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PRIMARY MANTLE CELL LYMPHOMA OF GASTROINTESTINAL TRACT- A CASE REPORT

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Mantle cell lymphoma (MCL) represents a relatively rare type of mature B cell neoplasm, which arrises from the CD5+ cells of the mantle zone of lymph follicles. It often has the extranodal or leukemic presentation. It is characterized by the relative insensitivity to applied chemotherapy and high relapse rate after treatment. Median survival is about 3-4 years, and highly aggressive protocols may shift the median up to 5 years.

Our patient was a typical example of the natural biological course of MCL. A male patient, 57 years old, was admitted to the Clinic for Oncology CC Nis, after he was diagnozed with primary mantle cell lymphoma of the digestive tract in the form of multiple lymphomatouos polyposis (MLP) of the colon and small intestine. After the colonoscopic biopsies, he was diagnosed with MCL. This case was regarded as advanced stage of lymphoma, with low MIPI index. He received 8 cycles of immunochemotherapy CHOP+Rituximab with excellent clinical response determined as complete remission (CR). After disease-free interval of two years, a relapse occurred in the stomach, which was histopathologically verified.

MCL is still a disease with poor prognosis. Therapeutic approach, given the poor prognosis and resistance to conventional immunochemiotherapy and even high dose therapy followed by the autologuos stem cell transplantation, still remains insufficiently defined. Newer therapeutic agents which are found in a large number of clinical trials provide relatively encouraging results. *Acta Medica Medianae 2012;51(3):41-46.*

Key words: *mantle cell lymphoma, multiple lymphomatous polyposis, gastrointestinal tract*

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Introduction

Mantle cell lymphoma (MCL) is aggressive Non-Hodgkin's lymphoma characterized by t(11;14) chromosomal translocation and overexpression of cycline D1. It participates with approximately 4-8% of all Non-Hodgkin's lymphomas, having the worst prognosis of all. Standardised and efficient treatment has not been established yet (1). Histologically, MCL is represented as small to intermediate-sized lymphoid cells with irregular nuclear shape and scant cytoplasm, like centrocytes. The other, rare form of MCL is a blastoid variant which is more aggressive and morphologically represented as large blastoid cells which look like lymphoblasts. Lymphoma cells of this type express typical pan B cell markers: CD20, CD19, CD79α, as well as CD5 and CD43, whereas CD10 and CD23 are negative. Cyclin D1 is almost allways strongly positive in the malignant cells' nuclei.

At the proposal of the Europian-American Classification of the International Lymphoma Study Group, it was established in 1994 as a separate entity. (2). Then, the old names from numerous old classifications were repealed (intermediate lymphocytic lymphoma, centrocytic lymphoma, lymphocytic lymphoma with intermediate differentiation, such as marginal zone lymphoma), which brought great confusion in terminological distinction of the same entity.

Clinically, MCL has standard appearance as nodal lymphoma, gastrointestinal lymphoma in a form of multiple intestinal polyposis of the digestive tube (MLP) and as mantle cell leukemia with splenomegaly. At the presentation, most of the patients are elderly males with advanced form of the disease. The disease often has extranodal localization, and poor outcome after the applied therapy (3,4).

Case report

A male patient, D. J., 57 years old, admitted to the Clinic for Oncology, Departmant of Malig-

nant Hemopathies with bacteriologically controlled and protected unit (BKZJ), in November 2009, after the council's decision.

Anamnestically, year and a half before coming to hospital, the patient had periodically non-specific digestive problems, in the form of irritated stomach and flatulency. He mentioned that from the beggining of 2009 he had frequent shifts of diarrhea and obstipation, and after that he noticed abdominal bloating and mucus in the stool. All the time, he had no B simptoms, which are typical for lymphoproliferative disease (loss of body weight more than 10kg in the past 6 months, night swealling, weakness, fatigue and subfebrility). In August, he visited the gastroenterologist who indicated the rigid rectosigmoidoscopy which revealed multiple rectal polyposis, when biopsy was performed. After that, total colonoscopy was performed, during which multiple poliposis of the whole colon was verified. Polyps were sized from 2mm to 5cm in diameter in all the parts of the colon (from rectum, transversum, cecum, reaching the distal parts of the ileum). Multiple biopsies of mucosa were performed.

The diagnosis was established in the Centar for Pathology of the Clinical Center Niš, and a consultative review of pathohistology was done in Histolab Belgrade, and it was: Lymphoma non Hodgkin-Mantle cell lymphoma with classic immunohistochemical profile: LCA+, C20+, CD5+, CD43+, Cyclin D1+(in 100% tumor cells nuclei), CD23-, CD10-, CD3-, CD79a+, CK8-, EMA-, Ki 67+ in 40-50%of the tumor cells.

After the diagnostic procedures, staging of the disease was performed in accordance with the Serbian Lymphoma Group Guidlines (SLG). CT scan of the neck showed: submentally and beneath the oral cavity there was microlimphadenopathy. On the neck isolated lymph nodes on the left 12mm in diameter. CT of mediastinum: hilar lymphadenopathy average diameter of 15mm right and 17mm left. CT of abdomen: splenomegalia IP diameter up to 151mm, and isolated lymphadenopathy caudal from junction of renal veins to aortic bifurcation 27mm in diameter (two lymph nodes in close contact). CT of pelvis: Pararectal and inguinal microlymhadenopathy and obturatory swallen lymph nodes to 18mm. Echocardiography: EF 55%, FS 29%.

Coombs test: negative. Total blood count: Hct 39.1%, Hgb 125, RBC 4.66, WBC 5.4, Neu 3.1,

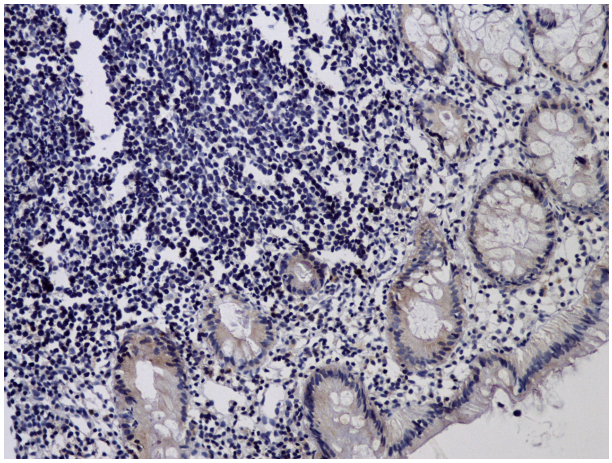

Figure 1. HE x 40 colon biopsy

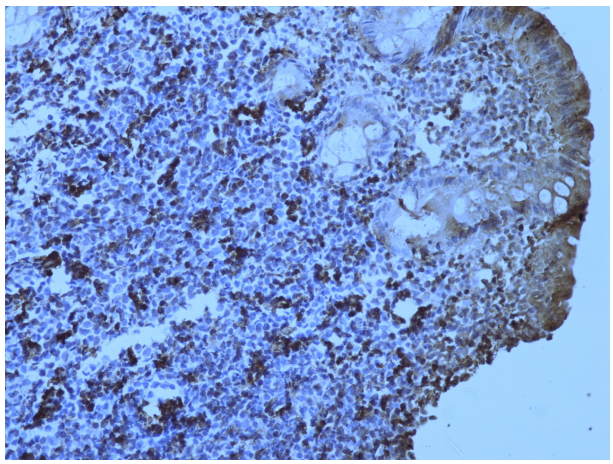

Figure 2. IHH: Cyclin D1+ colon

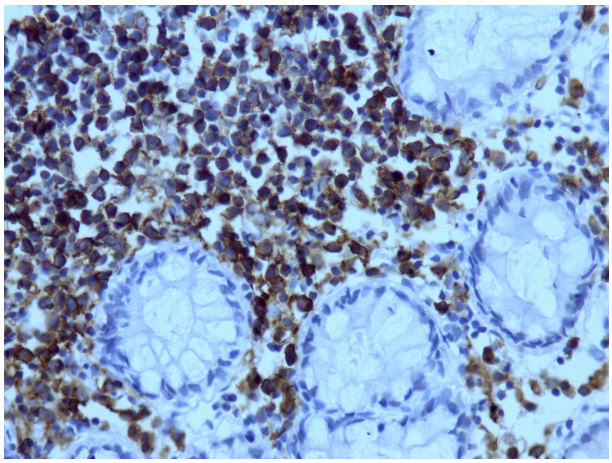

Figure 3. IHH: CD20+ colon

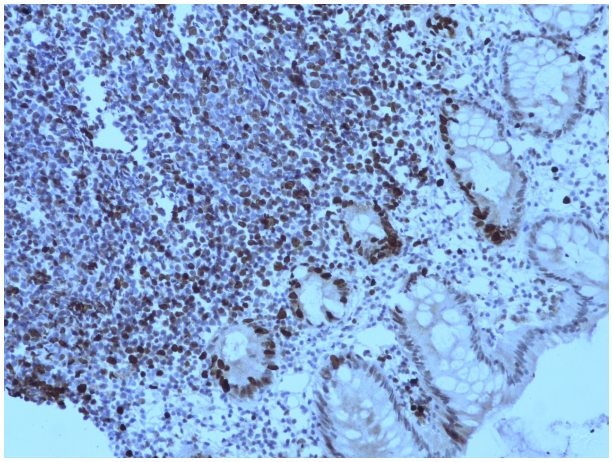

Figure 4. IHH: Ki 67 index 40-50% colon

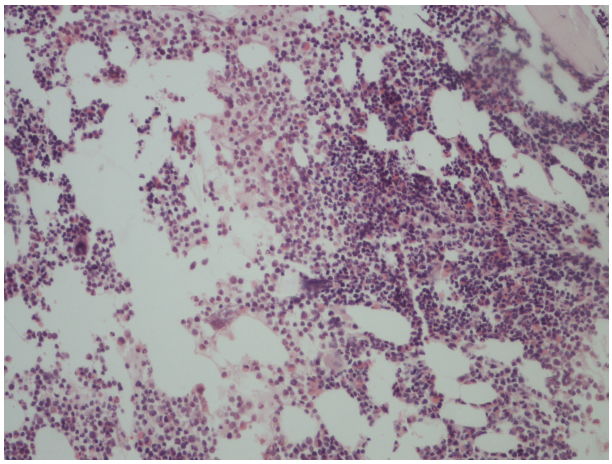

Figure 5. Bone marrow HE x 40 Infiltration of MCL

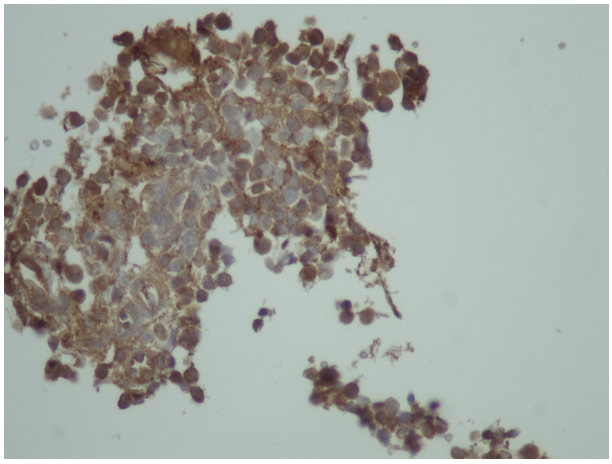

Figure 7. Bone marrow IHH: Cyclin D1+ MCL

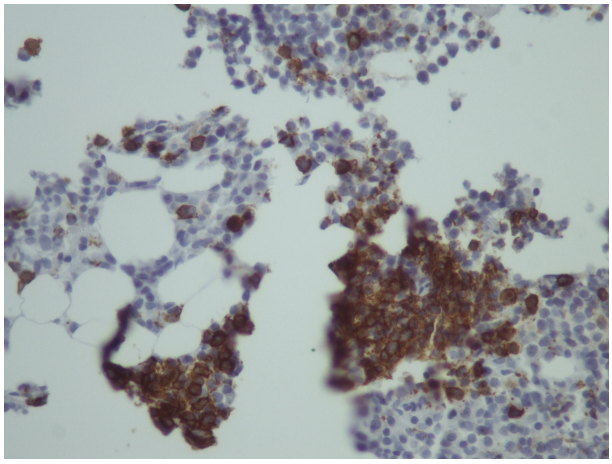

Figure 6. Bone marrow IHH: CD20+ MCL cells

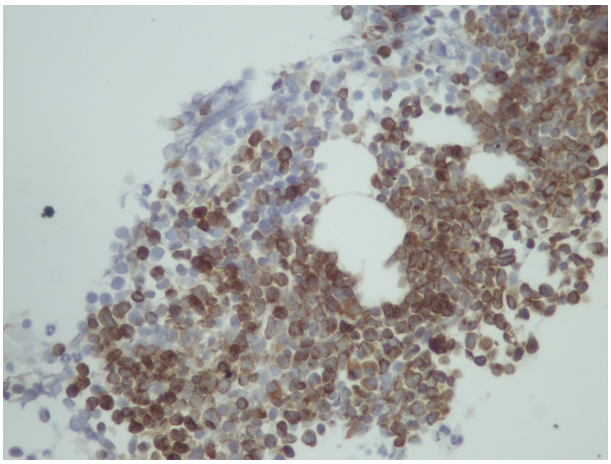

Figure 8. Bone marrow IHH: bcl2+ MCL

Ly 1.3, Plt 192. Biochemical parametres: SE 12/, fibrinogen 5.4 g/L, glucose 4.6 mmol/L, urea 4.3 mmol/l, creatinine 94.2 μmol/L, acidum uricum 251.1 μmol/L, Total proteins 55.6 g/L, albumines 32.2 g/L, AST 16 U/L, ALT 10 U/L, ALP 76 U/L, GGT 24.4 U/L, LDH 283 U/L, CRP 12.6 mg/L, Fe 6.6 μmol/l, TIBC 49.9 μmol/L, UIBC 43.3 μmol/l, TSAT 13%, Na 139 mmol/ g/L, K 3.8 mmol/L, Ca 2.17 mmol/L, Cl 104 mmol/L. Immunological analyses: IgG 7.80 g/L, IgM 0.34 g/L, IgA 1.48 g/L, beta 2 microglobuline 3.63 mg/L. Electrophoresis of the plasma blood proteins: no monoclonal protein in the blood was found. Virusological status: anti HIV negative, anti HCV negative, HbsAg negative. Peripheral blood smear: normal cells, small count of isolated lymphoid cells with notched nuclei. Flowcytometry of peripheral blood: no leukemic cells were found. Bone marrow biopsy: Approximate cellularity is 60-70%. All three haematopoetic cell lines ripen properly, reticular fibers are grade 1. Sporadically, spotty infiltrates of lymphoid cells were observed, which have monotonous appearance and are CD20+, Cyclin D1+, bcl2+, and CD3-, and which correspond to mantle cell lymphoma cells infiltration.

Following the completion of staging, the patient was recognized as Lymphoma non-Hodgkin in clinical stadium-CS IV A, a, V+ with Mantle cell lymphoma International Prognostical Index (MIPI) score 1-low risk, with no comorbidity, ECOG 0, KI 100%, according to Ann Arbour and Cotswald criteria.

Following the staging system and after defining the prognostical indexies, the patient started the inductional immunochemotherapy by protocol R-CHOP 21 in 8 consecutive cycles.

Induction has been ended in May, 2010. Response to therapy was defined as complete remission (CR). In the assessement of therapy response, new bone marrow biopsy was performed with immunohistochemical evaluation, which showed no presence of residual tumor cells.

All CT scans showed the absence of lymphadenopathy, and the spleen was of normal size. Repeated colonoscopy showed no polyposis. PET/CT evaluation was not performed. Patient maintained CR untill November 2011, when he relapsed. The relapse appeared in the stomach, which was detected during gastroduodenoscopy. New biopsies were done and it was pathohistologically verified - mantle cell lymphoma.

Discussion

Frequency of gastrointestinal involvement according to MCL diagnosies is about 30%, and it is

one of the most frequent extranodal localizations of the disease (5). The term multiple intestinal polyposis (MLP) was first presented by Corn in 1961 to describe the multiple polypoid lesions of the digestive tract consisting of mucosal infiltration of lymphoma (6). Farther immunohistochemical and citogenetic stadies confirmed that MLP was actually mantle cell lymphoma involving the gastrointestinal tract (7).

MLP has clinical presentation as abdominal pain, diarrhea, bowel bleeding, or rarely as protein losing enteropathy, intestinal malabsorption and chylous ascites. It most often occurs in the ileocecal region, and one third of patients have voluminous mass (8,9). It is necessary to differentiate other hamartomatous lesions from mantle cell lymphoma presented as an MLP. Not all polypoid lymphomatous lesions in digestive tract are MCL. Michopolous et al. showed in the study of 35 patients with MLP that only 12 of them had MCL (10). From the group of lymphoproliferative diseases, MLP presentation possibly may have follicular (FL) and extranodal marginal zone lymphoma (MALT), although quite rarely.

The basic diagnosis includes the proximal and distal endoscopy procedures, i.e. colonoscopy with multiple biopsies of the polyps. An experienced pathologist should diagnose the specific disease by using the required panel of immunohistochemical (IHH) analyses which includes CD79a, CD20, CD5, CD43, CyclinD1 which are standard positive, and CD10 and CD23 which are usually negative. In addition, cytogenetic FISH analyses which includes t(11;14),which represents bcl1 rearangements from chromosome 11 with IgH locus from chromosome 14, with cycline D1 over expression, are reliable markers for MCL (11). Abberant phenotypes of MCL have been described more recently, which are cycline D1 negative, as well combinations which deviate from well known classic IHH characteristic of MCL.

Our patient underwent the whole panel IHH analysis and diagnosis of MCL was set according to the criteria of modern guide for lymphoma. FISH analyses is not routinely done in Serbia, a conventional metaphase cytogenetics analyses were not performed, because this procedure is unable to detect specific structural chromosomal translocation. Clear symptomatic clinical presentation of MLP has completed the diagnosis of MCL.

Abstraction of bone marrow and peripheral blood is different and it ranges up to 70% of cases (12). The type of marrow infiltration is a very important prognostic factor, since it is diffuse, compared to the nodular type of infiltration. With respect to survival duration, diffuse pattern has worse prognosis (12,13,14). Our patient had nodular type of bone marrow infiltration. Patient was regarded as advanced form of the MCL –IV (fourth) stadium, with no simptoms typical of lymphoma-A, and with no biochemical activity of the disease, but as Bulky volume-V+, beacause of the diffuse pattern of tumor growth and abstraction of whole gastro-intestinal tube and presence of extraintestinal lymphadenopathy. Among the poor prognostic markers, he had high level of beta 2 microglobuline (greater than 3) and diffuse Bulky disease.

Therapeutic approach for MLP entity in MCL does not differ from general therapeutic strategy of any clinical form of MCL. Surgery has a legitimate place only in intuscuception or intestinal obstruction, but only as palliative, predominantly as a diagnostic measure. The optimal tretment of MCL remains insufficiently defined and is the subject of numerous studies. MCL is the primary resistant disease or illness with a high rate of relapse, after initial good response to induction treatment. Standard accepted induction regimen is CHOP+Rituximab. Induction with high dose chemotherapy HyperCVAD+Rituximab, followed with conditional protocol BEAM and auto-logous stem cell transplantation, may be an option for patients younger than 60 years with high MIPI index. This modality makes sense only if CR is achieved after the inductional treatment (sensitive disease). This scheme demonstrated promising results in uncontrolled trials.

The overal response rate to induction therapy ranges from 80-95%, with percentage of CR being 30-50% (15). Despite good results achieved in the aforementioned induction treatment regimens, overall survival remains poor due to high rates of early relapse. Median survival of patients after standard treatment is 3-4 years (16). Intensive immuno-chemotherapy with or without autologous support has successfully extended the period without disease progression for 5 years and over (17,18). Numerous controlled studies providing data to a newer agents may have a place in the future guidelines for the treatment of MCL. In this sense, proteasome inhibitor Bortezomib has shown response rate of about 31% as a single agent, acting on p27, Cyclin D1 i nF kappa B. Temsirolimus, as mTOR inhibitor leads to 38% remissions in patients with relapsed or refractory MCL. Lenalidomid, as immunomodulatory agent leads to 53% favourable response, of which 13% achieves CR (19). Total median 5-year survival for MCL at an advanced form of the disease is generally 50%, and 70% in the limited form (20,21).

In our patient, we decided to use conventional induction approach CHOP 21+Rituximab in 8 consecutive cycles. Achieved CR maintaned for 2 years, which is in apsolute correlation with known data from the literature. Secondary protocols which have their justified position are Fludarbine regimens, as mono or combined therapy with Mitoxantrone. ”Salvage”regimens with relative chance for disease control in a period of time are those involving high dose Citarabine (ESHAP, DHAP), given that MCL cells are relatively sensitive to the pyrimidine analogue.

Conclusion

Since MCL often affects the gastrointestinal tract, even up to one third of cases, during the staging procedures all patients should undergo endoscopic examination of digestive tube, even when there are no direct manifestations of gastrointestinal affection. This recomendation is in the guidlines for MCL staging procedures in the Serbian Lymphoma Group.

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PRIMARNI MANTLE CELL LIMFOM GASTROINTESTINALNOG TRAKTA-PRIKAZ BOLESNIKA

Ivan Petković, Dragan Mihailović, Miljan Krstić, Ivica Pejčić, Svetislav Vrbić i Mirjana Balić

Mantle cell limfom (MCL) predstavlja relativno redak tip zrelih tumora B ćelija, koji izrasta od CD5+ ćelija mantl zone limfnih folikula. Često ima ekstranodalnu i leukemijsku prezentaciju. Odlikuje ga relativna neosetljivost na primenjenu hemioterapiju i visoka stopa relapsa nakon terapije. Prosečno preživljavanje je oko 3-4 godine, a visoko agresivni protokoli mogu pomeriti medijanu do 5 godina.

Naš primer daje klasičan prikaz prirodnog biološkog toka MCL. Bolesnik, muškarac star 57 godina, primljen je u Kliniku za onkologiju KC Niš sa postavljenom dijagnozom primarnog mantle cell limfoma digestivnog trakta u vidu multiple limfomatozne polipoze (MLP) kolona i tankog creva. Nakon kolonoskopskih biopsija, postavljena je dijagnoza MCL. Stadiran je kao uznapredovali stadijum limfoma, sa niskim MIPI indeksom. Primio je 8 ciklusa imunohemioterapije u indukciji po CHOP+Rituximab protokolu sa odličnim kliničkim odgovorom tipa kompletne remisije (CR). Nakon dve godine bez bolesti, javlja se relaps bolesti u želucu koji je i patohistološki verifikovan.

MCL i dalje predstavlja prognostički lošu bolest. Optimalan terapijski pristup, s obzirom na lošu prognozu i rezistenciju na konvencionalnu imunohemioterapiju, pa čak i na visku dozu, praćenu autologom transplantacijom matične ćelije hematopoeze i dalje ostaje nedovoljno definisan. Noviji terapijski agensi koji se ispituju u velikom broju kliničkih trajala pružaju relativno ohrabrujuće rezultate. *Acta Medica Medianae 2012;51(3):41-46.*

Ključne reči: *Mantle cell limfom, multipla limfomatozna polipoza, gastro-intestinalni trakt*