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MANTLE CELL LYMPHOMA – A KILLER WITH A CHILD'S FACE

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Mantle cell lymphoma (MCL) is a distinct type of non-Hodgkin lymphoma with very aggressive clinical behavior. Despite its bland morphology, MCL remains incurable and deadly disease, although several variants with more indolent clinical course have been recognized. This study aimed to comprehensively analyze pathological features of MCL in patients from Southeastern Serbia and to determine the frequency of this devastating disease in our population. During the five-year period, the diagnosis of MCL was established in 47 cases, which constitutes 10.3% of all newly diagnosed lymphomas in our Center for Pathology, University Clinical Center Niš. The majority of the patients were men, 72.3%, and the average patients' age at the time of diagnosis was 66.1 years. Extranodal presentation was observed in 61.7%. Every fourth case of MCL was diagnosed on bone marrow biopsy. The oral cavity and the gastrointestinal tract were equally represented as extranodal diagnostic location with 17% each. MCL encompasses large spectrum of architectural patterns and cytological variants thus its diagnosis requires immunohistochemical analysis of CyclinD1 and SOX11 for correct diagnosis and distinction from other lymphoid neoplasms and reactive and hyperplastic conditions. Variant morphology of MCL may be easily confused with potentially curable or indolent lymphomas. Accurate and precise diagnosis of MCL may improve patients' outcome through timely application of new and promising treatment strategies. Pathologist role in proper recognition and rapid diagnosis of MCL and its subtype, especially in biopsies from extranodal locations, including endoscopic biopsies, may contribute significantly to longer survival and better clinical outcome of the disease.

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Key words: *mantle cell lymphoma, diagnosis, pathology, immunohistochemistry, CyclinD1*

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Introduction

Mantle cell lymphoma is a distinct type of non-Hodgkin lymphoma with very aggressive clinical behavior (1). Although several variants with more indolent clinical course have been recognized (2, 3), mantle cell lymphoma (MCL) remains incurable and deadly disease. MCL accounts for 5-10% of all non-Hodgkin lymphomas.

MCL belongs to a group of mature B-cell neoplasms, and it is usually composed of monomorphic population of small to medium-sized cells with irregular nuclei. MCL cells are quite homogenous, uniformly appearing, usually there is no large, transformed cells within neoplastic population. MCL cells may have angulated nuclear contours or slightly polygonal shaped or cleaved nuclei, and scarce pale cytoplasm. Generally, MCL cells are just slightly larger, but very similar to normal lymphocyte. On a small biopsy, it is not difficult at all to miss the bland morphology of MCL. MCL can easily go unnoticed, especially on biopsies from organs that are normally rich in lymphoid tissue content, like mucosa of digestive system or Waldeyer's ring (1, 4).

Diagnostic hallmark of MCL is aberrant expression of CyclinD1, which reflects pivotal molecular event in pathogenesis of this lymphoma, the translocation t(11;14)(q13;q32). This chromosomal aberration results in juxtaposition of the bcl-1 locus on 11q13 to the immunoglobulin heavy chain gene region, which leads to deregulation of gene encoding the cell cycle protein CyclinD1. CyclinD1 overexpression further deranges cell cycle control by breaching the tumor suppressor function of RB1 and p27.

Additional secondary genomic alterations are required for complete malignant transformation. Predominantly these necessary alterations affect genes involved in cell cycle regulation and repair mechanisms in DNA damage cell response. Recently, a rare CyclinD1-negative subtype of MCL has been identified. This rare variant shares clinical, morphological, and phenotypic characteristics with classic MCL, and usually carries translocations involving *CCND2*/CyclinD2 gene (4, 5).

Clinical manifestations of MCL may be quite non-specific and diverse. Usually, they are associated with the anatomic region affected, and may represent as regional lymphadenopathy, asymmetric enlargement of palatine tonsil accompanied by odynophagia or hoarseness, abdominal discomfort or pain, gastrointestinal bleeding or bowel obstruction. Systemic symptoms like weight loss, general malaise, fever and night sweats are only seldom encountered. Occasionally, only abnormalities in peripheral blood analysis (leukocytosis with lymphocytosis, anaemia, pancitopenia) may lead to bone marrow biopsy and establishment of MCL diagnosis.

The data about the incidence, diagnosis, therapy, and outcome of MCL in our country is scarce (6-10). This study aimed to comprehensively analyze pathological features of MCL in patients from Southeastern Serbia and to determine the frequency of this devastating disease in our population.

Materials and methods

A total of 455 lymphomas that were diagnosed in the Center for Pathology, University Clinical Center Niš between January 2016 and December 2020 were analyzed, among which MCL cases were selected. The patients' data were retrospectively collected from archived medical records. Baseline clinical characteristics were evaluated, including patients' age, gender, and localization of lymphoma presentation.

Formalin-fixed paraffin-embedded tissue sections stained with hematoxylin and eosin were used for diagnosis and assessment of pathologic parameters. Pathologic diagnosis of MCL was based on the current 2017 World Health Organization classification (1).

Immunohistochemical (IHC) analysis in all cases where suspicion of MCL was made during the review of HE slides comprised the following IHC panel: CD20, PAX5, CD3, CD5, CD10, Bcl-2, Bcl-6, MUM1, CyclinD1 and Ki67. Only cases from year 2020 were stained to SOX11, because this antibody was not available in our Center during the previous years.

Results

During the five-year period the diagnosis of MCL was established in 47 cases, which constitutes 10.3% of all newly diagnosed lymphomas in our Center for Pathology, University Clinical Center Niš. The majority of the patients were men, 72.3%, and the average patients' age at the time of diagnosis was 66.1 years (Table 1).

The majority of MCL had extranodal clinical presentation (29 cases, 61.7%). Every fourth case of MCL was diagnosed on bone marrow biopsy. Oral cavity and gastrointestinal tract were equally represented as extranodal diagnostic location, with 17% respectively (Table 2).

Micromorphology and immunophenotypic characteristics of MCL are shown in Figures 1-3.

Table 1. Clinical-pathological characteristics of newly diagnosed cases of Mantle cell lymphoma

Year	Total lymphoma	**Mantle cell lymphoma**		Average patients' age (yrs)	Male patients (N)	%
		(N)	**(%)**			
2016	82	12	14.6	64.8	10	83.3
2017	84	9	10.7	73.0	6	66.6
2018	88	7	8.0	67.1	6	85.7
2019	69	8	11.6	59.4	6	75.0
2020	126	11	8.7	66.2	6	54.5
Total	455	47	10.3	66.1	34	72.3

Table 2. Structure of diagnosed cases of Mantle cell lymphoma by initial primary nodal and extranodal locations

MCL diagnostic site	N	%
Total	47	100
Nodal localization	18	38.3
Cervical lymph nodes	13	27.7
Inguinal lymph nodes	5	10.6
Extranodal site	29	61.7
Bone marrow	13	27.7
Oral cavity	8	17.0
Tonsil	4	8.6
Epipharynx	2	4.2
Non specified	2	4.2
Gastrointestinal tract	8	17.0
Stomach	4	8.5
Colon	3	6.4
Intestine	1	2.1

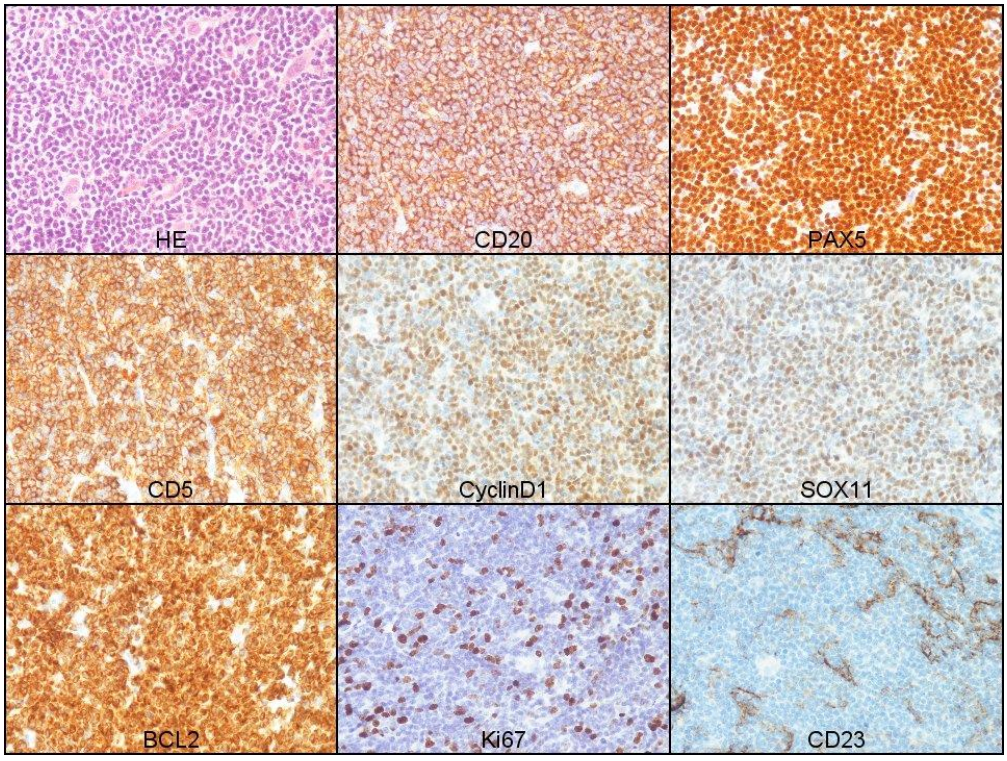

Figure 1. Morphology and immunophenotype of nodal Mantle cell lymphoma:
monomorphic medium-sized lymphoid cells population with scattered epithelioid histiocytes and hyalinized vessels.
Neoplastic cells express B-cell markers CD20 and PAX5 in addition to diagnostic CD5, CyclinD1 and SOX11 expression.
Bcl-2 is also positive, while Ki67 proliferative index is 15%.
CD23 highlights residues of follicular dendritic meshwork.
Original magnification x400.

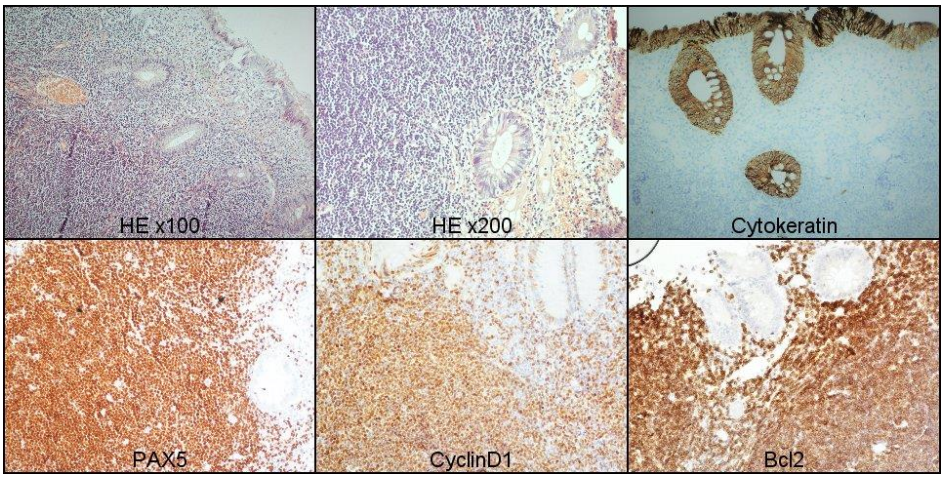

Figure 2. Lymphomatous polyposis of the colon – Mantle cell lymphoma of gastrointestinal tract.
Diffuse infiltration of colonic wall by small to medium sized neoplastic lymphoid cells.
Cytokeratin stains preserved superficial and cryptal epithelium.
Tumor cells strongly and diffusely express PAX5, CyclinD1 and Bcl-2.
Original magnification x100 and x200.

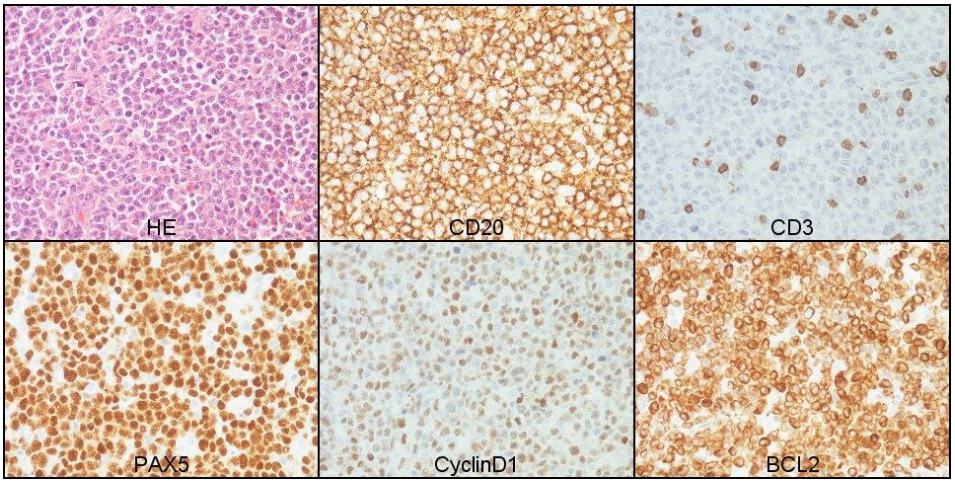

Figure 3. Pleomorphic mantle cell lymphoma, aggressive variant of MCL that closely resembles diffuse large B-cell lymphoma. Large lymphoid cells have irregular nuclei with prominent nucleoli,
and abundant cytoplasm, and are immunohistochemically positive to B-cell markers,
CyclinD1 and Bcl-2, and negative to T-cell marker CD3.
Original magnification x400.

Discussion

MCL most frequently occurs in older men, compared to other types of non-Hodgkin lymphoma, and the average patients' age is 65. The results of our study are in accordance with these findings. The majority of MCL in our Center was diagnosed in male patients, who comprised 72.3% of cases, with the average patients' age 66.1 years. In 2020, the percentage of female patients with MCL increased, which has no explanation other than pure stochastic probability, considering the fact that MCL is not significantly associated with autoimmune diseases, smoking, alcohol consumption, exposure to ultra-violet radiation or body mass index, unlike some other lymphoma types (11). The only significant risk factor, associated with a twofold increased risk of MCL, is family history positive for hematological malignancy among first-degree relatives.

Unfortunately, the data about family history of our patients was not available.

During the recent years, the definition of MCL has evolved from aggressive B-cell lymphoma with constitutive overexpression of CyclinD1 into a pathological spectrum of several clinical and biological subtypes. Major breakthrough was made with identification of CyclinD1 negative MCL and discovery of MCL with CyclinD2 translocations (5, 12, 13). Two distinct clinical subtypes are recognized: more aggressive, conventional MCL, and more indolent form, leukemic, non-nodal MCL. Conventional MCL originates from naïve B-cell of mantle zone, expresses transcription factor SOX11, develops numerous genetic aberrations because of high chromosomal instability, and usually presents with generalized lymphadenopathy. Leukemic non-nodal MCL originates from a B-cell that has experienced germinal center microenvironment, retains memory B-cell phenotype with more stable karyotype, and is negative for SOX11. Leukemic MCL shows minimal involvement of lymph nodes, it presents with leukemia and splenomegaly and can remain clinically indolent for years, but progression to aggressive disease may occur (3, 5, 14, 15). We initially diagnosed MCL from bone marrow biopsy in 27.7% of the cases, which is not surprising, since bone marrow infiltration and peripheral blood involvement with notable lymphocytosis are seen in the majority of MCL, up to 90%. These patients had hematologic disturbances, some had enlarged spleen, and the treating clinicians chose bone marrow biopsy as a diagnostic method of choice.

Mantle cell lymphoma *in situ* is a recently introduced entity in WHO classification of mature B-cell neoplasms (1). This lesion is usually an incidental finding of CyclinD1-positive B-cells in mantle zones of reactive lymphoid follicles, who carry translocation t(11;14) (2). Clinical significance of this lesion is not well understood. Its course may be associated with overt MCL, other small B-cell lymphoma or may remain silent long after diagnosis, even without any treatment (1, 2).

Differential diagnosis of MCL is not straightforward based on its histology, because MCL encompasses large spectrum of architectural patterns and cytological variants. Involvement of lymph nodes may represent in a form of mantle zone, nodular and diffuse pattern, and requires immunohistochemical analysis to CyclinD1 and SOX11 for correct diagnosis and distinction from other lymphoid neoplasms and reactive and hyperplastic conditions. Variant morphology may be easily confused with potentially curable or indolent lymphomas. Small cell MCL variant can be easily misdiagnosed as small lymphocytic lymphoma/chronic lymphocytic leukemia, while blastoid and pleomorphic variants (Figure 3) of MCL can mimic DLBCL or acute myeloid leukemia (16, 17). Opposite to DLBC which is curable in most of the cases, these aggressive variants of MCL are quite rare but deadly. Among our cases of MCL, only one had alarming morphology of pleomorphic variant, while two cases were small cell MCL.

We diagnosed MCL in gastrointestinal system in 17% of the cases, which is in accordance with the notion that MCL involves GIT in 10-25%. MCL can manifest in a form of multifocal lymphomatous polyposis, multiple polyps most frequently involving ileocecal region of the bowl (Figure 2). This gross finding may resemble much less perilous diagnostic possibilities, thus diagnostic biopsy is always indicated. Nevertheless, multifocal lymphomatous polyposis of small or large bowel is not specific for MCL only, and can be morphologic expression of other lymphomas (18, 19). Diagnosis of MCL in digestive tube is quite challenging, especially because of the presence of MALT, mucosa-associated lymphoid tissue, which may show hyperplastic and reactive changes in numerous conditions. Bland morphology of MCL can mimic benign entities. Therefore, MCL must be always considered in biopsies of polyps with large lymphoid aggregates (20, 21).

Clinical prognosis of MCL is poor, excluding the rare indolent forms. MCL usually follows the course of a very aggressive refractory disease. Patients are stratified according to the clinical prognostic factors clustered under MCL international prognostic index (MIPI) into low, intermediate, and high risk groups, and treated accordingly with various immunochemotherapy combinations, preferably with rituximab maintenance. In refractory cases or in early relapses newer targeted approaches are strongly recommended. Genomic landscape information, such as mutational status of *TP53* and *CCND1*, are gaining increased recognition as factors that increase prognostic value of MIPI index. Further understanding of molecular events in MCL which influence its clinical behavior could allow personalized therapeutic approach (22, 23).

Currently, MCL is an incurable disease, a killer with a child's face. However, accurate and precise diagnosis may improve patients' outcome through timely application of new and promising treatment strategies. The pathologist's role in a proper recognition and the rapid diagnosis of MCL and its subtype, especially in biopsies from extranodal locations, including endoscopic biopsies, and distinction from other less aggressive non-Hodgkin lymphomas may contribute significantly to longer survival and better clinical outcome of the disease.

References

1. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al., editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. Lyon: IARC; 2017.
2. Carvajal-Cuenca A, Sua LF, Silva NM, Pittaluga S, Royo C, Song JY, et al. In situ mantle cell lymphoma: clinical implications of an incidental finding with indolent clinical behavior. Haematologica 2012;97(2): 270-8. [CrossRef] [PubMed]
3. Schlette E, Lai R, Onciu M, Doherty D, Bueso-Ramos C, Medeiros LJ. Leukemic mantle cell lymphoma: clinical and pathologic spectrum of twenty-three cases. Mod Pathol 2001;14(11):1133-40. [CrossRef] [PubMed]
4. Jiang M, Bennani NN, Feldman AL. Lymphoma classification update: B-cell non-Hodgkin lymphomas. Expert Rev Hematol 2017;10(5):405-15. [CrossRef] [PubMed]
5. Veloza L, Ribera-Cortada I, Campo E. Mantle cell lymphoma pathology update in the 2016 WHO classification. Ann Lymphoma 2019;3. [CrossRef]
6. Petkovic I, Mihailovic D, Krstic M, Pejcic I, Vrbic S, Balic M. Primary mantle cell lymphoma of gastrointestinal tract – a case report. Acta Medica Medianae 2012;51(3):41-6. [CrossRef]
7. Petkovic I, Stojnev S, Krstic M, Pejcic I, Vrbic S. Synchronous mantle cell lymphoma and prostate adenocarcinoma-is it just a coincidence? Vojnosanitetski pregled 2016;73(11):1072-5. [CrossRef][PubMed]
8. Todorovic M, Pavlovic M, Balint B, Kraguljac N, Mihaljevic B, Bogdanovic A, et al. Immunophenotypic profile and clinical characteristics in patients with advanced stage mantle cell lymphoma. Med Oncol 2007;24(4):413-8. [CrossRef] [PubMed]
9. Knezevic S. Primary mantle cell lymphoma of tonsil – Case report. Opsta medicina 2017;23(1-2):37-42. [CrossRef]
10. Rašić DM, Knežević M, Terzić T, Vlajković G. Bilateral ocular panadnexal mass as initial presentation of systemic blastoid variant of mantle-cell lymphoma. Surv Ophthalmol 2017;62(1):83-8. [CrossRef] [PubMed]
11. Smedby KE, Sampson JN, Turner JJ, Slager SL, Maynadié M, Roman E, et al. Medical history, lifestyle, family history, and occupational risk factors for mantle cell lymphoma: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. J Natl Cancer Inst Monogr 2014;2014:76-86. [CrossRef] [PubMed]
12. Salaverria I, Royo C, Carvajal-Cuenca A, Clot G, Navarro A, Valera A, et al. CCND2 rearrangements are the most frequent genetic events in cyclin D1(-) mantle cell lymphoma. Blood 2013;121:1394-402. [CrossRef] [PubMed]
13. Royo C, Salaverria I, Hartmann EM, Rosenwald A, Campo E, Beà S. The complex landscape of genetic alterations in mantle cell lymphoma. Semin Cancer Biol 2011;21(5):322-34. [CrossRef] [PubMed]
14. Clot G, Jares P, Gine E, Navarro A, Royo C, Pinyol M, et al. A gene signature that distinguishes conventional and leukemic nonnodal mantle cell lymphoma helps predict outcome. Blood 2018;132:413-22. [CrossRef] [PubMed]
15. Fernàndez V, Salamero O, Espinet B, Solé F, Royo C, Navarro A, et al. Genomic and gene expression profiling defines indolent forms of mantle cell lymphoma. Cancer Res 2010;70(4):1408-18. [CrossRef] [PubMed]
16. Shrestha R, Bhatt VR, Guru Murthy GS, Armitage JO. Clinicopathologic features and management of blastoid variant of mantle cell lymphoma. Leuk Lymphoma 2015;56(10):2759-67. [CrossRef] [PubMed]
17. Yoshino T, Tanaka T, Sato Y. Differential diagnosis of chronic lymphocytic leukemia/small lymphocytic lymphoma and other indolent lymphomas, including mantle cell lymphoma. J Clin Exp Hematop 2020; 60(4):124-9. [CrossRef] [PubMed]
18. Hirata N, Tominaga K, Ohta K, Kadouchi K, Okazaki H, Tanigawa T, et al. A case of mucosa-associated lymphoid tissue lymphoma forming multiple lymphomatous polyposis in the small intestine. World J Gastroenterol 2007;13(9):1453-7. [CrossRef] [PubMed]
19. Mohammed A, Shariati F, Paranji N, Waghray N. Primary follicular lymphoma of colon: A case series and review of literature. Clin Case Rep 2021;9(7): e04486. [CrossRef] [PubMed]
20. Iwamuro M, Okada H, Kawahara Y, Shinagawa K, Morito T, Yoshino T, et al. Endoscopic features and prognoses of mantle cell lymphoma with gastrointestinal involvement. World J Gastroenterol 2010; 16(37):4661-9. [CrossRef] [PubMed]
21. Nassri R, Nassri A, Alkhasawneh A, de Souza Ribeiro B, Schey R. Colonic Mantle Cell Lymphoma with Multiple Lymphomatous Polyposis. GE Port J Gastroenterol 2020;27(4):296-8. [CrossRef] [PubMed]
22. Dreyling M, Campo E, Hermine O, Jerkeman M, Le Gouill S, Rule S, et al; ESMO Guidelines Committee. Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28(suppl 4): iv62-iv71. [CrossRef] [PubMed]
23. Ahmed M, Zhang L, Nomie K, Lam L, Wang M. Gene mutations and actionable genetic lesions in mantle cell lymphoma. Oncotarget 2016;7(36):58638-48. [CrossRef] [PubMed]

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MANTLE ĆELIJSKI LIMFOM – UBICA DEČIJEG LICA

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Mantle ćelijski limfom (MCL) je poseban tip non-Hodgkinovog limfoma sa veoma agresivnim kliničkim ponašanjem. Uprkos blagoj, uniformnoj morfologiji, MCL je neizlečiva i smrtonosna bolest, iako je prepoznato nekoliko varijanti sa indolentnijim kliničkim tokom. Cilj ove studije je sveobuhvatna analiza patomorfoloških karakteristika MCL-a kod bolesnika iz jugoistočne Srbije i određivanje učestalosti ovog limfoma u našoj populaciji. Tokom petogodišnjeg perioda, dijagnoza MCL-a postavljena je u 47 slučajeva, što čini 10,3% svih novodijagnostikovanih limfoma u Centru za patologiju Univerzitetskog kliničkog centra Niš. Većina obolelih bili su muškarci (72,3%), a prosečna starost bolesnika, u trenutku postavljanja dijagnoze, bila je 66,1 godina. Ekstranodalna prezentacija bila je prisutna kod 61,7% obolelih. Svaki četvrti slučaj MCL-a dijagnostikovan je biopsijom koštane srži. Usna duplja i gastrointestinalni trakt podjednako su zastupljeni kao ekstranodalna dijagnostička lokacija, sa po 17%. MCL obuhvata širok spektar histoarhitektonskih obrazaca i citoloških varijanti, te dijagnostika zahteva imunohistohemijsku analizu ekspresije CyclinD1 i SOX11 gena za tačnu dijagnozu i diferencijaciju od drugih limfoidnih neoplazmi i reaktivnih i hiperplastičnih stanja. Morfološke varijante MCL-a mogu se lako pomešati sa potencijalno izlečivim ili indolentnim limfomima. Tačna i precizna dijagnoza MCL-a može poboljšati ishod bolesti blagovremenom primenom novih i obećavajućih strategija lečenja. Uloga patologa u pravilnom prepoznavanju i brzoj dijagnozi MCL-a i određivanju njegovog podtipa, posebno u biopsijama sa ekstranodalnim lokacijama, uključujući endoskopske biopsije, može značajno doprineti dužem preživljavanju obolelih i boljem kliničkom ishodu bolesti.

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Ključne reči: *mantle ćelijski limfom, dijagnoza, patologija, imunohistohemija, CiclinD1*