Research of oral manifestations in blood dyscrasias (dysorders)

Abstract

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Among the many conditions that may be encountered in the oral cavity, those in the field of haematological disorders must represent, for the dental practitioner, an area of extreme responsibility in what concerns the approach of any treatment, due to the fact that a bleeding dental work performed without a prior detailed analysis of the patient's general condition may lead to serious complications and sometimes even death (2, 13, 19).

Clinical signs of various blood dyscrasias in the oral cavity are quite varied and sometimes very similar with other local or general conditions, this imposing to the dental practitioner thorough knowledge of the signs and symptoms specific to each condition reflected at this level, in order to be able to make an accurate positive and differential diagnosis. Of course, not all signs of blood dyscrasia are as frequently encountered in stomatological practice, but some of them, and we primarily refer to acute leukemia and all its forms, must always be in the attention of practitioners, both motivated by the fact that they are life threatening for the patient, but also because they are quite common nowadays, as a consequence of multiple ecological factors, incompletely elucidated, yet (1).

We have undertaken a series of investigations on patients suffering from blood dyscrasias, in collaboration with the hematology department of the Municipal Hospital Brasov (Spitalul Municipal Brașov), in order to study the characteristics of oral manifestations in patients with blood disorders and to define the possibilities and limits of stomatological interventions for this category of patients, as well as clinical and statistical studies in this field of expertise, conducted in the area of Brașov, in order to find the percentage of this illness category, encountered by dental practitioners in their daily practice. I hope this scientific research conducted with the help of competent specialists in haematology, laboratory physicians and recognized statisticians, based on an extensive current documentation will be useful to the practitioners that have to face such situations in the consulting room practice.

I have elaborated this doctoral thesis hoping that my endeavor will find its usefulness, putting at the disposal of interested parties the data necessary for solving more difficult cases.
CHAPTER 1

CLINICAL AND LABORATORY ASPECTS IN BLOOD DYSCRASIAS

The oral cavity is often the center of manifestation for several haematological conditions, sometimes through superficial injuries, other times through significant intra-oral lesions that may be traumatic. The aspect of these lesions is inseparable from the clinical examination for establishing the certainty diagnosis. The examination of the oral area will be supplemented by an examination of skin and other mucosa, or a general clinical examination, in case any diseases are suspected in the system. Theoretician or practitioner, the stomatologist, like a vast variety of specialists in medicine, is compelled to know and understand the patient’s medical history, before starting the dental treatment, which might eventually fail as a result of the patient’s malaise, who in the worst case scenario might die subsequent to an incorrectly or improperly administrated treatment.

Nowadays, the number of malpraxis lawsuits is continually increasing worldwide and it has to become very clear for the physicians in Romania that the responsibility is ascribed to them and declaring a patient clinically healthy at first sight may turn up to be a fatal choice.

In this study I intend to approach and evidence a series of clinical situations that the practitioner may encounter in his current professional activity, allegedly periodontal problems, but which may, in reality, hide haematological systemic diseases.
**Sequence of main disorders in AL (acute leukemia)**

Leukemic stimulus (virus, oncogenic mutations etc.)

Normal progenitor cell

Leukaemic progenitor cell

**Proliferation**  **Metabolic disorders**

Bone marrow  Spleen  Liver

Lymphatic  Skin

Ganglions  Kidney

CNS

Fever  Innapetence

Dislocation  Bone invasion  Hepatomegaly  Weight Loss

Skin lesions  Metabolic disorders

Renal failure  K⁺ Ca²⁺ and Nucleic acids

Leukaemic meningitis  (uric nephropathy)

Anaemia  Leukemia picture

Infections

Hemorrhagic  Bone  Splenomegaly

Syndrome  pains  Adenopathies

**Fig.1. Disorders in acute leukemia**
Leukemogenic factors

Among the agents incriminated for causing leukemia three have proven of having a significant statistic value: ionizing radiations, chemical substances and certain hereditary factors. Ionizing radiations have proven to be leukemogenic and carcinogenic, both subsequent to the Hiroshima and Nagasaki bombing and in the environments that use ionizing radiations (industry and medicine). For the atomic bombing survivors data collection began at 5 years after the bombing. Leukemia rate reached a peak between 1950 and 1954, whereafter it decreased constantly (9). Subsequent to doses of 40 Gy and lower, the excess of leukemia was evident in both cities (Hiroshima and Nagasaki). At a subtotal exposure of 100 cGy, the relative risk was of 6/100000 for leukemia. Children between 0 and 14 years old at the moment of the exposure, had a maximum rate of acute leukemia in 6 – 10 years from the exposure; it decreased with 50 % in the following 5 years, and after 18 years it became naught. Subjects over 50 years old had a maximum incidence in 10 years from the exposure, a rate which was maintained for a period of 23 years (31). The subjects between 15 and 50 years old had intermediary incidences as compared to the ones mentioned above (208, 209).

Acute myeloid leukemia is a clonal disease of hematopoietic stem cells with myeloid orientation, characterized by their neoplastic aberrant proliferation, with the stooping of the differentiation and maturation. A more accurate term is that of acute myeloid or nonlymphoid leukemia, as some morphologic variants differ among them from the point of view of the clinical picture, the morphological phenotype, in which are involved different bone marrow series, immunologic, chromosomal abnormalities as well the therapeutic strategy.

In acute myeloid leukemia the granulo-monocytic series is mainly involved, however at a great extent also the erythrocytic and megakaryocytic series, justifying their naming as “acute myeloid leukaemias”. Since these series derive from a common multipotent stem cell among them is established a strong functional solidarity, so that the proliferation of the granulo-monocytic series is often associated with the proliferation of the erythrocytic, megakaryocytic or monocytic series (34).

ACUTE PROMYELOCYTIC LEUKEMIA

Represents a particular form of AML with a distinct clinical, morphological and cytogenetic identity, as well as with special treatment, for this reason being set forth separately.

Acute promyelocytic leukemia was described by Hillestad in 1957 and studied in 1959 by Jean Bernard. It represents 10 % of the total AML cases and is characterized by the presence of promyelocytic blast cells– M3 in the peripheral blood and bone marrow, exceeding 50 % of the total of cellular elements (27).

Specific cytogenetic abnormalities. Translocation t (15:17) (q22; q12 - 21) represents in addition to the hemorrhagic syndrome, which appears as a major manifestation, the second characteristic of AML, on the clinical plan, from a biological point of view. The discovery of this translocation by Rowley signified a new stage both in what concerns the characterization
of the disease as well as in its modern therapy with agents that induce retinoic acid differentiation. This chromosomal abnormality also represents a specific marker as its frequency is around 70–90% in AML and is absent in other acute leukemias or myelodysplasias (5,6).

The patients are generally young, the average age being of 31 years.

**CHRONIC MYELOID LEUKEMIA**

CML is a clonal action resulted from the neoplastic transformation of a pluripotent stem cell (PSC), capable of hematopoietic differentiation towards all hematopoietic lines. The clonal origin was evidenced through cytogenetic studies, of molecular genetics, and following enzymatic studies.

Chronic myeloid leukemia is a blood tissue neoplastic disease, included in the group of chronic myeloproliferative diseases (BMPC), along with polycythemia vera (PV), essential thrombocythemia (ET) and myelofibrosis (Mf.).

Incidence and epidemiology. CML represents 15–20% of adult leukemias, with an incidence of 1 – 2 cases at 100 000 adults per year. By age, the maximum incidence is between 25 and 50 years. It is rare under the age of 18 and exceptional under the age 5.

There is a slight male predominance (♂ : ♀ = 1,4 : 1).

Clinical picture. The onset is extremely variable. The disease may be discovered accidentally by the patient or the physician when finding a splenomegaly causing abdominal distension or discomfort on the left upper quadrant. In some patients the first symptoms are represented by progressive anaemia with altered general condition or painful abdominal crisis caused by a splenic infarction. Sometimes the first clinical manifestation is the appearance of echymoses, gastrointestinal bleeding or postoperative bleeding, since around 30% of the patients suffer from uneven osteosclerosis, disease that may be discovered after a bone scan (199, 200).

**POLYCYTHEMIA VERA**

Polycythemia vera (PV) is a neoplastic condition of the blood tissue, included in the group of chronic myeloproliferative diseases, along with chronic myeloid leukemia (CML), essential thrombocythemia (ET) and myelofibrosis with agnogenic myeloid metaplasia (MMM).

The initial disorder consists of a gained mutation that appears in a stern pluripotent cell from the bone marrow. From this cell a clone of abnormal stern cell develops, producing an excessive number of cells from the erythrocytic, granulocytic and megakaryocytic (panmielosis) series. As a result the number of erythrocytes, granulocytes and platelets increases in the blood (pancitosis).

Distinctive for PV is the predominant growth of erythrocytes and of the erythrocyte mass with normal arterial $O_2$ saturation. Overproduction of erythrocytes (eritrocitosis) is often associated with low serum levels of erythropoietin (Epo) (43).
PV is the first myeloproliferative disease with a demonstrated functional, intrinsic abnormality of progenitor cells: „culture formation of erythroid colonies in the absence of exogenous Epo” (35, 37).

The main clinical manifestations are aquagenic itching, red-violet color of the teguments and mucosae, splenomegaly.

**ESSENTIAL THROMBOCYTHEMIA**

Essential thrombocythemia (ET) or primary thrombocythemia is a neoplastic disease of the blood tissue, included in the group of chronic myeloproliferative diseases along with polycythemia vera (PV), chronic myeloid leukemia (CML) and myelofibrosis with myeloid metaplasia (MMM). Like other chronic myeloproliferative disorders, ET is a clonal disease, which originates in a pluripotent stem cell from the bone marrow (15).

The main cytological disorder is megakaryocytic hyperplasia from the bone marrow, which leads to an excessive growth of blood platelets (at least > 600 000/mmc and frequently > 1 000 000/mmc).
CHAPTER 2

HAEMATOLOGIC DISORDERS IN THE ETIOLOGY OF PERIODONTAL DISEASE

Chronic marginal periodontitis (CMP), which we recognize nowadays in various morphoclinical forms, in terms of basic lesions, in early or advanced stages, appear at almost all examined persons, regardless of the age and geographical location of the researched human community.

Periodontal disease has a history equally long with that of humans. Anthropologic and paleopathologic studies show that the disease has constantly accompanied the phylogenetic evolution of the human species from prehistoric times.

Destructive bone lesions of the marginal periodontium were found using modern means of investigations at mummies embalmed 4000 years ago, in Ancient Egypt.

The papyrus discovered by George Ebers contains numerous references to gum related ailments and remedies based on plant extracts, minerals, inserted in honey or yeast (Ancient Egypt, around 1550 B.C).

Rudimentary tools for oral hygiene have been discovered in Mesopotamia, at UR, in the form of gold toothpicks, dating from 3000 B.C.

Babylonians and Assyrians used gum massage and washed their mouth with plant extracts.

In our country, the first writings about gum care using brushing and dentifrice date from 1828 and are ascribed to SELINGHER.

Victor Babeş (1854 - 1926), founder of modern microbiology, author of the world's first treaty of bacteriology (in collaboration with A.V. CORNIL), “Les Bactéries”, published at Paris in 1866, shows in its content that spirochetes are found at the teeth's collet, in the dental plaque. Agreeing with MALASSEZ and GALLIPP (1884) he believes that “alveolodental osteoperiostitis seems to be subject to salivary micro-organisms that penetrate between the cement and the alveolar wall. The alveodental ligaments and cement are destroyed”. In 1893, VICTOR BABEŞ published the article “About a bacillus that causes gingivitis and bleeding in scurvy”.

In 1924 the work “Alveolar pyorrhea” is published by Docent Ph.D. Ion Aleman.

Since 1926, at Bucharest, the Conference on pathology and oro-dental therapy is established, which became official in 1929, being conducted by Ph.D. C. Dimitrescu. During lectures “Alveolar pyorrhea and lesions of the oral mucosa” are being taught.

Dental education and practice of orodental and periodontal treatments have benefited from the contribution of specialists like Prof. Ph.D. D.D. Niculescu, Prof. Ph.D. Dan Theodorescu, Ph.D. Cicerone Mihail, Prof. Ph.D. Andrei Nass, Ph.D. Ana Sireteanu many others.

At present, Periodontology, as fundamental discipline of dental medical science has a solid foundation of theoretical and applicative researches in histology and histochemistry, microbiology and immunology, photoelasticity, functional surgery and immobilization, antimicrobial, immunomodulatory and biostimulation modern treatments.
MECHANISMS OF BACTERIAL PATHOGENESIS IN PERIODONTAL DISEASE

Microbiological studies enabled the determination of the pathogenicity of bacteria from the bacterial plaque in periodontal diseases, by means of various mechanisms (154). Thereby, are described:

Direct mechanisms, including the harmful action of bacterial factors related to their cellular structure, tissues’ invasion, production of exotoxins, endotoxins’ release, development of enzymes having a role of aggression against adjacent tissue components, toxic metabolites.

Indirect mechanisms include the host’s immune response, attempting to defend itself against the bacterial attack; mechanisms that may become themselves aggravating and progression factors for periodontal lesions.

1. DIRECT MECHANISMS OF BACTERIAL PATHOGENICITY

Adherence, subgingival bacterial colonization and invasion in periodontal tissues

Bacterial adherence in the subgingival area may be specific: Capnocytophaga adheres to the cement of the root; Eikenella adheres to epithelial cells.

Colonization of other species is achieved subsequent to the active adherence or, more often, if using for adherence the bacteria from the supragingival area.

Human and animal studies have clearly evidenced the mechanism of germs’ invasions in the form of necrotic ulcerative gingivostomatitis, respectively species of intermediate spirochetes.

Subsequent to the bacterial invasion of the junctional epithelium there were observed destructions of the basement membrane. The destruction of the periodontal tissue through invasion has been evidenced in the form of juvenile paradontis (59). The involved bacterium belongs to the species Actinobacillus actinomycetemcomitans, causing severe lesions of the gingival tissue, ascertained and experimental fact.

Harmful action of structure factors from the bacterial cell

The bacterial cell wall, through the peptidoglycan component; Lipopolysaccharide through is polysaccharide specific fraction “O” –antigen action, and through the K.D.O. fraction (lipid A reunited with core zone)

Thus, the endotoxin’s activity is multiple:

⇒ on leukocytes– produces leucopenia
⇒ on complement – causes its activation through the alternative path
on macrophages, causes the synthesis of interleukin 1, TNF, PGE and hydrolytic enzymes α

Harmful action of synthesized factors released from the bacterial cell

Exotoxins

Predominant bacteria in subgingival plaque pertaining to gram-negative flora haven’t been proved of producing exotoxins, except for the species Actinobacillus actinomycetemcomitans, which, sometimes, is able to synthesize an exotoxin named leucotoxin, due to the toxic activity against the polymorphonuclears.

Species like: Porphyromonas gingivalis, Treponema denticola, Prevotella, Capnytophaga may cause collagenases.

Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans and other species can release collagenases from polymorphonuclears, macrophages, fibroblasts.

Both gram-negative germs as well as gram-positive-germs in the subgingival plaque determine, during their metabolism, factors that may contribute to tissue destructions: butyric acid, propionic acid, amines, indole, volatile sulfides, ammonia, methyl mercaptan, hydrogen sulfide, dimethyl sulfide, which are inhibitors of collagen and other proteins (241).

2. INDIRECT MECHANISMS OF BACTERIAL PATHOGENICITY

ROLE OF HOST FACTOR IN PERIODONTAL DISEASES

Against the factors of bacterial aggression, the host’s organism responds through non-specific and specific defense factors.

Non-specific defense (immunity) in periodontal diseases

It is achieved at the level of the periodontium through the natural barrier represented by the anatomic integrity of the junctional epithelium, the humoral factors in the fluid of the gingival groove and the periodontal pocket, as well as the cellular factors from the tissue.

- Natural barrier

It is represented by the junctional and sulcular epithelium, which, through their anatomic integrity, prevent the generation of bacteria and their metabolites in tissues. Non-
adherence, ulceration of the epithelium modify the permeability of the tissue, allowing the diffusion of bacterial solvable compounds and their corpora.

- **Humoral defense factors**
  
  May be found in saliva and gingival fluid.  
  Saliva contains numerous antibacterial factors such as: Lysozyme, lactoferrin, peroxidase system.

- **Gingival groove fluid**
  
  As compared to saliva, in the gingival groove fluid are found defense factors such as:
  
  - complement (extravasated serum);
  - IgG class antibodies in high percentage (extravasated serum but also locally synthesized) and in a lower percentage IgM class antibodies.
  
  The complement from the gingival fluid is activated by the opsonized bacteria, by their metabolic products, by the released bacterial endotoxins.

- **Cellular factors**
  
  Polynuclears play an important part in this inflammatory process. Leukocytes margination is produced, their migration by means of diapedesis in the chemotactic outbreak.

  Macrophages derived from blood monocytes which have migrated in the tissue, play an important part, being involved both in the non-specific chronic inflammatory process as well as in the specific defense processes by presenting antigenic information to lymphocytes B or T, activating the specific humoral or cell response.

  Other cells involved in the inflammatory process are the ones of the periodontal tissue: epithelial cells, endothelial cells, fibroblasts.

**Specific defense (immunity) in periodontal diseases**

Antigens and antibodies in gingival groove and periodontal tissue

  Bacterial antigens may be structural: capsule, coating antigens, wall fragments or fragments synthesized by the bacteria: exotoxins, some enzymes.

  Antibodies in gingival groove fluid and the periodontal tissue belong in great majority to the IgG class immunoglobulin, with an increased power of opsonization and fixation of the complement, as well as, in a lower extent to the IgM class without opsonigenic potential, but with a high capacity of activation and fixation of the complement.

  The antibodies from IgA class are found in small quantities in the gingival groove and tissue, having an important part in the protection against supragingival plaque with slightly larger concentrations in saliva.
• Humoral and cell immune response in periodontal disease

Local production of antibodies has been evidenced experimentally for the antigens deriving from the gram-negative bacilli of species: Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Fusobacterium nucleatum, Campilobacter rectus.

• Antigen-antibody reactions in the periodontal tissue

Through the specific union of the antigen and the determined antibody are created complexes that have the capacity of fixating the complement on the specific position in the antibody molecules.

The complement’s fixation confers to the antibody the capacity of antigen lysis. In the gingival fluid the complement has concentrations close to those from the serum being extravasated from it at the level of the gingival groove.

Humoral mediated hypersensitivity reactions:

• Hypersensitivity reaction type I (anaphylactic) - Has been associated with the periodontal disease. The antibodies from the IgE class named “reagins” involved in this type of hypersensitivity are fixed on the mastocytes. Through the union with the bacterial antigens occurs the degranulation of mastocytes with the release of some mediators, especially histamine with secondary anaphylactic effects.

• Hypersensitivity reaction type II (cytotoxic-cytolitic) – In this type of reaction the antigen is on the surface or inside a cell from the tissue; the union of the antibody with the antigen is followed by the fixation of the complement, with the destruction of the antigen and, therefore the implicit lesion of the tissue. This type of reaction occurs in the autoimmune diseases (211).

• Hypersensitivity reaction type III (ARTHUS) – occurs through the precipitation of antigen-antibody complexes with secondary complexes, causing diseases by the, so called, “immune complexes”. The onset of this type of reaction is caused by an antigen excess leading to the formation of a large quantity of antibodies and, respectively, immune complexes.

Cellular immune response

In this specific response form, the antigen information from the macrophage is taken by T lymphocyte, which transforms blastically under the mitogenic action of the antigen, leading to the synthesis of lymphokines, factors that may also contribute to the amplification of the inflammatory process with the stimulation and release of other mediators in the location of the antigenic aggression.
BACTERIA CONSIDERED POSSIBLE PERIODONTAL PATHOGENS

- In gingivitis

Model experiments have shown the onset of a gingival inflammation in 10-21 days after a poor oral hygiene. During this time, the bacterial plaque's constituents are, in great majority, from the Actinomyces group, especially Actinomyces viscosus. These species have proven to be associated with gingival hyperplasia. However, other studies have shown that the entire mass of bacterial plaque, in contact with the gum, causes its inflammation, therefore in gingivitis can not be taken into consideration a single specific etiologic factor.

- In periodontitis

The identification of pathogenic species in periodontitis is more difficult as compared to gingivitis. However, laborious isolations have shown a specificity of etiologic agents, depending on the clinical form of the disease. Therefore, a series of microbial species have been shown to possess virulence factors, toxicity and cellular destruction.

PERIODONTAL DISORDERS IN ANAEMIA

GINGIVITIS FROM ANAEMIA
1. Hyperchrom, macrocytic, pernicious anemia
   Addison-Biermer anaemia characterized by Hunter's Glossitis whose specific is the smooth lingual mucosa with papillary atrophy, having a bright red color.
2. Iron Deficiency Anemia Microcytic Hypochromic
   Plummer Vinson syndrome from hyperchrom anaemia. Sideropenic anaemia is at the basis of atrophic glossitis, angular cheilitis, generalized atrophy of the oral mucosa, oral ulcerations and secondary candidiasis.
3. Drepanocitary, sickle cell anaemia, sickle cell disease
   This condition is characterized by a pale, slightly yellowish mucosa, and the development of osteoporosis at the level of maxillary bones. Homozygous sickle cell disease is commonly a severe hemolytic anaemia, most patients suffering from this disease not reaching adulthood.
4. Hemolytic normocytic, normochromic anaemia
   Appears as a result of the toxic action of medication against haematopoiesis. The gingival mucosa is pale and shows overinfected ulcerations caused by leucopenia.
5. Gingivitis from thrombocytopenia
   Thrombocytopenia may be idiopathic – Werlhof disease, or secondary – in leukemias, malignant tumors, poisoning with benzene, arsenic, aminofenazone or irradiation.
Pathognomonic for thrombocytopenia is purpura on the skin and mucosae. Petechiae and haemorrhagic blisters may appear on the cheek mucosa and palate and hemorrhages occur at the slightest touches.

6. Hyperplastic gingivitis from Wegenger granulomatosis
   Acute necrotic and granulomatous lesions of the respiratory and renal tract. The gum has a red-violet color, ulcerations and bleeding occur.

HAEMOPHILIA

Haemophilia A is the most frequent and severe form. The disease has a familial character and affects males. Transmission is recessive gonosomal and occurs with an incidence of 1/10,000 male newborns.

Clinical manifestations depend on the severity of the factor VIII. Patients with severe condition have less than 1% factor VIII in circulation, and the ones suffering from a moderate condition have between 1 and 5% factor VIII and patients with mild condition have a level of the factor VIII varying between 6 – 30%.

Haemophilia B (CHRISTMAS disease) also has a recessive transmission, however, it affects both sexes. It is encountered rarer than haemophilia A, but the differences regarding the intensity of clinical signs is practically insignificant.

Haemophilia C. In this type of haemophilia, hemorrhagic manifestations are moderate. Both sexes in equal proportions may develop haemostatic defect. The disease’s transmission is recessive.

MACROGLOBULINEMIA

(Waldenström disease)

Is a rare condition, characterized by the presence of an IgM monoclonal protein in the serum, leading to an abnormal proliferation of B lymphocytes.

The disease especially develops at men, after the age of 50.

Evolution is variable. There are fulminate forms and forms with a long evolution.

The common symptoms of the disease are the following:

◊ Asthenia
Pallor
Weight loss,
Indisposition
Adenopathies
Neurological disorders
Hepatosplenomegaly

Characteristic signs are persistent gingival hemorrhages, petechiae, echymoses, epistaxes, mucosa ulcerations.

ADDISON DISEASE
(Chronic Primary Cortico-Adrenal Failure)

The condition occurs most often through the autoimmune induced destruction of the adrenal gland. Other causes include infectious diseases, adrenal gland removal, gram-negative septicemia, pituitary insufficiency, tumoral invasion and idiopathic causes.

Intraorally, the disease is manifested through the development of hypermelanosis, apparently similar with melanoplakia. The pattern isn’t small and consists of multiple, focal spots, having a black-bluish color, being generalized or having a linear, diffuse pigmentation (dark brown), brown.
CHAPTER 3

Existent correlations between irritations and oral manifestations in blood dyscrasias

ULCERATIVE CONDITIONS

Ulcerations are one of the most frequent lesions in dental practice. They involve an extremely varied etiology and may be classified as it follows:

REACTIVE LESIONS

⇒ Ulcerations:
  ▪ mechanical
  ▪ chemical
  ▪ thermal

BACTERIAL DISEASES

⇒ Syphilis
⇒ Gonorrhea
⇒ Tuberculosis
⇒ Actinomycosis
⇒ Noma
FUNGAL DISEASES

⇒ deep fungal infections:
  → Histoplasmosis
  → Blastomycosis
  → Coccidioidomycosis
  → Cryptococcosis

CONDITIONS ASSOCIATED WITH IMMUNOLOGIC DYSFUNCTIONS

⇒ Mouth ulcers
⇒ Behcet syndrome
⇒ Reiter syndrome
⇒ Erythema multiforme
⇒ Lupus erythematosus (205)
⇒ Allergic Reactions
⇒ Wegener's granulomatosis
⇒ Centro-facial malignant granuloma
⇒ Cyclic Neutropenia

REACTIVE LESIONS

MECHANICAL ULCERATIONS

Most of the ulcerations of soft oral parts are mechanical, being located on the lower lip, tongue and cheek mucosa. They are not determined by age or sex. Traumatic ulceration that develops at infants with natal or neonatal teeth located on the ventral tongue in foregoing 1/3 is known with the name of Riga-Fede disease.

CHEMICAL ULCERATIONS

Chemicals may cause ulcerations through their compounds (acids or bases) having an irritant effect or because of their allergic nature. Therefore, mucosal lesions appear, either caused by the patient or iatrogenic.

We may encounter mucosal burns caused by aspirin or alcohol which was administrated by the patient in the area of the aching tooth. In this way there appears a tissue necrosis with painful erosions which heal within a week’s time.

THERMAL ULCERATIONS

Ulcerations determined by thermal burns are rarely encountered intraorally.

They may be caused by hot liquids or foods, being located especially at the level of lips, tongue and palate.
PERSONAL CONTRIBUTION

CHAPTER 4

Oral manifestations in blood dyscrasias
MOTIVATION OF THE RESEARCH

Given the importance of knowing the oral manifestations determined by the presence of blood dyscrasias at certain patients I have considered useful the presentation of some cases encountered in current practice and outlining all clinical aspects that may important for establishing an early diagnosis, avoiding in this way the possibility of serious therapeutic errors.

Oral manifestations in these diseases are frequent both in acute forms as well as chronic forms, regardless of the affected cellular line. Blood dyscrasias create, from an immunological point of view, a state similar to immunodeficiency, and following the impairment of the erythrocytic and platelet line disorders appear in the hemostatic system and also various forms of anemia.

In his daily professional activity the dental practitioner faces a rather various range of manifestations at the level of the oral cavity, which he should know in depth, avoiding in this way incorrect interventions, which may sometimes cause severe complications to patients.

In this context are especially included blood dyscrasias, which may manifest at the level of the gingival mucosa or other areas of the oral mucosa, clear signs of disease.

The understanding of these signs and symptoms is very important due to the fact that in dental therapy there are interventions which applied without proper discernment, could considerably aggravate the general disease or could even endanger the patient's life, by provoking uncontrollable haemorrhages.

Considered from another point of view the oral manifestations related to blood dyscrasias could represent the first signs of development of this disease in the organism, enabling in this way an early diagnosis and a successful collaboration with the specialists in haematology.

These are the main reasons for considering that the profound examination of this topic could represent an essential aid for all dental practitioners, through the definition of all clinical aspects that may guide us to an early diagnosis, avoiding in this way the possibility or serious therapeutic errors.
RESEARCH OBJECTIVES

The understanding of blood dyscrasias is of great importance due to the fact that in dental therapy there are interventions which applied inappropriately may aggravate considerably the general disease, or may even endanger the life of the patient.

Certain oral manifestations are among the first signs that appear in these diseases, enabling the establishment of an early diagnosis and indicating the existence of blood disorders, thus making possible the administration of an appropriate specialty treatment.

Oral manifestations developed at patients suffering from leukemia may be ascribed to the malignant disease itself as well as to different therapy methods. Up to 40% of all patients suffering from cancer who underwent chemotherapy develop oral pathology (177, 181, 184).

Oral pathology may lead to significant complications: morbidity, impaired nutrition, delays in treatment, dose reductions affecting disease prognostication. Many researchers have undertaken a series of clinical studies intended to study the modalities of treatment for this pathology.

In the hereby study will be presented acute complications, oral manifestations at patients suffering from blood dyscrasias, which are, sometimes, determined by treatments (chemotherapy, radiotherapy) as well as the prevention and the modalities of management related to these complications, since these modifications of the physiological process are still an issue that needs further investigations.

Within the studies undertaken in order to lay out this paper there have been strikingly highlighted the signs and symptoms specific to each entity from the group of blood dyscrasias encountered in the consulting room practice, but also in the specialized sections of hospitals from the county or city of Brașov, with which a close cooperation was established, for a period of several years. We envisioned that the picture of various oral manifestations, related to these diseases, would be as better as possible defined so that we would be able to distinguish it from that of other diseases with rather similar manifestations, at the level of the oral cavity.

Clinical manifestations as well as a series of laboratory investigations have attempted to present, based on an extensive documentation from the current specialty literature, essential elements that depict the presence of these diseases, reflected by the changes occurred in the aspect of oral mucosa.

The extremely large range of diseases that may appear at the level of the oral cavity has to be well known by practitioners, in order to develop a proper treatment plan, sometimes after a prior consultation with other medical specialists. For this reason in this paper I have depicted a broad range of diseases, most often encountered by dental practitioners in their
daily practice, representing a guide, hopefully, of wide utility, in achieving an accurate management of these conditions.

The study lots consist of 8802 cases with blood dyscrasias from the above mentioned hospitals, out of which 312 cases were selected, and for which I have examined and analyzed the existent oral manifestations.

Thorough investigation of medical statistics have been made according to different criteria (by hospital areas, environment of origin, age, sex, diagnosis, risk factors, etc.), achieving a detailed picture of oral manifestations in blood dyscrasias in these areas, extremely useful for planning concentrated actions for their prevention and treatment. The detailed analysis carried out in localities from the county of Brașov may be extrapolated to the entire country, representing a valuable point of orientation for sanitary authorities in the activity of prevention and control of these diseases.

A series of laboratory tests specific for these pathology forms bring certain support elements in evidencing and diagnosing these diseases, and the presentation of some clinical cases at adults and children clearly depicts the aspects that the practitioners face in their everyday work.
CHAPTER 5

Methodological aspects

In Romanian medical literature there are only a few scientific publications on the correlational study of blood dyscrasias vs. oral manifestations.

Existent studies and guidelines at international level may not be entirely extrapolated in our country: most of them are based on mixed lots, that include both pediatric population as well as adults, the etiology of blood dyscrasia differs depending on the geographic populations, the type of treatment, administrated differently depending on the equipment and experience of each centre.

For all these reasons the main objective of this paper is to regard the gained experience in what respects the diagnosis of blood dyscrasias through their manifestation at the level of the oral cavity and treatment of oral manifestations, either in the acute or the chronic stage of the disease with the purpose of drawing up general recommendations, adjusted to the possibilities and particularities existent in Romania.

For the clinical-statistical analysis there was conducted a study, during 2004-2008, on 8802 cases selected within the hospitals of Brașov county, presenting blood dyscrasias. Out of these cases a number of 312 cases were selected and the existent oral manifestations were examined and analyzed. In order to undertake a comparative study there was set a control group consisting of 100 patients who didn’t have blood dyscrasias.

Statistical method
Based on an appropriate method of understanding the processes which are randomly conducted and on the probability theory, medical statistics succeeds to decipher with a known and acceptable error – the multiple correlation between the studied phenomena and the determinant factors, in view of establishing their main trends. For this purpose are used programs dedicated for processing statistical data and obtained results. The variation may be expressed by absolute, relative values, fractions or properties.

By grouping data into classes it is noticed the assimilation of all values of a class to a unique value, that of the median point (in this way the reduction to the case of a discontinuous variable is achieved).

The number of a value (or class) represents its absolute frequency, that is, the number of occurrences of this value (or class) in the distributed assembly.

Relative frequency is obtained by reporting absolute frequency at the number of individuals. The sum of relative frequencies will equal 1, which is the lot, that is, 100 percent or 100 distribution cases.

Cumulative frequency represents the number of cumulated individuals up to a certain value of the study variable; it may be either absolute or relative. Starting from the smallest value (the first from the order of the picture), successively are added the frequencies of each value (or class); therefore for each value is considered not only its own frequency, but the total of this frequency with all lower values. In this way is obtained the frequencies’ distribution, called cumulated, leading to clear conclusions regarding the studied phenomena.

With the help of statistical indicators the quantitative analysis may be conducted, enabling assessments and comparisons from the point of view of data location and distribution. They numerically express, according to the study values, either the location or the variation of data.

Correlation and regression indicators are used to express the functional, causal connections, between two or several characteristics of a phenomenon or collectivity.

The average values are indicators of the essential qualitative property of the studied collectivity’s phenomena, the measure of the central trend of the variable’s frequency distribution.

The median is the average value that is being used in large series of values, with close levels, therefore homogenous collectivities. The median divides the series of values in two equal halves. The median doesn’t consider all sizes taken by the values of the respective variant in frequency distribution and doesn’t yield to algebraic calculations, being less influenced by extreme values as compared to the average and also more stable to selection fluctuations.

The mode, module or dominant is an average value corresponding to the maximum frequency of a distribution series. The calculation is simple, considering the value with the maximum frequency as the average value.
Quartiles represent the value for which cumulative relative values reach 25%, 50% (median) respectively 75%. In other words, 25% of the subjects up to 54 year old. Interquartile range. The quartiles divide the data into four classes of frequencies equal to 25%. 3 values Q1, Q2, Q3 representing the quartiles are needed.

Standard error helps to determine the variation range of the average for a given confidence (95%). Standard deviation show how far apart is data around the average value.

Arithmetic mean error. The arithmetic mean determined by us doesn’t represent, most of the times, more than an empiric mean and not an absolute one, since we are not researching the total collectivity, but only a sample, a large or smaller part of the total.

ANOVA analysis of variance may not be used except for the case of normal frequency distributions (which have the same standard deviation). Otherwise, is used with good results the Kruskal-Wallis non-parametric test, based on the analysis of “assigned” ranks, similar with the Mann-Whitney tests and using the tabular data of the distribution $\chi^2$ (chi –square).

Comparison test “U” Wilcoxon is used in order to compare two results when the compared values are series of relative digits or the number of elements differs between the respective series.

Mann-Whitney test is non-parametric test, having a more complex method of data comparison, thus giving more information on the frequencies distribution of variables. It is especially used in testing the difference of average values of two series of values, in case the «t» test may not be conducted.

Opportunity Report (OR) – the opportunities of the exposed individuals to develop a certain characteristic are OR times higher than the opportunities of non-exposed individuals.

Risk Report (RR) – the risk of exposed individuals is RR times higher as compared to that of non-exposed individuals.

Risk difference RD represents the percentage wherewith the risk of exposed individuals is higher as compared to the risk of non-exposed individuals. A negative difference indicates the fact that the exposure is beneficial.
CHAPTER 6

Clinical-statistical study of oral manifestations in blood dyscrasias

Many systemic diseases have oral manifestations. The oral cavity is an important anatomic location having a critical role in many physiological processes, such as digestion and respiration. It is also, unique by the presence of the tissue surrounded by the excessively exposed mucosa. The oral cavity is frequently involved if there are present other multi-organ diseases.

In many cases oral involvement precedes the onset of symptoms and lesions from other locations.

This paper is, in particularly, focused on the study of the conditions in which oral manifestations are involved in various blood diseases.

Oral manifestations have to be duly recognized so that appropriate diagnosis and treatment measures are taken in respect to the patient.
In oral manifestations are involved lesions of the oral mucosa, tongue, gum, teeth, periodontium, salivary glands, facial skeleton, extraoral skin and other structures (3).

Leukemia, extremely severe disease that represents a neoplastic proliferative process of the leukoblast mesenchyme, is generally characterized by the unlimited increase of myeloid leukocytic or lymphoid elements accompanied by metaplasies of the haematopoietic organs and the appearance in the peripheral circulation of some young elements, which have not reached maturity yet (162).

It is a neoplastic disease, encountered at all races and at any age, however the highest incidence being recorded at younger ages. (162).

In what respects the form of manifestation, the illness may be myeloid, which is the most frequent acute form of manifestation in adults. It may evolve, per se, from the beginning or may be the consequence of a chronic myeloid leukemia. Whereas chronic leukemias have an evolution extending for a period of several years, acute leukemias evolve more suddenly, an extremely high number of immature cellular forms being developed, such as myeloblasts, lymphoblasts or reticular-hystiocitic cells (monoblast), the presence of the later determining the monocytic form of leukemia (monoblast) (156, 159).

Acute leukemia is frequently accompanied by oral manifestations that may often be extremely important, however we should keep in mind that local irritants are the ones activating manifestations at the level of the mucosa; in their absence the persons suffering from leukemia present a normal mucosa. The most common aspect is that of papillary hyperplasia or free gingival margins accompanied by intense hemorrhagic phenomena, and sometimes ulcerative lesions.

In acute leukemia occurs a maximum alteration of the function of haematopoietic organs. The result is a drop-off of all central and peripheral mature blood elements, being developed only young, immature, malign and proliferative cells (126, 133).

Oral manifestations are dominated by gingival hyperplasia and gum bleeding.

Hyperplastic gingivitis may be a first clinical manifestation or may occur during the evolution of the disease; the gum has a pale or pale-red color, sometimes violaceous with cyanotic character; petechiae and echymoses may be found on the mucosa. To these are added hyperplasia which sometimes develops into severe aspects through superficial ulcerations that appear in the form of necrotic gingivitis extended also to other areas of the mucosa. Hyperplastic tumefaction extends covering the vestibular and lingual side of the gum, being possible the complete covering of teeth, a distinctive sign as compared to common hyperplasia which develops only vestibularly. Secondary, superinfections may occur and fetid halitosis appears. Adenopathy and sometimes high dental mobility are manifested.
Gum bleedings appear at the slightest touch, sometimes even suddenly and they have to direct us towards a possible presence of leukemia, especially when the hemorrhage doesn't stop.

The dental practitioner is required to recognize the disease and refrain from any bleeding intervention and sometimes even dental brushing.

DISEASES WITH MANIFESTATIONS SIMILAR TO THE ONES FROM BLOOD DYSCRASIAS

DIFFERENTIAL DIAGNOSIS

ERYTHEMA MULTIFORME

It is an acute condition of mucosa and teguments with highly variable clinical aspects which heal spontaneously.

Although the erythema multiforme is often included in the group of vesiculobullous diseases, clinical manifestations also include ulcerative, erythematous or erosive lesions.

Clinical manifestations. Erythema multiforme appears more frequently during spring and autumn at young persons, age 30 - 40, especially males.

The most severe form of erythema multiforme is the Stevens-Johnson syndrome.

The disease is mainly related to mucosae. General symptomatology is more pronounced, and mucosal and skin lesions are more extensive as compared to the common form of erythema multiforme (16).

Oral mucosa is constantly implicated. Very painful, extended superficial ulcerations, covered by white-grey or hemorrhagic pseudomembranes are preceded by bubbles.

Simultaneously erosions may appear at the level of pharynx, larynx, esophagus, respiratory system.

Eye injuries manifested through conjunctivitis, corneal ulcerations, anterior uveitis may cause corneal opacity, symblepharons and even blindness.

LUPUS ERYTHEMATOSUS

It is an autoimmune collagenosis that presents various clinical forms that also include mucocutaneous manifestations.
Three types may be described: acute, subacute and chronic.

The acute form corresponds to systemic lupus erythematosus and the subacute one to cutaneous lupus erythematosus, and the chronic one to discoid lupus erythematosus.

The most severe form from the spectrum of this disease is represented by systemic lupus erythematosus, because of the disease’s generalization.

The least aggressive form is represented by discoid lupus erythematosus. This disease tends to remain located in the tegument and sometimes mucosae (81).

Clinical manifestations. Discoid lupus erythematosus may appear at any age; however it is predominantly encountered at women around the age of 40.

Oral mucosa is implicated in proportion of - 15-20% of the cases, in association with cutaneous lesions. In clinical rare situations, oral lesions may be isolated (197, 201).

The most implicated locations are the following:

- cheek mucosa
- lower lip
- gingival fibrous mucosa
- tongue

A typical oral lesion is characterized by a red, central, atrophic area, well defined, clearly bounded at the periphery by a more prominent area with white striations arranged in the form of rays. On the entire surface of the lesion keratosis pilaris may be found.

In some cases, oral lesions may be present in the form of ulcerations, white plaques having an appearance similar to leukoplakia or erosions that evolve towards atrophic scars.

Since the clime aspect of oral lesions is not pathognomonic, the disease may be suspected only in the presence of cutaneous lesions.

ALLERGIC REACTIONS

Allergy is a hypersensitive reaction of the organism against one or several foreign substances, acquired through repeated exposure at the same allergen.

Allergic manifestations may be generalized or localized and may develop at any age (14). Usually, a genetic predisposition to allergies or a permanent sensitivity is discovered.

Hypersensitivity reactions were classified into various types according to:
• onset rate of the symptomatology:
  - immediate
  - late
• clinical manifestations
• cellular response
In this way five types of allergic reactions may be named:

- type I – immediate hypersensitivity (anaphylactic), mediated by Ig E
- type II - cytotoxic-cytolytic reactions
- type III – immune complexes reactions type IV – cellular mediated hypersensitivity or late hypersensitivity
- type V – induced hypersensitivity

The ones that have importance for the dental practitioner are the immediate reactions type I (anaphylactic shock, urticaria, angioedema, allergic stomatitis) and late reactions type IV (contact allergy).

The mucosa of the oral cavity may be implicated in these types of reactions, but may also be the place of contact with the allergen that may trigger these reactions.

Anaphylactic shock – is a brutal and often dramatic event that may occur in several minutes after reintroducing an antigen in the organism (usually by injection). It is characterized by cardiovascular collapse accompanied by agitation and anxiety, subsequent to which paresthesia appears around the mouth and at the level of extremities, and also vertigo, dizziness, loss of consciousness, respiratory manifestations, (acute respiratory failure), digestive manifestations (abdominal pains, nausea, vomiting, diarrhea).

Acute angioedema (Quincke edema) – also known as acute circumscribed angioedema is another allergic pathologic manifestation, characterized by the rapid development of a oedematous tumefaction, especially of the head and neck, without inflammatory signs.

It appears locally, not clearly defined and doesn’t change the color of teguments.

According to the frequency order, it may affect:
- eyelid
- lips
- lingual mucosa
- soft palate
- larynx

If the edema obturates the glottis there is the risk of acute asphyxia.

Its origin and etiology is not fully elucidated. Allergic stomatitis also known as allergic mucositis appear as a result of combining dental materials with the tissue proteins, by contact. At the level of the oral mucosa 4 types of allergic reactions may develop (classified according to Gell and Coambs) (215).

a) Anaphylactic stomatities (systemic) are characterized by urticaria, vesiculo-ulcerative eruption of the oral mucosa associated with general manifestations that may lead to anaphylactic shock.

They are induced by food, but also a series of drugs such as quinine, quinidine, penicillin, chloramphenicol, etc.

In this category a special interest is represented by vesiculobullous allergic stomatities, encountered in the Steven-Johnson syndrome or Lyell syndrome, having a special severity.

WEGENER’S GRANULOMATOSIS
It is a rare chronic disease of unknown cause that affects middle-aged adults.

From the clinical point of view it is characterized by necrotizing granulomatous lesions of the respiratory tract, necrotizing vasculitis and arteries that simultaneously implicate veins and arteries and a necrotizing glomerulonephritis that may progress to a granulomatous glomerulonephritis.

Oral lesions are common and are manifested by single or multiple ulcerations surrounded by an inflamed area. The most common locations are on the tongue, palate or cheek mucous. Rarely an early sign of the disease may be a particular gum tumefaction. The gum is hypertrophied, showing an intense congested granulomatous papilla (193).

CENTROFACIAL MALIGNANT GRANULOMAS

It is characterized by ulcerative-necrotic lesions of the nasal cavity, palate and median portion of the face with irreversible evolution.

The etiopathogenesis of this disease is unknown. Some authors consider it an atypical form of lymphoma, others as a hyperimmune response to a non-identified antigen.

Clinically, the disease onsets with prodromal signs characterized by epistaxis, mild pains, nasal obstruction with purulent discharge (154, 157).

There are being developed necrotic ulcerations of the gum, retromolar trigone and nasal cavity without any healing tendency. Lesions worsen rapidly, destroying and perforating the palate, nasal septum and the surrounding bone structures, resulting in severe disfigurement.

CYCLIC NEUTROPENIA

Cyclic neutropenia is a blood dyscrasia of unknown cause characterized by a cyclic decrease of neutrophils.

The disease is transmitted in an autosomal dominant manner with variable expressivity.

The reduction of the number of neutrophils occurs regularly, at three weeks intervals, and lasts for 1-3 days. After a recovery period of 5-8 days the number of neutrophils returns to normal (160).

Usually, the disease manifests during the childhood, nevertheless it may onset at any age.

During an episode of severe neutropenia the patients develop moderate fever, malaise, headache, dysphagia, arthralgia, cervical adenopathies and skin infections.

The ulcerations of the oral cavity’s mucosa are painful, covered with whitish deposits, surrounded by a discreet erythema (99).

WHITE LESIONS
White lesions on oral mucosa owe their specific aspect to the modification of the mucosal surface through the thickening of the keratin layer, the hyperplasia of the malpighian layer or the intercellular edema.

At the same time, white or white-yellowish lesions may appear as a consequence of covering the ulcerated areas with fibrin deposits or fungal colonization.

Etiologic factors are extremely varied, but there are clinical situations in which the cause may not be identified.

Regezi and Sciubba classify lesions in the following way (166):

**HEREDITARY DISEASES**
- White sponge nevus
- Hereditary benign intraepithelial dyskeratosis
- Follicular dyskeratosis

**REACTIVE LESIONS**
- Frictional hyperkeratosis
- Nicotine Stomatitis
- Solar Cheilitis

**OTHER WHITE LESIONS**
- Idiopathic leukoplakia
- Hairy leukoplakia
- Hairy tongue
- Geographic tongue
- Lichen planus

**NON-EPITHELIAL LESIONS**
- Candidiasis
- Submucous fibrosis

**HEREDITARY DISEASES**

**WHITE SPONGE NEVUS (Cannon Disease)**
Intraorally, lesions are distributed in a symmetrical manner, being most often located on the cheek mucosa.

In descending order, lesions may be found along the lateral edges of the tongue, the mucosal lip line, on the alveolar mucosa and mouth floor.

The lesions’ sizes vary from one individual to another and from one period to another.

**INTRAEPITHELIAL DYSKERATOSIS**

**HEREDITARY BENIGN (Witkop Disease)**
Clinically, oral lesions appear as white, thick, wrinkled, soft, asymptomatic plaques which may be located in any region of the mucosa, except for the dorsal surface of the tongue. When the implicated location is the cheek mucosa along the occlusal plane appears a sensation of mucosa roughness.

FOLLICULAR DYSKERATOSIS
(Darier – White Disease)

It is a rare genetic disease, transmitted in autosomal dominant manner.

It appears more frequently in boys, during childhood, or adolescence.

The disease, mainly, implicates skin and nails.

Oral mucosa lesions are encountered in approximately 50% of skin lesions cases and tegumentary lesions succeed in a short time (137).

Typical oral lesions appear in the form of small, white, confluent papules (2-3 mm in diameter), having a squamous appearance. The bias location is the hard palate and immobile gum, followed by the cheek mucosa and tongue.

NICOTINE STOMATITIS
(Pipe smokers’ palate)

It is a reactive condition of the palatal vault mucosa caused by the prolonged, irritating action of heat and chemical substances released during tobacco burning.

The lesion is the exclusive attribute of excessive pipe or cigar smokers.

From a clinical point of view, in the early stages, a diffuse erythema of the hard palate mucosa develops. Subsequently, through the epithelium’s hyperkeratinization the appearance changes, the mucosa thickens and gains a white-gray or white-ashy tint. On the lesion’s surface are found red dots having a diameter of 1-5 mm, representing dilated and inflamed openings of the accessory salivary glands.

SOLAR CHEILITIS

Solar Cheilitis also known as actinic cheilitis is a lesion that appears, especially, on the lower lip, being caused by the prolonged, excessive action of solar radiation.

It is exclusively encountered at the white race, in persons working outdoors for long periods of time (sailors, farmers, builders, etc.).

Gradually, the lip becomes firm, slightly swollen, showing crusts on its surface, in addition there may appear ulcerated areas which may indicate either a loss of elasticity or a possible carcinomatous transformation (35, 56, 193).

IDIOPATHIC LEUKOPLAKIA
It is a clinical term indicating a spot or a white plaque located on the oral mucosa that can not be removed by wiping and can not be clinically classified in any other diagnosable disease.

HAIRY LEUKOPLAKIA

Hairy leukoplakia is a clinical entity reported for the first time at homosexuals infected with HIV- positive (1981) (24).

Similar lesions have been subsequently reported at patients with other forms of immunosuppression, namely, patients who have underwent organ transplant. Clinically the lesion is described as a white spot, of variable sizes (from a few mm to a few cm) having an irregular, cutaneous surface that confers it a "hairy" appearance.

It doesn’t get removed when scratching and it doesn’t regress spontaneously or subsequent to antifungal treatment.

It is usually located on the lateral edges of the tongue, in 90% of cases, bilaterally. Sometimes the lesions may also extend on the ventral or dorsal surface of tongue.

HAIRY TONGUE

It is a relative frequent lesion, caused by the hypertrophy and elongation of the filiform papillae which confer to the dorsal surface of the tongue a hairy appearance.

The lesion develops more frequently in men after 30 years and the incidence tends to increase with age (26).

The lesion onsets next to a foramen cecum and subsequently extends laterally and backwards. Filiform papillae are hypertrophied, elongated and may reach sizes of up to 10 mm.

Color varies from white-yellowish to brown or black, being influenced by: diet, smoking, oral hygiene and the presence of chromogenic bacteria (58, 62).

GEOGRAPHIC TONGUE

(Benign migratory glossitis, migratory erythema)

It is a benign inflammatory condition caused by the dekeratinization and desquamation of the filiform papillae.

Clinically, it is characterized by multiple erythematous areas having a round shape, bordered by a white edging.

The lesions’ sizes are variable, from a few millimeters to several centimeters.
A characteristic of this entity is that its appearance is in continuous change (sometimes from one day to another), the lesion healing completely in one area and appearing in another.

**LICHEN PLANUS**

Lichen planus is a chronic inflammatory disease of the tegument and mucosa, which equally implicates all races.

Lichen planus, like cutaneous-mucosal dermatitis is more common in women after the age of 40.

The distinctive characteristic of lichen planus is lesion polymorphism, determined, among others, by the long clinical evolution of the disease.

On the tegument the elementary lesion consists of a papule having 2-3mm in diameter, red-lilac color, round or polygonal form, with a smooth, shinny surface showing in the middle a hollow punctiform area.

**INTRAVASCULAR FOCAL DEVELOPMENTAL ABNORMALITIES**

**HEMANGIOMA**

The term hemangioma is used in a generic sense to encompass a variety of vascular neoplasias and malformations that predominantly develop at birth or shortly thereafter.

Within the category of development abnormalities, hemangioma, as clinical manifestation may be encountered in a series of syndromes:

- **STURGE-WEBER syndrome**
- **KLIPPEL-TRENAUXAY-WEBER syndrome**
- **RENDU-OSLER-WEBER syndrome**

**STURGE-WEBER syndrome** (encefalotrigeminal angiomatosis) is a rare congenital disease that implicates both sexes, characterized by:

- venous angioma of the cerebral conex’s leptomeninges
- macular hemangioma on the same side of the face
- neurological disorders
- oral and ocular lesions

**Klippel - TRENAUNAY - WEBER Syndrome** (angiooostehypertrophy) is also a rare vascular dysplastic disease. It is characterized by multiple flat facial hemangiomas, vascular tumor formations of the soft tissues and bone with asymmetrical hypertrophy of the extremities, ocular lesions (pigmentation of the sclera, cataract, glaucoma, and iris heterochromia), visceral and oral hemangiomas.
From a clinical point of view oral hemangiomas are most commonly located on the soft and hard palate, and the gum, having a hypertrophic appearance. It causes facial asymmetry, eruption disorders and, implicitly, dental occlusion.

RENDU - OSLER – WEBER syndrome (hereditary hemorrhagic telangiectasia) is a genetic disease with an autosomal dominant transmission that implicates both sexes.

The disease is characterized by multiple, mucosal, cutaneous and visceral telangiectasias (liver, kidney, stomach, etc.).

Lesions have 1-3 mm in diameter, may have a dark red, mauve or violet color, and disappear at vitropression.

NEOPLASIAS
ERYTHROPLASIA

The term of erythroplasia is used for any area of the mucosa that has a red, velvet appearance and may not be classified based on the clinical aspect and the histopathological examination in any other disease.

The lesion may be found in any area of oral mucosa, however, there is ascertained an increased incidence in the mouth floor, soft palate, foregoing pillars.

VITAMIN B DEFICIENCIES

The individual deficiencies of some of these vitamins may cause distinct clinical manifestations, including oral.

This category may include:
- Ariboflavinosis (riboflavin or vitamin B₂ deficiency)
- Pellgra (nicotinic acid deficiency)
- Megaloblastic anemia (folic acid deficiency)
- Pernicious anemia (vitamin B₁₂ deficiency).

b. IRON DEFICIENCY ANAEMIA

(Iron Deficiency Anaemia)

It is the most common type of anaemia.

Oral manifestations are characterized by a burning sensation especially at the level of the tongue, pale mucosa and progressive atrophy of filiform and fungiform papilla, so that in later stages the dorsal surface of the tongue turns red, shiny and smooth. Angular cheilitis is also present.

IMMUNOLOGICAL DISORDERS

PLASMA CELLS GINGIVITIS
It is the disease that owes its initial name to the presence of dense plasma cells infiltrate in the affected tissue.

From a clinical point of view, plasma cells gingivitis mainly affects adults and may last for several months or even years.

Free and adherent gums are edematous and have a deep red color. At the same time, the lingual mucosa is atrophic, red, and at corners become noticeable cracks and ulcerations.

Subjectively, the patients complain of burning sensation especially at tongue and lips level.

**DRUG REACTIONS AND CONTACT ALLERGY**

**EXTRAVASCULAR**

**PETECHIAE AND ECHYMOSES**

Intraoral petechiae and echymoses are determined by trauma or blood dyscrasias.

Blood dyscrasias include:

- Acute leukemias
- Chronic leukemias
- Agranulocytosis
- Infectious Mononucleosis
- Idiopathic and secondary thrombocytopenic purpura
- Hemophilia
- Macroglobulinemia

**ORAL AND PERIORAL PIGMENTATIONS**

In the course of various diseases, the mucosal tissue may suffer a variety of color modifications.

Blue, brown or black chromatics represent the pigmentary lesions of the oral mucosa and such discolorations may be ascribed to the deposit of both endogenous and exogenous pigments (173)

Although there are many biochemical substances and metabolic products that cause pigmentation, only a few deposit at the level of the oral soft tissues forming oral and perioral pigmentations.

They classify as follows:

**BENIGN LESIONS HAVING THE FOLLOWING ORIGINS**

**MELANOCYTIC**

- physiological pigmentations
- smoker's melanoses
- ephelides
- Peutz-Yeghers syndrome
- Addison disease
- lentigo
- oral melanotic maculae

Neoplasie

- pigmentation nevi
- melanomata
- neuroectodermal tumor of child

EXOGENOUS PIGMENTATIONS

- amalgams tattoo
- heavy metal-induced pigmentation
- drug-induced pigmentation

BENIGN MELANOCYTIC LESIONS

Melanin producing cells (melanocytes) have their embryological origin in neural crests. These cells extend up to the epithelial surfaces and are located among basal cells.

PHYSIOLOGICAL PIGMENTATIONS

SMOKER’S MELANOSES

Tobacco smokers show a distinctive color change of the exposed mucosal surfaces, referred to as cigarette smokers’ melanosis (173).

EPHELides

Ephelides or freckles are small maculae with a regular diameter under 5 mm, of yellowish color varying to dark brown, appearing on the lips or skin, as a result of the accumulation of melanotic pigment following the exposure to sunlight (207, 218).

Peutz-Yeghers syndrome is an autosomal dominant disease associated with multiple, mucocutaneous, melanotic maculae and gastrointestinal polyposis. These polyps have limited neoplastic potential, usually are found in the jejunileum, but may also be found in the stomach and colon causing abdominal pain, rectal bleeding (rectoragy) and diarrhea.

ADDISON DISEASE

(Primary chronic cortico-adrenal deficiency)
The disease develops most often subsequently to the autoimmune induced destruction of the adrenal gland. Other causes include infectious diseases, adrenal ablation, gram-negative septicemia, pituitary insufficiency, tumor invasion and idiopathic causes.

Intraorally, the disease is manifested through the development of hypermelanosis, apparently similar to melanoplakia. The pattern isn't small and consists of multiple, focal spots, having a black-bluish color, being generalized or having a linear, diffuse pigmentation - (dark brown), brown.

**LENTIGO**

It is a mainly tegumentary lesion, rarely encountered intraorally, that appears as a macula of brownish color, specific for the palate, gum and lips areas (206).

**ORAL MELANOTIC MACULAE**

Oral melanotic maculae are usually single, raised, well circumscribed lesions, of brown to black color, with a diameter under 1 cm, which mainly develop at persons with white skin, between the age of 25 -45.

**NEOPLASIAS**

**PIGMENTATION NEVI**

Nevi are lesions usually located at skin level which exceptionally may appear at the level of the oral cavity.

The term of "nevus" is a general term that may refer to any congenital or acquired lesion, having as starting point various cellular types such as: epidermis, vessels and pigmentary cells.

**MELANOMATA**

Melanomata are malignant lesions of melanocytic origin that can appear at tegumentary level as well as intraorally, having 2 times higher frequency in men as compared to women and, manifested especially after the age of 50 (30, 31). Intraorally, pre-existing melanosis onsets prior to the development of the melanoma, this pigmentry process representing a primary stage in the lesions’ growth.

**NEUROECTODERMAL TUMOR OF CHILD**

Is a rare benign tumor, being formed by pigment producing cells, relatively primitive. Like melanocytes and nevus cells, these cells originate in the neural crest cells.
Clinical characteristic – The disease is frequent at newborns under the age of 6 months, being located especially at maxillary level. The tumor consists of a nonulcerated mass, occasionally pigmented in black, pigmentation owed to the melanin generated by tumor cells.

ANALYSIS RESULTS FOR THE STUDIED LOT

The study was conducted for a lot of 8802 cases of blood dyscrasias within hospitals of Brașov county. Of these cases a number of 312 cases was selected and the existent oral manifestations were examined.

General characterization elements of Brașov county.

The healthcare provided to the population is divided into a system of 7 hospital areas, as per the proportion shown in the following study.

<table>
<thead>
<tr>
<th>Locality</th>
<th>Brasov</th>
<th>Fagăraș</th>
<th>Zărnești</th>
<th>Victoria</th>
<th>Codlea</th>
<th>Săcele</th>
<th>Rupea</th>
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<td>15202</td>
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<td>41117</td>
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<td>7.1%</td>
<td>2.6%</td>
<td>5.7%</td>
<td>6.9%</td>
<td>5.0%</td>
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<tr>
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<td>591.995</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Fig. 4. Percentage distribution for Brașov county by hospital areas

Fig. 5. Percentage distribution of the population of Brașov county according to the environment of origin
Fig. 6. Death rate by age groups

Fig. 7. Percentage distribution of cases according to the sex of the patients
Fig. 8. *Percentage distribution of cases according to the patients’ environment of origin*

Fig. 9. *Percentage distribution of cases with blood dyscrasias according to the diagnosis*
Fig.10. Annual distribution of cases diagnosed with blood dyscrasias

Fig.11. Death rate during the analyzed period
Fig. 12. Annual incidence of death in the studied lot

Fig. 13. Annual reparation of diagnosed cases vs. sex of the patients
Fig. 14. Annual distribution of diagnosed cases vs. environment of origin

Fig. 15. Annual distribution of diagnosed cases vs. environment of origin
**Fig. 16.** Distribution of cases from the studied sample by age groups

**Fig.** Frequency of blood dyscrasias by age
Fig. 17. Distribution of blood dyscrasias cases by diagnosis

Fig. 18. Frequency of oral manifestations in the studied lot
Fig. 19. *Frequency of oral manifestation in blood dyscrasias*

Fig. 20. *Distribution of cases by the frequency of oral manifestations*
**Fig. 21.** Distribution of cases by diagnosis and oral manifestations

**Fig. 22** Frequency of cases with oral manifestations depending on the oral hygiene
MULTIVARIATE ANALYSIS OF ORAL MANIFESTATIONS IN BLOOD DYSCRASIAS

The analysis of oral changes in relation with the diagnosis of blood dyscrasia was conducted using multivariated analysis methods. In this study were reviewed the results of multiple correlation taking into consideration oral impairment and the presence of blood impairment.

ORAL MANIFESTATIONS IN LEUKEMIA

Acute leukemia

In acute leukemia a decrease of the production of erythrocytes, granulocytes and platelets generates clinical signs of anaemia, infections and hemorrhages.

Oral manifestations are encountered in 80% of the patients. They are frequent, sometimes early, especially in acute myelomonocytic leukemia and are characterized by:
- petechiae
- echymoses
- spontaneous gingival hemorrhages or hemorrhages induced by minor trauma
- hyperplastic gingivitis
- necrosis and ulceration of the mucosa
- submandibular and cervical adenopathies

Hyperplastic Gingivitis may be a first clinical event or may occur in the evolution of the disease.

The gum has a pale of violaceus color, with cyanotic character.

Hyperplastic tumefaction covers both the vestibular side as well as the oral one, the complete covering of teeth being possible.

Chronic myeloid or lymphoid leukemia especially implicate elder persons and have an insidious onset.

Oral manifestations are similar with the manifestations of the acute form, but are less severe. Oral mucosa is pale and may show petechiae and superficial ulcerations. Gingival hypertrophy is more frequently encountered in its lymphoid form, like it is the case for adenopathies. At the same time, leukemic nodules may appear at the level of the palatal fibrous mucosa.

Hemorrhagic manifestations (bleeding, petechiae and echymoses) appear at 11-20% of patients and are based on thrombocytopenia, or intravascular coagulation.

![Graph showing partial correlation coefficients in the association of oral manifestations vs. leukemia](image.png)

**Fig.22.** Partial correlation coefficients in the association of oral manifestations vs. leukemia
ORAL MANIFESTATIONS IN ANAEMIA

Iron deficiency is the main cause of anaemia and is the most common haematological disorder.

This type of anemia is developed provided one of the following four conditions is met:

1. excessive loss of blood
2. increased request of red blood cells
3. low iron intake
4. low capacity to absorb iron

Manifestations may appear as early as three or four months, but in the majority of cases the symptoms are manifested late, during the first year or later.

The most common lesions which have been encountered are ulcerated lesions, gingival infection that respond to conventional treatment, hematomata, petechiae or echymoses.

**Fig.23. Partial correlation coefficients in associating oral manifestations vs. anaemia**

HEMOPHILIC ORAL MANIFESTATIONS

Represent a severe blood disease with plasmatic coagulation deficit, consisting of the absence in plasma of some thromboplastin factors: factor VIII or antihemophilic globulin A, factor IX Christmas factor, resulting haemophilia B and factor XI P.T.A. (Plasma thromboplastin antecedent), causing haemophilia C.
This deficiency is characterized by bleeding, frequently in the mouth, as well as joints and skin.

**Fig.24.** Partial correlation coefficients in associating oral manifestations vs. haemophilia

**ORAL MANIFESTATIONS IN OTHER BLOOD DYSCRASIAS**

Since a series of blood dyscrasias have similar oral manifestations, they were included in the same analysis sublot. We mention here: aplastic anaemia, leukopenia, thrombocytopenia, agranulocytosis, purpura, medullary aplasia, eosinophilia

**Fig.25.** Partial correlation coefficients in associating oral manifestations vs. other forms of blood dyscrasias
Conclusions

As in the case of all neoplastic diseases, in early diagnosis and treatment of leukemia is important to improve the chance for remission of the patients’ disease. The cases of acute leukemia should be considered as a medical emergency and, consequently, should be immediately directed to the specialized medical facilities.

The dental practitioner may play an important role in identifying oral manifestations in this disease and in ordering appropriate haematological test so that the diagnosis of leukemia is confirmed.

![Distribution of cases according to the patients’ age](image1)

**Fig. 26. Distribution of cases according to the patients’ age**

![Frequency of cases with oral manifestations in the studied lot according to the patients’ age](image2)

**Fig. 27. Frequency of cases with oral manifestations in the studied lot according to the patients’ age**
ORAL MANIFESTATIONS AT THE CHILD SUFFERING FROM BLOOD DYSCRASIAS

Within the studied lot a number of 11 children have shown oral manifestations representing 4.1% of the analyzed lot. Taking into account the importance of this issue we have especially addressed oral manifestations at children suffering from blood dyscrasias. In order to obtain a significant clinical-statistical analysis, the study focused on a sample lot which included 30 patients aged between 0-19 years who didn’t manifest blood dyscrasias. In this way was assessed the risk of occurrence of blood manifestations at children with blood dyscrasias, caused both by the disease as well as the administered treatment.

Fig.28. Frequency of oral manifestations in the study lot according to the patients’ age

Fig.29. Contingency table oral manifestations vs. blood dyscrasias at patients aged between 0-19 years
Table 33. Dental treatment protocol

<table>
<thead>
<tr>
<th></th>
<th>Diagnosis protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before chemotherapy</strong></td>
<td>Thorough examination – radiography, ortopantomography</td>
</tr>
<tr>
<td></td>
<td>Teeth extraction with affection and reserved prognosis</td>
</tr>
<tr>
<td></td>
<td>Treatment if caries</td>
</tr>
<tr>
<td></td>
<td>Oral hygiene using fluoride toothpaste (2/day)</td>
</tr>
<tr>
<td></td>
<td>For children with a high degree of caries risk, the use of mouthwash twice a day (0.12% chlorhexidine content)</td>
</tr>
<tr>
<td><strong>During treatment</strong></td>
<td>Further use of mouthwash twice a day (0.12% chlorhexidine content)</td>
</tr>
<tr>
<td></td>
<td>Temporary stop of dental brushing if lesions are too painful</td>
</tr>
<tr>
<td></td>
<td>Administration of de nystatin in oral suspension 4 times per day</td>
</tr>
<tr>
<td></td>
<td>in case there are clinical signs of oral candidiasis</td>
</tr>
<tr>
<td></td>
<td>Administration of acyclovir in case there are signs of infection</td>
</tr>
<tr>
<td></td>
<td>with herpes simplex</td>
</tr>
<tr>
<td></td>
<td>Use of artificial saliva and 5%, bicarbonate for rising the mouth</td>
</tr>
<tr>
<td></td>
<td>at children suffering from xerostomy</td>
</tr>
<tr>
<td><strong>Remission</strong></td>
<td>Basic care for preventing oral manifestations:</td>
</tr>
<tr>
<td></td>
<td>• fluoride toothpaste (2/day)</td>
</tr>
<tr>
<td></td>
<td>• use of mouthwash twice per day</td>
</tr>
<tr>
<td></td>
<td>• permanent advice and consultation</td>
</tr>
<tr>
<td></td>
<td>Normal treatment of patients, if remission is complete, except for invasive interventions.</td>
</tr>
</tbody>
</table>

Long term effects of the blood dyscrasias’ treatment associated with oral manifestations

Xerostomy caused by chemotherapy may be completely remedied in children by continual oral care.

The results reported in relation to the caries of the children who underwent treatment for malign diseases as compared to a sample lot consisting of children who underwent dental treatment evidenced no significant difference regarding the dental caries rate, while other studies have reported an increasing caries’ incidence.

The youngsters who have been treated by chemotherapy during the most active growing period don’t seem to manifest a significantly altered development. Nevertheless, there may appear enamel disorders – mineralization, frequently encountered in these patients.

In contrast, teeth disorders appear as frequent complications subsequent to the radiotherapy performed in the head and neck area. Oral manifestations include hypoplasia, problems regarding the growing of the teeth in formation, growth disorders etc.
Conclusion

Dental care for children suffering from leukemia is very important. The understanding of the disease’s nature and treatment are an essential part in the caring of the patient. Preventive treatment aims to avoid the complications of oral manifestations during chemotherapy, since oral care involves the treatment of oral diseases and the improvement of acute symptoms, which could complicate the therapy of blood dyscrasias.

Dental care during remission has to focus on maintaining the dental health of the affected child. The treatment’s principle should remain the same also in the case of children with other types of blood dyscrasias.

![Distribution of cases according to the patients’ sex](image)

**Fig.32. Distribution of cases according to the patients’ sex**
**RISK FACTORS ASSOCIATED TO THE ORAL MANIFESTATIONS AT PATIENTS SUFFERING FROM BLOOD DYSCRASIAS**

INFLUENCE OF RADIOTHERAPY IN THE DEVELOPMENT OF ORAL MANIFESTATIONS AT PATIENTS SUFFERING FROM LEUKEMIA

**Fig.34. Clinical aspect – patient suffering from leukemia (G.T. 62 years, male)**

Recent studies have shown that the effects of radiation may consist of the weakening of the defense system. (134). The dose of the applied radiation and the volume of the exposed glandular tissue are two „key” factors in determining the degree of glandular hypofunction and this independently of the secretory type of the glands affected by radiations. The irreversibility of the xeroinducing process appears when the dose of the focal radiation applied in the area of salivary glands has reached and exceeded 70 Gy. The quick reduction of the quantity of saliva drives the patient to consume, on a frequent basis, sweetened liquids,
which cause the modification of the oral flora in favor of Streptococcus mutans and cariogenic lactobacilli. In these conditions it is generated an acceleration in the evolution of new lesions during the period of one year. These phenomena occur in a very short period of time and directly proportional with the dose of received radiation, with the degree of the lesions developed at the level of the salivary glands and the duration of the hyposialia.

Periodontal lesions are developed, with gingival recessions and even periodontal disease with the generation of root caries.

The reduction of the rest and stimulated salivary flow is correlated with the number of received radiotherapy sessions. If the number of sessions is limited, hyposialia is temporary and may completely return to normal.

Radiotherapy induces acinar atrophy and chronic inflammation at the level of salivary glands. (183). The early response is the atrophy of secretory cells without inflammation, being possible to have been caused by the radio-induced apoptosis. Otherwise, the late response, with inflammation may be the result of radio-induced necrosis. The dry mouth symptom seems to be in a small degree correlated with the objectives found in the dysfunction of salivary glands.

It is necessary to establish a dental management before applying cervical-facial radiotherapy, insisting on the collaboration between the dental practitioner and the specialist in oncology-radiotherapy. The use of a pre-radiotherapy dental assessment document enables the specialist to conduct a complete clinical and radiographic examination.

RADIOTHERAPY IN THE STUDIED LOT

Fig.35. Frequency of radiotherapy treatment in the studied lot
**Fig.36. Frequency of oral manifestations vs. radiotherapy**

**Fig.37. Average values of the rest salivary flow RFR**
Categ. Box & Whisker Plot: **Flux salivar stimulat RFS**

Kruskal-Wallis-H = 42.555, p = 0.0000; F = 63.8796, p = 0.0000

**Fig.38. Average values of RFS – Stimulated salivary flow**

**Fig.39. Regression line in the correlation between the studied lot vs. stimulated salivary flow (RFS)**

**CONCLUSIONS**

- Our ascertainment confirm the fact that oral manifestations are in direct correlation with the lower values of RFR, RFS and pH.
- In case of the patients who have their general condition affected, salivary analyses may guide us in assessing the risks of oral manifestations and are indicated in clinical studies as well as current practice. Normal salivary function is essential for protecting the integrity of teeth and soft oral tissues. For the patients suffering from blood dyscrasias and especially those who have underwent cervical-facial radiotherapy and
who manifest xerostomy, the management of oral diseases should also include the assessment of the salivary functions.

Factors that influence the composition of total human saliva (acc. Dawes C., 1993, 47):

- Proportional contribution at different glandular sources;
- Contribution of blood and gingival crevicular fluid;
- Quality of oral hygiene;
- Plasma composition;
- Flow rate;
- Nature of stimulus;
- Duration of stimulation;
- Time after the previous stimulation;
- Circadian rhythm, circannual;
- Genetic polymorphism;
- Antigenic stimulation;
- Exercise;
- Medication,
- Conditions to stop the flow;
- Different diseases.

The analysis of results shows significantly increased values of urea in saliva and blood at the two studied groups of patients as compared to the sample lot.

![Categ. Box & Whisker Plot: Urea](image)

**Fig. 41. Statistic indicators of urea values in the studied lots**
CONCLUSIONS

- Analysis of salivary organic compounds has gained weight in recent years and plays an increasingly important role in establishing the diagnosis of oral manifestations.

- In our study we wanted to emphasize the importance of saliva analyses as well as the necessity to recommend them to patients whenever needed, having the advantage that they don’t require painful dental work.

- These studies have a greater importance in monitoring the oral health condition and are indicated especially to patients with a high risk of oral diseases.

- The results confirm the previous observations showing that as a consequence of different diseases or cervical-facial irradiation the parotid salivary glands - source of main organic salivary compounds (amylase, etc.) - are affected.

- The variation of these organic compounds in saliva has repercussions on the protective effect of saliva against microbial, cariogenic agents and may eventually cause an increasing risk of oral disease.

- In the case of patients suffering from blood dyscrasias, dental management should be individualized per patient and should include frequent visits to the dental practitioner who regularly assesses the diet and the consumption of xerogenic drugs.

INFLUENCE OF CHEMOTHERAPY IN THE DEVELOPMENT OF ORAL MANIFESTATIONS IN PATIENTS SUFFERING FROM LEUKEMIA

Oral manifestations encountered at patients suffering from leukemia may be ascribed to the malign disease, per se, as well as to different therapy modalities. Up to 40% of the patients that developed cancer and who receive chemotherapy present an oral pathology. Mucosal ulcerations and necroses may be caused by vascular thrombosis through the leukemic cells or may appear as a consequence of minor traumas or the chemotherapy treatment.
**Fig. 46. Frequency of chemotherapy treatment in the studied lot**

**Fig. 47. Frequency of oral manifestations vs. chemotherapy**
CASE PRESENTATIONS

Case 1

Female, age 22 who came to the emergency dental consulting room, showing manifestations of acute leukemia. The presence of oral lesions in this diagnosis is ascertained, and it is pointed out the importance of the immediate notification of the disease, by the dental practitioners.

The patient presented a four days history of pain associated with increased gingival ulceration. The patient, also showed lethargy symptoms, however they weren’t accompanied by fever or indisposition. There was no history of previous gingival trauma or episodes of oral ulcerations.

The location of the gingival inflammation was on the right side of the mandible (figure 48).

Fig. 48. Inflammations at gingival level (F.R. female, 22 years old)
At gingival level is noticed a large ulceration surface extended at apical level (figure 49).

The ulceration has been covered by „snake skin” and shows necrosis surrounded by an erythematous plaque.

A periapical radiography or even an ortopantomography does not reveal significant results.

Analgesics were administered and the use of chlorhexidine mouthwash was recommended. The patient was advised to return in the following days for consultation. During the consultation, she reported increasing pain; however the clinical signs were not changed.

Several investigations have included haematological investigations, erythrocyte sedimentation rate, values of iron and the investigation of the level of vitamin B12. Haematological results showed a low hemoglobin value, a level characteristic for anaemia. A very low level of platelets, a very high value of white blood cells and high values of monocytes. All other haematological findings were insignificant. These results have confirmed the diagnosis of acute leukemia and the patient was immediately admitted in the general oncology department of the hospital for bone marrow biopsy and further investigations and treatment as necessary.

Fig. Frequency of leukemia cases in the studied lot
CASE 2

Patient S.V., male, age 15, suffering from acute lymphocytic leukemia, shows a generalized gingival outgrowth, with spontaneous bleeding, intense red color of the gums, "bell clapper" papillae, caused by edema and the infiltration of white blood cells.

![Image of acute lymphocytic leukemia, gingival, hemorrhagic hyperplasia](image)

Fig.50. Acute lymphocytic leukemia, gingival, hemorrhagic hyperplasia

The patient presented vague pain at the level of the maxillary bones, cervical ganglions with a slightly increased volume, light facial pallor. The patient was hospitalized in a specialized clinic, was subject to the same hygiene measures observing all appropriate precautions in order to avoid bleeding and he underwent mouth rinses with antihemorrhagic and anti-inflammatory solutions that lead to improved symptoms.
OTHER CLINICAL CASES

Fig. 51. Neutropenia (G.F. male, age 33)

Fig. 52. Neutropenia
**Fig. 53.** Neutropenia subsequent to systemic corticosteroids therapy

**Fig. 54.** Lymphoma (T.P. age 42, male)

**Fig. 55.** Lymphoma in Acute Myeloblastic Leukemia
Fig. 56. Lymphoma in Acute Myeloblastic Leukemia

Fig. 57. Lymphoma in acute lymphocytic leukemia

Fig. 58. Lymphoma in acute lymphocytic leukemia
ADDISON DISEASE

Oral manifestations in Addison disease consist of the development of hypermelanosis, apparently similar to melanoplakia. During the consultation are distinguished multiple, focal, black-bluish spots, being generalized or with diffuse linear pigmentations (dark brown), brown.

32 patients (9.97%) of the studied cases made at least one visit to the dental practitioner from the first signs of illness until the diagnosis was made. Of these, five have been referenced to other specialty physicians, two of them with a presumptive diagnosis close to reality (vitamin deficiencies of iron).

Fig. 35. Frequency of cases with Addison disease in the studied lot

Fig. 59. Addison Disease (P.L. male, age 52)
Fig. 60. Addison Disease (G.D. male, age 43)

Fig. 61. Addison Disease (A.L. male, age 34)
Conclusions

As it is the case for all neoplastic diseases, early diagnosis and treatment of leukemia are important to improve patients' chances for remission of the disease. Cases with acute leukemia should be considered a medical emergency and therefore should be immediately directed to the medical specialty departments.

The dental practitioner may play an important part in identifying oral manifestations related to this disease and in ordering appropriate haematological test to confirm the diagnosis of leukemia.

- In his daily practice the dental practitioner faces a very extensive range of pathologic manifestations at the level of the oral cavity, which he should know in depth, in order to make an accurate positive and differential diagnosis and to elaborate the appropriate therapeutic interventions.

- The collaboration with other medical specialties is often required for conducting clinical and laboratory investigations, in order to precisely determine the elements necessary for defending with certainty a diagnosis.

- In what respects blood dyscrasias, detailed knowledge of their manifestations in the entire body and especially at the level of the oral cavity, prevents the dental practitioner from intervening without any discernment, existing the possibility of him causing extremely severe complications, and we mainly refer here to the generation uncontrollable hemorrhages.

- Knowledge of clinical and laboratory aspects of blood dyscrasias helps the dental practitioner to establish a correct diagnosis needed for implementing an appropriate therapy.

- Cooperation with specialists in haematology is recommended in order to provide a treatment with satisfying results.
One of the blood dyscrasias, frequently encountered in practice is acute leukemia, with its different variants, which may develop its first manifestations at the level of the oral mucosa, case in which the dental practitioner has to act with caution in what respects any bleeding intervention and to closely collaborate with the specialist in haematology, in order to avoid any complication, and to implement, in due time, the most appropriate therapeutic measures.

Only through careful examination, detailed and well conducted anamnesis and a successful interdisciplinary cooperation, the dental practitioner may offer the necessary support for the correct discovery and treatment of these conditions.

Oral disorders may take very different aspects that could be confused with those of other local or general diseases, reason for which the collaboration with the specialist in haematology and the execution of specific laboratory tests are compulsory for a good management of the disease.

Discoloration of gingival mucosa or other areas of the oral mucosa, induced or spontaneous gum bleeding, echymoses, ulcerations, gingival overgrowths, regional adenopathies are signs that the dental practitioner has to observe and analyze with discernment in order to take appropriate measures.

Not only oral signs should be examined by the dental practitioners, but also general signs such as the presence of some forms of anemia, fatigue, echymoses, epistaxis, melena, petechiae, fever, paresthesiae, paralysis, liver and spleen function disorders, impaired general condition and others may represents the guiding elements in determining the presence of blood dyscrasias in the body.

The treatment of these diseases will be administrated in a specialized clinic. The dental practitioner has to recognize the disease and refrain from performing any bleeding intervention.

Dental treatment will focus on a cautious oral cavity hygiene, without any brutal manipulations; sometimes even brushing causing unmanageable hemorrhages. For this purpose will be used cotton swabs dipped with mild antiseptic solutions (chlorhexidine 0.1%) to which, eventually will be added small amounts of bicarbonate for a more efficient removal of plaque. Medication may be used for an antiseptic effect and the stopping of the bleeding.

Any intervention that may cause bleeding must be conducted only with the approval of the specialist in haematology, who has under supervision the patient in question.

Observing these principles, the dental practitioner will bring a significant contribution to the fight against various manifestations of blood dyscrasia at the level of the oral cavity and the unpleasant consequences of unjustified interventions.
will be avoided.

- Investigations using modern methods of medical statistics highlighted the percentage distribution of blood dyscrasias, in seven hospital areas from Brasov county.

- Out of 8802 researched cases, 312 were selected, presenting clear oral manifestations; they were analyzed from the point of view of their distribution by different criteria, such as the environment of origin, diagnosis, sex, age, death rate, the manifestation forms at oral level in various forms of disease encountered in children and adults, the effects of underwent treatments, risk factors detected. The analyzed parameters highlighted a series of very useful data for assessing the health condition of the population in the researched areas.

- The collected data could provide valuable support for the authorities responsible for health management in the researched areas, for establishing preventive and early treatment measures related to these diseases.

- A series of laboratory investigations such as the value of the rest and stimulated salivary flow, pH of saliva, saliva composition, blood urea compared to saliva urea, salivary amylase in case of irradiations, the effect of chemotherapy, all of these have filled in the data regarding the health condition of the investigated patients and enabled a complex vision, supported by relevant tables and graphics.

- A representative casuistic reflected through pictures that highlight the distinctive elements of the researched pathology, confirms the veracity of the foregoing and outlines the signs according to which have been diagnosed the individuals in this comprehensive study.

- A considerable part of the general hematological diseases have an impact on the oral sphere.

- The most common signs found in the oral cavity are gingival hyperplasias, spontaneous and induced bleeding gums, interdental papillae having a pale color with red to violaceous areas, echymoses and petechiae, multiple ulcerations with irregular forms, sometimes diffuse maxillary pain, and, especially, cervical and submaxillary lymphadenopathies.

- An accurate, well conducted anamnesis may direct us towards the manipulations allowed in some cases and especially towards those which are FORBIDDEN.

- Our findings confirm that oral manifestations are directly correlated with low values of RFR, RFS and pH.

- In patients with an impaired general condition, salivary analysis may guide us in assessing the risk of oral manifestations and are indicated both in clinical studies.
and current practice. Normal salivary function is essential to protect dental integrity and the integrity of oral soft tissues. In patients suffering from blood dyscrasias and especially in the case of those who have undertaken cervico-facial radiotherapy and developed xerostomy, oral diseases management should also include the assessment of salivary functions.

- Analysis of salivary organic compounds has gained weight in recent years and plays an increasingly important role in establishing the diagnosis of oral manifestations.

- In our study we wanted to emphasize the importance of saliva analyses as well as the necessity to recommend them to patients whenever needed, having the advantage that they don’t require painful dental work.

- These studies have a greater importance in monitoring the oral health condition and are indicated especially to patients with a high risk of oral diseases.

- The results confirm the previous observations showing that as a consequence of different diseases or cervico-facial irradiation the parotid salivary glands - source of main organic salivary compounds (amylase, etc.) - are affected.

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- In the case of patients suffering from blood dyscrasias, dental management should be individualized per patient and should include frequent visits to the dental practitioner who regularly assesses the diet and the consumption of xerogenic drugs.