which are not included as distinct forms in the WHO-EORTC for cutaneous lymphomas and the WHO classification (2008, 4th).

Primary cutaneous B-cell lymphomas (CBCL) account for approximately 25 to 30% of all primary cutaneous lymphomas. Both forms of low-grade malignant CBCL, primary cutaneous follicle center lymphoma (PCFCL) and primary cutaneous marginal zone lymphoma (extranodal MALT type lymphoma) (PCMZL) represent the vast majority of CBCL and show an indolent, slowly progressive course and an excellent prognosis despite a high recurrence rate. The more common class switched and the non class-switched form of PCMZL can be distinguished two distinctive subsets which differ in the cellular composition, IgM expression and biologic behavior with extracutaneous involvement found in the non class-switched form. In contrast to PCMZL and PCFCL, primary cutaneous diffuse large B-cell lymphoma, leg type, and other rare forms of large B-cell lymphomas such as intravascular large B-cell lymphoma have an unfavorable prognosis.

Final diagnosis in cutaneous lymphomas follows the rule of the multiparameter approach as outlined in the WHO-EORTC classification and the WHO classification. In this context clinico-pathologic correlation is crucial for the diagnosis of primary cutaneous lymphomas.

References

SYMPOSIUM ON PLASMA CELL DISORDERS AND SECRETORY LARGE CELL LYMPHOMA

L-03
IgG4 sclerotic disease and related lymphoproliferation
*Mueller-Hermelink H. K.*
Medical Faculty, University of Wurzburg, Wurzburg, Germany

L-04
Follicular lymphomas
*Nathwani B.*
Cedars-Sinai Medical Center, Los Angeles, CA USA

Although, diffuse large B cell lymphoma is the most common lymphoma in every country in the world, it is not a distinct disease entity; it is a highly heterogeneous category consisting of 22 separate variants & subtypes. Of all lymphomas that are distinct disease entities, nodal follicular lymphoma (FL) is the most common in the west occurring in all ages and all anatomic sites. The incidence of FL in the USA is ~30% and the highest in the world.

A FL starts in the bone marrow when a pro B-cell acquires the t(14;18) translocation that has not been exposed to antigen. This t(14;18)+ cell reaches the germinal center, and after an exposure to antigen, it can be recognized as an in situ FL. In the USA, the t(14;18) translocation is found in 85% of FL.

The outline of my presentation, today, will be as follows:
1. Introduction
2. Definition
3. Molecular Pathogenesis of FL - In situ FL & overt FL
4. Histologic Progression and Transformation of FL
5. Histologic criteria for diagnosing FL: patterns, cytologic features, differentiation, grading
6. Low Grade FL with High Proliferation Index
7. Differences between FL Grade 3A and 3B
8. Diffuse Large B-cell Areas (Lymphoma) in FL
9. Values and Limitations of Immunostains
10. Multiplex PCR Increases the Sensitivity of Detection of IgH & IgL Gene Rearrangements
11. Clinical Significance of the Host Immune Response Gene Expression Profiles in FL
12. Diffuse Follicular Lymphoma
13. Primary Extranodal FL: Cutaneous, Pediatric, Intestinal, other

SYMPOSIUM ON SMALL CELL LYMPHOMAS AND PTCL

L-05
An update on EBV associated lymphoproliferations

Dojcinov S.
All Wales Lymphoma Panel, University Hospital of Wales, Cardiff, UK

Epstein-Barr virus (EBV) infects more than 90% of the population and following asymptomatic infection or infectious mononucleosis, the virus establishes a lifelong latency in the memory B-cells. Its oncogenic properties were noted for the first time in the 1960s in association with Burkitt lymphoma. It has since become evident that EBV plays an important role in the aetiology of a range of malignancies originating from lymphoid, epithelial, smooth muscle or dendritic cells. More than 50 years after the discovery of the EBV, more new entities associated with it are emerging as well as new concepts of immune system dysregulation which result in lymphoproliferations (LPs). An update on aetiology, pathogenesis, classification, pathology and differential diagnosis of EBV associated LPs of all lineages is provided.

EBV plays a major role in the aetiology of LPs in the immunosuppressed host. This could be in a setting of primary immunodeficiency, iatrogenic induction of immunosuppression including organ transplantation as well as in HIV infection. Post-transplant lymphoproliferative disorders (PTLD) represent a spectrum of immunosuppression related LPs which have been well characterised and classified in four categories including reactive lesions, polymorphous and monomorphic LPs and Hodgkin lymphoma. These could be EBV positive or negative, monoclonal and polyclonal, early or late in the course of transplantation. A combination of these features helps somewhat in predicting prognosis and choosing management but the correlation of the pathological parameters of PTLD with outcomes is far from perfect. Novel immunomodulatory therapies have been tested for PTLD, including infusion of EBV specific CD8 positive cytotoxic T-cells.

Recently a concept of immunosenescence has been better characterised and associated with EBV driven B-cell LPs which occur in elderly individuals. Immunosenescence is a naturally occurring process of decay of the immune system which takes place with aging. When advanced, there is a state of significant immunosuppression resulting in a spectrum of EBV positive B-cell LPs. These include
reactive lymphoid hyperplasias, clinically indolent and localised mucocutaneous ulcers, but also aggressive large B-cell lymphomas, often with Hodgkin-like features. The polymorphous lesions and large B-cell lymphomas in this setting frequently harbour Hodgkin/Reed-Sternberg (HRS) cells characterised by co-expression of CD30 and CD15. Angioinvasion and necrosis are also frequently present. The differential diagnosis with classical Hodgkin lymphoma and lymphomatoid granulomatosis is difficult. It relies on a combination of clinical patterns of presentation and morphological features including the characteristics of the background inflammatory infiltrate. Differential diagnosis with angioimmunoblastic T-cell lymphoma is also problematic and relies on the recognition of specific germinal centre T-cell phenotypes and morphological features such as prominence of high endothelial venules.

Chronic lymphocytic leukaemia / small lymphocytic lymphoma (CLL/SLL) has been recognised to be immunosuppressive and therefore associated with proliferation of EBV positive HRS-like cells. More recently it has also been noted that some treatments for CLL/SLL including fludarabine and anti CD52 antibody may induce EBV positive B-cell polymorphous lymphoma which may clinically mimic Richter’s transformation. These B-cell LPs usually represent clones unrelated to the underlying CLL/SLL and may regress spontaneously upon withdrawal of the therapeutic agent involved.

The 2008 revision of the WHO lymphoma classification incorporated new T/NK-cell EBV positive entities associated with dysregulation of the immune control over EBV in young patients. The EBV positive T-cell lymphoproliferative disorder of childhood and hydroa vacciniforme-like lymphoma are included which are monoclonal, predominantly T-cell EBV positive lymphomas prevalent in the geographical areas of the world with a high incidence of EBV associated lymphomas. They are considered to be under the umbrella of a wider spectrum of EBV positive LPs named chronic active EBV infection. This spectrum also includes polyclonal and cytologically polymorphous T-cell LPs which may develop after acute EBV infection in a minority of susceptible patients as a result of a defective T-cell response to the virus.

L-06
Bone marrow diagnosis of malignant lymphomas and plasma cell disorders
Pajor L.
UPMC, Department of Pathology, Pecs, Hungary

For the evaluation of lymphoid compartment / infiltrate the histological investigation of trephine biopsy is superior to that of marrow clot section which is followed in efficacy by the cytology of smear / touch preparation of bone marrow. The normal lymphocyte’s content doesnot exceed 10% of nucleated cells with 6 to 1 T vs B lymphocytes, 2 to 1 T8 vs T4 cell ratio and appr. 1% plasma cell content. Six accumulation / infiltration patterns can be recognized which are as follow. 1. interstitial, 2. nodular, 3. paratrabecular, 4. random focal, 5. intrasinusoidal, 6. diffuse infiltrate / packed marrow. The benign nodular infiltrate might be more difficult to differentiate from a malignant one. For those with larger nodules than 0.6 mm and more nodules than 4/1 cm trephine the term of nodular lymphoid hyperplasia has been introduced. It may arise in autoimmune disorders and upon aging. The more central location, the mature cellular composition, heterogeneous cytology, well defined borders, presence of germinal centers and fine reticulin network in the background are rather indicative of the benign nature of the lymphoid accumulation. However, no clearcut criteria for the differentiation between the bening and malignant ones merely on morphological ground are available. Random focal depositions, irregular shape and margins, paratrabecular infiltrate or packed marrow, increased
reticulin deposition, homogeneous cytology, no small lymphocytic appearance, homogeneous B- or T-cell infiltrate, pathognomonic immunophenotype might refer to the pathomorphology associated with malignant lymphomas. Flow phenotyping, IgH/TCR\gamma antigen gene rearrangement PCR tests and iFISH studies represent assets to morphology in revealing the nature of infiltrates.

Precursor B- and T-cell ALL /LBL are usually characterized by packed marrow as well as CD10, CD19, CD34, CD79a, TdT positivity and CD1a, CD2, CD3, CD4, CD5, CD7, CD8, CD34, TdT expression, respectively, or by their combinations. In case of the previous lesion CD66c, CD58 and myeloid coexpression might serve as aberrant markers and it can be partially CD20+, too. Flow phenotyping and molecular techniques are needed for the subtyping of these lesions. The t(12;21)+ and the high hyperdiploid pre-B-ALL are the two most common forms, both of them with major genetic heterogeneity at the subclonal landscape. In course of the follow up the various number of haematogoniums and the leukaemia ancestor cells with monoallelic derangement might course diagnostic challlange.

The overall bone marrow involvement by peripheral B-cell lymphomas is high, reaches 70% of cases. Among the mature peripheral B-cell lymphomas of CLL, FL, MCL, MZL types any form of infiltration may occur, the paratrabecular one being most characteristic for FL and frequently an FDC networks by CD21/23 in the background for the last three lymphomas. Cytology gives a clue to the subtype of lymphoma, the IHC by CD5+, CD20+, CD23+, by CD10+, CD20+, bcl2+/-, bcl6+ and by CD5+, CD20+, CD1c+, immunophenotype provide definite diagnosis for CLL, FL and MCL, respectively. Some lymphomas, e.g., FL may affect bone marrow in form of a different lymphoma, e.g. LPL, due to altered differentiation, a phenomenon called dysconcordant lymphoma presentation in the marrow. MZL might exhibit massive plasmacytic differentiation making the differential diagnoses from LPL difficult. MZL, especially SMZL (SLVL), HCL, HCL variant and SDRP-SBCL represent differential diagnostic group. The first three might produce morphologically the honeycomb/fried egg patterns, all variantly overlap in immunophenotype. Only the HCL exhibits invariably the CD11c-CD20-CD25-CD103-DBA44-Annexin-HBME-1-TRAP positive phenotype and SDRP-SBCL the peculiar intrasinusoidal infiltration pattern. In MPNs the marrow exhibit a morphologically discernable lymphoid infiltrate in appr. 30% of cases, but monoclonality according to IgH-R by PCR only in 5%. In the last cases, however, coexistant lymphoma with clonal identity to the MPN can be revealed.

In neoplastic plasmacytic disorders of the bone marrow the plasma cell exhibit the CD20-, CD38+, CD45-, CD138+, aberrant phenotype, monoclonality and heterogeneous genetics, 14q32, 13q14 and t(4;14) being the most common. They appear in multiple myeloma (MM) with more than 30g/L M-protein in the serum or urine as well as with related organ impairement (CRAB) rather in groups or homogeneous sheets frequently with Russel bodies or Mott cells, whereras in the supposed precursor lesions, MGUS less than 10%, rather evenly distributed clonal plasma cells are present. IgM MGUS will progress to LPL /WM, non-IgM MGUS might, but not necessarily, progress to MM, the genetic predisposition, the role of 13q14 deletion, is uncertain. LPL is featured by the presence of two populations: CD20+, CD38-, CD45+, CD138- small lymphocytes and CD20-, CD38+, CD45-, CD138+ plasmacytic elements. Peripheral mature B-cell lymphomas, especially MZL, represent the differential diagnosis. The infiltrate might be other than IgM type, the γ-HCD is a subtype of LPL. Solitary plasmacytoma of the bone (SPB) is composed of homogeneous plasmacells with the aberrant phenotype as above and in 2/3 of cases represents a forunner of MM. (Lympho)-plasmacytic disorders of the marrow might by complicated with amorphous e.c. deposition of monoclonal immunoglobulins, crystal storing histiocytosis or amyloidosis of AL type.
DLBCL lymphoma infiltrate bone marrow rarely, in appr. 10% of cases, usually nodular or random focal lesions are present. The diagnosis by morphology is more obvious because of the definite cytological atypia, by CD10, CD20, bcl6, mum1, heavy and light chain IHC the subtyping is possible. DLBCL might be manifested in the bone marrow in form of TCRBCL which need to be differentiated from cHL (see below). Intravascular LBCL exhibits an intrasinusoidal infiltration pattern.

Among the granulomatous bone marrow infiltrates cHL, TCRBCL, lymphomatoid granulomatosis (multifocal EBV+ TCRBCL), ALCL, PTCL-lymphoepithelioid variant need to be considered and supposed to be differentiated from granulomatous infectious diseases, sarcoidosis or systemic mastocytosis. Both cHL and TCRBCL have scattered mono-, multinucleated tumor cells, but the HRS cells in cHL exhibit a CD15+/-, CD20--/+, CD30+, BOB1-, OCT2-, fascin+, whereas scattered giant tumor cells in TCRBCL the CD15-, CD20+, CD30--/+, CD45+, BOB1+, OCT2+, fascin- phenotype.

The hepatosplenic γ/δ-T-cell lymphoma (HSL) is – beside SDRP-SBCL and ILBCL - the third lymphoma causing a unique intrasinusoidal bone marrow infiltrate, which can be easily overlooked and frequently discernible only by IHC. In case of defective CD8+ cytotoxic T-lymphocytes, EBV infection in children casuses a severe chronic active EBV (SCAEBV) infection resulting in fulminant T-lymphoproliferative disorder with homogeneous, diffuse infiltrate of bone marrow by CD8+, EBV+ clonal T-cells.

SYMPOSIUM ON GRAY ZONE LYMPHOMAS

L-07
The borderline of Hodgkin’s lymphoma
Maclellan K.
Institute of Cancer and Pathology, St James’s University Hospital, Leeds, UK

Hodgkin’s lymphoma (HL) is now known to be a neoplasm of germinal centre derived B cells. Two distinct subtypes are recognised; lymphocyte predominant nodular (LP) and classical Hodgkin’s lymphoma (CHL). Differences in morphology, phenotype and genotype are present between the two forms of HL as well as differences in their clinical presentation and course. Both forms of HL are believed to be absolutely separate from the B cell derived non-Hodgkin’s lymphomas (NHL).

In recent years it has become apparent that the two forms of HL are not quite as distinct as was originally thought with cases of LP relapsing as clonally related CHL and vice versa and there exist cases of B-cell lympho-proliferative disease with morphological, phenotypic and genotypic features intermediate between CHL and NHL, so-called gray zone lymphomas. The separation of LP from the B cell NHLs is also not clear, as up to 5% of cases of LP will transform in to clonally related diffuse large B cell lymphomas.

In addition to the biologic borderline between HL and the B cell NHLs there is a morphologic borderline with some rare NHLs closely mimicking HL but having a very different clinical presentation, response to therapy and outcome.

The lymphocyte rich subtype of CHL can be a close morphologic mimic of LP but differs in clinical presentation and course. T cell / Histiocyte rich B cell lymphomas may prove difficult to distinguish from LP HL, particularly when the latter is predominantly diffuse, but has a very different stage
distribution and is much more aggressive. Anaplastic large cell lymphoma may prove problematic to separate from lymphocyte depleted variants of nodular sclerosis CHL, especially when the former is ALK negative, but the therapeutic approach required for these two entities is quite different and the clinical outcome is prejudiced if the incorrect diagnosis made.

In this presentation I will attempt to outline the biologic and morphologic borderline of HL and discuss the diagnostic and clinical implications.

WORKSHOP ON EXTRANODAL LYMPHOMAS AND EXTRANODAL LOCALIZATION OF LYMPHOMAS

L-08
Extranodal lymphomas - an update
Dotlic S.
Department of Pathology and Cytology, Clinical Hospital Center, Zagreb, Croatia

Classifications of tumours change according to our knowledge of cell biology and histogenesis. Hence, better understanding of lymphoid cell subpopulations and their subspecialisation results in better characterisation of lymphoid entities. This has also resulted in the realisation that certain cell populations are functionally, but also anatomically and tissue restricted and give rise to lymphomas in specific compartments, not only lymph nodes but also skin, soft tissue, gut, mucosal portals of entry, nerves and brain. One of the consequences of this approach has been a separate classification of cutaneous lymphomas, appreciating all aspects of their clinical characteristis, pathology and known histogenesis. Good examples of this correlation could be seen from characterisation of T-cell subsets. The highly subspecialised effector T-cells of the adoptive immunity such as follicular helpers or T-regts reside in nodal tissue and circulate. The components of the innate immunity which function at an antibody and antigen- independent way reside at portals of entry such as skin, gut and spleen.

As result of this specialisation presentations are different: nodal or leukaemic disease of alpha/ beta TCR phenotype in case of cells participating in the adoptive immune response, while the components of the innate immune defence (anatomically concentrated around the bodily portals of entry) result in extranodal lymphomas such as hepatosplenic T-cell lymphoma, enteropathy type T-cell lymphoma and some cutaneous lymphomas. There are also examples in the B-cell compartment with lymphomas resulting from post-follicular terminally differentiated cells and memory cell subtypes giving rise to cutaneous diffuse large B-cell lymphoma of leg type, splenic diffuse red pulp lymphoma and also those where homing features and restriction to certain anatomical sites could be verified such as intestinal follicular lymphoma. Our understanding of such facts impact on the way we interpret histological finding and diagnose lymphomas. For example, in the recent years it has become evident that gamma/delta T-cell lymphomas represent a much wider spectrum than just hepatosplenic lymphoma and have a lot in common across a range of anatomical sites. So hepatosplenic, some enteropathy types and subcutaneous panniculitis types share many common features. In addition, upon presentation lymphomas do not tend to sit in restricted tissue or anatomical boundaries and unusual crossovers do occur.
For a range of other extranodal presentations, however, there is yet no identification of underlying specialised cell populations and it is more likely that a range of lymphomas with different histogenesis and cells of origin may populate these sites. As a consequence, for example, attempts to classify bone presentations of diffuse large B-cell lymphomas as a separate clinicopathological entity have not been successful. In many instances, intimate knowledge of histogenesis and phenotypes is helpful in recognising unusual unexpected presentations (for example primary effusion lymphoma in the lymph node).

This presentation will provide an update on some newly recognised extranodal entities and borderline conditions and also examples of some very rare, but well defined lymphomas which may not be part of systematic reviews covered by other presentations, and are problematic for diagnosis. They represent two extreme ends of a spectrum, namely indolent proliferations which could be interpreted as aggressive lymphomas and, on the other end, innocuous lesions which could be interpreted as reactive, but pursue a very aggressive clinical course.

Primary intestinal follicular lymphoma presents with polypoid mucosal lesions. In a substantial number of cases it is an incidental finding on endoscopies for other reasons. It is usually found in the duodenum. Histologically it is composed of well formed follicles with CD10 and BCL2 expression. The tumour cells show specific intestinal mucosa homing receptors indicating the fact that this lymphoma is indeed originating from the locally resident, specific intestinal B-cell pool. It pursues a very indolent clinical course and seldom requires treatment. There is no bone marrow involvement and patients do not need to be subjected to this investigation. On a basic biological level, many features for intestinal follicular lymphoma overlap with follicular lymphoma in situ. Another lymphoma where diagnosis is contentious on several different levels is paediatric follicular lymphoma. It is a very rare condition occurring during the first 2 decades of life. However, the paediatric type has recently been described in adults as well. Most of the cases present in pharyngeal tonsils and neck lymph nodes, but also distinctively involve the testis. The clinical course is indolent and requires little treatment. In the nodal setting the morphology of paediatric FL simulates reactive hyperplasia with large irregular follicles populated exclusively by centroblasts. This is extended on the immunocytochemical level where paediatric FL is BCL2 negative and does not harbour BCL2 rearrangement, so distinction from hyperplasia could be very difficult. Clonality studies show rearranged IgH.

Another extranodal condition which has not yet reached classification tables is NK cell enteropathy described by Mansoor et al from E. Jaffe's group. It is important to emphasise as many of these cases have been diagnosed as aggressive lymphomas and, as a result very aggressively treated. Patients present with widespread ulcerations throughout the GI tract. Similar cases were reported by Takeuchi et al. in the stomach. The disease is chronic in character. Histologically the mucosa is filled by small and medium size blastic cells with clear cytoplasm which display a NK phenotype. TCR rearrangement studies are negative. On a similar theme, a range of extranodal CD8+ lymphoproliferations have been described recently which have not yet been officially classified. They sit at the border between neoplasia and reactive conditions and are potentially prone to misdiagnosis as aggressive lymphomas. Petrella et al. have described cases of CD8+ lymphoid proliferations in the ear which seem to represent a distinct clinicopathological entity. There is a dense non-epidermotropic proliferation of small clonal CD8+ cells. The disease is non-aggressive and requires minimal treatment. This may be a spectrum of more systemic indolent CD8+ lymphoproliferative process. A series of cases have been previously identified by Egawa et al and Renheim et al. and more recently by A.M. Perry et al. (EAHP Meeting Lisabon 2012 and personal communication). These involved mucosal and intestinal sites with a relapsing course and non-progressive disease. Most have been misinterpreted as idiopathic inflammatory bowel disease.
Another very rare extranodal condition in which there is a discrepancy between aggressive looking histology and clinical behaviour is seroma-associated anaplastic large cell lymphoma. This lymphoma is seen with a variety of breast implants, saline and silicone, many years after implantation. They present with fluid accumulation surrounding the implant. The diagnosis could be made by fluid cytology as the lesional cells grow within the cavity and the seroma fluid. The other interesting example is a very rare form of diffuse large B-cell lymphoma described by N. Harris’ group – primary lymphoma of peripheral nerve. It is exceptionally difficult to diagnose clinically and pathologically, and has an aggressive clinical course. Patients present with variable nerve related symptoms, mostly loss of power and sensation. Pathologically there is a mixed lymphocytic infiltrate involving nerves. The lesions are clonal and the disease pursues aggressive course with frequent extension to the brain and relapses restricted to nerves.

Extranodal lymphomas are certainly intriguing and familiarity with the types of lymphomas that may occur in different organs is essential for establishing a correct diagnosis.

L-09
Extranodal lymphomas and extranodal localizations of nodal lymphomas - clinicians perspective

Aurer I.
Division of Hematology, Department of Internal Medicine, University Hospital Centre Zagreb and Medical School, University of Zagreb, Croatia

The WHO classification of lymphoid neoplasms does not have a gold standard but most disease entities are defined by their morphologic, immunologic and genetic characteristics. In few cases the diagnosis requires a specific localization (e.g. extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), primary cutaneous follicle centre lymphoma (FL), primary diffuse large B-cell lymphoma (DLBCL) of the central nervous system, primary mediastinal LBCL, cutaneous LBCL, etc.). Some entities almost always present as extranodal disease, although this is not an absolute prerequisite for diagnosis (e.g. hairy cell leukemia (HCL), T-cell prolymphocytic leukemia (T-PLL), T-cell large granular leukemia (T-LGL), chronic lymphoproliferative disorder of NK cells, etc.). On the other hand, nodal lymphomas can involve extranodal organs, either as primary (stage I-IIIIE) or as secondary localizations (stage IV). The latter but not the former is usually related to a worse prognosis.

The distinction between primary extranodal marginal zone lymphomas (eMZL) and extranodal spread of nodal MZL is important because eMZLs have an excellent prognosis and are treated differently. Primary treatment of gastric and ocular eMZLs consists of antibiotics and, only in cases of failure, mild immunochemotherapy such as R-CVP or rituximab + chlorambucil. Almost no one dies of these diseases. Splenic MZL is best treated with splenectomy; mild immunochemotherapy should be given after relapse. In contrast, nodal MZLs have an inferior prognosis with average survival of 7-9 years and are treated similar to follicular lymphomas with immunochemotherapy, rituximab maintenance, and, in younger patients in 2nd or 3rd remission, autografting.

In FL it is important to distinguish between primary cutaneous forms and dissemination of systemic FL. PET and bone marrow biopsy are helpful for staging. The former are treated (and very frequently cured) by local radiotherapy, while the latter are treated (when treatment is needed) with systemic immunochemotherapy, rituximab maintenance and sometimes autografting. On the other hand, neither
the approach to nor prognosis of primary cutaneous FL differs from that of localized (stage I) nodal FL.

The localization of extranodal LBCL affects treatment and prognosis. Primary mediastinal disease has a somewhat different presentation from the NOS type, but no consistent differences in treatment and prognosis have been shown. Primary CNS DLBCL needs different treatment because drugs commonly used for NOS DLBCL do not penetrate well through the blood-brain barrier. While its prognosis is inferior to that of the NOS type, it is still better than in NOS cases disseminating to the CNS. Intravascular LBCL has an unusual presentation, with skin and brain involvement and no lymphadenopathy but is treated similar to the more common types. Optimal treatment of primary effusional DLBCL is unknown and its prognosis is dismal. Primary cutaneous LBCL of the leg type should be treated with standard immunochemotherapy (R-CHOP-like) and irradiation, the prognosis is similar to that of localized DLBCL NOS.

In peripheral T-cell lymphomas (PTCLs) the problem is that the optimal treatment of NOS PTCL is unknown. Most centers use CHOP-like therapy, younger patients are frequently autografted in 1st remission. A group from the UK reported favorable results in enteropathy-associated PTCL treated with an aggressive chemotherapy scheme. However, it remains unclear whether such results would be obtained with the same treatment also in the NOS type. Hepatosplenic PTCL usually presents with exclusive extranodal involvement and has a dismal prognosis. As series from East Asia have shown, extranodal NK lymphomas respond better to asparaginase-based than to CHOP-like regimens but this is probably true also for the (rare) nodal NK lymphomas.

Different diseases present with the same type of extranodal involvement but are treated differently or differ in prognosis.

CLL, splenic MZL, HCL, T-PLL, T-LGL, chronic lymphoproliferative disorder of NK cells, FL and mantle-cell lymphoma (MCL) can all present as chronic leukemias. HCL, splenic MZL, FL, MCL, diffuse red pulp lymphoma and HCL variant present as splenic lymphomas. A number of B and T lymphomas differing in aggressivity are characterized by primary skin involvement.

Finally, not all extranodal localizations of primary nodal lymphomas are equal. CNS involvement is always very unfavorable. So is bone marrow involvement in patients with aggressive disease, albeit to a lesser extent. Patients with bone involvement (which must be differentiated from bone marrow involvement) should probably be treated with radiotherapy. Lung involvement in Hodgkin lymphoma carries a worse prognosis unless treated with escalated BEACOPP. Testicular DLBCL has a high propensity for CNS dissemination. There are also favorable localizations: leukemic MCL with splenic involvement is frequently indolent, and preliminary reports suggest that localized gastric DLBCL responds to antibiotics similar to eMZL.

L-10
First line treatment of diffuse large B-cell lymphoma

Basic-Kinda S.
Division of Hematology, Department of Internal Medicine, University Hospital Centre Zagreb, Zagreb, Croatia

If faced with the need to define a single standard treatment for DLBCL most physicians would undoubtedly chose 8 cycles of the combination of rituximab, cyclophosphamide, doxorubicin, vincristine and steroids administered every 21 days (R-CHOP21). This treatment cures 60% of patients, which means that 40% will still die of their disease. Patients with high risk of failure might
benefit from more aggressive approaches while treatment reduction might be useful in low-risk patients.

Approaches to identify reliable immunohistochemical prognostic factors have so far failed, so we are left with clinical prognostic factors, most of which are included in the IPI: age, stage, extranodal involvement, LDH and performance status. An important prognostic factor not included in the IPI is bulky disease.

Studies have shown that more than 90% of patients with stage I disease and no adverse prognostic factors are cured with 3 CHOP21 cycles and involved-field radiotherapy. The prognosis of those with stage I and risk factors or stage II and no risk factors is only slightly worse if treated with 6 cycles of R-CHOP21, 2 additional doses of rituximab with and (in cases of bulk) radiotherapy.

For intermediate risk patients (aIPI=1), it seems that shortening the period between R-CHOP cycles to 2 weeks does not improve outcome but less cycles need to be given, so 8 cycles of R-CHOP21 or 6 cycles of R-CHOP14 can be regarded as optimal, resulting in cure rates of 60-70%. This is also the treatment of choice for patients over 60 years who do not tolerate more aggressive approaches. In younger high-risk patients (aIPI > 1) the situation is less favorable and less clear. Less than 50% are cured with R-CHOP21. Studies suggest that their outcome can probably be improved with R-ACVBP or R-CHOEP14 regimens.

Finally, patients with cardiac systolic dysfunction cannot tolerate CHOP. For them, infusional R-EPOCH or R-CEOP, a regimen in which doxorubicin is replaced by etoposide, offer a realistic possibility for cure.

WORKSHOP ON PLASMA CELL DISORDERS, SECRETORY LARGE CELL LYMPHOMAS AND PITFALLS AND DIFFICULT CASES

L-11
Historical and immunohistochemical study of malignant lymphomas in Macedonia-Study of 222 cases


¹Medical Faculty, University “Ss. Cyril and Methodius”, Skopje, Macedonia; ²Medical Faculty, University of Leeds, UK; ³Hospital Hotel de Diue, Medical Faculty, University of Paris, Paris, France; ⁴Cedars-Sinai Medical Center, Los Angeles, CA USA; ⁵City of Hope National Medical Center, Department of Pathology, Duarte, CA USA; ⁶Medical Faculty, University of Wurzburg, Wurzburg, Germany

The recognition of several new types of non-Hodgkin's lymphoma (NHL) in the beginning of 1990-ties has led to proposals for changing lymphoma classifications to the new WHO classification of NHL-s by the International Lymphoma Study Group (ILSG). (1) The proposed classification defined NHL subtypes using contemporary morphologic, immunologic and molecular techniques, but did not include original data on patients characteristics and outcome, nor the distribution of the various NHL subtypes.
In 1995, a group of leading hematopathologists, clinicians and statisticians conducted a retrospective clinical evaluation of the ILSG classification of NHL. In this study, besides the main clinical characteristics and treatment outcomes for the common NHL subtypes, the distribution of the major subtypes of NHL-s across geographic regions, was also presented. This study provided evidence that the distribution of NHL subtypes differed by geographic region. Since then, many regional epidemiological studies were done by the ILSG together with the local leaders. The clinical significance of the new entities and the practical application of the new WHO Classification of malignant lymphomas in Macedonia has been done by the help of the leaders of the ILSG. In this presentation we present the main results from this study: the distribution of the major subtypes of NHL with their main histological and immunophenotypic features; main epidemiological features of the diagnosed NHL-s; pitfalls in the differential diagnosis of NHL-s. The results from the clinical data will be presented elsewhere.

**Material and methods:** According to the design of the study, we have collected 222 consecutive cases of previously untreated NHL that were representative of the geographic region, in the period between January 1, 2009 and July 31, 2010. The study included cases diagnosed mainly at the Institute of Pathology and University Clinic of Radiotherapy and Oncology at the Medical Faculty in Skopje (two main referent centers in the country).

In all cases, tissue biopsy samples that were adequate for diagnosis and classification before initial therapy were included; positive bone marrow specimens were included in the pathology review, as well. Clinical data, treatment data, and some follow-up information were also collected for all cases from the medical records by a clinician at the University Clinic of Hematology. All the data were recorded on a standardized form for direct computerized data entry given from the ILSG – Nebraska University.

These data included coded patient, patient sex, ethnic origin, and date of birth; the date and site of the diagnostic biopsy; a tabulation of nodal and extranodal sites of involvement; Ann Arbor stage at the time of diagnosis.

Available laboratory data, performance status and maximum diameter of the largest tumor mass were recorded, as well as the initial therapy and therapeutic response, details of remission, progression and follow–up were tabulated in each case.

The pathology slides and reports were collected at the Institute of Pathology in Skopje, including the cases from the Laboratory for Histopathology and Cytology at the University Clinic of of Radiotherapy and Oncology. All the slides were stained by H&E, Giemsa, PAS and Reticulin and immunostained with LSAB technique at the Institute of Pathology.(2,4) All the cases were restained at the Institute of Pathology, University of Wuerzburg . The original stained slides and restained slides were organized for review from five expert hematopathologist, and additional sections, immunostains, as well as molecular analyses, were performed if deemed necessary by the expert pathologists. These results were recorded on a standardized form for direct computerized data entry. These additional analyses were done at the Institute of Pathology in Wuerzburg by courtesy of Prof. Konrad Muller-Hermelink and Prof. A. Rosenwald. Diagnostic slides were previously diagnosed from a domestic pathologist (Petrusheska G., Zografski G., Ivkovski Lj.). Afterwards, they were reviewed and classified independently by each expert hematopathologist (Muller-Hermelink H. K., Weisenburger D., Diebold J., Natwani B., Maclellan K.). In addition to independent diagnoses rendered by each of the expert pathologists, a consensus diagnosis was reached in each case on multi-headed microscope by discussion of the five expert pathologists at the end of each day. If there was no agreement, additional immunostains, molecular analyses and additional information were required, (mainly done from the Prof. Hermelink laboratory in Wurzburg). Few additional clinical informations were available for this purpose. Finally,
all the data were sent to Prof. Weisenburger, who made final consensus diagnoses of the Macedonian cases with NHL. Molecular analyses done from the Prof. Hermelink laboratory in Wurzburg were as follows: Case#6, #14; #85; #141: EBER (-) ; Case# 45; #112; #217: PCR-IgH: FR3A (oligoclonal), FR2A (monoclonal); Case#53; #72: FISH c myc BAP; Case #106; #112: Bcl2-BAP FISH; Case # 125: PCR-TCRg.

Results: Fourteen from the 222 cases (6.8%) were diagnosed as other than NHL and, thus, were excluded from further analysis. Approximately 32.7% of the cases were forms of diffuse large B-cell lymphoma. Approximately 11.21% of the cases were types of marginal zone lymphoma (extranodal, nodal and splenic marginal zone NHL). SLL/CLL was observed in 9.21% of the cases and follicular lymphoma was observed 7.31 of the cases. There were solitary plasmacytic lesions (bone and extraosseal lesions in 6.34% of the cases. All types of T cell proliferations made up only 5.85% from the cases and anaplastic large T/null-cell lymphoma was present in 1.46% of the cases.

Percent of disagreement was lower for low grade NHL-s, probably due to insufficient immunophenotyping in the domestic laboratories. However, for these low grade lymphomas, information on the immunophenotype did not increase significantly the diagnostic accuracy even in the expert hematopathologists group. From this point of view, further molecular analyses were significantly helpful, as well as clinical data. Immunostains for other NHL-s were significantly accurate and resulted in greater agreement in the diagnoses. For some cases, clinical data were very important for final decision for making a diagnosis. Opposite to this, precise histologic diagnosis of a specific type of lymphoma provides both clinically and prognostically important information. Immunophenotyping added significantly to the accuracy of diagnosis of many of the lymphoma types, including MCL, DLBCL and PTCL. This was not the case with the other low grade NHL-s, such as FL, SLL and MZL, where major pitfalls were observed. Also, it is very important to have tissue available for immunostaining and other special analyses to facilitate proper patient care.

That implies the need for more intensive communication among the surgeon, hematologist and pathologist. One of the final conclusions of this study was that besides the importance of the clinical presentation for the precise diagnosis of the NHL, it is also important to have other clinical parameters such are prognostic factors as defined by the International Prognostic index. They must be combined with the histologic classification for appropriate clinical decisions (3,5).

References

L-12

Plasma cell disorders and secretory large cell lymphoma

Jovanović R.

Institute of Pathology, Medical Faculty, University “Ss. Cyril and Methodius”, Skopje, Macedonia

Plasma cell neoplasms (PCs) are clonal expansion of Ig-secreting, heavy-chain class-switched, terminally differentiated B-cells that secrete monoclonal (homogenous) Ig – paraprotein or M-protein. A pre-neoplastic state is recognized - Monoclonal gammopathy of undetermined significance (MGUS), in which there is a clonal expansion of Immunoglobulin secreting clone, but not overt neoplastic proliferation.

In addition, neoplastic PC proliferations including PC myeloma (Multiple myeloma), Solitary plasmacytoma of bone and Extraosseous plasmacytoma will be discussed, with short overview on the monoclonal immunoglobulin deposition diseases.

Secretory Large B-cell lymphomas are heterogeneous group of neoplasms with a common feature – presence of plasmacytic/blastic/oid differentiation. The main focus will be on the plasmablastic lymphoma and variants and subtypes of DLBCL that in some cases can express plasmacytoid differentiation (DLBCL NOS – Immunoblastic var. with plasmacytoid differentiation, DLBCL associated with chronic inflammation, Lymphomatoid granulomatosis (rare cases), ALK+ large B-cell lymphoma, Large B-cell lymphoma arising in HHV8-assoc. multicentric Castleman disease, and Primary effusion lymphoma - extracavitary variant).

L-13

Diffuse large cell lymphoma - advance in the diagnosis and treatment in last decades in Macedonia

Stojanovik A.

University Clinic for Hematology, Medical Faculty, Skopje, Macedonia

Nowadays, goal of treatment approach in diffuse large B cell lymphoma is cure and first step towards it is to achieve complete remission. DLCBL is a potentially curable disease, with curability highly dependent on clinical and biological features. According to the WHO classification of Hematological Malignancies, the entity of DLCBL is characterized by rapidly growing mature B cell tumors with large or relatively large cells and includes a number of disease variants.

Non Hodgkin’s lymphomas are majority of lymphoid neoplasms in Europe with the incidence rate of nearly 15 new cases per 100,000 inhabitants. More than 90% of aggressive lymphomas are derived from B cells (1).

In patients with DLCBL initial diagnosis should be based on adequate sample of tissue obtained with an excisional biopsy of an abnormal lymph node or a generous incisional biopsy of an involved organ (2). Once the diagnosis of DLCBL is established, the second mandatory step is evaluation of patient to determine sites of involvement by the lymphoma and the presence or absence of key prognostic factors to complete a staging evaluation.

Results of the pre-therapeutic staging are also the basis for determining the response to therapy. Imaging studies include at least computed tomography of the chest, abdomen and pelvis and PET scan if available. Bone marrow biopsy is routine diagnostic procedure. Cure of the disease need a complete response to therapy. The new response criteria were developed to incorporate PET scan, as the most
sensitive and specific imaging modality currently available for patients with aggressive lymphoma (3,4).

The International Prognostic Index (IPI) is considered to be the most important prognostic factor for survival and the strongest indicator for identification of high-risk patients, who are unlikely to be cured with standard chemotherapy. IPI is based on only 5 clinical characteristics (age, performance status, stage, extranodal involvement, LDH level). The Vancouver group evaluated the significance of the IPI in the modern rituximab era when initial treatment is R-CHOP. R-IPI remains the most clinically tool to predict prognosis (5).

The chemotherapy has transformed DLCBL from a fatal disease into one that can be cured and the development of curative combination chemotherapy for patients with advanced stages of aggressive NHL has been one of the major successes of cancer therapy. The backbone of that treatment is the CHOP regimen, initially proposed for an aggressive lymphomas in the 1970s. Decades after, there were several attempts to improve CHOP regimen with more intensive chemotherapy (m-BACOD, Pro-MACE-CytaBOM, MACOP-B) named as second and third generation regimen with six to eight chemotherapy drugs. These regimens, despite their promising initial results did not prove to be better than standard CHOP regimen (6).

Although CHOP is considered as a gold standard, the search for the optimal chemo-therapy regimen for treating DLCBL continues. ACVBP regimen shown to be superior than CHOP according to GELA in subgroup of poor risk patients (7). Results are better in older patients whereas CHOP is administered at 14 rather than 21 days.

A major shift in the frontline management of DLCBL and changed practice throughout the world has been the addition of the monoclonal chimeric antibody against CD20, rituximab, to anthracycline based chemotherapy (8). Rituximab is chimeric human/murine antibody that binds specifically to the B-cell surface antigen, CD20. Rituximab induces lymphoma cell lysis through different immunologic or direct mechanisms, including direct induction of apoptosis and both complement mediated lysis and antibody dependent cellular toxicity. When combined with chemotherapy, there is marked synergy with substantial gains in both PFS and OS and there are now several large-scale randomized trials demonstrating the superiority of rituximab-containing regimens for both older and younger patients.

There are still patients who failed to obtain complete remission after initial treatment and patients relapsing, earlier or later, after achieving complete remission. These patients are candidates for salvage regimen (R-DHAP or R-ICE, efficacy is broadly similar) to induce complete remission and then proceed to autologous peripheral blood stem cell transplantation (9).

In Republic of Macedonia annually more than 100 cases of NHL are diagnosed at the population of cca 2 million inhabitants (67 cases in 2002, 84 cases in 2007, and 119 cases on 2012). The percent of DLCBL is relatively low comparing with statistic data from other countries (less than 25% of all lymphoma cases). The incidence of lymphomas in Macedonia is low, 5-6 cases on 100,000 inhabitants, probably the result of important number of unrecognized cases.

The results of the treatment of DLCBL in last two decades in Macedonia with overall survival and progression free survival will be presented, together with our experience with CHOP regimen before and after introducing rituximab in the regular treatment.

References


Case 1
Testicular plasmacytoma
Domazetovski I., Dukovski D., Petrushevska G.1
1Institute of Pathology; 2University Clinic for Hematology, Medical Faculty, University “Ss Cyril and Methodius”, Skopje, Macedonia

In December 2008 58-years old male underwent a surgical treatment because of a tumor mass on the right testicle.
The gross examination at the Institute of Pathology showed a testicle, which measured 8.5 x 6 x 2cm with smooth and intact tunica albuginea. On dissection a grey-reddish tumor mass was present, replacing most of the normal testicular tissue, leaving just a small part of it.
The microscopic examination showed presence of a neoplasm, composed of large, partially polygonal cells with predominantly plasmacytoid appearance. Some of the cells were plasmablastic. The cells had large, vesicular nuclei with prominent nucleoli. Individual seminiferous tubules, inlaid by Sertoli cells were present in the neoplastic infiltrate.
The neoplastic cells were positive for CD43, CD79 and LCA, and negative for CD20, CD3 and CD5, while the proliferative index Ki67 was 50%. A diagnosis of non-Hodgkin’s lymphoma-NOS was established with a recommendation for additional typization.
Additional immunostainings for CD20(-), CD79a(+), cKappa(-), cLambda(+), CD5(-), CD3(-), CD138(-), EBER(-), Cyclin D1(-), MUM(+) and Ki-67>50% were performed at the Institute of Pathology in Würzburg, were a diagnosis of plasmacytoma was established.
In January 2009 the patient was presented at the University Clinic for Hematology with a medical history of a non-Hodgkin’s lymphoma, NOS. Physical examination disclosed a palpable tumor mass on the right side of the neck, which measured 10 x 10 cm. There were no signs of organomegaly.
Diagnostic investigations that were performed included: blood count ESR 32mm/h; Hgb
140g/l; WBC 8.3x10⁹/l; Plt 325x10⁹/l LDH 738U/l and urea 14.1 mmol/l. Other laboratory tests including liver functional tests, urine analyses, serum protein electrophoresis, and creatinine were within normal limits. The CT scan of the chest revealed a mediastinal tumor mass and the one of the abdomen showed presence of peritoneal tumor mass and ascites. The patient received eight cycles of CHOP regimen, achieving partial remission. December 2010 a relapse of the disease occurred with extranodal tumor infiltration of the major pectoral muscle and flexor muscles of the hands and fingers, and an abdominal tumor mass. The patient received one CHOP cycle and was put on hemodialysis because of the acute renal failure (urea 19.6mmol/l; creatinine 695µmol/l), finishing with a lethal outcome.

Case 2

**Diffuse large B-cell lymphoma, immunoblastic variant with plasmablastic differentiation**

*Bogdanovska-Todorovska M.¹, Petrushevska G.¹, Popova-Simjanovska M.²*

¹Institute of Pathology, ²University Clinic for Hematology, Medical Faculty, University “Ss Cyril and Methodius”, Skopje, R. Macedonia

A 60-years old male presented with fatigue, malaise, dyspnea and oliguria was admitted at the University Clinic for Hematology in May 2010. Physical examination revealed scleral icterus and enlarged lymph nodes, in neck, axilla and inguinal region. There was no hepato-splenomegaly. Abdominal ultrasonography examination revealed enlarged paraaortic lymph nodes. Computerized tomography scan was also performed and showed enlarged mediastinal lymph nodes and bilateral pleural effusion. Laboratory tests included: blood count, Hb 88; Le 11.8; Plt 798; urea 23.6; creatinine 156; ac.uricam 1092; LDH 1205 and TP 60g/L. Lymph node biopsy was performed.

The microscopic evaluation revealed completely effaced lymph node architecture due to diffuse infiltration with large atypical lymphoid cells. The neoplastic lymphoid cell population consisted predominantly of immunoblasts with large nuclei, vesicular chromatin and single, large, centrally placed nucleoli. Plasmablasts and centroblasts were also observed. Mitotic figures were common. Immunohistochemical analysis showed that atypical cells were positive for MUM1, CD79a and negative for CD20, CD138, CD56, CD5, bcl1, bcl2 and bcl6. The proliferation index Ki 67 was positive in 90% of the tumor cell population.

A diagnosis of diffuse large B-cell lymphoma (DLBCL), immunoblastic variant with plasmablastic differentiation was established. The differential diagnosis included other CD20 negative B-cell non-Hodgkin lymphomas (Plasmablastic lymphoma, Primary effusion lymphomas, Anaplastic lymphoma kinase (ALK)–positive large B-cell lymphoma).

Additional immunostainings for MUM1(+), CD20(-), cKappa(+), cLambda(-), CD5(-), CD10(-), CD138(-), CD56(-), bcl1(-) and Ki67 (high) were performed at the Institute of Pathology in Wuerzburg, and the diagnosis for DLBCL was confirmed.

The patient was treated with CHOP chemotherapy regimen. After 2 cycles of CHOP he died due to acute renal failure, on July 2010.
Case 3
Osseal diffuse large B-cell lymphoma with plasmablastic differentiation

Dukovski D.1, Dukova B.2, Petrushevska G.2

1University Clinic for Hematology, 2Institute of Pathology, Medical Faculty, University “Ss Cyril and Methodius”, Skopje, R. Macedonia

In June 2009 49 years-old male presented at University Clinic for Hematology with a medical history of maxillary tumor. An ex tempore biopsy was performed in April 2009 with the finding of undifferentiated carcinoma, followed with a radical surgical resection and a diagnosis of Non Hodgkin Lymphoma-Diffuse large B cell lymphoma (DLBCL). Physical examination disclosed no palpable lymphadenopathy and no organomegaly. Routine laboratory test revealed: ESR 50/; Hgb 133; WBC6,1; Plt325 and other laboratory tests including liver functional tests, urine analyses, serum protein electrophoresis, blood urea, and creatinine were within normal limits except LDH 738. Radiologic findings were normal in chest X-ray and abdominal ultrasound. Performed bone marrow biopsy revealed no infiltration.

Radical surgical resection of right eye enucleation, maxillary sinus tissue and right neck dissection was analyzed by routine histohemical and immunohistochemical techniques. The histopathologic evaluation showed diffuse growth pattern of large blastoid cells involving maxillary sinus mucosa, periorbital soft tissue and neck lymph nodes. The neoplastic cells were positive for CD20, CD79 and MUM1. T-cell markers were negative, as well as bcl-6. Proliferative marker Ki67 showed nuclear positivity in more than 60% of tumor cell population.

The diagnosis of DLBCL was made. Additional immunostainings for EBER iSH (-) and Perforin (-) was performed at the Institute of Pathology in Wuerzburg, and diagnosis of plasmacytoma was made. The patient underwent Rituximab-CHOP regimen (6 cycles), radiotherapy on eye orbit and maxilla. In January 2010 there was relapse of DLBCL involving soft tissue in orbital cavity (CT scan findings) without peripheral lymphadenopathy, and no organomegaly. In July 2010 the patient underwent high-dose chemotherapy with autologus peripheral stem cells transplantation with achieving complete remission.

Case 4
Diffuse large B cell lymphoma- small cell plasmacytoid type

Kostadinova-Kunovska S.1, Trajkova S.2, Petrushevska G.1

1Institute of Pathology, Medical Faculty, University “Ss. Cyril and Methodius”, Skopje, Macedonia; 2University Clinic of Hematology, Clinical Center, University “Ss. Cyril and Methodius”, Skopje, Macedonia

Primary bone lymphoma is a rare entity with an incidence of less than 1% of all lymphomas and 7% of all malignant bone tumors. We present a case of a 49-year-old female with pathological fracture of the left humerus and previous history of breast carcinoma.

The breast carcinoma had been diagnosed 2,5 years prior to the fracture, treated surgically, with chemo- and radiotherapy. 15 months after the surgery, she developed metastatic infiltration of the paravertebral soft tissue and pleura, treated with chemo- and radiotherapy.

The histopathological analyses of the bone tumor curretage revealed highly cellular tumor tissue with non-cohesive growth pattern and necrotic areas, composed of pleomorphic lymphoid cells with
prominent nucleoli and high mitotic index, among which centroblasts, immunoblasts and plasmacytoid cells were recognised. The initial immunohistochemistry showed that tumor cells were positive for LCA and bcl2; ruled out metastatic breast disease (Cytokeratin -), and other small round cell neoplasms (Vimentin -, CD99 -). Further investigations showed that the cells were CD20 +, bcl6 -, and the proliferative index (Ki67), was >90%. The tumor cells were also negative for CD10, MUM1, CD23, CD30, CD138, kappa, positive for lambda light chains, and some were positive for CD5. The initial, as well as consensus diagnosis was Diffuse Large B Cell Lymphoma, small cell plasmacytoid type. The DLBCL with plasmacytoid features have tendency for extranodal localization, poor response to chemotherapy and short survival, which was also the case with our patient, who died less than 17 months after the diagnosis of DLBCL.

Case 5
Lymphoplasmacytic lymphoma
Popova-Simjanovska M.1, Jovanovik R.2, Petrushevska G.2
1University Clinic for Hematology, 2Institute of Pathology, Medical Faculty, University “Ss Cyril and Methodius”, Skopje, Macedonia

In January 2009 73-years old male presented at the University Clinic for Hematology with a medical history of increased susceptibility to infections. Physical examination revealed no lymphadenopathy or hepatosplenomegaly, neither other remarkable findings. Diagnostic investigations that were performed included: blood count, ESR 72/; Hgb 134; Le 12,2; Plt 314; and other laboratory tests (urea 4.2 mmol/L, creatinine 65 mmol/L, uric acid 284 mmol/L, negative Bence-Jones proteins, positive paraproteins, β2-microglobulin 1.78, IgM 33.2, IgA 0.4, IgG 6.0). Radiologic findings included chronic bronchitis and no signs for osteolysis in the scull, sacral and vertebral column bones, although osteoporosis and degenerative changes were detected. Bone marrow (BM) biopsy was performed. The histopathologic evaluation revealed hypercellular BM with interstitial and focal-patchy infiltration with small lymphocytes, admixed with lymphoplasmacytic and plasma cells occupying approximately 50% of the bone marrow. Some of the plasma cells contained intranuclear pale inclusions. There were also residual normal hematopoietic elements with increased presence of mastocytes. The neoplastic lymphocytes were positive for CD20, IgG positive (some of the lymphocytes), IgM-negative, non-specific background signal for CD15.

A diagnosis of Lymphoplasmacytic lymphoma (LPL) was established with a differential diagnosis of CLL/SLL with immunocytic differentiation. Additional immunostainings for CD20(+), CD79a(+), cKappa(+), cLambda(-), CD5(-), CD30(-) and CD138(+) were performed at the Institute of Pathology in Wuerzburg, and LPL was confirmed.

Initially the patient was treated with Rituximab (4 doses). Because of persistent disease the treatment continued with CVP (8 cycles). One month afterwards BM showed residual disease, high total proteins and paraprotein positivity (IgM 10,96). The treatment proceeded with FCR regimen (4 cycles) resulting in IgM reduction (3,31). Therapy with Thalidomide and corticosteroids followed. From February 2011 until March 2013 the patient was stable and receiving bisphosphonates.
Epithelioid angiosarcoma mimicry (Case Ma-128)

In November, 2009 66-years old female with decreased body weight was admitted at the Hematology Clinic. Laboratory investigations showed elevated SR 46/--; Hb 101; Le 5.5; Tr 369 and other laboratory investigations were in normal range (urea - 4.1, creatinine - 101, AST - 24; ALT – 27; LDH – 400; AP 98; total proteins - 68g/L). On physical examination there were found multiple ulcerative lesions on the anterior abdominal wall with diameter of 5-6 sm. CT of chest and abdominal cavity: increased lymph nodes in anterior mediastinal cavity. Surgical biopsy from tumor lesion was done.

On histological examination two irregular skin excisions measuring 1.7x1.5x0.8cm and 1.6x1.4x0.7cm with central ulcerative lesions with diameter of 0.5cm. were seen. On dissection one found fleshy tumor tissue with largest diameter of 1.3cm, and infiltrative borders. The histological examination demonstrated infiltrative malignant lesion in dermal and subcutaneous fatty tissue with surface epidermal ulceration. Tumor cells had pleomorphic large nuclei with central nucleoli and eccentric bluish rather than eosinophylic cytoplasm, and high mitotic rate (Fig.1). The cells were positive for CD138, vimentin negative, with suspicious positivity for kappa light chain and diagnosis of plasmablastic lymphoma was made. The patient was treated with CHOP C8 regimen, followed by partial remission. Treatment was continued with CVP V9 regimen and patient died after two years.

After reviewing of the case additional immunostain for CD31 (Fig.2) strong positivity in the tumor cells and consensus diagnosis of epitheloid angiosarcoma followed.WHO classification of vascular tumors include : hemangiomas, epitheloid hemangioma, angiomatosis, lymphangioma, Kaposiform hemangioendothelioma, retiform haemangioendothelioma, papillary intralymphatic angioendothelioma, Kaposi sarcoma, other intermediate vascular neoplasms, epitheloid hamangioendothelioma, angiosarcoma of soft tissue including epitheloid angiosarcoma. Although epithelial angiosarcoma may occur as cutaneous tumors, most segregate in deep soft tissue. Patient’s ages range from 2 to 97 years and usually appear as a scalp tumor, facial lesions, within irradiated skin regions.

Histologically the tumor is composed from packed polygonal cells with focal evidence of endothelial differentiation. Diverging phenotype is consisted from sinitial growth of large cells with clear nuclei and prominent nucleoli in the dermis, predominance of discohesive plasmacytoid polygonal cells with abundant bright eosinophylic cytoplasm. This phenotype posed further diagnostic challenges simulating lymphoma, melanoma, lymphoepithelioma like carcinoma. Immunohistochemical studies reveal positivity for CD31 and CD34 and no immunoreactivity for other antigens including cytokeratins, S100, melanocytic antigens, leukocytic common antigens and desmin. Alternatively one can find focal positivity for panCK, EMA, SMA.

This tumor is highly aggressive tumor and therapeutic modalities: combine local excision, chemotherapy and radiotherapy. For diagnosis CD31 combines both relative specificity with excellent sensitivity and is positive in approximately 90%.
In conclusion epitheloid cutaneous angiosarcoma is rare neoplasm and may have a broad morphological spectrum, raising interpretative challenges on microscopy in the histopathology lab. Clinical features of the disease are important for the right interpretation of the histological findings and for the further treatment of the patients.

**Fig.1. H&E, 400x.**

**Fig.2 CD31, PT-LINK**

**Thymoma B1 and its differential diagnosis (Case Ma-130)**

In October, 2009 40-years old male with aches in the left side of mediastinal cavity was admitted at the University Clinic of Haematology. On physical examination there was no hepato- and splenomegaly as well lymphadenopathy. Laboratory investigation showed ESR – 76/--; Hb – 127; Le – 6.8; Tr – 395; glycaemia 12.5; urea 5.7; creatinine 76; acidi urici 263; AST 26; ALT 24; AP 116; Total proteins 74 g/l; IgG 18.79; IgA 5.52; IgM – 0.83. Examination of the bone marrow showed normal morphology. On CT there was found infiltration of the right pulmonary artery by large tumor mass. Surgical biopsy was done followed with diagnosis of T-cell lymphoblastic lymphoma. Patient was treated with R-CHOP C8 regimen until 04. 2010. In January 2012 the disease relapsed with increased mediastinal lymph nodes on CT (upper mediastinal space, paratracheal at the level of hilus on the right side and infiltration into the pulmonary artery). Treatment was continued with R-CVP C8 protocol and the patient was last seen October 2012.

Reviewing of the histological specimens showed histological analysis of 4 tissue fragments, largest one measuring 4x4x2cm. Microscopical examination revealed tumor mass consisting of lymphocytes with hyperchromatic nuclei, resembling to lymphoblasts separated by thick collagenous bands. There was found CK18 positivity in the meshwork of epithelial cells, and diagnosis of Thymoma B1 was done by the consensus group. WHO classification of thymic tumors describe thymic thymoma B1 as „tumour of thymic epithelial cells, histologically indistinguishable from the normal thymus, composed predominantly of areas resembling cortex epithelial cells scattered within in a prominent population of immature lymphocytes and areas of medullary differentiation“.

Differential diagnosis includes: normal thymic tissues; B2 thymoma, T Lymphoblastic lymphoma. B1 Thymoma has large excess of cortical areas compared to small areas resembling the thymic medulla, fewer Hassaall corpuscles, less regular lobulation and thick fibrous septa and capsule (Fig. 3). Infiltrative pattern of lymphocytes in septa and capsule favors lymphoma that are Tdt+ (Fig.4).
Expression of cytokeratin meshwork (CK19+, CK7+, CK focal+, CD5-, CD20-, Ki67 low) are important signs of thymoma B1. Presence of cortical T lymphocytes (CD1a+, CD4+, CD8+, CD5+, CD99+, TdT+) could be found in both entities. Mature medullary T lymphocytes (CD3+, CD5+, CD1a-, CD99-, Tdt-) are rare. B2 Thymoma is a tumor of organotypic thymic epithelial cells with large polygonal cells with vesicular nuclei and prominent nuclei arranged in a loose network. A background population of immature T cells is always present. The cells are CK19+(100%), CK5/6+(90%), CK7 (80%), CD5-, CD20-, CD70- and always there are immature T lymphocytes (CD1a+, CD4+, CD8+, CD5+, CD99+, TdT+) (Fig.5).

Atypical lymphoid hyperplasia (Case Ma-125)

In September 2009, 25 years old male with neck lymphadenopathy was admitted at the Clinical Hospital of Hematology. On laboratory investigations there was found: Hb – 117; Leu – 38; Tr -127; Total protein 112 gr/L; LDH – 391; AP – 153; Coombs+; IgG>34.7; IgA – 5.5; IgM – 0.43. CT of abdominal cavity showed splenomegaly, increased number of lymph nodes with regular dimensions. Lymph node biopsy was indicated and histological diagnosis of NHL – Immunocytoma was done that was confirmed from the referral center in Wuerzburg. The patient was treated with FCR C5 until 06.2010. On control examination with PET CT scan normal findings were gain and the patient is on maintenance with Rituximab.

Histopathology: two adhered lymph nodes were admitted at the pathology lab with largest diameter of 2.5cm. Standard histochemical and immunohistochemical stainings (H.E., Giemsa and CD20, CD3, CD15, CD30, Ki67) were done. Microscopically one could found few regressive follicles and
widen the disturbed paracortical area with abnormal vascular proliferation (epitheloid venules?). There were areas of remaining marginal zones with proliferation of atypical lymphoid cells and plasma cells. Although further molecular clonality analyses for the FR2A-region appeared to be oligoclonal the destructive character favours a diagnosis of indolent B-cell lymphoma. Consensus diagnosis was diagnosis other than lymphoma because of no proof of clonality – neither by IHC-ry for kappa and lambda nor by molecular analyses. This type of destructive architectural lesion is indicative for new entity of ATYPICAL LYMPHOID HYPERPLASIA (Fig.6).

Fig.6. PAS: 250x

Unclassifiable case, probably peripheral T-cell lymphoma of cerebellum

Janevska V.¹, Petrushevska G.¹, Filipche V.², Jovanovik R.¹, Ognenoska-Jankovska B.³
¹Institute of Pathology, Medical Faculty, Skopje, Macedonia; ²University Clinic of Neurosurgery, Skopje, Macedonia; ³University Clinic of Radiotherapy and Oncology, Skopje, Macedonia

A 53 years old woman was admitted to the hospital because of three day long vomiting, few weeks long headache and psychomotor slowness. The computed tomography showed hypodense area in right cerebellum with compressive effect to fourth ventricle and the MRI showed tumor lesion in cerebellum and two others small lesions in supratentorial region. A surgical removing of the cerebellar tumor was done. Two days after the surgery the patient’s general condition was worse and the control CT showed multiple hypodense areas in basal ganglia. The patient passed away seven days after the surgery.

Macroscopically the cerebellar tissue was finely granulated and at cut surface there were large areas of necrosis and hemorrhage. Microscopically there were multiple necroses in the cerebellar tissue with patchy lymphoid infiltrate in vital areas. Many plasma cells, lymphocytes and histiocytes were recognized among pleomorphic lymphoid cells. Immunohistochemically the cell population was predominately positive for T cell lymphocytes: CD3+, CD4+, CD8+, CD20-, MUM1-, PCA+, CD68+, CD34-, CK-. The second prominent morphological feature was endothelial proliferation in some blood vessels, presence of intraluminal thrombi and perivascular cuffing of lymphocytes and plasma cells in outer layer.

The differential diagnosis was made between peripheral T-cell lymphoma NOS and vasculitis.
L-15

**Indolent B-cell lymphomas and mantle cell lymphoma in Romanian lymphoma series**

*Fetica B.*

Institute of Oncology “Ion Chiricuta”, Cluj-Napoca, Romania

**Objective:** Indolent b-cell lymphomas generate a health problem world wide representing roughly 40% of non-hodgkin lymphoma. Unfortunately these slow-growing malignancies produce no symptoms until they are in advanced stages. Although in Western Europe and USA follicular lymphoma is reported to be the most prevalent indolent lymphoma this pattern is not met in developing countries such as Romania. My presentation will focus on the distribution of indolent B-cell lymphoma in the Romanian lymphoma cases and on the importance to have a quality and complete diagnosis for the mantle cell lymphoma.

An important issue will be to see if there are similarities between the proportions of indolent B-cell lymphoma and mantle-cell in Romania and the other countries from the Balkans-region.

**Material and methods:** We have included in our study 198 consecutive lymphoma cases diagnosed in our Institute between 2004 and 2007, followed-up until April 2010. The consensus diagnosis was reached by a panel of 4 independent haemopathology experts from the International Lymphoma Study Group. Age, sex and overall survival (Kaplan Meier estimate) were compared among all lymphoma categories.

**Results:** Indolent B-cell lymphoma represented 30.81% of all cases with a distribution as follows: 4% Extra-nodal MALT lymphoma with 3 year overall survival of 85%, 19.7% Chronic Lymphocytic Leukemia with 3 year overall survival of 66% and 7% Follicular Lymphoma with 3 year overall survival of 62%. Mantle cell lymphoma represented 5.56% of all cases with 3 year overall survival of 9%.

**Conclusions:** Most of the indolent b-cell lymphomas have a memory b-cell as counterpart logically leading to the conclusion that inflammatory response plays an important role (sometimes central) in lymphoma-genesis of these malignancies.

The follicular lymphoma prevalence is evidently distinct from Western Europe opening the door to speculations about a possible environmental trigger.

Mantle cell lymphoma even if is a small cell lymphoma and shares sometimes morphological cellular features and pattern of invasion with indolent B-cell lymphomas has in general a more aggressive clinical course. For these reason it is important to have a good morphological, immunohistochemical and molecular diagnosis to separate the mantle cell lymphoma from the indolent lymphomas.
SATELLITE SYMPOSIUM LECTURES

HOFFMAN-LA ROCHE SATELLITE SYMPOSIUM

SS-01.
Diagnostic algorithm of malignant lymphomas, classification and pathohistological characteristics
Petrushevska G.
Institute of Pathology, Medical Faculty, Skopje, Macedonia

SS-02.
MabThera treatment of NHL and CLL
Georgievski B.
University Clinic for Hematology, Medical Faculty, Skopje, Macedonia

NOVARTIS ONCOLOGY SATELLITE SYMPOSIUM

SS-03.
The evolution in CML continues...
Karanfilski O.
University Clinic for Hematology, Medical Faculty, Skopje, Macedonia
PROFFERED PAPERS

PP-01
Distribution of lymphoid neoplasms in Serbia
Perunicic-Jovanovic M.¹, Cemerikic-Martinovic V.², Terzic T.³, Krstic M., Mihailovic D.⁴, Stojnev S.⁴, Nikin Z.⁵, Jakovic Lj.⁶
¹Department of Pathology, Clinical Center of Serbia, Belgrade; ²Beo-lab, Belgrade; ³Institute for Pathology, Medical Faculty, University of Belgrade; ⁴Center for pathology, Clinical Center, Nis; ⁵Department for Pathology and Cytodiagnostics, Oncology Institute of Vojvodina, Sremska Kamenica, Serbia; ⁶Clinic for Hematology, Clinical Center of Serbia, Belgrade

The subtype distribution of lymphoid neoplasms in Serbia was analyzed according to WHO classifications excluding plasma cell myeloma/plasmacytoma. We conducted a comprehensive analysis, based on subtype, age, sex, and localisation of primary biopsy specimens of 1,999 lymphoid neoplasms diagnosed from January 2011 to December 2012 at 5 institutions.

Of the 1,999 patients, mature B-cell neoplasms accounted for 79.43% of all lymphoid neoplasms, Hodgkin lymphoma for 14.85%, and mature T/NK-cell neoplasms for 4.3%. The most common subtype was diffuse large B-cell lymphoma (27.91%), followed by chronic lymphocytic leukemia/small lymphocytic lymphoma (22.6%), Hodgkin lymphoma (14.85%), marginal zone lymphoma (9.50%), follicular lymphoma (8.35%), and mantle cell lymphoma (5.90%). Lymphoid neoplasm subtypes were seen more often in male subjects (57.73%), than in female subjects (42.27%). The common sites of primary diagnosis of lymphoid neoplasms diagnosis were lymph nodes (44.07%), bone marrow (32.66%), gastrointestinal tract (8.90%), and skin (3.5%). The patients age ranged from 7 to 90 years, with a mean age of 58 years.

In summary, our study showed that the epidemiologic features of lymphoid neoplasms in Serbia are similar to those in Western countries in many ways, whereas some subtypes showed distinct features. Our study found a higher rate of Hodgkin lymphoma and marginal zone lymphoma.

PP-02
Descriptive epidemiology of lymphomas: What is going on in Slovenia in the last few years
Gaslievic G.¹, Zadnik V.², Gacic B.³, Gjidera M.¹, Grcar-Kuzmanov B.¹, Volavsek M.¹
¹Institute of Oncology, Department of Pathology, Ljubljana, Slovenia; ²Institute of Oncology, Department of Epidemiology and Cancer Registry, Ljubljana, Slovenia; ³Institute of Pathology, Medical Faculty, Ljubljana, Slovenia

Background and aim: Among all malignancies in Slovenia, malignant lymphomas account for 2.5-3%. The incidence of HL is consistently lower than that of NHL. In NHL, incidence increases with advancing age with a median age of diagnosis in the 7th decade and is generally somewhat higher in men, except for the period 2005-2009 when more women patients was documented (52%). Lymphomas comprise an important part of malignancies in childhood and among young adults (NHLs 7%, HLs 10%). Comparison of lymphomas' incidence over the time is partially complicated by the fact that major, still ongoing changes in the classification of the hematolymphoid malignancies have occurred in recent years, as new diagnostic methods and techniques are developed. The aim of this
study is to present and analyze data on lymphomas' distribution in Slovenia in a period from 2005-2012 (2005-2009 and 2008-2012) according to ICD-O-3 morphology codes.

**Materials and methods:** The present data were collected from the Slovenian Cancer Registry (for the period from 2005 to 2009; the latest available processed data were available for 2009). Since more than 60% of all Slovenian lymphomas are diagnosed at the Institute of Oncology in Ljubljana, data for the period between 2008 to 2012 (period that coincides with 4th edition of WHO classification of tumors of hematopoietic and lymphoid tissue), were collected from the files of the Department of Pathology, Institute of Oncology. Only solid tumors (except for CLL/SLL and excluding plasma cell neoplasms), were encountered in this analysis.

**Results:** Between 2005 and 2009 there were 1 671 cases of newly diagnosed lymphomas in Slovenia, 1 791 (88%) of NHLs and 242 (12%) of HLs. All cases were verified microscopically, either by histology (85-90%) or cytology (10-15%). During the five years period, crude incidence for HL and NHLs remained almost stable or rose modestly, being 2-3/100 000 for HL and 12-13/100 000 for NHLs.

Among HL, nodular sclerosis was the most frequent subtype (45%). More than 80% of the NHLs were represented by five mature B cell neoplasms: DLBCL (33%), CLL/SLL (25,9%), FL of all grades (10,8%), nodal and extranodal MZL (7,1%) and MCL (5,3%), while other B cell NHLs were diagnosed more rarely. Crude incidence rate for DLBCL was 8,3-8,8, for FL 2,7-3,9 and for T cell lymphomas <1. T cell lymphomas (mature T cell neoplasms) represented only a minor part of the NHL group (4,0%), namely PTC NOS 2%, AILT 0,6%, ALCL 1,6% . NOS morphology constituted 4,5% of all diagnosed NHLs.

In the period between January 2008 and the end of December 2012, 1 164 lymphomas were newly diagnosed at the Institute of Oncology in Ljubljana, 1 002 (86,1%) representing NHLs and 162 (13,9%) HLs. The most frequent among NHL diagnoses was DLBCL (29,9%), followed by CLL/SLL (18,5%), FL (14,2%), nodal and extranodal MZL (9,1%) and MCL (7,9%). T cell neoplasms represented 7,2% of all NHLs, the most frequent being PTC NOS (4,5%), followed by ALK+ ALCL (1,5%) and AILT (0,9%).

**Conclusions:** Crude incidence rate for HLs, NHLs and different NHL subtypes, as well as distribution of lymphoma subtypes, are similar to those seen in other countries of the region (Central Europe). Number of cases with poorly defined morphology represented 4.5% of all newly diagnosed lymphomas during 2005-2009. Since somewhat more T cell lymphomas have been diagnosed in the period from 2008-2012, it is very likely that a proportion of them were not recognized previously and therefore placed into an unknown morphology group.

It can be expected that further education in hematopathology with centralized revision of the slides, as well as introduction of the new diagnostic methods and techniques, would improve the accuracy of diagnosis with reducing the number of cases with NOS morphology and improve quality of data that could enable more accurate comparisons of disease incidence and survival over time and across regions.

**PP-03**  
**Bone marrow involvement in non-Hodgkin lymphoma**  
*Terzić T.*  
Institute of Pathology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia

Lymphoproliferative disorders (LPD) in bone marrow (BM) biopsies are generally diagnosed based on histomorphological and immunophenotypical features. All patients with LPD require BM examination for staging propose, but sometimes for diagnosis, especially in cases when lymph node biopsy is not available. However, a trephine biopsy performed for staging may show discordant histological subtype or discordant grade between the type of lymphoma seen in the marrow and that present in lymph node or other tissues, with clear therapeutical implications. A trephine biopsy is also essential for evaluation of therapy response and residual/relapsing disease.

The following topics will focus on the applications of paraffin immunohistochemistry: differentiation of various forms of reactive nodular hyperplasia from neoplastic BM infiltration, patterns of BM lymphomatous infiltration, subtyping B-cell lymphomatous infiltration of BM, detection of occult lymphomatous infiltration of BM, determining prognosis.

**PP-04**  
**Splenectomy for hemathological disorders**  
*Jankulovski N.*  
University Clinic for Digestive Surgery, Skopje, Macedonia

Splenectomy is therapeutic for a large host of conditions. It is a consequence of expanding the list of disorders and liberalizing the indications for splenectomy in many diseases. Red blood cells disorders: autoimmune hemolytic anemia, hereditary spherocytosis, hemoglobinopathies and thalassemia are prone to splenectomy after failure of medical therapy. A variety of thrombocytopenic disorders are improved by splenectomy, and the most common indication for splenectomy is ITP (idiopathic thrombocytopenic purpura). Splenectomy is successful in reversing hypersplenism in a spectrum of disease called myeloproliferative disorders. Relief of symptoms from splenomegaly is also achieved, but it does not affect the inexorable course of the disorder. The role of splenectomy in white blood cells disorders (leukemias and lymphomas) is only palliative and facilitates chemotherapy. Splenectomy in patients with hematologic disorders imparts a risk of fulminant and life threatening infection “overwhelming postsplenectomy sepsis” that can be obviated by appropriate treatment. Although splenectomy for hemathologic disorders is only therapeutic and not curative, the relief of symptoms and for some disorders facilitation of chemotherapy leads to better quality of life and longer survival.

**PP-05**  
**Primary gastric diffuse large B-cell lymphoma**  

¹Clinic for Hematology, Clinical Center Serbia, Medical Faculty, University in Belgrade, Belgrade, Serbia; ²Clinic for Hematology, Clinical Center, Belgrade, Serbia; ³Institute for Medical Statistic and Informatic, Medical Faculty, University in Belgrade, Belgrade, Serbia

27-29 May, 2013  
Skopje, Macedonia
Objective: The aim of this study is to compare two treatments (immunochemotherapy alone and surgery plus immunochemotherapy) as well as to define most important prognostic factors.

Materials and methods: Records of all-stages patients with a diagnosis of PG-DLBCL which were treated in the Clinic for Hematology Clinical Center of Serbia, between 2002 and 2012, were reviewed. Patients fulfilling the following criteria were included in this study: patients with histologically proven large-cell B lymphoma of the stomach who received Rituximab plus CHOP (R-CHOP) regimen as first-line immunochemotherapy with or without additional surgical resection.

Results: From 73 patients who were fulfilled inclusion criteria 44 received R-CHOP and 29 underwent surgical resection followed by R-CHOP. All clinical and pathological features were similar between the two groups. Tumor resection did not improve 5-years OS (75.9% and 65.9%, for surgery plus immunochemotherapy and immunochemotherapy alone, respectively; p=0.293). Ann Arbor clinical stage II (p=0.047), ECOG2 (p=0.008), IPI2 (p=0.038), stage-modified IPI (for II2 grade of the Lugano staging system) (p=0.036), trombocytosis > 450x10^9/l (p=0.001), level of CRP 5mg/l (p=0.028) and albumins level low than 28g/l (p=0.047) were predictors of OS in patients with PG-DLBCL. A new inflammatory stage IPI (IS-IPI) risk score (smIPI plus level of CRP) was recognized as the best prognostic tool (p=0.045) in multivariate analysis. There were significant differences among patients with low-risk (score 0,1) and intermediate/high-risk groups (score 2) in 5-years OS (89.5% vs 50.0%, p=0.021).

Conclusion: IPI staging system modified for high level inflammation has shown to be the best prognostic tool for overall survival of PG-DLBCL patients. Adition of tumor resection to immunochemotherapy did not improve survival.

PP-06 Prediction value of the immunohistochemical GCB/NON GCB classification and outcome of diffuse large B-cell lymphoma patients treated with R-CHOP regimen-single centre experience

Trajkova S., Panovska-Stavridis I., Stoanovik A., Petrushevksa G., Ivanovski M., Dukovski D., Popova-Simjanovska M., Chadievski L., Chevreska L.

University Clinic for Hematology, Medical Faculty, Skopje, Macedonia

Diffuse large B-cell lymphoma (DLBCL) is sub-classified in to molecular subgroups that correspond to different stages of lymphocyte development- namely germinal center B-cell (GCB) and non-GCB DLBCL. Results of different studies showed that prognosis of GCB DLBCL are better than of non-GCB DLBCL if treated initially with CHOP like regimens. However, recently the results from one large prospective study indicated that in Rituximab (R)-CHOP treatment settings other markers than immunohistochemical features predict the outcome of the DLBL. In order to investigate the prediction value of the immunohistochemical GCB/non GCB classification of DLBCL and the outcome of our DLBL patient treated with the R-CHOP regimen we conducted a retrospective study.

A total of 132 DLBCL patients diagnosed and treated with R-CHOP regimen at the University Clinic of Hematology in the period between February 2002 and December 2007 were enrolled in our study. The median follow-up of the patient was 36 months. The biopsy samples were immunostained and analyzed for markers of germinal center (Bcl6), post-germinal center (MUM1) and apoptosis (Bcl-2). The patients were categorized as GCB subtype (68; 51, 6%) or non-GCB subtype (64; 48, 4%). The median overall survival time (OS) were 65; 25 months in GCB group and 61, 1 month in non-GCB group, and time to treatment (TT) were 60, 85 and 57.75months respectively for the both groups. The groups were statistically comparable regarding the both parameters. They were also comparable
The prognostic significance of bcl-2, tumor associated macrophages and total lymph node involvement by neoplastic and inflammatory cells in advanced stage classical Hodgkin's lymphoma

Jakovic Lj.¹, Mihaljevic B.¹,², Perunicic-Jovanovic M.³, Bogdanovic A.¹,², Andjelic B.¹, Bumbasirevic V.⁴

¹Clinic for Hematology, Clinical Center of Serbia, Belgrade, Serbia; ²Faculty of Medicine, University of Belgrade, Belgrade, Serbia; ³Department for Histopathology, Clinical Center of Serbia, Belgrade, Serbia; ⁴Institute of Histology and Embryology, Faculty of Medicine University of Belgrade, Belgrade, Serbia

Although Hodgkin’s lymphoma (HL) is a curable cancer, current treatment strategies are not precise enough. The predictive power of biological and morphological parameters is controversial and prognostic models have not reached wide acceptance.

The aim of the study was to determine whether tissue-based variables could add prognostic value to standard clinical parameters and contribute to better risk stratification of HL patients. We analyzed the prognostic relevance of 8 parameters in 85 advanced stage classical HL patients.

Univariate analysis confirmed five indicators of shorter OS: Bcl-2 overexpression by HRS cells (>50%Bcl-2+HRS); increased CD68 tumor-associated macrophages (>25%CD68+TAM); IPS>2; bulky disease; and total involvement of the lymph node by neoplastic and inflammatory cells (TLNI) (p=0.007, p=0.003 p=0.000, p=0.002, p=0.017, respectively). These factors also influenced lower EFS (p=0.031, p=0.035, p=0.004, p=0.014, respectively), apart from TLNI.

Multivariate analysis identified five independent factors for OS: >50% Bcl-2+HRS; >25% CD68+TAM; TLNI; IPS>2; and bulky disease (p=0.025, p=0.042, p=0.003, p=0.000, p=0.003, respectively). Furthermore, >25% CD68+TAM; IPS>2 and bulky disease affected EFS (p=0.044, p=0.009, p=0.018, respectively).

Based on the cumulative score of unfavorable prognostic factors for OS, we designed a prognostic model stratifying patients into 4 risk groups (low 0-1, intermediate 2, high 3, very high 4-5 risk factors) each with a progressively reduced OS (100%, 78%, 45%, 0% respectively, p<0.001).

Our findings support the combination of tissue based variables with clinical parameters, identifying patients who are at higher risk of poor outcome at initial diagnosis.
POSTER PRESENTATIONS

P-01
Acute renal failure in a patient with diffuse large B-cell lymphoma
Domazetovski I.¹, Jovanovik R.¹, Kostadinova-Kunovska S.¹, Duganovska S.¹, Labachevski B.¹, Nikolov I.², Ivanovski N.², Shikole A.², Petrushevska G.¹
¹Institute of Pathology, Medical Faculty, University “Ss. Cyril and Methodius”, Skopje, Macedonia; ²University Clinic of Nephrology, Medical Faculty, Skopje, Macedonia

Objectives: The aim of the report was to update the literature concerning this topic and highlight the importance of renal biopsy in obtaining a correct diagnosis, selecting the appropriate therapy and improving the final outcome.

Materials and methods: After the physical examination, laboratory tests and urine analysis, an abdominal ultrasound and peripheral blood smear were made. Autopsy samples were taken from the kidneys, enlarged lymph nodes, and bone marrow, fixated with 10% formalin, sliced and processed with Hematoxylin and eosin (H&E), and immunohistochemical staining methods for CD20, CD79, Bcl-2, Bcl-6 and Ki67.

Results: The laboratory tests showed high levels of degradation products and severe anaemia, while the peripheral blood smear showed presence of dysplastic erythroblasts and hypo-granular neutrophils. The amount of proteins in the 24 hour urine was 1.5 g/l. The ultrasound showed enlarged kidneys, with signs of first degree urinary obstruction and a swollen, hypo-echogenic parenchyma. At autopsy, diffuse, confluent zones of necrosis and bleeding were present in both kidneys. Histologically the interstitial space was heavily infiltrated by a mononuclear substrate, mainly in the medullar part. The glomeruli were spared, with slight capillary congestion, whereas the tubules were atrophic, with notable focal presence of casts. The vast majority of infiltrating cells were CD20, CD79, Bcl-2 positive and Bcl-6 negative. Ki67 was above 80%.

Conclusions: Acute renal failure by a lymphomatous infiltration of the kidneys is extremely rare and usually occurs due to bilateral infiltration. The absence of other causes, together with enlarged, slightly obstructed kidneys with hypo-echogenic parenchyma on ultrasound strongly suggested an infiltrative process in our patient. The noted massive interstitial lymphomatous infiltration, tubular compression and atrophy in our patient might have been the cause of acute renal failure.

P-02
Biological differentiation of diffuse large B-cell lymphoma patients associated with bulky disease and advanced stage using immunohistochemistry
Trajkova S.¹, Panovska-Stavridis I.¹, Stojanovik A.¹, Ivanovski M.¹, Dukovski D.¹, Pivkova-Veljanovska A.¹, Georgievski B.¹, Popova-Simjanovska M.¹, Stankovik S.¹, Chadievski L.¹, Petrushevska G.², Chevreska L.¹
¹University Clinic for Hematology, Medical Faculty, University “Ss. Cyril and Methodius”, Skopje, Macedonia; ²Institute of Pathology, Medical Faculty, University “Ss. Cyril and Methodius”, Skopje, Macedonia
Objective: Diffuse large B cell lymphoma with initial bulky disease and advance stage, might have diverse immunophenotype, adverse prognostic presentation may originate from activated rather than germinal center B cells. In order to investigate the prediction value of the immunohistochemical GCB/non GCB classification of DLBCL of the outcome of our DLBCL patient with bulky presentation advance stage of the disease, we conducted a retrospective study.

Materials and methods: Our study enrolled 70 DLBCL patients diagnosed and treated at the University Clinic of Hematology, in the period between January 1999 and December 2006. We analyzed the biopsy samples immunohistochemically for markers of germinal center (Bcl6), post-germinal center (MUM1) and apoptosis (Bcl2) using the modified Hans algorithm.

Results: The patients were categorized as GCB subtype (37;53%) or non-GCB subtype (33;47,1 %), Bulky initial presentation was noticed at 36,4% of GCB and 43,2% non-GCB subtype. There were no statistical differences in the frequencies of GCB and non-GCB subtypes bulky primary sites with diameter of >10 cm. DLBCL patients of 71,4% have III,IV stage according to Ann Arbor (p=.0000), and there were no statistical differences in the frequencies of GCB and non-GCB subtypes. GCB patients with advance stage of disease were 73% (p=.0002), and 69,7% (p=.0021) from non-GCB respectively.

Conclusion: Our results did not show any statistical survival difference in GCB and non-GCB phenotypes with bulky disease and advance stage of the disease. Prospective clinical trials with a large number of patients are needed to elucidate reliable molecules that are predictive markers of survival in DLBCL patients.

P-03
Using immunohistochemistry for biological characterization of nodal versus extranodal presentation of diffuse large B-cell lymphoma patients

Dukovski D.¹, Trajkova S.¹, Panovska-Stavridis I.¹, Stojanovik A.¹, Ivanovski M.¹, Pivkova-Veljanovska A.¹, Georgievski B.¹, Popova-Simjanovska M.¹, Stankovik S.¹, Chadievska L.¹, Petrushevska G.², Chevreska L.¹
¹Univeristy Clinic for Hematology, Medical Faculty, University “Ss. Cyril and Methodius”, Skopje, Macedonia; ²Institute of Pathology, Medical Faculty, University “Ss. Cyril and Methodius”, Skopje, Macedonia

Objective: Patients with Diffuse large B-cell lymphoma (DLBCL) of primary nodal (PN) or primary extranodal (PEN) origin might have diverse immunophenotype, PEN lymphoma cells may originate from activated rather than germinal center B cells. We evaluated the relationship between DLBCL clinico-pathological features, including expression of B-cell differentiation markers, and primary tumor site.

Materials and methods: Our study enrolled 80 DLBCL patients diagnosed and treated at the University Clinic of Hematology, in the period between February 2002 and December 2007. Expression of Bcl6, Bcl2, and MUM1 was determined in paraffin-embedded tissues from 80 patients with DLBCL at Institute for Pathology, Skopje, R. Macedonia

Results: The patients were categorized as GCB subtype (48;60%) or non-GCB subtype (32;40 %),64 % of patients showed disease involvement at PEN sites (p=.0009),68%of the patients with GCB showed disease involvement at PEN sites(p=.0026), and 61% of patients with the non-GCB phenotype respectively(p=.0423). Most frequent localization was tonsilo-pharingeal region, stomach.
There were no differences in the frequencies of GCB and non-GCB subtypes among primary sites. There were no differences in the frequencies of GCB and non-GCB subtypes between patients with PN and PEN DLBCL.

**Conclusion:** Our results did not show any statistical survival difference in GCB and non-GCB phenotypes between patients with PN and PEN DLBCLs. Immunohistohemical markers do not really reflect the molecular diversity of the tumor. Additional studies are needed to further assess molecular differences between the two groups of patients.

**P-04**

**Rituximab maintenance therapy in diffuse large B-cell lymphoma: single center experience**

*Popova-Simjanovska M., Chevreska L., Trajkova S., Dukovski D., Ivanovski M., Stankovik S., Panovska-Stavridis I.*

University Clinic for Hematology, Medical Faculty, Skopje, Macedonia

**Objective:** Diffuse large B cell lymphoma (DLBCL) are curable group of lymphoma with improved outcome mainly due to the incorporation of the anti-CD20 monoclonal antibody, Rituximab (R) to the standard chemotherapy regimens. So far, initial findings are not promising in regard to the overall survival (OS) and progression free survival (PFS). We present our experience with the Rituximab maintenance treatment of DLBCL patients (pts) that were treated at the University Clinic of Hematology in the past 4 years.

**Materials and methods:** Since 2006, 42 Pts received Rituximab (375 mg/m2) every 3 months for 2 years. Our control group consisted of 65 DLBL pts that were treated in same period and did not undergo maintenance treatment. All evaluated pts initially received 8 cycles of standard R-CHOP regimen. Only pts in complete remission (CR) underwent R maintenance treatment. CR was required for entrance in the control group two. We evaluated and compared PFS, OS and quality of life (QoL) between the two groups.

**Results:** After a median follow up of 42 months, PFS was 32,5% in the treatment group and 27.7 % in the control group. Maintenance therapy was well tolerated, but we noticed marked, prolonged hypogammaglobulinaemia in the maintenance group. Statistical correlations of those results showed that maintenance group has statistically significant lower IgG levels (t-test, P<0,05).

**Conclusion:** In our experience R maintenance therapy did not improve PFS or OS in pts with DLBCL. Evaluation of a larger patient population, with a longer follow-up is needed before establishing R-maintenance treatment as standard therapeutical approach for DLBL pts.

**P-05**

**AIDS and non-Hodgkin’s lymphoma**

*Durbaku A.¹, Ivanaj A.², Kokciu M.³, Nina H.¹*

¹Oncologic Service, University Hospital Center “Mother Theresa”, Tirana, Albania; ²Hematologic Service, University Hospital Center “Mother Theresa”, Tirana, Albania; ³Clinical-Biochemical Laboratory, University Hospital Center “Mother Theresa”, Tirana, Albania

**Objective:** To review retrospectively the clinical outcome of patients with AIDS-associated non-Hodgkin Lymphoma (NHL) at oncological service of a tertiary hospital.
Material and methods: Medical records and histopathologic tissue of patients with HIV-associated NHL seen from 2000 to 2011 at the Oncological Service of University Hospital Centre “Mother Theresa” in Tirana. Survival time was calculated from date of diagnosis to death, or to the date on which the patient was last seen.

Results: Thirty four HIV-positive patients were diagnosed with NHL. Twenty eight patients never received HAART, and 59 received. Overall, 38 patients (43.7%) achieved complete response to NHL therapy, including only 14.3% patients in the non-HAART compared with 57.6% in the HAART group (p<0.01). Two patients (7.1%) in the non-HAART were alive compared with 37 (63.8%) in the HAART group (p<0.01). Mean survival time for all patients was 12 (T=15.3) months. Survival was significantly shorter in patients not receiving HAART (3.9 T=6.5.6 months) compared with those who did (12 T=17.1) (p=0.01).

Conclusion: Patients with NHL-HIV who were able to receive optimal chemotherapy treatment showed a significantly better prognosis. The treatment with HAART is a good choice.

P-06

Kikuchi disease presenting as axillary lymphadenopathy - case report

Kubelka-Sabit K.1, Jashar Dj.1, Filipovski V.1, Jovanovik R.2, Petrushevska G.2

1Clinical Hospital Acibadem Sistina, Skopje, Macedonia; 2Institute of Pathology, Medical Faculty, Skopje, Macedonia

Introduction: Kikuchi disease is a rare, benign, idiopathic, generally self-limiting lymphadenitis occurring in young adults. It can be clinically and histologically mistaken for lymphoma, granulomatous disease or systemic lupus erythematosus.

Case report: We present a case of Kikuchi disease occurring in a 34 year old female patient. The patient complained for a swelling in the axillary fossa of a 2 months duration. The surgical specimen consisted of 4 lipomatous fragments measuring 0.6 to 6.2 cm, from which two lymph nodes were isolated, measuring 0.6 and 0.9 cm. The detailed histological examination revealed only remnants of discernible lymphoid follicles, whereas most of the nodal tissue was necrotic. The node capsule was thickened with perivascular fibrosis. The morphology of the marginal sinuses was blurred due to fibroblastic proliferation with mixed mononuclear inflammatory infiltrate. Remnants of lymphoid follicles were seen in the cortex, whereas massive coagulative necrosis was seen in the paracortex. Large cells with vesicular nuclei were present, some of them with apoptotic features. Fibrin thrombi were also seen. The immunohistochemical phenotype of the T cells was: CD3+, CD5 (inconclusive), CD8 partially positive with high proliferation rate. The B–cell population was CD20+, kappa (+) and lambda (+). Bcl-2 positivity was seen in the perifollicular area. These findings were suggestive of acute necrotizing lymphadenitis - Kikuchi disease.

Conclusion: Differentiating this disease from similar lymphocytic disorders and especially lymphoma is extremely important. Early recognition of this entity should minimize unnecessary evaluations and prevent inappropriate treatment of this disease.
P-07

Diffuse large B-cell lymphoma diagnosed in a minor salivary gland biopsy - case report

Benedetti A., Popovski V., Monevska D., Kirkov A., Panchevski G., Bozhovic S., Iliev A.
University Clinic for Maxillofacial Surgery

Lymphomas of salivary glands account for 5% of all cases of extra nodal lymphomas and historically they comprise 1.7% to 3.1% of all malignant salivary gland tumors. Most primary salivary gland lymphomas are non-Hodgkin, B marginal zone lymphomas arising on the background of sialadenitis associated with autoimmune disorders, such as Sjögren's syndrome. Primary B cell lymphomas of a minor palatine salivary gland are uncommon. The aim of the study was to report on this rare entity.

A 55 year-old woman sought medical attention for a large, painless ulceration of the palate, with central position, late September at the clinic for maxillofacial surgery in Skopje. The painless ulceration had gradually increased in size over a period in excess of 3 months, with a history of small bleeding. In the last month, she felt that the ulceration had extremely grown in size. The intraoral examination showed a solitary, firm, painless mass attached to the deeper structures of the palatine bone with central, ulcer-like cancer lesion. Minimal bone destruction was present. The growth measured 2 x 1.5cm and wasn’t clearly demarcated from the surrounding normal tissue. The mucosa, surrounding the lesion was inflamed. The mass was subsequently excised under general anesthesia, with preservation of the nearby bone structures (fig.7, 8, 9). One week post-operatively the patient recovered fully. The histopathologic examination, showed presence of a tumor mass, composed of heterogenic cell population, predominantly of large lymphocytes, infiltrating minor salivary glands. Mitotic activity was also seen. With immunohistochemical analyses of the tissue samples, a diffuse large B-cell lymphoma was diagnosed. The vast majority of the infiltrating cells were positive for CD20 and CD79, while some of the cells were CD57 positive.
AUTHOR`S INDEX

Andjelic B...........................................40, 42
Antic D.............................................40
Aurer I................................................21
Basheska I.........................................23
Basic-Kinda S....................................22
Benedetti A.........................................47
Bila J..................................................40
Bogdanovic A......................................42
Bogdanovska-Todorovska M..............23, 29
Bozovic S............................................47
Bumbasirevic V..................................42
Cemrikic-Martinovic V.........................38
Chadievski L.......................................41, 43, 44
Chevreska L.......................................23, 41, 43, 44, 45
Diebold J...........................................12, 23
Djurasinovic V....................................40
Dojcinov S.........................................15
Domazetovski I..................................28, 43
Dotic S...............................................19
Duganovska S.....................................43
Dukova B...........................................23, 30
Dukovski D..........................................23, 28, 30, 41, 43, 44, 45
Durbak A.............................................45
Fetica B.............................................36
Filipche V..........................................35
Filipovski V........................................46
Gastjevic G.........................................38
Gazic B..............................................38
Georgievski B.....................................37, 43, 44
Gjidera M...........................................38
Grcar-Kucmanov B..............................38
Iliev A................................................47
Ivanaj A.............................................45
Ivanovski M........................................41, 43, 44, 45
Ivanovski N........................................43
Ivkovski Lj........................................23, 32
Jakovic Lj..........................................38, 40, 42
Janevska V.........................................23, 35
Jankulovski N.....................................40
Jashar Dz...........................................46
Jelicic J.............................................40
Jovanovik R.................................23, 26, 31, 35, 43, 46
Karanfilski O......................................37
Kempf W...........................................12
Kirkov A............................................47
Kokciu M...........................................45
Kostadinova-Kunovska S....................23, 30, 43
Krstic M............................................38
Kubelka-Sabit K..................................46
Labachevski B....................................43
Macclennan K.................................18, 23
Mihailovic D......................................38
Mihaljevic B......................................40, 42
Milic N.............................................40
Monevska D........................................47
Muller-Hermelink H. K......................11, 14, 23, 32
Nathwani B........................................14, 23
Nikin Z..............................................38
Nikolov I............................................43
Nina H..............................................45
Ognenoska-Jankovska B.....................35
Pajor L..............................................16
Panchevski G.....................................47
Panovska-Stavridis I.........................41, 43, 44, 45
Perunicic-Jovanovic M......................38, 40, 42
Petrushevka G.............................23, 28-32, 35, 37, 41, 43, 44, 46
Pivkova-Veljanovska A.......................43, 44
Popova-Simjanovska M......................23, 29, 31, 41, 43, 44, 45
Popovski V......................................47
Shikole A..........................................43
Stankovik S.......................................43, 44, 45
Stojanovik A.................................23, 26, 41, 43, 44
Stojnev S..........................................38
Terzic T.............................................38, 40
Todorovic M......................................40
Trajkova S.................................23, 30, 31, 41, 43, 44, 45
Volavsek M........................................38
Vukovic V..........................................40
Weisenburger D..............................11, 23, 32
Zadnik V..........................................38
First choice for staining in pathology laboratories and deliver the highest standards and accuracy in cancer diagnostics

Pharmachem
Kloveska 1, P.C. Box 38, 1060 Skopje, R. Macedonia
Tel.: +389 2 20 51 193
Fax: +389 2 20 51 454
farmachem@farmachem.com.mk

Dako
www.dako.com
MabThera во терапија на CD20 позитивни лимфопролиферативни забољувања

8 циклуни на MabThera плус хемотерапија се стандартен третман кој нуди најдобра шанса за излекување кај пациентите со DLBCL*

Стандартен третман за пациентите со FL** се 8 циклуни на индукциона терапија плус 12 циклуни на терапија на одржување

Терапијата на одржување со MabThera ја удвојува шансата за живот без прогресија на забољувањето кај пациентите со FL**

MabThera 500mg/m² плус хемотерапија го продолжува вкупното преживување и преживувањето без прогресија на забољувањето кај SLCL***

*DLBCL – дифузен крупноклеточен B лимфом
** FL – фоликуларен лимфом
*** SLCL – хронична лимфоцитна леукемија

Податоци за лекот:
MabThera (rituximab): химерно моноклонално антти CD20 антитело добиено со генетски инженеринг. Терапевтички индикации: Non-Hodgkin's лимфом (NHL) - MabThera е индициран за третман на претходно неетергери пациенти во III-IV стадиум на фоликуларен лимфом во комбинација со хемотерапија. MabThera како антикорпел за одржување е индициран за пациенти со фоликуларен лимфом кои одговараат на индуцирани терапији. MabThera како монотерапија е индицирана за третман на пациенти со III-IV стадиум на фоликуларен лимфом кои се хеморезистентни или се во втор репапс или репапс кој следи по првично хемотерапија. MabThera е индицирана за третман на пациенти со CD20 позитивен дифузен кратоклеточен B нон-Ходжкин лимфом во комбинација со CHOP хемотерапија. Хронична лимфоцитна леукемија (CLL) - MabThera во комбинација со хемотерапија е индицирана за третман на пациенти со претходно неетергери и релапирани рефракторна хронична лимфоцитна леукемија. Регулаторен артикул: Дозволено: Non-Hodgkin's лимфом 375 mg/m² телесна површина по циклу, во тек на 8 циклуни. Терапија за одржување 375 mg/m² телесна површина еднаш на секои два месеца до прогресија на болните или максимум во тек на два години. Хронична лимфоцитна леукемија 375 mg/m² телесна површина при првото циклу на третман, прослеодено со 500 mg/m² телесна површина во секоја последователна циклу до шестото циклу вкупно. Контралечење: Присушност на активната супстанца, на некој од експериментални или на протеини од луизис активни, тешки инфекции; пациентите со сериозно компромитиран имунолошки статус. Несигурни дејства: Реакции поврзани со вакцината (вклучувајќи синдром на ослободување на цитокини, синдром на лица на туморот), инфекции, кардиоваскуларни појаси, реактивиране на хепатит В и РМЛ. Содржина на лекувањето: 2 вицили х 100mg/10ml Луцита или 1 вицила х 500mg/50ml Луцита.

Носител на одобрение за ставање на лекот во промет: ХОФФМАНН-ЛА РОШЕ ЛТД од Швајцарија-ПРЕСТАВНИШТБО во Р. Македонија. Број на одобрение: MabThera 100mg/10ml 15-13218/08 MabThera 500mg/50ml 15-13219/08. Датум на последна ревизија на текстот: Јули 2011.

Релеванси: