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KAKO PREPOZNATI AKUTNU LEUKEMIJU U STOMATOLOŠKOJ ORDINACIJI

HOW TO RECOGNIZE ACUTE LEUKEMIA IN DENTAL PRACTICE

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ABSTRAKT
Akutna leukemija je maligna bolest hematopoetskog tkiva koja se karakteriše klonalnom proliferacijom i akumulacijom abnormalnih leukemijskih ćelija u kostnoj srži i insuficijentnom hematopoezom. Klinička slika se karakteriše pojavom simptoma i znakova usled insuficijencije normalne hematopoeze, infiltracije tkiva i organa malignim ćelijama i metaboličkih poremećaja. Zbog insuficijentne hematopoeze prisutna su tri klinička sindroma: anemije, krvarenja i infekcije. Akutne leukemije nastaju iz punog zdravlja i imaju veoma brz tok. Nelečene dovode do letalnog ishoda za par meseci najviše. Lečenje se bazira na modernim polihemioterapijskim protokolima, koji se razlikuju za svaki podtip leukemije. Stomatološkim pregledom se mogu uočiti krvarenja i infiltracije desni, koje su među prvim oralnim manifestacijma akutne leukemije. Takođe se mogu naći i znaci oralnog mukozitisa, koji se može manifestovati samo eritemom, a u težim slučajevima progredirati do ulceracija. Adekvatna nega usne duplje je obavezan i izuzetno važan deo u terapiji akutnih leukemija, i može ga sprovoditi samo vrhunski obučeno osoblje. Oralne manifestacije akutnih leukemija su brojne i raznovrsne, bitno utiču na kvalitet života ovih pacijenata ali i na ukupan terapijski uspeh u lečenju akutnih leukemija.
Ključne reči: *Akutna leukemija, terapija, oralne manifestacije*

ABSTRACT
Acute leukemia is a malignant disease of hematopoietic tissue, characterized by clonal proliferation and accumulation of abnormal leukemia cells in the bone marrow and by insufficient hematopoiesis. Clinical picture is characterized by the appearance of symptoms and signs arising from the insufficiency of norm.al hematopoiesis, the infiltration of tissues and organs by malignant cells and the metabolic disorders. Due to the insufficient hematopoiesis, three clinical syndromes are present: anemias, bleedings and infections. Acute leukemias occur in the conditions of perfect health and they develop very rapidly. If not treated, they have the lethal outcome in a few months at the latest. The treatment is based on modern poly-chemotherapeutic protocols, which are different for each leukemia subtype. Stomatological examination may reveal gum bleedings and infiltrations, which are among the first oral manifestations of acute leukemia. Indications may also be found for oral mucositis, which can be manifested only by erythema, or progress into ulcerations in more severe cases. Adequate oral cavity care procedure represents an obligatory and extremely important part of treating acute leukemias and it can be administered exclusively by the best-trained medical staff. *There is a great number of various oral manifestations of acute leukemias, significantly impacting the quality of life of these patients, as well as the total therapeutic success in treating acute leukemias.*
Key words: Acute leukemia, therapy, oral manifestations

Akutne leukemije

Akutna leukemija je maligna bolest hematopoetskog tkiva koja se karakteriše klonalnom proliferacijom i akumulacijom abnormalnih leukemijskih ćelija u kostnoj srži i insuficijentnom hematopoezom.

U momentu postavljanja dijagnoze normalna populacija ćelija kostne srži je u velikoj meri zamenjena leukemijskim klonom uz hematogenu diseminaciju u raznovrsne ekstramedularne lokalizacije. Blastne leukemijske ćelije

Acute leukemia

Acute leukemia is a malignant disease of hematopoietic tissue, characterized by clonal proliferation and accumulation of abnormal leukemia cells in the bone marrow and by insufficient hematopoiesis.

In the time of diagnosis, the normal population of bone marrow cells was largely replaced by the leukemic clone, accompanied by the hematogenous dissemination to different extramedullary localizations. Blastic leukemia cells are characterized by extremely limited function

se karakterišu ekstremno ograničenom maturacionom funkcijom, sa zadržavanjem proliferacione sposobnosti koja je nezavisna i varijabilna. Takodje je prisutan značajan poremećaj apoptoze.

Etiologija akutnih leukemija je još uvek uglavnom nepoznata. U nastanku akutnih leukemija učestvuje više faktora, kako naslednih tako i faktora sredine, od kojih su najznačajniji virusi, radioaktivno zračenje, razni hemijski agensi i lekovi. Navedeni etiološki faktori aktiviraju ćelijske onkogene i dovode do maligne transformacije progenitorne ćelije. Veoma važan faktor je i zatajenje imunog sistema koji nije prepoznao i uništio ovako maligno izmenjenu ćeliju, čime su se stvorili uslovi za njenu klonalnu proliferaciju[1].

Akutna leukemija se može javiti u bilo kojem životnom dobu, od fetusa do pozne starosti, sa incidencom javljanja od 3 na 100 000 stanovnika. Klasifikacija akutnih leukemija podrazumeva postojanje dve glavne grupe : akutne limfoblastne leukemije i akutne nelimfoblastne (mijeloidne) leukemije. U okviru ove dve glavne grupe postoje podgrupe, a klasifikacija se može vršiti na osnovu morfoloških, imunofenotipskih i citogenetskih karakteristika leukemijskih ćelija.

Klinička slika se karakteriše pojavom simptoma i znakova usled insuficijencije normalne hematopoeze, infiltracije tkiva i organa malignim ćelijama i metaboličkih poremećaja. Simptomi se javljaju obično par nedelja pre javljanja lekaru, i mogu se značajno razlikovati od pacijenta do pacijenta. Zbog insuficijentne hematopoeze prisutna su tri klinička sindroma: anemije, krvarenja i infekcije.

Najčešći simptomi se javljaju zbog anemije, i to su malaksalost, slabost, zamaranje i bledilo. Obično je prisutna značajna inkorelacija ovih simptoma u odnosu na laboratorijske nalaze. Hemoragijski sindrom na početku bolesti ne mora biti prisutan ili je blažeg stepena. Uglavnom se javlja zbog trombocitopenije. U početku su najčešća krvarenja kože i sluzokože, u vidu petehija, hematoma i slivenih hematoma, krvarenja desni, konjuktiva,itd. Sa padom broja trombocita ispod 25 hiljada može doći do ozbiljnijih krvarenja, koja se mogu manifestovati raznim krvarenjima digestivnog, urogenitalnog i respiratornog sistema. Kada su trombociti ispod deset hiljada, postoji velika opasnost od značajnijih unutrašnjih krvarenja, od kojih su

of cell maturation, together with retaining the independent and variable proliferation capability. A significant disorder of apoptosis is also present.

The etiology of acute leukemia is still unknown in most cases. The acute leukemia generation is associated with many agents, both hereditary and environmental, where the most significant factors are viruses, radiation exposure, various chemical agents and medicaments. The mentioned etiologic agents activate cellular oncogenes and lead to a malignant transformation of progenitory cells. Another very important factor reflects in the immune system failure to recognize and destroy such malignantly altered cell, thus creating the conditions for its clonal proliferation[1].

Acute leukemia may occur at any point in life, from the stage of fetus to the old age, with the incidence of 3 cases per 100000 population. The classification of acute leukemias includes two principal groups: acute lymphoblastic leukemias and acute non- lymphoblastic (myeloid) leukemias. These two main groups are divided into subgroups, while the classification may be made on the basis of morphological, immunophenotypic and cytogenetic characteristics of leukemic cells.

Clinical picture is characterized by the appearance of symptoms and signs arising from the insufficiency of norm.al hematopoiesis, the infiltration of tissues and organs by malignant cells and the metabolic disorders. The symptoms usually appear a few weeks before turning to a doctor for help, and they may significantly differ from patient to patient. Due to the insufficient hematopoiesis, three clinical syndromes are present: anemias, bleedings and infections.

The most frequent symptoms are caused by anemia, such as exhaustion, weakness, fatigue and paleness. Usually, there is a significant incorrelation of these symptoms with the laboratory findings. At the illness outset, the hemorrhagic syndrome may be of a mild scale or it may not occur at all. It usually appears due to thrombocytopenia. In the early stages, bleedings of skin and mucous membrane are the most frequent and they appear in the form of petechiae, single and multiple hematomas, bleeding gums, conjunctival hemorrhage, etc. The thrombocyte number decrease below 25 thousand may cause serious hemorrhages, manifested by various bleedings of digestive, urogenital and respiratory systems. When the thrombocyte number falls below 10 thousand, there is a great risk of considerable internal bleedings, the most dangerous of which being the central nervous system hemorrhages. Secondary fibrinolysis and

najopasnija u centralnom nervnom sistemu. Pojava sekundarne fibrinolize i diseminovane intravaskularne koagulacije je redovna u pacijenata sa akutnom promijelocitnom leukemijom, a česta u akutne monoblastne leukemije i uzrok je značajnih hemoragijskih događaja. Bakterijske infekcije su najčešći i najveći problem u pacijenata sa akutnom leukemijom. Javljaju se usled neutropenije. Mogu biti fokalne (orofaringijalni mukozitis, otitis, pneumonija), ali i sistemske (sepsa), pogotovu učestale i teške u pacijenata sa manje od 500 granulocita u apsolutnom broju. U većini slučajeva su praćene temperaturom[2].

Zbog infiltracije može se javiti bol u kostima, abdomenu. Akutna limfoblastna leukemija se karakteriše infiltracijom limfnih žlezdi, slezine, centralnog nervnog sistema, testisa i kože, što se kod ovih pacijenata ispoljava generalizovanom limfadenopatijom, organomegalijom, simptomima povećanog intrakranijalnog pritiska (glavobolja, mučnina, povraćanje). Značajnije infiltracije su karakteristika i monoblastne i mijelomonoblastne akutne leukemije, ali bez zahvatanja centralnog nervnog sistema.

Pacijenti u većini slučajeva odaju utisak teških bolesnika, a fizikalni pregled mora biti detaljan i kod sumnje na akutnu leukemiju, da se ne bi propustili znaci infekcije i krvarenja.

Laboratorijske analize imaju značajnu ulogu u postavljanju dijagnoze i određivanju podtipa leukemije. Krvna slika pokazuje značajnu leukocitozu u najvećem broju pacijenata, ali broj leukocita može biti normalan ili smanjen u obolelih od akutne leukemije. Zbog toga je važan pregled razmaza periferne krvi, i nalaz mladih ćelija (blasta) u njemu će potvrditi sumnju na akutnu leukemiju. Anemija i trombocitopenija su skoro uvek prisutne. Pregled kostne srži nakon aspiracione punkcije i biopsije je neophodan za postavljanje dijagnoze akutne leukemije. Nalaz hipercelularne kostne srži sa više od 30% blasta je dovoljan za dijagnozu akutne leukemije, mada je ovaj procenat skoro uvek veći od 50%. Citohemijska bojenja preparata kostne srži (PAS, peroksidaza, alfa naftil esteraza) i imunofenotipizacija su bitni u postavljanju dijagnoze kao i u određivanju tipa leukemije. Takodje se rade i citogenetske analize koje imaju i prognostički značaj[3].

Akutne leukemije nastaju iz punog zdravlja i imaju veoma brz tok. Nelečene dovode do letalnog ishoda za par meseci najviše.

disseminated intravascular coagulation regularly occur in the patients with acute promyelocytic leukemia, while they are also frequent in acute monoblastic leukemia, and they cause substantial hemorrhagic events. Bacterial infections represent the most frequent and the greatest problem to the patients with acute leukemia. They are caused by neutropenia and they can be focal (oropharyngeal mucositis, otitis, pneumonia), as well as systemic (sepsis), particularly frequent and severe in the patients with the absolute granulocyte count less than 500. In most cases, they are followed by increased body temperature[2].

Infiltration may induce pain in the bones or abdomen. Acute lymphoblastic leukemia is characterized by the infiltration of lymph glands, spleen, central nervous system, testicles and skin, which is manifested in these patients through generalized lymphadenopathy, organomegaly and symptomes of increased intracranial pressure (headache, nausea, vomiting). Significant infiltrations are also characteristic for monoblastic and myelomonoblastic acute leukemias, but without affecting the central nervous system.

In most cases, patients give the impression of seriously ill persons, while physical examination has to be detailed when acute leukemia is suspected too, in order not to miss the signs of infection and hemorrhage.

Laboratory analyses play an important role in diagnosing and determining the leukemia subtypes. Although blood tests reveal significant leukocytosis in most of the patients, the number of leukocytes may also be normal or decreased in acute leukemia. Therefore, it is important to examine the peripheral blood smear, as the suspected acute leukemia shall be confirmed by detecting young cells (blasts) in it. Anemia and thrombocytopenia are almost always present. After the aspiration puncture and biopsy, bone marrow examination is required for acute leukemia diagnosing. A hypercellular bone marrow finding with more than 30% of blasts is sufficient to diagnose acute leukemia, although the percentage almost always exceeds 50%. Cytochemical stainings of bone marrow specimens (PAS, peroxidase, alpha-naphtil-esterase) and immunophenotypization are essential in making a diagnosis, as well as in determining the type of leukemia. Additionally, cytogenetic analyses are performed, as they have a prognostic significance, too[3].

Acute leukemias occur in the conditions of perfect health and they develop very rapidly. If not treated, they have the lethal outcome in a few months at the latest.

Ipak, danas su akutne leukemije izlečive bolesti. U odraslih pacijenata se potpuno izleči 30-40%. Neposredni terapijski cilj je postizanje kompletne remisije, zatim njeno konsolidovanje i održavanje sve do postizanja konačnog cilja – izlečenja. Lečenje traje od dve do tri godine.

Lečenje se bazira na modernim polihemioterapijskim protokolima, koji se razlikuju za svaki podtip leukemije. Pre otpočinjanja polihemioterapije, neophodno je pacijenta dobro pripremiti u cilju izbegavanja nastajanja težih infekcija, tumor lizis sindroma i krvarenja. Suportivna i simtomatska terapija su neophodne, pogotovu u uvodnoj i terapijama konsolidacije, koje usled primene većih doza citostatika dovode do aplazije kostne srži i teške citopenije. Osim citostatika, u lečenju akutne promijelocitne leukemije se koristi oltransretinoična kiselina – modulatorni lek koji se pokazao veoma efikasnim u lečenju ovog oblika akutne leukemije. Takodje i primena raznih citokina je našla svoje mesto u cilju skraćenja aplazijske faze.

Kod jednog broja pacijenata sa lošijim prognostičkim faktorima se primenjuje alogena transplantacija koštane srži, odnosno u zadnje vreme transplantacija matične ćelije hematopoeze. Pored neophodnosti nalaženja odgovarajućeg donatora, potrebno je da oboleli ispuni više uslova (godine života do 50, dobar performans status, i drugo) da bi se obavila transplantacija[4].

Oralne manifestacije

Oralne manifestacije imaju veliki značaj za pacijente obolele od akutne leukemije. Dosta pacijenata se prvo obrati zbog raznih oralnih problema upravo stomatologu, koji pažljivim i detaljnim pregledom može posumnjati na akutnu leukemiju i omogućiti raniju dijagnostiku i terapiju. Ovi pacijenti imaju značajno veću šansu za duže preživljavanje i izlečenje[5].

Stomatološkim pregledom se mogu uočiti krvarenja i infiltracije desni, koje su među prvim oralnim manifestacijma akutne leukemije. Prisutna su najčešće difuzno, češće se javljaju u pacijenata sa akutnim mijeloidnim nego u pacijenata sa akutnim limfoblastnim leukemijama. Krvarenja i infiltracije se mogu videti i u drugim delovima oralne šupljine. Takođe se mogu naći i znaci oralnog mukozitisa, koji se može manifestovati samo eritemom, a u težim slučajevima progredirati do ulceracija[6]. Nisu retki slučajevi

Nevertheless, acute leukemias are nowadays curable illnesses. In adult patients, 30-40% cases get fully cured. The immediate therapeutic aim is to achieve a complete remission, to consolidate it and to maintain it until the final aim - full cure - is attained. The treatment duration is two to three years.

The treatment is based on modern poly-chemotherapeutic protocols, which are different for each leukemia subtype. Prior to the application of poly-chemotherapy, the patient should be well prepared in order to avoid heavier infections, tumor lysis syndrome and hemorrhage. Supportive and symptomatic therapies are necessary, especially during the introductory and consolidation treatments, since they cause bone marrow aplasia and serious cytopenia due to the administration of large doses of cytostatics. Beside cytostatics, the acute promyelocytic leukemia treatment includes ultrans-retinoic acid - a modulatory medicament that proved to be very effective in treating this form of acute leukemia. The application of various cytokines has also found its place in the endeavors to shorten the phase of aplasia.

Some patients with poorer prognostic factors underwent alogenous bone marrow transplantation, or more recently, transplantation of hematopoietic stem-cells. Apart from the necessity to find a suitable donor, the patient has to fulfill several requirements (age of up to 50 years, solid performance status, and other) for the transplantation to be performed[4].

Oral manifestations

Oral manifestations are of a great significance for the patients suffering from acute leukemia. Due to different oral problems, many patients first contact a stomatologist, who can suspect acute leukemia through careful and thorough examination and thus enable early diagnosis and therapy. Such patients have substantially greater chances of longer survival and cure[5].

Stomatological examination may reveal gum bleedings and infiltrations, which are among the first oral manifestations of acute leukemia. They are mostly diffuse, and they appear more frequently in the patients with acute myeloid leukemias as compared to the acute lymphoblastic leukemia patients. Bleedings and infiltrations may be observed in other oral cavity areas, too. Indications may also be found for oral mucositis, which can be manifested only by erythema, or progress into ulcerations in more severe cases[6]. It is not rare that the suspicion for acute leukemia is made after some stomatologic intervention, most often tooth extraction. In a

kada se sumnja na akutnu leukemiju postavi posle neke stomatohirurške intervencije, najčešće ekstrakcije zuba. Krvarenje koje se ne zaustavlja ili neočekivani i brzo progredirajući apscesi brzo dovode ove pacijente do hematologa.

Lezije oralne mukoze su od velikog značaja u pacijenata sa akutnim leukemijama zbog svoje učestalosti i jer predstavljaju mesta ulaska infektivnih agenasa u nastajanju teških sistemskih infekcija. Infekcije su najčešće bakterijske,jer se dosta bakterija nalazi u usnoj šupljini, a pored patogenih mogu ih izazvati i uslovno patogeni mikrorganizmi jer se radi o imunokompromitovanim pacijentima. Česte su i gljivične infekcije koje su u našem podneblju najčešće iz roda Candida, a od virusa su najčešći Herpes simplex i zoster. Glavni problem je ovde neutropenija, koja je pogotovu teška u fazi aplazije posle primene polihemioterapije, ali ne treba zanemariti ni oštećenje sluzokože citotoksičnim lekovima[7]. U prevenciji i lečenju se koriste razni antiseptični rastvori, ali i gotovi preparati koji često sadrže i lokalne anestetike i supstance koje oblažu sluzokožu i pomažu njeno obnavljanje, kao i razni lokalni antimikotici. Adekvatna nega usne duplje je obavezan i izuzetno važan deo u terapiji akutnih leukemija, i može ga sprovoditi samo vrhunski obučeno osoblje. Perikoronitis kao i druga akutna periodontalna stanja mogu značajno komplikovati intenzivnu polihemioterapiju i terapiju kondicioniranja za transplantaciju matične ćelije hematopoeze, te je od velikog značaja učešće raznih specijalnosti stomatologije u lečenju istih[8].

Zaključak

Akutne leukemije su i danas najteže i za lečenje najkomplikovanije bolesti u onkohematologiji. Savremeni terapijski postupci su značajno unapredili lečenje ovih bolesti, te možemo reći da su akutne leukemije izlečive bolesti.

Oralne manifestacije akutnih leukemija su brojne i raznovrsne, bitno utiču na kvalitet života ovih pacijenata ali i na ukupan terapijski uspeh u lečenju akutnih leukemija.

Uloga stomatologa u dijagnostici akutnih leukemija, kao i u prevenciji i lečenju njenih komplikacija je izuzetno značajna, te zahteva i stalno stručno usavršavanje i saradnju sa hematolozima.

short time, bleedings that cannot be stopped or unexpected and rapidly progressing abscesses bring these patients to a hematologist.

Oral mucosal lesions are greatly significant in the patients with acute leukemias since they are frequent and represent the points of intrusion of infectious agents in the development of serious systemic infections. Infections are mainly bacterial, as numerous bacteria exist in the oral cavity, and, beside pathogenic microorganisms, their causative agents can be conditionally pathogenic microorganisms as well, being that immunocompromised patients are involved. Fungal infections are also frequent and they are mainly of the Candida species in our climate, while most frequent viruses are Herpes simplex and zoster. The main problem here reflects in neutropenia, which is especially grave in the phase of aplasia upon the application of poly-chemotherapy, though the mucous tissue damage caused by cytotoxic drugs should not be ignored, too[7]. Prevention and treatment include different antiseptic solutions, ready-made preparations often containing local anesthetics and substances that cover the mucous membrane and help its regeneration, as well as various local antimycotics. Adequate oral cavity care procedure represents an obligatory and extremely important part of treating acute leukemias and it can be administered exclusively by the best-trained medical staff. Pericoronitis, as well as other acute periodontal problems, may substantially complicate the intensive polychemotherapy and the conditioning therapy for the transplantation of hematopoietic stem-cells. Therefore, the participation of different stomatologic specialists is of great importance in their treatment[8].

Conclusion

Acute leukemias are still the most severe and for the treatment most complicated illnesses in oncohematology. Modern therapeutic procedures have substantially improved the treatment of these illnesses, so it may be stated that acute leukemias are curable.

There is a great number of various oral manifestations of acute leukemias, significantly impacting the quality of life of these patients, as well as the total therapeutic success in treating acute leukemias.

The role of stomatologists in the diagnosis of acute leukemia and in prevention and treatment of its complications is extremely important, therefore requiring constant professional development and collaboration with hematologists.

LITERATURA / REFERENCES

1. Ilić S. i sar. : Interna medicina, knjiga I, Medicinski fakultet Niš, Prvo izdanje, 2004.

2. Lichtman MA et al. Williams Hematology. 7th ed. New York. McGraw-Hill Professional Publishing, 2007.

3. Wiernik P et al. Neoplastic Diseases of the Blood. Fourth edition. Cambridge University Press, 2003.

4. Provan D et al. Oxford Handbook of Clinical Haematology. Second edition. Oxford University Press, 2004.

5. Hou GL, Huang JS,Tsai CC. Analysis of oral manifestations of leukemia: a retrospective study. Oral Diseases 1997; 3: 31-38.

6. Meyer U et al. Oral findings in three different groups of immunocompromised patients. J Oral Pathol Med 2000; 29: 153-158.

7. McKenna SJ. Leukemia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000; 89: 137-139.

8. Neville WB et al. Oral & Maxillofacial Pathology. Second edition. W.B. Sanders Company. 2002.

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