Hronična limfocitna leukemija u ordinaciji opšte medicine

Prikaz slučaja. Pacijentkinja, stara 66 godina, domaćica, dolazi na pregled zbog zamora koji traje oko mesec dana i gubitka 3-4 kg, ostale tegobe negira. Na pregledu svesna, orijentisana u vremenu, prostoru i prema ličnostima, eupno-ična, limfadenopatija na vratu, aksilama i ingvinumu, odaje ...

Krvna slika je pokazala povećan broj leukocita 181,30x10^9/L i limfocitozu 92,2%, ostali parametri su bili normalni. Upućena je hematologu Opšte bolnice u Kraljeva, gde je urađena daljnja dijagnostika. Potvrđena je dijagnoza HLL. Konzilijarno je odlučeno da se sprovede imunohemioterapijsko lečenje (IHT) sa Fludarabine i Rituksimabom. 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. Dakle, povremenost i povećanje broja limfocita su očigledni i potrebno je provesti daljnju dijagnostiku.

Ključne reči. Hronična limfocitna leukemija, leukocitoza, limfocitoza.

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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 181.30x10^9/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.
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 blood.

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 common. 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. 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 3 new cases per 100,000 people per year over the age of 65.

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. The onset of the disease is usually insidious and CLL is often diagnosed accidentally during a routine blood check or treatment of asymptomatic lymphadenopathy. 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 cells. Over time, abnormal lymphocytes 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 izazvanog 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 preobrađena, prisutna limfadenopatija u vratu, aksilama i ingvinumu do 4 cm u konglomeratima, odaje utisak laškog bolesnika.

Objektivnim pregledom nađeno je: glava uobičajene konfiguracije, nos prohodan, jezik vlažan i neobložen, tonsile uvećane, očni bulbi 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, srednje intenzivna, nesnažna, TA 140/80 mmHg. Abdomen je u ravni grudnog koša, palpatorno bolno neosetljiv, kardiogram simetričan, respiratorno obostrano pokretan, 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 palpatated 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 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 palpatated 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 181.30x10^9/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 izmjenjene strukture, zbrisani hilus, promera 10 mm i 7 mm. Obostrano parajugularno uočava se više pojedinačnih LN u nizu, izmjenjene strukture, zbrisanih hilusa, očuvanog L/W indeksa, najveći promjer do 14 mm. Obostrano aksilarno uočava se više grupisanih uvećanih LN, ali očuvane strukture i hiperegogenog hilusa, očuvanog L/W indeksa, promera do 20 mm. Obostrano ingvinalno uočava se više grupisanih uvećanih LN, očuvane strukture i hiperegogenog hilusa, očuvanog L/W indeksa promera do 23 mm. Nalaz RTG puča u graničama normalne, nalaz EHO srca uređan. Virusologija (ELIZA test) na HbsAg, HCV i HIV Ag negativan. Coombs dir. i ind. negativan. Biohimijijski nalaz: leukociti (WBC) (193...207,85 x 10^9/L), eritrociti (RBC) (3.95...4,06 x 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), NEUTROFILO (4,5%), LYMFOCITI (92,5%), MONOCITI (2,6%), EOZINOFILI (0,3%), BAZOFILI (0,1%) ostali biohimijijski parametri uredni.

Pod sumnjom na hroničnu limfocitnu leukemiju upućena je u Klinički centar Srbije na dalju dijagnostiku i lečenje. Virološke ispitivanja za HepB, HepC i HIV Ag je negativno. Coombs dir. i ind. tests negativni. CBC findings: leukocytes (WBC) (193...207,85x10^9/L), erythrocytes (RBC) (3.95...4,06x10^12/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, CD38-, CD49d-. She was presented to the Medical Council in CCS: Le 193,4x10^9/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
Hronična limfocitna leukemia je jedna od najčešćih leukemia kod odraslih. Incidencija dostiže 13 oboljelih 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. Nažalost, lečenje u prvom redu se vodi standardnom terapijom. Najčešće se koriste radiologija, hemioterapija, imunohemioterapija, palijativna terapija i transplantacija. U lečenju se koristi hemioterapija, imunohemioterapija, radiološka, palijativna terapija koštane srži, opšte mere i hemioterapija se obično sastoji u kombinaciji više lekova.

**Diskusija**

300 mg/dan, Aciclovir i Bactrim 2 x 2 u dane vikenda. Kontrola krvne slike jednom nedeljno. Primenu II cy rituximaba 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, kontrolle hematologa na tri meseca. Sadašnja biohemija je u normalnim granicama WBC 4,19 x10^9/L, RBC 4,12x10^12/L, HGB 135 g/L.

Imajući u vidu sporu progresiju bolesti kod većine bolesnika, međutim se vrši njihova imunofenotipizacija (IF), tj. određivanje karakteristika limfocita u perifernoj krvi14. Kod čelija HLL uglavnom je dokazano prisustvo markera CD5, CD19, CD23, CD20. Ukoliko se dokaze da su limfociti istog porekla, kao i da ih ima više od 5.000 u uzorku periferno krvi, može se postaviti dijagnoza HLL. Znaci, za ranu dijagnozu nisu potrebni invazivni testovi poput punctije i biopsije koštane srži.

Imajuci u vidu sporu progresiju bolesti kod većine bolesnika, 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, hipogammaglobulinemije što može dovesti do ozbiljnih bakterijskih, virusnih gljičenih infekcija. Često su kod HLL prisutne hromozomske abnormalnosti, stoga je važno pročitavanja lečenja uraditi FISH analizu kojom se utvrduje prisustvo specifičnih hromozoma. Del (13 g) – najčešća genetska promena na hromozomu 13, otkriva se kod 40% do 60%, oni imaju povoljniju prognozu, dok Del 17p (deleciju hromozom 17) ima oko 5% bolesnika i oni imaju najlošiju prognozu, jer ne reaguju na standardne terapije16. Metodi lečenja su višestruki, a pristup pacijentu individualan. U lečenju se koristi hemoterapija, imunohemoterapija, biološka terapija, radiološka, palijativna transplantacija koštane srži, opšte mere. Hemoterapija 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 x10^9/L, RBC 4.12x10^12/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 (monoklonal lymphocytosis). Therefore, their immunophenotyping (IF) is performed, i.e. determination of lymphocyte characteristics in peripheral blood. 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 diagnosis.

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
Ciklofosfamid, Hlorambucil, Bendamustin. Citostatiki 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.

Imunohemoterapija je kombinacija citostatika i leka koji predstavlja antitelo koje se vezuje za određeni protein na malignoj čeliji. Ova terapija predstavlja napredak u lečenju, za razliku od hemoterapije koja deluje manje specifično. Terapija monoklonskim antitetima ima za cilj da uništi samo čelije HLL. Koriste se Rituximab, Obinutuzumab i Ofatumumab7,8,9.

Biološka terapija se koristi kod relapsa bolesti, kada bolesnik ne reaguje na klasičnu terapiju, ali i kod pacijenata sa visokokrizičnom HLL. Najčešće korишćen lek je Ibrutinib koji blokira Bruton-ovu tirozin kinazu7,8,9.

Palijativna terapija podrazumeva transfuzije eritrocita i /ili trombocita, primenu antibiotika, kortikosteroida, eventualno operativno vadenje slezine. Transplantacija koštane srži svrši podrazumeva korišćenje matičnih čelija davaoca. Opšte preporuke podrazumevaju izbegavanje faktora rizika za male 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 čelijskom 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 pojava simptoma ili progresije. Izlečenje je, po pravilu, nemoguće pa je lečenje usmereno na suzbijanje simptoma i produženje života5.
Zaključak

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.

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Conflict of Interest: None declared

Autori izjavljuju da nemaju sukob interesa

Primljen - Received - 30.01.2021.
Ispрављен - Corrected - 11.03.2021.
Prihvaćen - Accepted - 16.03.2021.