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Case report ■

Burkitt Lymphoma in Elderly Patients

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SUMMARY

Burkitt lymphoma (BL) is a disease of predominantly young population, while in the elderly it occurs as a rare neoplasm. Elderly patients (age >60 years) represent a significant problem because of the inability to apply effective aggressive chemiotherapy in these cases. The risk of induction death is very high and unacceptible. Mainly, palliative treatments are applied, whose goal is not curing but maintaining the quality of life. We present the case of a person 75 years old with a diagnosis of sporadic, typical BL treated with CHOP+R in the induction therapy with excellent response but rapid progression after the abolition of rituximab. In discussion, the authors are looking for relevant data on the therapeutic approach in BL in the elderly.

Key words: **Burkitt lymphoma, elderly patients**

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INTRODUCTION

Burkitt lymphoma (BL) is a highly aggressive B cell non-Hodgkin's lymphoma (NHL) and the fastest-growing human tumor (1). The incidence is 1-2% of adult lymphomas and 40% of lymphomas in children in the United States and Western Europe (2). Denis Burkitt first described this type of lymphoma in children in equatorial Africa in 1958 (3).

2007 National Cancer Institute Surveillance, Epidemiology and End Results (SEER) database suggests that "older" adult patients (age >40 years) account for roughly 59% of all adult Burkitt lymphoma cases in the United States. About 30% of BL cases are diagnosed after the age of 60 years, according to the same source. BL has three peaks of incidence in relation to age-specific observation, the first and second peak are the same in both men and women aged between 10 and 70 years; a third peak is only in men aged 40 years (4).

BL is a disease of predominantly younger population, while in the elderly it occurs as a rare neoplasm. Elderly patients (>60 years) represent a unique problem because of the inability of application of the effective and aggressive chemotherapy. The risk of induction death is very high, almost unacceptable. Generally, palliative treatments are applied, whose goal is not healing but maintenance of the quality of life. We illustrate the case of a person aged 75 years with the diagnosis of sporadic, typical BL, who was treated with CHOP+R as the induction therapy with an excellent response but rapid progression after the abolition of Rituximab.

In discussion of this article, the authors are looking for relevant data on the therapeutic approach to BL in elderly.

CASE REPORT

A female patient, Lj. M., aged 75, was admitted to the Oncology Clinic, Department of hematological malignancies with bacteriologically controlled and protected unit (BKZJ), on December 12, 2011, following the council's decision for lymphoma.

At the beginning of October in 2011, the patient noted an enlarged gland in the neck to the left. The gland was growing relatively fast over the short period. During the disease, besides the gland enlargement, there were no other symptoms of the disease. She visited her physician in Leskovac, early in November, and was first prescribed empirical antibiotic therapy, which was without clinical effect. Given the clear clinical suspicion of a possible malignant process, she was sent to the Center for Radiology, Clinical Center Niš, where on November 22, 2011 MRI imaging of the neck soft tissue was performed. After this review, biopsy was performed on November 24, 2011 at the Clinic for Maxillofacial Surgery in Niš. Histopathological report was received on December 15, 2011 and it read: **Non-Hodgkin's Lymphoma-Burkitt lymphoma** with classical immuno-histochemical profile: **C20+, CD10+, bcl6+, bcl2-, TdT-, CD79α+, CD38+,** CD5-, Cyclin D1-, CD23-, CD99-, CD3-, CD15-, CD117-, CD30-, **Ki 67+** in over 95% of tumor cells. With these findings she was presented to the council's for lymphoma at the Oncology Clinic, Clinical Center Niš. In a period of just a few days, after the council's decision, the tumor reached a very rapid progression of the volume with the effects of compression on the airways. She was admitted to hospital as an emergency because of major choking, being unable to take food and for severe pain in the neck and head. Upon receipt, because of the urgency of the situation, hydration was undertaken, high-dose corticosteroids were prescribed, and 300 mg dose of Alopurino was included. She immediately went to the emergency immunochemotherapy induction by R+CHOP regime (Rituximab 375 mg/m^2 d0, Cyclophosphamide 750 mg/m^2, Doxorubicin 50 mg/m^2, Vincristine 1.4 mg/m^2 d1, Methylprednisolone 80 mg d1-5). The administered therapy lead to the prompt response and reduction of tumor volume by almost 50% within 48 hours. After stabilizing her condition, we approached the staging of lymphoma by applying the recommendations of the Serbian Lymphoma Group (SLG).

She brought **MRI scan** of the neck soft tissue (22.11.2011.): On the left side of the neck conglomerates present, pathologically enlarged lymph nodes of diameter 42x43mm. Spread of the mandibular bone to the upper thoracic aperture caudally. Multiple enlarged lymph nodes on the right side of the neck, but smaller in size. Left jugular vein was compressed and dislocated. Muscles of the floor of the oral cavity had normal signal, as well as salivary glands. **Echosonography of the upper abdomen** was performed: Liver with no focal lesions. Gallbladder calculosis with large caliber of 20 mm-3 biliary stones were vizualized, biliary ducts were normal. Both kidneys, spleen and pancreas were normal. Without enlarged retroperitoneal lymph nodes. **X-ray of the chest**: normal findings. **Echocardiography:** EF 65%, FS 43% normal heart echomorphology.
Coombs test: negative. **KKS:** Hct 0.42, Hgb 14.4 g/dl, RBC 4.90, WBC 13.8, Neu 11.2, Ly 1.8, PLT 265. **Biochemical parametres:** SE 8/, fibrinogen 3.6 g/L, glucose 3.9 mmol/L, urea 15.0 mmol/l, creatinine 115.4 μmol/L, uric acid 547.2 μmol/L, Total proteins 67.8 g/L, albumines 39 g/L, AST 32 U/L, ALT 31 U/L, ALP 45 U/L, GGT 14.7 U/L, LDH 1002.6 U/L, CRP 12.6 mg/L, Fe 4.1 μmol/l, Na 145 mmol/ g/L, K 4.3 mmol/L, Ca 2.22 mmol/L. **Immunological status:** IgG 8.46 g/L, IgM 0.42 g/L, IgA 2.07 g/L, beta 2 microglobuline 2.65 mg/L. **Plasma protein electrophoresis:** no monoclonal secretion was found, hipoalbuminemia.

Virulogical status: anti-HIV negative, anti-HCV negative, HbsAg negative, EBV IgM negative, ***EBV IgG ++++ (extremely high positive***). **Periferal blood smear:** no leucemic cells were found. Flowcitometry was not performed, due to normal blood smear findings.

Bone marrow aspirate: Hypercellularity (grade 4). All three hematopoietic lineages were found but overpopulated by limphoblastic cells infiltrates. Morphologically, those cells were of blastic charcteristics but without typical vacuoles in the cytoplasm, which could be seen in Burkitt leukaemia ALL-L3 type. Bone marrow infiltration of malignant cells was approximately 40-50%**. Bone marrow cytogenetics**: 46XX, **t(8:14) (q24: q34)-**c-myc/IgH loci. Initial hyperploidy was found in some of the analyzed mitoses.

Following the clinical tests, the patient was studied according to Ann Arbour criteria as Lymphoma non-Hodgkin in clinical stage (CS) IV A, b, V+, with "age-adjusted International Prognostical Index"-aaIPI 2 (medium high risk) and with the comorbidities (angina pectoris stabilis, arterial hypertension and incipient renal failure), ECOG 1, KI 70%.

Given the excellent clinical response to the first cycle of induction therapy, the second cycle was continued with the same regime. The reduction of tumor volume was nearly 90% after the second cycle of induction. Upon arrival for the third cycle of therapy due to the health fund limitation, we had to discontinue a further use of monoclonal antibody Rituximab and continue the therapy only with CHOP21. Upon arrival for the fourth cycle for the first time we observed the progression of the tumor volume on the neck, so the decision was made to administer the fourth cycle of CHOP21 induction. Upon arrival for the fifth cycle, the tumor had grown to more than 50% since the last hospitalization, the occurrence of pain in the neck and head, nasal, almost unintelligible speech, and it was decided to continue the treatment with some of the secondary protocols DHAP (Dexamethason 40 mg d1, Cisplatin 100 mg/m^2 d1 CIV and the reduced total dose of Cytarabine 3000 mg d2). After this therapy, we achieved a satisfactory clinical response with significant subjective improvement and reduction of tumor volume. Upon arrival for the second cycle of DHAP therapy, there was a significant decrease in creatinine clearance (42ml/min/m^2), and Cisplatin dose was reduced by 70%. Then in the seventh hospitalization, there was a significant occurrence of thrombocytopenia and leucopenia grade 3, but without the occurrence of major complications. Soon after, in the course of the eighth hospitalization, there was a significant progression of tumor volume, with the appearance of suffocation, disorientation, and headaches. MSCT of the endocranium and brain was urgently made and showed no signs of CNS infiltration; MRI scan was recommended. Palliative therapy with high doses of corticosteroids was performed with Dexamethason 40 mg d1-4, d9-12. The effect of this therapy had transient palliative effect, and since the patient was not a candidate for high dose regimes and transplantation, it was the only choice we could afford. We made the decision to apply the palliative radiation on the "bulky" volume of the neck. However, disease progression lead to strong attenuation, disorientation and coma, and soon the outcome was lethal. The overall survival was eight months after the onset (Figures 1-6).

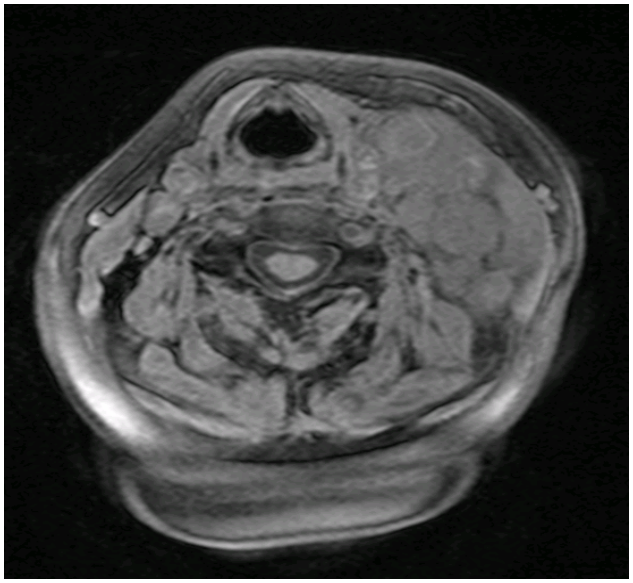

Figure 1. *MRI of the neck presents „bulky“ voluminous tumor mass on the right side*

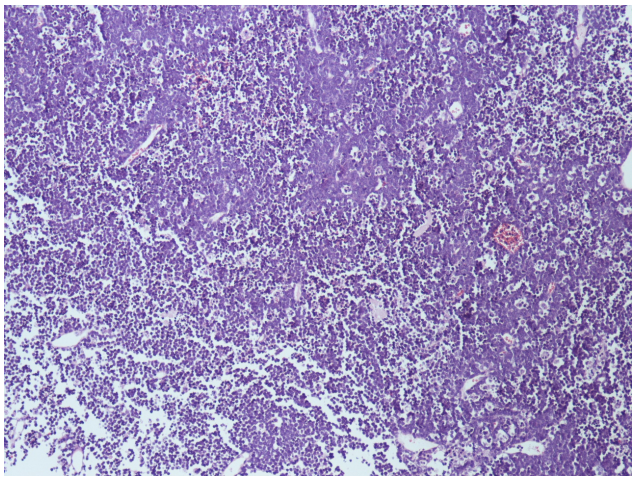

Figure 2. *Burkitt lymphoma. HEx10. The growth pattern of the tumor is diffuse , tumor cells look like centroblasts. „Stary sky“ pattern is presented*

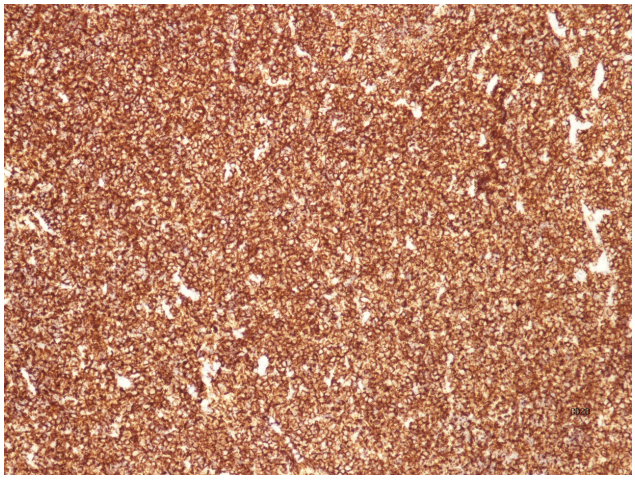

Figure 3. *HEx10. Tumor cells are highly CD20 positive*

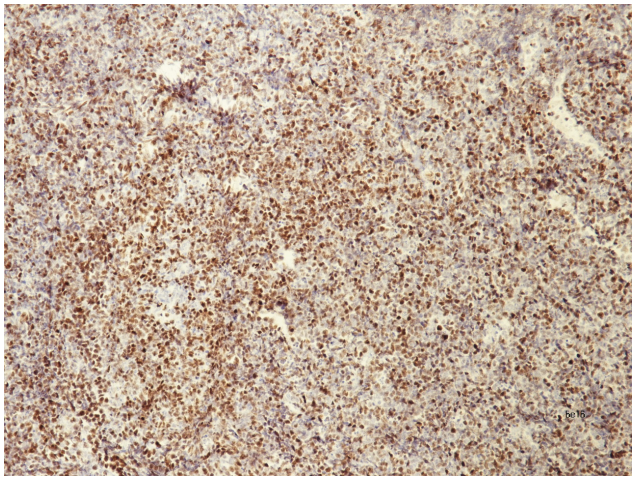

Figure 4. *Hex10. Tumor cells are bcl-6 positive*

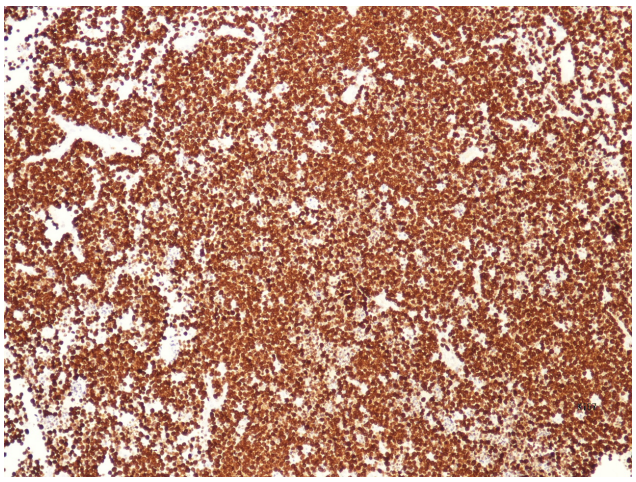

Figure 5. *Ki67 index is over 95%*

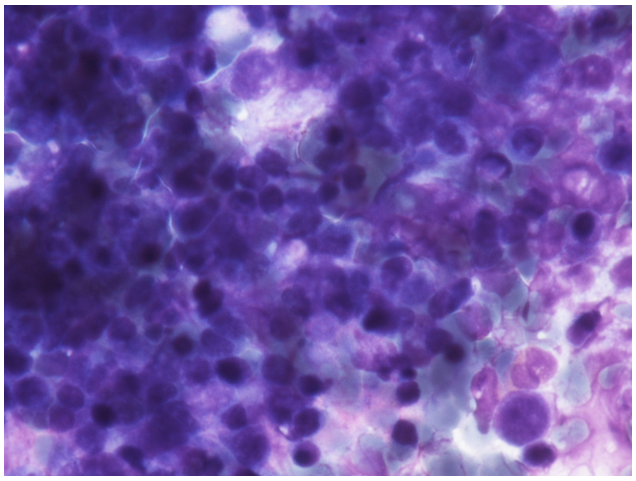

Figure 6. *Bone marrow aspiration-BL infiltration „packed marrow“*

DISCUSSION

According to the classification of the World Health Organization (WHO), three clinical variants of the typical BL have been described: endemic, sporadic and the type associated with immunodeficiency. Endemic Burkitt, which occurs in African children, usually 4-7 years old, with a male to female ratio 2:1, affects the jaw bones and other bones of the face, then kidneys, gastrointestinal tract, gonads, breast, and other extranodal sites (5). It is highly associated with EBV infection, in 98% (6). Sporadic BL occurs outside Africa. The most common location is the stomach-ileocoecal region. The association with EBV is about 20% (6). The immunodeficiency type is associated with HIV infection (7), or occurs in the post-transplant patients who are on chronic immunosuppressive therapy. The frequency of EBV infection in these patients is 30-40% (6).

A special entity is "atypical" Burkitt, which is characterized by diffuse boundary characteristics to diffuse large B cell lymphoma (DLBCL). This type has all characteristics typical of BL, but differs in pronounced cellular polymorphism, less prominent image of "starry sky" or atypical immunophenotype. This form is relatively common in elderly patients who were diagnosed with typical BL. In fact, it is c-myc aggressive lymphoma which is not BL than the variety of DLBCL.

BL have two clinical presentations, such as lymphoma and acute lymphoblastic leukemia (ALL-L3 type). Micromorphological features, a monotonous lymphoblastic cell morphology, round to oval nuclei, loose chromatin with multiple nucleoli, strongly basophilic, scanty cytoplasm, usually with numerous lipid vacuoles in the cytoplasm. Characteristic is the existence of numerous macrophages that engulf apoptotic cellular debri, creating a picture of the "starry sky". The typical immunophenotype is the pan B cell: CD20 +, CD79α +, CD19 +, CD22 +, sIgM +, then germinal center like CD10 +, bcl6 +, but MUM1-, TdT-, bcl2-, CD5-, CD138- and CD23-. Proliferative fraction (Ki67) is approximately 100% (5, 7).

Molecular basis of BL is the activation of c-myc gene at position 8q24 through translocation with some of the immunoglobulin locus. In 80% of cases, it is in the 14q34 region in switch class of heavy chains. In 15% of cases, it is the translocation for locus of kappa light chains in position 2p11, and in 5% it is the translocation of 22q11 of lambda light chains.

These translocations lead to the overexpression of the c-myc encoded proteins and destabilize the control of cell division and growth, due to c-myc gene as the transcriptional regulator. In our patient we detected typical t(8;14) (q24;q34) in the bone marrow aspirate. Incipient hyperploidy explains the clonal evolution of advanced disease, with the presentation of secondary chromosomal aberrations.

The role of EBV infection is not fully understood, however, it is known that prelymphoma stage plays a role in stimulating B cells, but its importance after the development of lymphoma is not clear. Our patient had a highly positive IgG titer of the EBV presence (defined as IgG++++).

Staging procedures of BL is in accordance with the Ann Arbor staging system, while Murphy system is

abandoned. With regard to bone marrow infiltration and presence of cervical "bulky" mass, our patient was in the fourth clinical stage, with aaIPI 3 (high risk). Therapeutic approach in BL, in younger patients, is based on the use of highly aggressive, high dose chemotherapy and its frequent use, the forcing of the dose intensity, and mandatory CNS prophylaxis with high doses of systemic therapy, intrathecal therapy, or both. Optional therapies are Hyper CVAD (MD Anderson), an alternation CODOX-M/IVAC (Magrath) or dose-adjusted EPOCH, all with the addition of Rituximab. Standard doses of chemotherapy used to treat DLBCL such as CHOP are inadequate for the treatment of BL (8). During the first cycle of induction therapy, mandatory measures are the use of extensive hydration with application of uricostatics as a measure of prevention of the acute tumor lysis syndrome (ATLS).

Data on the treatment of persons older than 60 years that were included in a prospective randomized study is extremely small so that there is no consistent view on the approach to induction therapy in this selected group of patients. The treatment was left to the single center experience. The goal of treatment in the elderly is not curing but maintaining the quality of life with possible prolongation of survival. There is a small number of patients older than 60 who received HyperCVAD + Rituximab and who had a favorable response (9). Elderly patients have difficulties in tolerating this regimen, which carries a high risk of early induction death, and they also are difficult to withstand high doses of Methotrexate and Cytarabine, which are included in many current protocols and are not candidates for autologous stem cell transplantation (ASCT). Age was defined as one of the strongest adverse prognostic factors in patients with NHL. Numerous studies have demonstrated that older patient's age was significantly correlated with shorter disease-free survival (DFS) and overall survival (OS) (10-13). This shorter survival has been mainly related to a trend in prescription of weaker treatments assumed to be better tolerated (10) and a poorer tolerability of standard treatments widely due to the presence of concomitant diseases (13). In the absence of concomitant diseases, the survival was not shortened in patients of >70 years compared with younger patients (14).

The treatment decision should be guided by prognostic scores. Scoring systems which are important are aaIPI, Charlson scale and its modifications. French authors Coiffier and Thiemblemonts consider that the most important prognostic factors in elderly are performance status (PS) and the level of plasma lactate dehydrogenase (LDH).

In addition, elderly patients often present with alterations of pharmacokinetics and biodisponsibility of drugs modifying the pharmacodynamics of molecules (15). Thereby, drugs used and their dosage should be tailored to creatinine clearance, liver function, and hematopoietic reserve. A decrease in chemotherapy drug, however, has been found to be associated with a lower treatment efficacy (10). General recommendations, in relation to comorbidity score, advocate for induction with CHOP+R, or some modification of the said regime, with intrathecal prophylaxis metotrexat, of course, with palliative rather than curative purpose (16). Recently, it has been demonstrated that the addition of Rituximab to CHOP regime dramatically prolongs survival in elderly patients, without raising toxicity of treatment (17). Patients older than 80 years can also receive CHOP+R, except those with serious comorbidities (17). Only a small number of patients may have benefit from a "salvage" therapy after relapse (17). There are sparce data on the level of case reponted by the Israeli authors on low dose therapy which must include Rituximab, with low doses of cytostatics, as was in this case: Vincristine 1.4 mg/m^2 with oral Etoposide 100 mg/m^2 d1 and 50 mg/m^2 d2-6, in 78-year old female patient, who relapsed a year after CHOP induction therapy in the fourth cycle, and who had a stable complete remission (CR) two years after mentioned therapy (18).

CONCLUSION

Although the primary goal of treatment of elderly patients with BL is not healing (older than 80 years) because the risk of death due to aggressive therapy is very high in the population aged 65-70 years, however, we should look for a stable remissions that prolong life. What is important is that best supportive care, with more aggressive therapy as definitely a better measure of survival. Protocols with lower doses are not effective and have the effect of palliative care. It is encouraging that the leading drug for which there is evidence that prolongs life in elderly is definitely Rituximab in combination with some chemotherapeutic agents. Older patients with lower scores and aaIPI lower risk could be treated with this approach. The patients with high scores of aaIPI remain in the domain of ineffective therapy. It is of ultimate importance to introduce new agents for the treatment of the selected group of elderly patients.

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BURKITT-OV LIMFOM KOD STARIJE OSOBE

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Sažetak

Burkitt-ov limfom (BL) je bolest pretežno mlade populacije, dok je kod starijih retka neoplazma. Stariji bolesnici (>60 god) predstavljaju svojevrstan problem zbog nemogućnosti primene efektivne agresivne hemioterapije. Rizik od indukcione smrti je jako visok, neprihvatljiv. Uglavnom se pribegava palijativnim tretmanima, čiji cilj nije izlečenje nego održanje kvaliteta života. Prikazan je slučaj osobe stare 75 godina sa dijagnozom sporadičnog, tipičnog BL, koja je tretirana CHOP+R terapijom u indukciji sa odličnim odgovorom, ali brzom progresijom nakon ukidanja Rituximaba.

Autori u diskusiji tragaju za relevantnim podacima o terapijskom pristupu kod BL starijih osoba.

Ključne reči: **Burkitt limfom, stariji bolesnici**