

HEMATOLOGICAL PATHOLOGY BETWEEN DIAGNOSIS AND TREATMENT IN THE CONTEXT OF ORAL MANIFESTATIONS. MANAGEMENT OF THE PATIENT WITH LEUKEMIA IN THE DENTAL PRACTICE. REVIEW

Maria-Alexandra Martu¹, Oana Ciurcanu^{2*}, George-Alexandru Maftei^{3*}, Liliana Pasarin¹, Cristina Popa³, Darius Sandu⁴, Oana Butnaru⁵, Ionut Luchian¹

¹ "Grigore T. Popa" University of Medicine and Pharmacy Iasi-Romania, Faculty of Dental Medicine, Department of Periodontology.

² "Grigore T. Popa" University of Medicine and Pharmacy Iasi-Romania Faculty of Dental Medicine, Department of Dento-alveolar surgery.

³ "Grigore T. Popa" University of Medicine and Pharmacy Iasi Romania, Faculty of Dental Medicine, Department of Oral Pathology.

⁴ Student "Grigore T. Popa" University of Medicine and Pharmacy Iasi Romania, Faculty of Dental Medicine.

⁵ "Grigore T. Popa" University of Medicine and Pharmacy Iasi Romania, Faculty of Dental Medicine, Department of Biophysics.

Corresponding author: Oana Ciurcanu^{*}, e-mail: onutza73@gmail.com

George-Alexandru Maftei^{*}, e-mail: george.maftei@gmail.com

#All authors have contributed equally as the first author

Abstract

Periodontal pathology and early clinical manifestations in the context of leukemia are influenced by the host organism, by immunological, microbiological and genetic factors, but also by environmental factors (physical agents (ionizing radiation, x-rays) and chemical agents (drugs such as cytostatics, exposure to organic solvents or to pesticides, herbicides, exposure to cigarette smoke). The purpose of this article is to emphasize both the importance of the health status of the marginal periodontium and the severity of gingival-periodontal manifestations in the context of haematological diseases. We also want to draw attention to the role of periodontal treatment: the elimination of periodontal inflammation, the reduction of periodontal pockets, the maintenance of rigorous oral hygiene and the periodic check-up in a dental practice in this category of patients. Clinical and radiological evidence-gathering is very important in the recognition and diagnosis of gingival-periodontal manifestations in haematological diseases, as when they are not treated in time, they become a source of infection of the oral cavity and in the entire body. **Conclusions.** It is essential to analyze this interaction in all aspects, from a clinical, microbiological, immunological and genetic point of view, in order to make a diagnosis and implement a correct and complete treatment plan.

Keywords: oral disease, periodontal disease, leukemia, management therapeutic.

Introduction

Periodontal disease is a frequent oral disease of bacterial cause which comprises of gingivitis and periodontitis. In this pathology, the tissues that surround and support teeth are affected to various degrees according to severity.[1]

Gingivitis is the most frequent form, and it is expressed through edema, bleeding and pain, and if left untreated it develops into periodontitis in which

periodontal attachment and supporting bone is lost gradually.[2,3]

Periodontitis is a highly prevalent disease that affects approximately 50% of adults in its mildest forms, this percentage being higher in subjects over 65 years of age. Severe periodontitis is the sixth most common human disease and it affects nearly 12% of the global adult population.[4]

The severe form of the disease is characterized by major loss of periodontal tissues, both superficial and profound, which leads to tooth loss if left untreated, this in turn leads to an affected nutrition, speech impediments, low self-esteem, and an overall diminished quality of life.[5]

All things considered, severe periodontal disease constitutes an important social, healthcare and economic strain, and is at the crux but also an outcome of social disparity worldwide. Moreover, in the near future, the prevalence of periodontitis is likely to increase globally because of an aging population and therefore an elevated preservation of teeth.[6]

Another major issue is the association of periodontal disease with other common systemic conditions such as cardiovascular disease, adverse pregnancy outcomes, diabetes, kidney disease, rheumatoid arthritis, Alzheimer's disease, chronic obstructive pulmonary disease, and cancer.[7-12]

Microorganisms and their products, which form the oral biofilm, together with inflammatory mediators, disseminate from periodontal tissues via blood vessels in the entire body, thus accounting for the link between periodontitis and other systemic diseases and conditions.[13-15]

Recently, major advances have been made in the etiopathogenesis of periodontal disease, in the recognition and description of the significant risk factors that increase the risk of developing periodontal diseases, and in the increasing proof of the epidemiologic and mechanistic associations between systemic diseases and periodontitis.[16]

Even though systemic inflammation, diabetes, cardiovascular diseases and adverse pregnancy outcomes are still the focal point of research regarding these correlations, nowadays other systemic diseases, such as rheumatoid arthritis, obesity and metabolic

disease, respiratory diseases, cancer, and neurodegenerative diseases, have been linked with periodontal disease.[17-19]

Leukemia is a blood disease of a malignant nature that is defined as a disorganized proliferation of red and white and blood cells in the bone marrow, resulting in undifferentiated cells (called blasts) that lose normal cell functionality.[20]

These undifferentiated cells, in time, are able to infiltrate other tissues and organs, including the oral cavity. The infiltration of the tissue, along with blood modifications, can significantly alter the oral environment, for example causing edema and gingival bleeding, which in most patients are the initial signs and symptoms of the disease.[21-26]

Moreover, leukemia patients are treated with high doses of chemotherapy and/or radiotherapy, which have various effects on the oral cavity and on periodontal tissues. Another issue is the reduced capacity of hospitalized patients to maintain proper oral hygiene during systemic disease treatment.[27]

The effects of cancer treatment on oral and periodontal health

Considering the importance of the cancer pathology and its potential life-threatening implications, dental practitioners should be aware of oral modifications and of management strategies in leukemia patients.[28]

A clear estimation of oral modifications in these patients can be challenging, however this could yield an explicit outlook of the overall management strategies and necessary measures to improve the oral health and outcome of these patients.

The treatment of patients diagnosed with acute or chronic leukemia is based on following certain protocols, which differ from one patient to another, both in terms of the type of medication and in terms of doses.[29,30]

The studies show which types of drugs lead to a remission of this condition, but also which is the length of time that must be observed in order to achieve remission. Therefore, cytostatics are administered in combination with chemotherapy.[28]

Several types of cytostatic drugs are used in cancer therapy, and together they have various types of effects.[31-33]

In addition to the cytostatic medication used in this pathology, other pharmaceuticals can induce changes in the oral mucosa, which are described as adverse effects of the drugs. (Table 1).[28]

Table 1. Pharmaceuticals that induce changes (lesions) of the oral mucosa. Stef L. 2011,[28]

Cytotoxic drugs – Methotrexate, Ciclosporin, Propylthiouracil, Vincristine, Cisplatin, Leukeran
Antirheumatic medication – Azathioprine, Penicillamine, potassium chloride
Non-steroidal anti-inflammatory drugs - Aspirin, Ibuprofen, Ketorolac
Antiparasitics – Levamisole, Chloroquine
HBP medication – Losartan, Captopril
Antibiotics – Vancomycin, Penicillin, Tetracycline, Doxacycline, Chloramphenicol
Hydrogen peroxide

These protocols are individualized from one patient to another, depending on age (acute forms are most often found in young patients, while chronic leukemias occur in the adult population), on the type of leukemia, on the severity of the disease or on the moment when it was diagnosed, but also on the associated neoplasms or pathologies.[32,33]

Cytostatics are drugs with an anti-cancer effect, and the treatment with cytostatics is called chemotherapy. Chemotherapy is considered effective if the cancer cells die after treatment with a cytostatic drug (apoptosis = programmed cell death or necrosis) or turn into a less immature cell (a process called differentiation).

Depending on their specific mechanism of action, cytostatic drugs interfere with the process of mitosis in various ways, for example by affecting the genetic material (DNA) of a cell.

The most common method is to administer a combination of several different cytostatic drugs.[34] The effectiveness of chemotherapy depends on the type of tumour, its composition, rate of growth, etc. Sometimes cytostatics are

given as high-dose chemotherapy. This is used in the treatment of leukaemia, lymphomas, and of other haematological pathologies.

Chemotherapy and radiotherapy affect cell proliferation, their growth mechanisms are affected, growth stops and the cells die.[34]

Antimetabolites interfere with the growth of DNA and RNA by replacing the normal building blocks of RNA and DNA and affect cells at the stage in which the cell's chromosomes are copied. They are most often used to treat leukemia, and the drug that responds best is Methotrexate.

According to studies, the treatment with Methotrexate will have a better result when administered together with Prednisone (corticosteroid), the two being interspersed in equal doses.

Even after remission, the two drugs must be administered intravenously for another 3 weeks, this time Prednisone being administered 1 hour before each dose of Methotrexate.

Mitotic inhibitors are compounds derived from natural products such as plants. They act by stopping cell division, and can affect cells in all stages by

maintaining enzymes. Vincristine has a very good result in the leukemia treatment protocol, and this drug will also be administered intravenously.

Corticosteroids and *cyclophosphamides* are part of the category of indispensable drugs for the leukemia treatment protocol: Prednisone, Dexamethasone, Methylprednisone.

Folinic acid is a drug used to reduce the toxicity of chemotherapeutic antagonists, and in leukemia therapy, Citrovorum is administered 36 hours after each dose of Methotrexate.[26]

Studies show that in order to reach a remission of this condition, the duration of treatment, on average, is 116 weeks, but it can also fall within a period of 36 - 117 months. Practitioners have studied the fact that, in each patient, there may be very high chances of treatment failure, which is considered true when, on the 42nd day of treatment, there is no sign of improvement in the condition.[34]

Oral tissues are very vulnerable to the adverse effects of cytostatics, which affect swallowing, speech, mastication; all these effects were presented in the first part of this work.

Adverse reactions are simply unwanted effects caused by the patient's medication.[31] Such reactions can be conventionally classified, according to the production mechanism, into type A reactions (augmentative reactions) or type B reactions (strange reactions).

Type A reactions are the result of an exaggerated but normal pharmaceutical action of a drug prescribed in a usual therapeutic dose. Examples include xerostomia following the use of the antimuscarinic agent atropine, and prolonged bleeding as a result of the prolonged action of aspirin.

Type A reactions are predictable and usually dose-dependent, and although their incidence is common, the mortality they cause is generally low.

By contrast, type B reactions have aberrant effects because they are not predictable based on the known pharmaceutical actions of a drug given in usual therapeutic doses to a patient whose body reacts normally.

Among the adverse reactions with effects on the oral cavity we note:

- troubles of the salivary glands - xerostomia - sialorrhea;
- changes in taste;
- damage to the oral mucosa: ulcers, lichen planus lesions, discoloration;
- gingival hypertrophy;
- changes in dental structure and color.

However, it has been demonstrated that xerostomia is the most frequent manifestation of the oral cavity related to the consumption of pharmaceuticals.

Frequently, for patients diagnosed with leukemia, due to their inability to maintain a satisfactory oral hygiene, but also for reasons that include stopping the super-infection of the mucosa in the oral cavity, practitioners recommended oral rinses with chlorhexidine.

Studies show that, over time, chlorhexidine is responsible for the appearance of enamel discoloration. Also, the use of chlorhexidine can lead to the occurrence of brown coloration of the tongue (hairy black tongue).

In most patients, gingival hyperplasia was mostly resolved after the first stage of chemotherapy, without periodontal interventions.

Gingival recession and dental tartar were observed even after drug therapy. The cervical and proximal areas of the patient's teeth were stained due to prolonged use of chlorhexidine.

During the chemotherapy period, patients are advised to use chlorhexidine mouth rinses and a soft toothbrush in order to prevent infection and oral inflammation. After several cycles of chemotherapy, patients recover completely, but some have

other pathologies, secondary to the use of cytostatic drugs.

These cannot be prevented, due to the diversity of the patients and especially to the fact that it is not possible to know every patient's response to any type of treatment.

It is important to keep the patients strictly under control, with constant adjustments, on a case to case basis, in order to be able to manage these changes earlier and more easily.

The management of periodontal pathology in patients diagnosed with leukemia

Once the diagnosis has been made, consultation with the attending physician or oncologist is mandatory before beginning dental treatment. [35]

The main problems in the dental treatment of patients with malignant haematological tumours of white cells are:

- Bleeding tendency
- Increased risk of infection - odontogenic infections and opportunistic infections
- The risk of osteonecrosis of the jaw
- Anaemia
- Corticosteroid treatment - may show evidence of secondary adrenal insufficiency.
- Secondary malignant tumours

Dentists may face a dilemma: any dental treatment will worsen the leukemic situation and alter the patient's systemic condition.[34]

There are concerns that a dentist, while carrying out a routine dental treatment, or even the patient, while carrying out his own hygiene routine at home, could increase the risk of bacteremia; untreated, this could contribute in a sudden and spontaneous way to morbidity. First, patients with hematologic malignancies, including leukemia, should be examined clinically and radiologically

for oral manifestations, malignancies, periodontal disease, and osteolytic lesions. Secondly, strict oral hygiene instructions and removal of potential sources of infection should precede any cancer treatment. Clinicians frequently encounter periodontal disease of varying degrees, and it is known that chronic periodontitis can worsen without specific clinical signs.

Therefore, root planing, subgingival debridement, mouth rinsing, extraction of irrecoverable teeth, and administration of antibiotics should be performed prior to cancer therapy.[36-38] However, all procedures must be supervised by hematologists, and blood tests for preoperative evaluation are mandatory.[39,] Furthermore, patients in a severe or recurrent condition should be treated only with palliative or emergency treatment.

However, some studies state that, although it is very important for the dentist to know exactly how to manage all these oral manifestations in order to suppress them, most of the time, targeted treatments for periodontal pathology are not always helpful on their own.[40]

Thus, in association with them, it is very important to administer the appropriate medication recommended by the haematologist. As we specified in the previous sub-chapter, most studies demonstrate the fact that gingival hyperplasia progressively remits after the first chemotherapy session.

Periodontal treatment of patients with leukemia requires the consent of the haematologist. Root planing should be performed in association with the administration of prophylactic antibiotics. Patients should be advised to use chlorhexidine 0.2%, mouth rinses after oral hygiene procedures. However, certain complications of chemotherapy and radiation, such as mucositis, xerostomia, haemorrhage, and recurrent HSV infection, must be identified and the treatment plan modified accordingly.[34,41]

The literature suggests that gingival hyperplasia secondary to leukemia is completely or at least partially treated with effective chemotherapy sessions.[23] Some studies report resolution of hyperplasia within 10 days, while others report resolution after 8 weeks. However, no resolution, growth or extension of periodontal pathology was noted after chemotherapy. Therefore, it follows that the role of oral hygiene and of other factors influencing the resolution of spread in leukemia patients needs to be studied and investigated further.

Some recommendations published in the "Practice Guide in Periodontology", Coordinators: Prof. dr. Silvia Martu and Prof. dr. Anca Dumitriu, 2010:[25]

The dentist must refrain from performing any procedure that entails bleeding.

It is recommended to perform:

1. plaque control
2. repeated rinses at short intervals (1-2 hours) with antiseptic substances.
3. light tamponade to remove fibrin deposits
4. application of slightly antiseptic, soothing solutions,
5. local applications of thrombin covered with gauze dressing and surgical cement;
6. local applications of complex rinses with antibiotics

In periodontal abscesses, antibiotics are administered generally, and locally gentle maneuvers are made in order to evacuate the purulent exudate through the natural opening of the periodontal pocket; if this is not possible, microincisions are made, washes with gentle antiseptics are performed, antibiotics are applied topically, thrombin is applied, as well as light compressive dressing (20 minutes).

1. Gum brushing will be avoided because of the trauma and bleeding it can trigger.

2. Personal oral hygiene will be done by washing with antiseptic solutions typified by chlorhexidine.

3. The patient will be sent urgently to a specialized haematology clinic,

4. After the disappearance of the acute phenomena, preferably non-traumatic descaling will be done with ultrasound equipment, followed also by antibiotic gargles and especially antibiotic paste applications.

The surgical treatment of hyperplasia *can only be performed* with the haematologist's advice, following appropriate specialized treatment.

Acute leukemia absolutely contraindicates any dental treatment, including periodontal treatment!

The treatment of periodontal diseases in chronic leukemia:

1. any work will be done only with the consent and following the recommendations of the haematologist.
2. scaling and periodontal surgical treatments may only be performed after determining, on the same day, the bleeding time and the number of platelets (mandatory over 80,000/mm³) and under antibiotic prophylaxis.
3. The practitioner must take into account that chronic leukemia raises the following possible problems related to periodontal treatment: prolonged bleeding, infections, changes in the healing process.
4. Unfavourable evolution: lack of response to treatment/evolution of gingival volume changes
5. Complications: prolonged bleeding, infections

Dentists, especially dentists specializing in periodontology, must recognize that gingival hyperplasia may represent an initial manifestation of an underlying systemic disease.[25,34]

Leukemia, especially the acute myeloid form, is a haematological disorder in which periodontal symptoms frequently

occur, therefore practitioners may encounter such patients in the dental office.[42,43]

Periodontal manifestations appear either early or late, but if they are diagnosed on time, they can be resolved well with timely treatment. Therefore, gingival hyperplasia is the manifestation that most of these patients face, a manifestation that prevents the patient, first of all, from achieving good oral hygiene, especially due to the occurrence of gingival bleeding associated with hyperplasia.[44]

The petechiae, bruising and even necrosis that appear on the periodontium can be counted among the many manifestations that occur in this area, changes that occur due to the general pathology: thrombocytopenia, pancytopenia, neutropenia.[45]

Ulcerations that appear especially on the tongue, the jugal mucosa or in the periodontium, contribute to the occurrence of oral manifestations either early or late, both in the acute and chronic stages of leukemia.[46]

Other changes in the cephalic extremity are diffuse lymphadenopathy, with the presence of large nodules, enlarged tonsils and even pharyngitis, through leukemic infiltration of these tissues.

It is well known, however, that the chronic forms of leukemia present less serious oral manifestations, by comparison

with the acute forms, where they are of a significant magnitude. As mentioned above, gingival hyperplasia has a significantly increased contribution to the periodontium, in patients diagnosed with acute leukemia, where oedema can cover almost the entire surface of the teeth, extending both at the maxillary and mandibular levels.[47]

Some studies demonstrate the fact that it is installed, most of the time, in an acute but also chronic form, at the level of the front teeth, both vestibular and oral, and later on the hyperplasia becomes generalized, since it is a rapidly progressing condition.

Conclusions

The dental treatment plan for a patient diagnosed with leukemia must be made in collaboration with a haematologist. Any procedure will be performed only with the consent and following all the recommendations of the haematologist. Any procedure that entails bleeding is contraindicated in acute leukemia. For personal oral hygiene a soft or extra soft toothbrush will be used, in association with antiseptic chlorhexidine based solutions.

Although such patients have a poor prognosis, early diagnosis and rigorous recommendations, followed precisely, may improve the quality of life of the patient diagnosed with leukemia.

References

1. Germen M, Baser U, Lacin CC, Fıratlı E, İşsever H, Yalcin F. Periodontitis prevalence, severity, and risk factors: a comparison of the AAP/CDC case definition and the EFP/AAP classification. *Int J of Environmental Research and Public Health*. 2021 Mar 26;18(7):3459.
2. Barrett AP. Gingival lesions in leukemia. A classification. *J Periodontol* 1984;55:585-588.
3. Brito LF, Taboza ZA, Silveira VR, Teixeira AK, Rego RO. Diagnostic accuracy of severe periodontitis case definitions: Comparison of the CDC/AAP, EFP/AAP, and CPI criteria. *Journal of Periodontology*. 2022 Jun;93(6):867-76.
4. Eke PI, Borgnakke WS, Genco RJ. Recent epidemiologic trends in periodontitis in the USA. *Periodontology* 2000. 2020 Feb;82(1):257-67.
5. Şteţiu A, Ştef L, Boţa G, Vulcu C, Şteţiu M., Manifestări clinice ale parodonţiului marginal in leuceemiile cronice, *AMT*, vol II, nr. 2, 2010, pag. 117

6. Botelho J, Machado V, Leira Y, Proença L, Chambrone L, Mendes JJ. Economic burden of periodontitis in the United States and Europe: An updated estimation. *Journal of Periodontology*. 2022 Mar;93(3):373-9.
7. Genco RJ, Sanz M. Clinical and public health implications of periodontal and systemic diseases: An overview. *Periodontology 2000*. 2020 Jun; 83(1):7-13.
8. Nicolaiciuc O, Mihai C, Sufaru IG, Mârțu I, Solomon SM, Tatarciuc D, Rezus C, Martu S. Study on the TNF- α , IL-1 β and IL-6 Levels in Patients with Chronic Periodontitis and Cardiovascular Diseases. *Rev.Chim. (Bucharest)*, 2017, 68(3): 619-623
9. Veisa G, Donciu M, Segal L, Hurjui L, Nistor I, Ursarescu I, Martu S, Burlea L, Solomon S. Albumin as a prognostic factor for malnutrition and inflammation in chronic kidney disease *Rev. Chim. (Bucharest)*, 2016,67(1):103-105
10. Solomon S, Pasarin L, Ursarescu I, Martu I, Bogdan M, Nicolaiciuc O, Ioanid N, Martu S. The effect of non-surgical therapy on C Reactive Protein and IL-6 serum levels in patients with periodontal disease and atherosclerosis. *Int. J. of Cl and Experimental Medicine*, 2016;9(2):4411-4417.
11. Luchian AI, Martu I, Goriuc A, Martu C, Beldiman A, Martu S. Changes in biochemical parameters associated with periodontal disease. *Rev. Chim. (Bucharest)*, 2016,67 (6):1073-1075
12. Boatcă RM, Scutariu MM, Rudnic I, Mârțu-Ștefanache MA, Hurjui L, Rezus E, Mârțu S. Evolution of inflammatory Biochemical Markers Within Periodontal Therapy to Patients with Rheumatoid Arthritis. *Rev. Chim. (Bucharest)*, 2016,67 (4):741-744
13. Bui FQ, Almeida-da-Silva CL, Huynh B, Trinh A, Liu J, Woodward J, Asadi H, Ojcius DM. Association between periodontal pathogens and systemic disease. *Biomedical journal*. 2019 Feb 1;42(1):27-35.
14. Teodorescu AC, Martu I, Teslaru S, Kappenberg-Nitescu DC, Goriuc A, Luchian I, Martu MA, Solomon SM, Mârțu S. Assessment of Salivary Levels of RANKL and OPG in Aggressive versus Chronic Periodontitis. *J of Immunology Res, Hindawi*, 2019, Article ID 6195258, 6 pg. <https://doi.org/10.1155/2019/6195258>
15. Martu MA, Solomon SM, Sufaru IG, Jelihovschi I, Martu S, Rezus E, Surdu AE, Onea RM, Grecu GP, Foia L. Study on the Prevalence of Periodontopathogenic Bacteria in Serum and Subgingival Bacterial Plaque in Patients with Rheumatoid Arthritis. *Rev. Chim. (Bucharest)*. 2017; 68(8): 1946-1949
16. Anton DM, Martu A, Maris M, Maftai GA, Sufaru IG, Tatarciuc D, Luchian I, Ioanid N, Martu S. Study on the Effects of Melatonin on Glycemic Control and Periodontal Parameters in Patients with Type II Diabetes Mellitus and Periodontal Disease *Medicina – Lithuania*, 2021, 57:140.
17. Relation between Chronic Periodontitis and Prevalence of Head-Neck Carcinoma in Association with Quality of Life. Nitescu D, Solomon S, Ursarescu I, Martu I, Martu C, Martu S. *Balk J Dent Med*. 2015;19:145-149.
18. Study regarding the association between chronic periodontitis and the prevalence of head-neck Carcinoma. Nițescu D, Solomon S, Ursărescu I, Martu I, Martu C, Martu S. *Rom J of Oral Rehab*, 2015,7(1):101 -106.
19. Hirschfeld J, Chapple IL, editors. *Periodontitis and systemic diseases: clinical evidence and biological plausibility*. Quintessenz Verlag; 2021 Apr 19
20. Gundesen MT, Lund T, Moeller HE, Abildgaard N. Plasma cell leukemia: definition, presentation, and treatment. *Current oncology reports*. 2019 Jan;21(1):1-0.
21. Quispe RA, Aguiar EM, Oliveira CT, Neves AC, Santos PS. Oral manifestations of leukemia as part of early diagnosis. *Hematology, Transfusion and Cell Therapy*. 2022 Oct 10;44:392-401.
22. Chowdhri K, Tandon S, Lamba AK, Faraz F, Leukemic gingival enlargement: A case report and review of literature, *Febr 2, 2018, IP: 81.30.162.38*

23. Paunica S, Giurgiu M, Dumitriu A, Oral Manifestations in Acute Leukemia as the First Sign; The Interdisciplinary Approach of Diagnosis and Treatment, Journal of Mind and Medical Sciences, JMMS. 2015, 2(2):186- 192.
24. Alirezaei S, Bakhshi M, Taheri J, Mafi A, Moghaddas O. Oral ulcerations as the first manifestations of acute leukemia. A case report. Open J of Stoma. 2013;3:507-9
25. Dumitriu HT, *Tratat de parodontologie*, Ed Didactica, Buc. 2014
26. Bojan A, Dima D, Frînc I, Parvu A, Pațiu M, Petrov L, *Procoale de diagnostic si tratament in hematologie*, 2012, pg 10-29.
27. Angst PD, Maier J, dos Santos Nogueira R, Manso IS, Tedesco TK. Oral health status of patients with leukemia: a systematic review with meta-analysis. Archives of oral biology. 2020 dec. 1;120:104948.
28. Ștef L, Boța G, Ștetiu A, Săceleanu A, *Aspecte ale aatologiei aucoasei orale determinate de reacțiile adverse ale medicamentelor*, AMT, 2011, vol II, nr.2, pg. 145
29. Bojan A, Dima D, Frînc I, Parvu A, Pațiu M, Petrov Ljubomir, *Procoale de diagnostic si tratament in hematologie*, 2012, pg 10-29.
30. Bîcleșanu C, Pangică A, Stanciu D, Mihai LL. Efecte adverse ale medicamentelor asupra cavității orale. Rev. Rom de Stomatologie, 2008, vol. LIV nr 2-3.
31. Kappenberg-Nițescu DC, Mihai C, Oanță C, Mârțu I, Volovăț SR, Mihaela S, Martu S. Evaluation of cumulative effects of chemotherapy and bevacizumab (Avastin®) in oncological patients with periodontal disease. Rev. Chim. (Bucharest), 2017, 68(3):549-552
32. Kappenberg-Nitescu DC, Pasarin L, Teodorescu CA, Sioustis IA, Solomon SM, Martu S. Analysis of possible Cisplatin therapy effects on the periodontal status in oncology patients Rom J of Medical and Dental Education 2019, 8(2):39-46
33. Kappenberg-Nițescu DC, Solomon SM, Teodorescu C, Sioustis I, Păsărin L, Martu S. Comparing the subgingival microbiome composition during oxaliplatin chemotherapy in a patient with colon cancer. Case report .Rom. J of Medical and Dental Education, 2018, 7(2): 75 -80.
34. Kappenberg-Nițescu DC, Luchian I, Martu I, Solomon SM, Martu S, Păsărin L, Martu A, Sioustis IA, Goriuc A, Tatarciuc M. Periodontal effects of two innovative oral rinsing substances in oncologic patients. Experimental And Therapeutic Medicine, 2021, 21:98
35. Elitsa G. Deliverska, Assya Krasteva, Oral Signs of Leukemia and Dental Management – literature data and Case report. Journal of IMAB - Annual Proceeding (Scientific Papers) 2013, vol. 19, issue 4
36. Solomon SM, Stoleriu S, Timpu D, Agop-Forna D, Martu-Stefanache A, Tanculescu O, Ioanid N, Martu S. E-SEM Evaluation of Root Surface after SRP with Periotor Tips. Materiale Plastice , 2016,53(4):796-798
37. Solomon SM, Timpu D, Agop Forna D, Martu Stefanache MA, Martu S, Stoleriu S. AFM Comparative Study of Root Surface Morphology After Three Methods of Scaling. Rev. Materiale Plastice, 2016,53(3): 546-549
38. Becker, A; Zogakis, I; Luchian I; Chaushu, S. Surgical exposure of impacted canines: Open or closed surgery? Seminars in Orthodontics 2016, 22 (1), pp.27-33
39. Martu I, Luchian I, and Martu, C. Comparative Analysis of Some Antioxidant Markers in Periodontal Disease. Rev. de Chimie . 2016, 67 (7):1378-1381.
40. Martu, MA; Surlin, P; and Foia, LG. Evaluation of Oxidative Stress before and after Using Laser and Photoactivation Therapy as Adjuvant of Non-Surgical Periodontal Treatment in Patients with Rheumatoid Arthritis. Antioxidants. 2021,10 (2)
41. Martu, MA; Maței, GA; and Foia, LG. Wound healing of periodontal and oral tissues: part II - patho-physiological conditions and metabolic diseases. Review. Rom. J.of Oral Rehab. 2020, 20(3):30-40.
42. Lim HC, Kim CS. Oral signs of acute leukemia for early detection, J Periodontal Implant Sci, 2014;44:293-299.
43. Dean AK, Ferguson JW, Marvan ES. Acute leukaemia presenting as oral ulceration to a dental emergency service. Aust Dent J. 2008 Sep;48(3): 195-7

44. Guan G, Firth N, Oral manifestations as an early clinical sign of acutemyeloid leukaemia: a case report, *Australian Dental Journal*. 2015; 60: 123–127
45. Cooper CL, Loewen R, Shore T. Gingival hyperplasia complicating acute myelomonocytic leukemia. *J Can Dent Assoc*. 2000;66:78-79.
46. Felix DE, Lukens J. Oral symptoms as a chief sign of acute monoblastic leukemia: Report of case. *J Am Dent Assoc*. 1986;113:899-900.
47. Franch AM, Esteve CG, Perez, GS. Oral manifestations and dental management of patient with leukocyte alterations. *J Clin Exp Dent*. 2011; 3(1):e53-59.