Hronična limfocitna leukemija u ordinaciji opšte medicine

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Chronic lymphocytic leukemia in general practice

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Sažetak

Uvod. Hronična limfocitna leukemija (HLL) je najčešća leukemija kod odraslih, retko obolevaju deca. Češće se javlja kod osoba muškog pola starosti preko 60 godina. Etiopatogenetski, predstavlja nenormalno bujanje limfocita u koštanoj srži, koji su disfunkcionalni iako morfološki liče na zrele.

Prikaz slučaja. Pacijentkinja, stara 66 godina, domaćica, dolazi na pregled zbog zamora koji traje oko mesec dana i gubitka 3 kg do 4 kg, ostale tegobe negira. Na pregledu svesna, orijentisana u vremenu, prostoru i prema ličnostima, eupnoična, limfadenopatija na vratu, aksilama i ingvinumu, odaje utisak lakšeg bolesnika. Klinički pregled: na plućima disanje vezikularno bez propratnih šušnjeva, srčana radnja ritmična, tonovi jasni, krvni pritisak (TA) 140/80 mmHg, abdomen u ravni grudnog koša, palpatorno bolno neosetljiv, jetra se ne palpira a slezina se palpira 2 cm ispod rebarnog luka. Krvna slika je pokazala povećan broj leukocita $181,30 \times 10^9/L$ i limfocitozu 92,2%, ostali parametri su bili normalni. Upućena je hematologu Opšte bolnice u Kraljeva, gde je urađena dalja dijagnostika. Ponovljena je krvna slika, urađen radiološki pregled (RTG) pluća, ultrazvuk (EHO) abdomena, vrata, aksila, ingvinuma, srca, virusologija, pregled ORL. Ultrazvuk abdomena je pokazao patološki nalaz sa uvećanom jetrom, slezinom, limfnim nodusima (LN). Pregled ORL: uvećane tonzile, ostali nalaz uredan. Pod sumnjom na hroničnu limfocitnu leukemiju, pacijentkinja je upućena u Klinički centar Srbije (KCS). Urađena je imunofenotipizacija (IF) i kompjuterizovana tomografija (CT) vrata, grudnog koša i abdomena. Potvrđena je dijagnoza HLL. Konzilijarno je odlučeno da se sprovede imunohemioterapijsko lečenje (IHT) sa *Fludarabinom* i *Rituximabom*. Posle 6 primljenih ciklusa, bolesnica se subjektivno dobro oseća a nalazi krvne slike su normalni.

Zaključak. Kod velikog broja pacijenata HLL može proticati asimptomatski ili sa nespecifičnim i blagim simptomima. Stoga su pregledi krvne slike i nalaz leukocitoze i apsolutne limfocitoze presudni da se posumnja na ovo oboljenje i da se sprovede dalja dijagnostika.

Ključne reči. Hronična limfocitna leukemija, leukocitoza, limfocitoza.

Abstract

Introduction: Chronic lymphocytic leukemia (CLL) is the most common leukemia in adults, rarely affecting children. It is more common in males over 60. Etiopathogenetically, it represents an abnormal proliferation of lymphocytes in the bone marrow, which are dysfunctional although morphologically similar to mature ones.

Case report: Female patient, 66, a housewife, comes for an examination due to fatigue lasting about a month and weight loss of 3-4 kg. She denies other health problems. On the examination, she is alert, oriented to time, space, and persons, eupnoeic, lymphadenopathy on the neck, axillae and groins. She gives away the impression of a patient with mild clinical symptoms. Clinical examination: clear breath sounds in all lung fields, regular heartbeat, clear tones, BP 140/80 mmHg, abdomen at chest level, painless to palpation, liver not palpable, and spleen palpated 2 cm below the costal arch. CBC (complete blood count) showed an increased number of leukocytes $181.30 \times 10^9/L$ and lymphocytosis 92.2%, other parameters were normal. She was referred to the hematologist in the Kraljevo General Hospital, where further diagnostics were performed. Blood count was repeated, Chest X-ray was performed, ultrasound (US) of the abdomen neck, axillae, groins, and heart, virology tests, ENT examination. Abdominal US showed a pathological finding with enlarged liver, spleen, lymph nodes (LN). ENT examination: enlarged tonsils, other findings unremarkable. Since chronic lymphocytic leukemia was suspected, she was referred to the Clinical Center of Serbia. Immunophenotyping (IF) and computed tomography (CT) of the neck, chest, and abdomen were performed. The diagnosis of CLL was confirmed. A Medical Council decided to perform immunochemotherapy (IHT) with *fludarabine* and *rituximab*. After 6 received cycles, the patient feels well and the CBC parameters are normal.

Conclusion: CLL may be asymptomatic or nonspecific and with mild symptoms in a large number of patients. Therefore, blood tests with leukocytosis and absolute lymphocytosis findings are crucial to suspect the disease and perform further diagnostics.

Keywords: Chronic lymphocytic leukemia, leukocytosis, lymphocytosis.

Uvod

Leukemije su maligne bolesti krvi. Prema dužini trajanja dele se na akutne i hronične, a prema vrsti leukocita koji maligno bujaju, na granulocitne i limfocitne. Predstavljaju nenormalno, generalizovano razmnožavanje jedne od leukocitnih loza, često praćeno povećanim brojem leukocita u perifernoj krvi¹.

Hronična limfocitna leukemija (HLL) je maligno oboljenje krvnih ćelija - limfocita. Morfološki se malo razlikuju od normalnih, ali su nefunkcionalni, što se posledično odražava na imunitet. Postoje dve vrste HLL: *B ćelijska*, koja je češća i javlja se kod 95% pacijenata i *T ćelijska* koja je ređa¹. Etiologija je nepoznata. Okrivljuje se jonizujuće zračenje, genetika, patogeni agensi, virusi, bakterije, pesticidi i herbicidi, stres. Postoje dokazi da je učestalo izlaganje pesticidima i herbicidima glavni spoljašnji faktor rizika^{1,2}. Porodična istorija bolesti može povećati rizik do tri puta više nego kod onih koji nemaju pozitivnu porodičnu anamnezu. Hronična limfocitna leukemija je, uglavnom, bolest muškaraca starijeg životnog doba, preko šezdeset godina. Rizik od HLL se značajno povećava sa godinama života. Postoji oko 13 novih slučajeva na 100.000 stanovnika starosti preko 65 godina^{1,2}.

U kliničkoj slici se javljaju uvećane limfne žlezde, uvećana jetra i slezina, ali i mnogi atipični znaci kao što su umor, noćno znojenje, gubitak težine, osećaj nadutosti, svrab i hiperpigmentacija kože, herpes zoster i drugo. Određivanje stadijuma može se izvršiti po *Rai* i *Binet* klasifikaciji. Postoje četiri stadijuma: nulti kada je prisutna samo limfocitoza, I stadijum kada pored limfocitoze postoji i limfadenopatija, II stadijum limfocitoza, limfadenopatija i uvećana jetra i/ili slezina. U III stadijumu, pored navedenog, postoji i anemija a u IV stadijumu postoji još i trombocitopenija^{1,2}. Početak bolesti je obično podmakao i HLL se često dijagnostikuje slučajno pri rutinskom pregledu krvne slike ili pri obradi asimptomatske limfadenopatije². Pregledom krvne slike nađe se leukocitoza sa izraženom limfocitozom. U leukocitarnoj formuli procenat limfocita se u početku kreće od 60% do 75% a kasnije i do 90%. Iako zreli, ovi limfociti su atipični, nefunkcionalni sa posledicama na imunološki sistem. U većini slučajeva pacijent sa povećanim brojem leukocita se dobro oseća. U ređim slučajevima klinički simptomi i znaci prate početak bolesti. Normalno, koštano srž čine matične ćelije, koje tokom vremena postaju zrele krvne ćelije. Kod HLL, previše matičnih ćelija krvi postaju abnormalni limfociti koji ne dostižu određenu zrelost i time gube funkciju. Ako se broj leukemičnih ćelija povećava u perifernoj krvi, posledično dolazi do povećanja broja i u koštanoj srži, čime se smanjuje prostor za normalne ćelije¹. Vremenom dolazi do nakupljanja abnormalnih leukocita u limfnim čvorovima, jetri i slezini kao i u drugim organima. Evolucija HLL je duga, akutizacije su retke a bolesnici imaju probleme sa čestim infekcijama, opštim propadanjem zbog autoimunih pojava, čestim hemoliznim krizama ili posledicama zbog insuficijencije koštane srži.

Introduction

Leukemias are malignant blood diseases. In relation to the duration, they are divided into acute and chronic, and according to the type of leukocytes, which flourish malignantly, into granulocytic and lymphocytic. They represent an abnormal, generalized proliferation of one of the leukocyte lines, followed very often by an increased number of leukocytes in the peripheral blood¹.

Chronic lymphocytic leukemia (CLL) is a malignant disease of the blood cells-lymphocytes, which are morphologically slightly different from normal cells but are non-functional, which consequently affects immunity. There are two types of CLL: *B-cell*, which is more common and occurs in 95% of patients, and *T-cell*, which is less common¹. The etiology is unknown. The culprits are ionizing radiation, genetics, pathogenic agents, viruses, bacteria, pesticides and herbicides, stress. There is evidence that frequent exposure to pesticides and herbicides is a major external risk factor^{1,2}. A family history of the disease can increase the risk by up to 3 times than in people who do not have a positive family history. Chronic lymphocytic leukemia is a disease mainly of older men, over 60. The risk of CLL increases significantly with age. There are about 13 new cases per 100,000 people over the age of 65^{1,2}.

The clinical presentation is remarkable for enlarged lymph glands, liver, and spleen, but also many atypical signs such as fatigue, night sweats, weight loss, bloating, itching, and hyperpigmentation of the skin, herpes zoster, and others. Disease staging can be performed according to *Rai* and *Binet* classification. There are 4 disease stages: Zero, when only lymphocytosis is present, I when there is lymphadenopathy in addition to lymphocytosis, II lymphocytosis, lymphadenopathy, and enlarged liver and/or spleen. In stage III, in addition to the above, there is also anemia, and in stage IV there is also thrombocytopenia^{1,2}. The onset of the disease is usually insidious and CLL is often diagnosed accidentally during a routine blood check or treatment of asymptomatic lymphadenopathy². CBC reveals leukocytosis with pronounced lymphocytosis. Leukocyte formula initially shows lymphocyte percentages ranging from 60%-75%, and later up to 90%. Although mature, these lymphocytes are atypical, dysfunctional with consequences for the immune system. In most cases, the patient with an increased number of leukocytes feels well. In rare cases, clinical symptoms and signs accompany the onset of the disease. Normally, the bone marrow is made up of stem cells, which become mature blood cells over time. In CLL, too many blood stem cells become abnormal lymphocytes that do not reach a certain maturity and thus lose function. As the number of leukemic cells increases in the peripheral blood, there is a consequent increase in the number of cells in the bone marrow, thereby reducing the space for normal cells¹. Over time, abnormal leukocytes accumulate in the

Prikaz slučaja

Pacijentkinja stara 66 godina, domaćica, dolazi na pregled zbog zamora koji traje oko mesec dana, u poslednja dva meseca izgubila je 3 kg do 4 kg, ostale tegobe negira. Leči se od povišenog pritiska, retko dolazi kod izabranog lekara, dugogodišnji je pušač, 20 cigareta dnevno, ne pije alkohol, u poslednjih nekoliko meseci imala je više stresnih situacija. Porodična anamneza pozitivna za kardiovaskularne bolesti i dijabetes.

Bolesnica je svesna, orijentisana u vremenu, prostoru i prema ličnostima, afebrilna, eupnoična, pokretna, normalno uhranjena, koža bledo prebojena, prisutna limfadenopatija u vratu, aksilama i ingvinumu do 4 cm u konglomeratima, odaje utisak lakšeg bolesnika^{1,2}.

Objektivnim pregledom nađeno je: glava uobičajene konfiguracije, nos prohodan, jezik vlažan i neobložen, tonzile uvećane, očni bulbusi pokretni u svim pravcima, zenice reaguju na svetlost i akomodaciju, vrat pokretan u svim pravcima, štitasta žlezda u fiziološkim granicama, grudni koš simetričan, respiratorno obostrano pokretan, na plućima vezikularno disanje bez propratnih šušnjeva, srčana akcija ritmična, tonovi jasni bez patoloških šumova; TA 140/80 mmHg. Abdomen u ravni grudnog koša, palpatorno bolno neosetljiv, jetra se ne palpira, slezina se palpira za 2 cm, čvrsta, glatkih ivica, bezbolna. Bubrežne lože neosetljive na grubu perkusiju. Ekstremiteti bez edema i deformiteta, očuvane periferne arterijske pulsacije na GE i DE. Bez vidljivih neuroloških ispada.

Urađena je kompletna laboratorija koja je pokazala visoke vrednosti leukocita $181,30 \times 10^9/L$ u perifernoj krvi, visoki procenat limfocita 92,2%. Ostali nalaz bio je u referentnim granicama. Odmah je upućena hematologu Opšte bolnice u Kraljevu, gde je hospitalizovana 15.10.2019. godine i gde je urađena dalja dijagnostika: radiološki pregled (RTG) pluća, ultrazvuk (EHO) abdomena, vrata, aksila, ingvinuma i srca, kompletna biohemija i ELISA test (*ELISA enzyme-linked immunosorbent assay*); pregled ORL lekara, EHO abdomena: jetra je veličinom u granicama fizioloških vrednosti, u njoj se uočavaju dve nejasno definisane, hiperehogene promene promera 14 mm i 15 mm koje mogu biti hemangiomi, ali se ne isključuju ni lezije sekundarne etiologije. Slezina je veličinom na gornjoj granici fizioloških vrednosti (120 mm x 55 mm) izrazito heterogene strukture, infiltrativno je izmenjena sa vidljivim difuzno raspoređenim hipoehogim mikroarealima koji su promera od 3 mm do 12 mm. U retroperitoneumu se zapaža veći broj izmenjenih limfnih nodusa (LN) promera 15 mm do 27 mm koji su hipohogene strukture, ostali nalaz uredan, EHO vrata, aksilarne i ingvinalne regije: štitasta žlezda je veličinom u granicama normale, simetrična, regularnih kontura, homogene strukture, u desnom lobusu uočava se heterogeni cistično izmenjen nodus 7,5 mm x 4,5 mm a u levom lobusu izoehogeni nodus veličine 5 mm x 6 mm. Sub-

lymph nodes, liver, and spleen as well as in other organs. The evolution of CLL is long, acutisations are rare and patients have problems with frequent infections, general deterioration due to the autoimmune phenomena, frequent hemolytic crises, or consequences due to bone marrow insufficiency.

Case report

A 66-year-old female patient, a housewife, comes for an examination due to fatigue that lasts for about a month. She lost 3-4 kg in the last two months, denies other health problems. She is treated for high blood pressure, rarely visits her GP, long-term smoker, 20 cigarettes a day, does not drink alcohol, had more stressful situations in recent months. She has got a family history of cardiovascular disease and diabetes.

She is alert, oriented to time, space, and persons, afebrile, eupnoeic, mobile, well-fed, with pale skin, lymphadenopathy on the neck, axillae, and groins up to 4 cm, in conglomerates. She gives away the impression of a patient with mild clinical symptoms.

Physical examination revealed: head of normal configuration, nose passable, tongue moist and uncoated, tonsils enlarged, eyeballs moving in all directions, pupils reacting to light and accommodation, neck movable in all directions, thyroid gland within physiological limits, chest symmetrical, respiratory bilaterally mobile, clear breath sounds in all lung fields, regular heartbeat, clear tones, without pathological noises, BP 140/80 mmHg. Abdomen in the plane of the chest, painless to palpation, the liver is not palpable, the spleen is palpated by 2 cm, firm, smooth edges, painless. Renal lodges are insensitive to rough percussion. Limbs without edema and deformity, preserved peripheral arterial pulsations on UE (upper extremities), and LE (lower extremities). No visible neurological deficits.

A CBC showed high values of leukocytes $181.30 \times 10^9/L$ in peripheral blood with a high percentage of lymphocytes 92.2%. Other findings were within the reference range. She was immediately referred to a hematologist at the Kraljevo General Hospital, where she was hospitalized on October 15, 2019, and further diagnostics were performed: chest X-ray, ultrasound (US) of the abdomen, neck, axillae, groins, and heart, complete biochemistry and ELISA test (*ELISA enzyme-linked immunosorbent assay*). ENT examination was performed. Abdomen US findings: the size of the liver is within the physiological limits; two vaguely defined, hyperechoic formations of 14 mm and 15 mm in diameter can be observed, which might be hemangiomas, but they also might be lesions of secondary etiology. The size of the spleen is at the upper limit of physiological values (120 mm x 55 mm) with a distinctly heterogeneous structure, it is infiltratively altered with visible diffusely distributed hypoechoic micro areas with a diameter of 3 mm to 12 mm. In the retroperitoneum, a larger number of altered lymph nodes (LN) with a diameter

mandibularno se uočava par uvećanih LN, od kojih su neki izmenjene strukture, zbrisanog hilusa, promera 10 mm i 7 mm. Obostrano parajugularno uočava se više pojedinačnih LN u nizu, izmenjene strukture, zbrisanih hilusa, očuvanog L/W indeksa, najveći promer do 14 mm. Obostrano aksilarno uočava se više grupisanih uvećanih LN, ali očuvane strukture i hiperehogenog hilusa, očuvanog L/W indeksa, promera do 20 mm. Obostrano ingvinalno uočava se više grupisanih uvećanih LN, očuvane strukture i hiperehogenog hilusa, očuvanog L/W indeksa promera do 23 mm. Nalaz RTG pluća u granicama normale, nalaz EHO srca uredan. Virusologija (ELIZA test) na *HbsAg*, *HCV* i *HIV Ag* negativan. Coombs dir. i ind. negativan. Biohemijski nalaz: leukociti (WBC) ($193...207,85 \times 10^9/L$), eritrociti (RBC) ($3,95...4,06 \times 10^{12}/L$), hemoglobin (HGB) 116...118 (g/L), HCT 0,369 (L/L), MCV 93,4 (fL), MCH 29,4 V (pg), MCHC 314 (g/L), RDW (13,8%), PLT 204...204 (10/L), MPV 10,7 (fL), NEUTROFILI (4,5%), LYMFOCITI (92,5%), MONOCITI (2,6%), EOZINOFILI (0,3%), BAZOFILI (0,1%) ostali biohemijski parametri uredni. Pregled ORL: uvećane tonzile.

Pod sumnjom na hroničnu limfocitnu leukemiju upućena je u Klinički centar Srbije na dalju dijaagnostiku i lečenje. U KCS - Klinika za hematologiju hospitalizovana je 02.12.2019. godine. Dijagnoza je potvrđena na osnovu imunofenotipizacije (IF): HLL scor 4, CD38-, CD49d-. Na prezentaciji Konzilijumu u KC: *Le* $193,4 \times 10^9/L$, *Hg* 116, *MCV* 93,4, *Tr* 204, *Ly* 92,5%, ostala biohemija uredna. Indikovana je hospitalizacija radi započinjanja lečenja. Tražena je kompjuterizovana tomografija (CT) vrata sa pregledom svih spratova farinksa zbog uvećanih tonzila.

Kompjuterizovana tomografija-CT pregled vrata, grudnog koša i abdomena: u regiji vrata na svim nivoima uvećani limfni nodusi, desno od 12 mm do 24 mm, pretežno u gornjoj trećini. Supraklavikularno uvećani limfni nodusi do 12 mm. U levoj partiji vrata uvećani i izmenjeni limfni nodusi promera od 14 mm do 35 mm, a supraklavikularno levo do 14 mm. Aksilarno obostrano uvećani i patološki izmenjeni limfni nodusi do 20 mm. U plućnom parenhimu bazalno desno subpleuralni nodus promera do 9 mm, sa trakastim adhezivnim promenama. Slezina heterodenzne strukture, regularnih kontura 143 mm x 59 mm. Jetra regularnih kontura, u AP dijimetru u MKL 160 mm, sa promenom u VII segmentu promera 13 mm po tipu hemangioma. Pored opisane promene, uočava se nejasno definisana hipodezna promena promera do 14 mm koja ne pokazuje PKPD. Uočava se i par hipodenznih jasno ograničenih subcentimetarskih promena u V i VI segmentu, bez PKPD, koje po svojim karakteristikama mogu odgovarati cistama.

U toku ove hospitalizacije konzilijarno je odlučeno da se kod pacijentkinje započne imunohemioterapijsko lečenje (IHT) po protokolu RFC, D1 I cy 03.12.2019.: *Fludarabin*, amp. 38 mg D1-3, *Ciklofosamid* amp. 380 mg D1-3, *Rituksimab* amp. 500 mg D4. Primena terapije je protekla bez komplikacija. Opuštena je kući uz savet da uzima *Alopurinol* tab.

of 15 mm to 27 mm are observed, which are of hypoechoic structures, the rest is unremarkable. Neck, axillary and groin regions US: The size of the thyroid gland is within normal limits, symmetrical with regular contours and homogeneous structure; in the right lobe, heterogeneous cystically degenerated nodule 7.5 mm x 4.5 mm and in the left lobe isoechoic nodule 5 mm x 6 mm. In submandibular area, there is a pair of enlarged LNs, some of which are of altered structure, with a deleted hilus, 10 and 7 mm in diameter. On both sides, parajugularly, several individual LNs are observed in a row, altered structures, erased hili, of preserved L/W index, maximum diameter up to 14 mm. On both sides, in axillae, several grouped enlarged LNs are observed, but with preserved structure and hyperechoic hili, of the preserved L/W index, up to 20 mm in diameter. In both groins, several grouped enlarged LNs, of preserved structure and hyperechoic hili, with preserved L/W index, up to 23 mm in diameter are observed. Chest X-ray findings are within normal limits. Heart US findings are normal. Virology tests (ELISA test) for HepB, HepC and HIV Ag are negative. Coombs dir. and ind. tests are negative. CBC findings: leukocytes (WBC) ($193 ... 207.85 \times 10^9/L$), erythrocytes (RBC) ($3.95...4.06 \times 10^{12}/L$), hemoglobin (HGB) 116 ... 118 (g /L), HCT 0.369 (L/L), MCV 93.4 (fL), MCH 29.4 V (pg), MCHC 314 (g /L), RDW (13.8%), PLT 204 ... 204 (10 /L), MPV 10.7 (fL), NEUTROPHILS (4,5%), LYMPHOCYTES 92.5 (%), MONOCYTES 2.6 (%), EOSINOPHILS 0.3(%), BASOPHILES 0.1 (%). Other biochemical parameters are normal. ENT examination: enlarged tonsils.

Due to suspected chronic lymphocytic leukemia, she was referred to the Clinical Center of Serbia for further diagnostics and treatment. She was hospitalized at the CCS, Hematology clinic, on December 2, 2019. The diagnosis was confirmed based on Immunophenotyping (IF): HLL score 4, CD 38-, CD 49d-. She was presented to the Medical Council in CCS: *Le* $193.4 \times 10^9/L$, *Hg* 116, *MCV* 93.4, *Tr* 204, *Ly* 92.5%, other lab work unremarkable. Hospitalization was necessary to start the treatment. Computed tomography (CT) of the neck, with the examination of all floors of the pharynx due to enlarged tonsils, was requested.

CT examination of the neck, chest, and abdomen findings: in the neck region there were enlarged lymph nodes on all levels, on the right-hand side ranging from 12 to 24 mm in diameter, mostly in the upper third. Supraclavicular enlarged lymph nodes were up to 12 mm. On the left-hand side of the neck, there were enlarged and changed lymph nodes with a diameter of 14 to 35 mm, and supraclavicular left up to 14 mm. Axillary bilaterally enlarged and pathologically altered lymph nodes were up to 20 mm. There was a subpleural node in the basal part of the right lung up to 9 mm in diameter, with banded adhesive changes. Spleen was of heterodense structure, regular contours, 143 mm x 59 mm. Liver of regular contours, in AP diameter in MCL 160 mm, with a formation in VII segment, 13 mm in diameter, which

300 mg/dan, *Aciklovir* i *Bactrim* 2 x 2 u dane vikenda. Kontrola krvne slike jednom nedeljno. Primenu II cy *rituksimaba* imala je preko dnevne bolnice KCS 13.01.2020, Primena II cy FC na hematologiji Opšte bolnice u Kraljevu. Primila je na opisani način ukupno 6 cy. Sada se subjektivno dobro oseća, kontrole hematologa na tri meseca. Sadašnja biohemija je u normalnim granicama WBC $4,19 \times 10^9/L$, RBC $4,12 \times 10^{12}/L$, HGB 135 g/L.

Diskusija

Hronična limfocitna leukemija je jedna od najčešćih leukemija kod odraslih. Incidencija dostiže 13 obolelih na 100.000 osoba starosti preko 65 godina. Budući da u početnoj fazi može imati vrlo blage i nespecifične simptome ili čak proticati asimptomatski, potrebne su rutinske analize krvne slike i preventivni pregledi koji su presudni za rano postavljanje dijagnoze i pravovremeno lečenje. Nalaz leukocitoze u krvnoj slici sa limfocitozom je *alarm* da se pacijent uputi hematologu na dalju dijagnostičku obradu. Takođe, u krvnoj slici može biti prisutna i anemija i/ili trombocitopenija ili hipogamaglobulinemija.

Da bi se potvrdila dijagnoza HLL, neophodno je dokazati da su svi limfociti istog porekla (monoklonska limfocitoza). Stoga se vrši njihova imunofenotipizacija (IF), tj. određivanje karakteristika limfocita u perifernoj krvi^{3,4}. Kod ćelija HLL uglavnom je dokazano prisustvo markera CD5, CD19, CD23, CD20. Ukoliko se dokaže da su limfociti istog porekla, kao i da ih ima više od 5.000 u uzorku periferne krvi, može se postaviti dijagnoza HLL. Znači, za ranu dijagnozu nisu potrebni invazivni testovi poput punkcije i biopsije koštane srži⁵.

Imajući u vidu sporu progresiju bolesti kod većine bolesnika, pre početka lečenja neophodno je odrediti fazu bolesti po *Binet* i *Rai*, uraditi imunofenotipizaciju (IF), kao i rizik progresije i prognozu (FISH – *Fluorescence in situ hybridization*).

U toku bolesti može doći do pada imuniteta zbog nefunkcionalnih limfocita, anemije, trombocitopenije, hipogamaglobulinemije što može dovesti do ozbiljnih bakterijskih, virusnih gljivičnih infekcija. Često su kod HLL prisutne hromozomske abnormalnosti, stoga je važno pre otpočinjanja lečenja uraditi FISH analizu kojom se utvrđuje prisustvo specifičnih hromozoma. Del (13 q) - najčešća genetska promena na hromozomu 13, otkriva se kod 40% do 60%, oni imaju povoljniju prognozu, dok Del 17p (deleciju hromozoma 17) ima oko 5% bolesnika i oni imaju najlošiju prognozu, jer ne reaguju na standardne terapije^{1,6}.

Metodi lečenja su višestruki, a pristup pacijentu individualan. U lečenju se koristi hemioterapija, imunohemioterapija, biološka terapija, radiološka, palijativna, transplantacija koštane srži, opšte mere^{5,6}. Hemioterapija se obično sastoji u kombinaciji više lekova. Najčešće se koriste *Fludarabin*,

might be a hemangioma. In addition to the described formation, a vaguely defined hypodense formation up to 14 mm in diameter is observed, which does not show PKPD. A pair of hypodense, clearly limited subcentimeter formations in the V and VI liver segments, without PKPD, can also be observed, and their characteristics may correspond to cysts.

During the hospital stay, the Medical Council decided to start immunochemotherapeutic treatment (ICT) according to the RFC protocol, D1 I cy on December 3, 2019: *Fludarabine*, amp. 38 mg D1-3, *Cyclophosphamide*, amp. 380 mg D1-3, *Rituximab*, amp. 500mg D4. There were no complications during the treatment. She was discharged home with the advice to take the *Allopurinol* tab. 300mg /day, *Acyclovir* and *Bactrim*, tab. 2x2 on weekends. CBC check was advised once a week. The application of II cy of *rituximab* was performed in the daily clinic of CCS on January 13, 2020, and the application of II cy of FC at Hematology Ward of the General Hospital in Kraljevo. She received a total of 6 cy, as described. Now she feels well and has got regular check-ups with a hematologist every three months. Current CBC is within normal limits WBC $4.19 \times 10^9/L$, RBC $4.12 \times 10^{12}/L$, HGB 135 g/L.

Discussion

CLL is one of the most common leukemias in adults. The incidence reaches 13 cases per 100,000 people, over the age of 65. Since in the initial phase it can have very mild and nonspecific symptoms or even be asymptomatic, routine blood counts and preventive examinations are needed, and they are crucial for early diagnosis and timely treatment. The finding of leukocytosis with lymphocytosis is an alarm, and a patient should be referred to a hematologist for further diagnostic evaluation. Anemia and/or thrombocytopenia or hypogammaglobulinemia may also be present in the blood count.

In order to confirm the diagnosis of CLL, it is necessary to prove that all lymphocytes are of the same origin (monoclonal lymphocytosis). Therefore, their immunophenotyping (IF) is performed, ie. determination of lymphocyte characteristics in peripheral blood^{3,4}. In the CLL cells, the presence of markers CD5, CD19, CD23, CD20 was mainly proven. If it is proven that the lymphocytes are of the same origin, and there are more than 5,000 of them in the peripheral blood sample, a diagnosis of CLL can be confirmed. So, invasive tests such as puncture and bone marrow biopsy are not needed for early diagnosis⁵.

Given the slow progression of the disease in most patients, it is necessary to determine the stage of the disease according to *Binet* and *Rai*, perform immunophenotyping (IF), as well as the risk of progression and prognosis (FISH - *Fluorescence in situ hybridization*), before starting treatment.

During the course of the disease, there may be a drop in immunity due to non-functional lymphocytes, anemia, thrombocytopenia, hypogammaglobulinemia, which can lead

Ciklofosamid, Hlorambucil, Bendamustin. Citostatici se mogu davati samostalno ili u kombinaciji sa ciljanom terapijom ili monoklonskim antitelima. Neželjena dejstva koja se mogu javiti su neutropenija, alergijske reakcije, temperatura, mučnina, povraćanje.

Imunohemioterapija je kombinacija citostatika i leka koji predstavlja antitelo koje se vezuje za određeni protein na malignoj ćeliji. Ova terapija predstavlja napredak u lečenju, za razliku od hemioterapije koja deluje manje specifično. Terapija monoklonskim antitelima ima za cilj da uništi samo ćelije HLL. Koriste se *Rituximab, Obinutumumab i Ofatumumab*^{5,6}.

Biološka terapija se koristi kod relapsa bolesti, kada bolesnik ne reaguje na klasičnu terapiju, ali i kod pacijenata sa visokorizičnom HLL. Najčešće korišćen lek je *Ibrutinib* koji blokira *Bruton*-ovu tirozin kinazu^{7,8,9}.

Palijativna terapija podrazumeva transfuzije eritrocita i /ili trombocita, primenu antibiotika, kortikosteroida, eventualno operativno vađenje slezine. Transplantacija koštane srži podrazumeva korišćenje matičnih ćelija davaoca. Opšte preporuke podrazumevaju izbegavanje faktora rizika za maligne bolesti, izbegavanje stresa, redovan san, dovoljno tečnosti, čuvati se infekcija i ujeda insekata jer ovi pacijenti imaju intenzivne reakcije na mestu ujeda.

Bolesnici sa B ćelijskom HLL ili njenim komplikacijama, prosečno žive 7 do 10 godina. Bolesnici u *Rai* stepenu od 0-II mogu živeti od 5 do 20 godina. Bolesnici stepena III ili IV umiru za 3 do 4 godine. Napredovanje prema insuficijenciji koštane srži ukazuje na kratko preživljavanje. Bolesnici sa HLL pokazuju sklonost ka drugim malignim tumorima, naročito karcinomu kože. Kako je HLL progresivna bolest neki bolesnici ostaju godinama asimptomatski, pa lečenje nije potrebno pre pojave simptoma ili progresije. Izlečenje je, po pravilu, nemoguće pa je lečenje usmereno na suzbijanje simptoma i produženje života².

to serious bacterial, viral, fungal infections. Chromosomal abnormalities are very common in CLL, so it is important to perform a FISH analysis to determine the presence of specific chromosomes before starting treatment. Del (13q) - the most common genetic change on chromosome 13, is detected in 40-60%, and they have a more favorable prognosis, while Del (17p) (deletion of chromosome 17) has about 5% of patients and they have the worst prognosis because they do not respond to standard treatment^{1,6}.

The treatment methods are multiple, and the patient approach is individual. Chemotherapy, immunochemotherapy, biological therapy, radiological, palliative, bone marrow transplantation, general measures are used in the treatment^{5,6}. Chemotherapy usually consists of a combination of several drugs. The most commonly used are *Fludarabine, Cyclophosphamide, Chlorambucil, Bendamustine*. Cytostatics can be administered alone or in combination with targeted therapy or monoclonal antibodies. Neutropenia, allergic reactions, fever, nausea, vomiting are the most common side effects.

Immunchemotherapy is a combination of cytostatics and an antibody that binds to a specific protein on a malignant cell. This therapy represents an improvement in the treatment, unlike chemotherapy which is less specific. Monoclonal antibody therapy aims to destroy only CLL cells. *Rituximab, Obinuturumab and Ofatumumab* are used^{5,6}.

Biological therapy is used in the disease relapses, or when the patient does not respond to conventional therapy, but also in patients with high-risk CLL. The most commonly used drug is *Ibrutinib*, which blocks *Bruton's tyrosine kinase*^{7,8,9}.

Palliative therapy includes transfusions of erythrocytes and/or platelets, use of antibiotics, corticosteroids, possible surgical removal of the spleen. Bone marrow transplantation involves the use of donor stem cells. General recommendations include avoiding risk factors for malignant diseases, avoiding stress, regular sleep, enough fluids intake, avoiding infections and insect bites because these patients have intense reactions at the site of the bite.

Patients with B-cell CLL or its complications live an average of 7-10 years. Patients in *Rai* grade of 0-II can live from 5-20 years. Grade III or IV patients die within 3-4 years. Progression to bone marrow failure indicates short survival. Patients with CLL are prone to other malignant tumors, especially skin cancer. As CLL is a progressive disease, some patients remain asymptomatic for years, so treatment is not necessary before symptoms or progression occurs. Healing is usually impossible, so treatment is aimed at suppressing symptoms and prolonging life².

Zaključak

Rutinske analize krvne slike i leukocitarne formule kao i preventivni pregledi od strane izabranog lekara, presudni su u ranom postavljanju dijagnoze HLL. Budići da ova bolest može dugo proticati asimptomatski ili sa blagim i nespecifičnim simptomima, nalaz leukocitoze i limfocitoze u perifernoj krvi je znak da treba misliti na ovo oboljenje i dalju dijagnostiku uraditi u tom pravcu. Poodmakle godine života, muški pol i pozitivna porodična anamneza idu u prilog tome. Diferencijalno dijagnostičke teškoće mogu zadavati infektivna mononukleoza i veliki kašalj. Dalja dijagnostika i lečenje sprovode se na sekundarnom i tercijarnom nivou. Nakon sprovedene specifične terapije, ovi pacijenti bivaju česti posetioci izabranog lekara zbog virusnih, bakterijskih ili gljivičnih infekcija, anemije i drugih posledica lošeg imuniteta.

Conclusion

Routine blood counts and leukocyte formulas, as well as preventive check-ups with GP, are crucial in the early diagnosis of CLL. Since this disease can be asymptomatic for a long time or with mild and nonspecific symptoms, the finding of leukocytosis and lymphocytosis in the peripheral blood is a sign that we should take into consideration and perform further diagnostics. Advanced age, male gender, and positive family history are risk factors. Infectious mononucleosis and whooping cough may cause differential diagnostic difficulties. Further diagnosis and treatment are carried out at the secondary and tertiary levels. After specific therapy, these patients become frequent visitors to the GP offices due to viral, bacterial, or fungal infections, anemia, and other consequences of poor immunity.

Literatura / Reference

1. Hronična limfocitna leukemija (Tumori hematopoetskog i limfoidnog tkiva). [Internet]. [cited 2021 Apr 8]. Available from: <https://bcell.rs/edu-hub/diseases/102>
2. Hronična limfocitna leukemija [Internet]. [cited 2021 Apr 8]. Available from: <http://www.msd-prirucnici.placebo.hr/msd-prirucnik/hematologija-i-onkologija/leukemije/kronicna-leukemija>
3. Ivančević Dragović T, Kurtović NK, Knežević V, Bogdanović A, Mihaljević B, Božić B, et al. *The role of immunophenotyping in differential diagnosis of chronic lymphocytic leukemia*. *Srp Arh Celok Lek*. 2014;142 (3-4):197-203.
4. Autore F, Strati P, Laurenti L, Ferrajoli A. *Morphological, immunophenotypic, and genetic features of chronic lymphocytic leukaemia with trisomy 12: A comprehensive Haematologica*, 2018;103(6):931-938.
5. Hallek M. *Chronic lymphocytic leukemia: 2015 Update on diagnosis, risk stratification, and treatment*. *Am J Hematol*. 2015 May;90(5):446-60.
6. Hallek M. *Chronic lymphocytic leukemia: 2017 update on diagnosis, risk stratification, and treatment*. *Am J Hematol*. 2017 Sep;92(9):946-965.
7. Otašević V, Mihaljević B, Antić D. *Prognosis and new therapeutic approaches in chronic lymphocytic leukemia treatment*. *Med Podml*. 2019;70(4):6-12.
8. Brown JR. *How I treat CLL patients with ibrutinib*. *Blood*. 2018 Jan 25;131(4):379-86.
9. Thompson PA, Burger JA. *Bruton's tyrosine kinase inhibitors: first and second generation agents for patients with Chronic Lymphocytic Leukemia (CLL)*. *Expert Opin Investig Drugs*. 2018 Jan;27(1):31-42.

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