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General Picture of Complications Arising in Oral Cavity Organs and Tissues During Treatment of Oncological Diseases with Chemotherapy Assistance

Nurova Shohsanam

PhD., Department of Orthopedic Dentistry and Orthodontics, Bukhara State Medical Institute, Bukhara, Uzbekistan

Abstract At the present stage of the development of dentistry, the diagnosis of periodontal pathology does not cause any special difficulties. The identification of clinical signs and characteristics of periodontal diseases, the prediction of the development of the disease, the relationship with the general condition of the patient requires additional analysis in relation to bone changes in the maxillary-alveolar system.

Keywords Dental defects, Periodontal disease, Hormones, Densitometer, Menopause, Periodontal pocket depth, Osteocalcin, Resorption

1. Introduction

Complications arising in oral cavity organs and tissues during treatment with chemotherapy assistance are very widespread. When chemotherapy is applied in standard doses, the probability of complication development constitutes from 20 to 80%, while in high doses of chemotherapy it reaches 100% [20,28,30].

Russian and foreign authors distinguish and indicate factors influencing the probability of complication appearance and their manifestation degree. It is possible to separate them into systemic and local factors. Systemic factors include:

- Types of means used in chemotherapy
- Weakening of immune system functions
- Long-term alcohol consumption and tobacco use during life
- Systemic diseases (diabetes mellitus, HIV-infection, cardiovascular system diseases, kidney diseases) [25,27,37,18,13].

According to Marylin J. Dodd and co-authors (1999), the patient's age also occupies an important place in complication development: complications are more often encountered before 20 years and after 65 years [36]. Gender differences are also observed in complication development: the risk is higher in women [35]. Local factors include dental status, ill-fitting prostheses, overhanging edges of fillings, low level of individual hygiene, as well as frequent recurrences of oral mucosa diseases in anamnesis (herpetic stomatitis, candidiasis, aphthous stomatitis) [25,27,36].

It should be noted that from the point of view of predicting complications in oral cavity organs and tissues, among all chemotherapy means, 5-fluorouracil, methotrexate, doxorubicin particularly attract attention [18,35]. The biggest problem of means used in chemotherapy is their cytotoxicity. 5-fluorouracil is an antitumor means belonging to the group of metabolites. Fluorouracil disrupts DNA synthesis, enhances formation of unfinished RNA structures, and thereby slows division of tumor cells [16]. 5-fluorouracil is used for treatment of gastrointestinal tract, breast, head and neck area tumors [16,19]. Study of 5-fluorouracil effect pathogenesis on mice showed that the means leads to oral mucosa atrophy, wherein proliferation decreases, cell death increases, release of inflammatory mediators activates, and protective function of oral mucosa decreases [18,19]. Genetic factors may influence development of oral mucositis during 5-fluorouracil therapy. Genes may affect enzymes metabolizing chemotherapy means. Thus, dihydropyrimidine dehydrogenase deficiency may increase potential toxic effect of 5-fluorouracil [35].

Methotrexate is a cytostatic means considered as belonging to the group of antimetabolites, antagonists of folic acid. Blocking tetrahydrofolate synthesis, the means disrupts DNA synthesis, which stops proliferative processes in the cell [37]. Methotrexate belongs to WHO essential medicines and is used for treatment of acute lymphoblastic leukemias, nervous system tumors, osteosarcoma and a number of autoimmune diseases [12].

* Corresponding author:
nurova.shohsanam@bsmi.uz (Nurova Shohsanam)
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Doxorubicin is a cytotoxic anthracycline antibiotic causing structural changes in nucleotide bases, which inhibits replication of nucleotides and activity of DNA- and RNA-polymerases. This condition leads to development of toxic effects on various organs. Doxorubicin is used for treatment of breast cancer, esophageal cancer, stomach cancer, brain and neck area malignant tumors, ovarian cancer, cervical cancer and a number of other tumors [34].

Oral mucositis is considered the most common complication of chemotherapy. This complex multicomponent process in oral mucosa arises in response to toxic effect of chemotherapy means or radiation therapy [30,20,35,17,30]. Oral mucositis may manifest differently: from erythema to oral cavity ulcers and necrosis. If necessary help is not provided to patients suffering from oral mucositis, hospital treatment period may prolong and treatment tactics need to be changed [27,30,35].

Pathogenesis of oral mucositis development includes several stages:Signal (mark) initiation, transduction (sequential initiation of inflammatory reactions), signal amplification, ulcer formation, ulcer healing [23,35,37]. The initiation stage begins with damage to DNA structure of cells in basal layer of oral mucosa epithelium, which deprives them of proliferation ability and disrupts cellular renewal sequence. In primary response to damage, activation of transcription factors is observed, increased regulation of proinflammatory cytokines, cytokine modulators, adhesion molecules, stress-reactants and matrix metalloproteinases is noted. This process leads to thinning and damage of oral mucosa epithelium caused by tissue damage and cell death [26,37,38].

Among all classifications of oral mucositis, the most widespread is the classification proposed by the World Health Organization [35].0 degree - no symptoms present, I degree - erythema and painful sensations; II degree - ulcer formation, possibility to consume solid food, III degree - ulceration requiring only liquid food consumption; IV degree - ulceration making oral food intake impossible.

Clinical symptoms of oral mucositis begin with erythema or patient complaints of dryness and burning sensation in oral cavity. It should be noted that in some cases clinical picture does not manifest severe forms [37]. Another part of patients suffers from forms of oral mucositis manifested by painful ulcers complicating swallowing and eating processes. According to research by Elting and co-authors (2007), in patients with oncological diseases of head and neck area, due to disrupted food intake process, in presence of oral mucositis, they may lose up to 5% of body weight during treatment [16,30]. Ulcers characteristic of oral mucositis differ from aphthous stomatitis and traumatic ulcers. Such ulcers have no clear boundaries, which is explained by deficiency of proinflammatory cytokines. Ulcers may be differently located, but are most often observed on buccal mucosa, oral floor, soft palate, lateral surfaces of tongue [19,30,35].

For patient, the most important sign of oral mucositis is ulcer formation. Ulcers form colonies in oral cavity in form of gram-positive and gram-negative bacteria [12]. Bacterial metabolism products may enhance damage of oral mucosa and stimulate additional release of proinflammatory cytokines. In oral mucositis, ulcers begin to heal by secondary intention, which requires several biological processes occurring in submucosal layer [28,34,36].

By preventing development of ulcerative lesions, it is possible to reduce probability of pain syndrome development, shorten hospital stay and eliminate need for nutritional support via tube [27]. In oral mucositis, ulcers become deep and prone to rapid colonization by microorganisms. Bacteria on ulcer surface are active participants in mucositis development process. Components of bacterial cell walls (lipopolysaccharides, lipoteichoic acid, antigens and alpha-glucans) penetrate into submucosal layer infiltrated by macrophages, which stimulates their subsequent secretion of proinflammatory cytokines [14,23,27]. In patients with existing granulocytopenia, there is risk of intact bacteria penetrating into submucosal vessels, leading to bacteremia and sepsis [17].

Most researchers have noted information about independent healing of oral mucositis after chemotherapy completion [17,20,24,32,36]. Ulcer healing is considered a result of active biological process, wherein signals from extracellular matrix of submucosal layer regulate proliferation, migration and differentiation of epithelial cells adjacent to ulcer. Cellular disorganization leads to prolonged ulcer healing periods, in minimal cases - to non-healing ulcers [12,26].

In patients undergoing chemotherapy, mucositis usually has acute course. First signs appear 3-5 days after drug administration, ulcer formation is noted at end of first week and improves within 2 weeks after therapy completion [6,12,29].

The most serious problem in oral mucositis is pain syndrome [26,28,30]. Special strategies have been developed to provide prevention and assistance to patients facing this problem [8]. According to recommendations developed by MASCC/ISOO (Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology) group of scientists, systemic and local analgesia is used. In severe cases, systemic opioid analgesics are used. In moderate cases, local application of doxepin, morphine, lidocaine, benzocaine, diphenhydramine is used [21,24,26,29,38]. If pain in oral mucositis is directly related to tissue damage and develops via neuropathic mechanisms, use of means aimed at reducing neuropathic pain is recommended [33,38]. There is also information about positive effect of artificial saliva means on reducing pain reactions in existing ulcers [8].

Chemotherapy treatment may seriously affect psycho-emotional state of patient. Thus, according to research by I.G. Romanenko and co-authors (2019), 60% of examined patients showed anxiety obsessive-phobic state affecting condition change processes and causing imbalance in hemostasis system [7].

Oral cavity contains various microorganisms: according to latest data, their species exceed 700 [10,14]. Such diversity makes oral cavity the most colonized by microorganisms environment in human body after intestine [4]. Flora composition

includes 50-200 differing species, widely distributed and found in almost every person. They are divided into microorganisms colonizing tooth surfaces (supragingival) and those living below gingival margin. The first group includes Actinomyces, Campilobacter, Capnocytophaga, Corynebacterium, Fusobacterium, Granulicatella, Neisseria, Prevotella, Streptococcus, Veilonella. The second group includes Filifactor, Fusobacterium, Parvimonas, Porfyromonas, Prevotella, Tannerella, Treponema. About half of oral cavity resident microflora is represented by anaerobic streptococci - S. mutans, S. mitis, S. sanguis, and peptostreptococci [14,29].

Oral cavity microbioma plays important role in implementation of specific and nonspecific, humoral and cellular immunity mechanisms. Bifidobacteria positively influence development of lymphoid apparatus and stimulate formation of protective barrier, increase proportion of properdin protein, lysozyme enzyme, prevent development of bacteremia and sepsis [10].

An important local factor affecting microbial composition is presence of orthopedic structures. They influence microbial adhesion, which stimulates increase in number of microbial colonies and thereby affects development of dental diseases [2]. Composite material restorations may also be colonized by microorganisms. However, there are patterns: the higher surface tension of material, the higher probability of microbial adhesion [17]. Highest tension is characteristic of ceramics and metal alloys, therefore, especially with unsatisfactory hygiene level, orthopedic structures are considered risk factor for development of oral cavity organs and tissues diseases [5,15].

Oral cavity microbioma plays important role in development of oral mucositis. Cytotoxic effect of chemotherapy means disrupts oral cavity microbial balance, damages oral mucosa and reduces neutrophil level [13]. Impaired protective function leads to disruption of resident microflora composition, as a result its representatives become causative agents of pathological processes in oral cavity [12]. Study of oral microbioma in breast cancer patients before and after chemotherapy conducted by Napenas JJ and co-authors (2010) showed that after treatment completion, using genetic sequencing method, 25 microorganism species were distinguished (85% of all flora), none of which were present in oral cavity before chemotherapy [31].

Influence of microflora representatives on severity of oral mucositis was studied by Hong B.Y. and co-authors [19]. According to scientists, chemotherapy means like 5-fluorouracil and docetaxel sharply change oral cavity microbial composition, which significantly affects condition of oral mucosa during treatment period. Under influence of these means, quantity of gram-negative microflora changes, which is associated not only with oral mucositis, but also with other inflammatory processes in oral cavity. At the same time, researchers note that decrease in representatives of Streptococcus, Actinomyces, Gemella, Granulicatella and Veillonella species is associated with increased severity of oral mucositis.

Based on available data, control of biofilm and qualitative -quantitative characteristics of oral cavity microflora is considered important in providing care to oncology patients [12].

Oral moisture is an important condition for maintaining patient comfort during antitumor therapy. Insufficient moistening of oral mucosa leads to its thinning, which increases susceptibility to microtraumas that may trigger development of inflammatory reactions [4].

Saliva is a dynamic system where processes ensuring physiological functions of teeth and mucosa occur [11]. Mixed saliva (oral fluid) is secreted by major salivary glands (parotid, submandibular, sublingual) and minor salivary glands located in oral mucosa (labial, buccal, palatal, lingual) [8]. Salivary glands are functionally diverse organs. They perform protective (preventing oral mucosa from drying out, protecting from irritants, neutralizing acids within buffer system activity), digestive (forming food bolus, primary processing with enzymes), communicative (ensuring proper speech and human communication), secretory, excretory, mineralizing functions (replenishing calcium and phosphorus in tooth enamel structure) [6,11].

Saliva is a viscous liquid with pH ranging between 6.4 and 7.8. Mixed saliva consists of 98.5-99.5% water, 0.5-1.5% dry residue - organic and inorganic components [7]. Organic components include proteins, peptides, amino acids, carbohydrates. Inorganic components include dissolved chlorides, phosphates, bicarbonates, thiocyanates, iodides, bromides, sulfates, microelement anions in saliva, as well as Na+, K+, Ca2+, Mg2+ cations. Additionally, microelements like Fe, Cu, Mn, Ni, Li, Zn, Cd, Pb, Li etc. are detected in saliva [7,8].

Some saliva components like lactoferrin, lysozyme, peroxidase, mucins, histatins, defensins, b-lysins, nordon glycoproteins play important role in formation of nonspecific oral resistance [4,6,17].

Lactoferrin is a glycoprotein of transferrin family with iron-binding properties. Lactoferrin is present in products of organism's exocrine secretion, including breast milk and saliva, and is also detected in neutrophil granules [11,31]. This substance is distinguished by wide spectrum of biological properties, including antimicrobial, antiviral and antifungal activity [20, 29]. Dentists pay special attention to lactoferrin due to its bactericidal and fungicidal effects [34]. In oncology patients, use of lactoferrin during chemotherapy may reduce taste and smell impairment [21].

Mucins belong to glycoprotein family. Mucin synthesis is provided by submandibular, sublingual and minor salivary glands. Specific structure of mucin is based on proline-rich polypeptide base, allowing retention of large number of water molecules, which ensures saliva viscosity [16]. Mucin functions include moistening food pieces for mechanical protection and covering oral mucosa [9].

Lysozyme is a factor of organism's nonspecific resistance, detectable in all biological fluids. Main function of lysozyme in oral cavity is cleavage of peptidoglycans in bacterial cell

walls, leading to their death [4].

Specific protective factors include immunoglobulins. Saliva contains 5 types: IgA, IgM, IgG, IgD, IgE. Highest concentration belongs to IgA, having 2 types: serum and secretory [24]. SIgA is considered main immunoglobulin isotype in saliva. It is formed by two polypeptide chains connected by disulfide bonds [2]. SIgA can prevent microbial adhesion to epithelium and tooth surfaces, maintaining integrity of oral mucosa. It is important to note that SIgA can neutralize enzymes, toxins and viruses independently and in combination with lactoferrin, lysozyme, peroxidase [2,21].

Chemotherapy affects salivary gland function, thereby changing activity of aforementioned saliva components, which makes oral cavity organs and tissues more vulnerable to biological and mechanical damaging agents.

Salivary gland dysfunction is a change in saliva quality or quantity, manifested by increased (hyperfunction) or decreased (hypofunction) secretion [3]. SGD is one of the most common complications of antitumor treatment [9]. Decreased salivation (xerostomia) may have objective (unstimulated mixed saliva volume ≤ 0.1 ml/min or stimulated ≤ 0.5 ml/min), subjective (patient feels dryness during speech and eating, develops burning mouth syndrome) symptoms [25,32].

According to Pinto VL and co-authors (2020), xerostomia occurs in 10% to 80% of chemotherapy patients. Usually, dryness appears by day 7-10 of chemotherapy and, unlike radiation therapy, disappears after treatment completion. Radiation-induced xerostomia may persist for several years [10]. Use of artificial saliva can relieve unpleasant symptoms of xerostomia [17]. Treatment regimens containing doxorubicin, cyclophosphamide, fluorouracil, methotrexate, vinblastine may cause changes in salivary gland function [12].

To increase salivation, along with artificial saliva, pilocarpine may be used. Pilocarpine is an M-cholinomimetic stimulating muscarinic receptors of smooth muscles, including salivary glands. In a study of Sjögren syndrome patients, pilocarpine showed significant effectiveness in relieving xerostomia symptoms compared to artificial saliva [13].

Along with antitumor efficacy, chemotherapy treatment is associated with development of adverse effects. Adverse effects significantly negatively affect quality of life of oncology patients [27]. In oncology, quality of life is assessed by several criteria: physical comfort (ability to perform basic body functions), functional comfort (ability to perform daily activities), emotional comfort, social comfort [9,15].

The most common oral complication is oral mucositis accompanied by pain syndrome, making basic processes like food/liquid intake, chewing, swallowing, breathing difficult. Pain syndrome and damage to oral and esophageal mucosa may lead to nutritional deficiency, patient weight loss, necessitating changes in antitumor treatment regimen [28,30,33,34]. Oral mucositis complications arise due to uncontrolled activity of microorganisms, negatively affecting patient quality of life, potentially leading to bacteremia and sepsis [22].

Modern oncology trends involve assessing treatment efficacy not only by overall and disease-free survival rates but also by quality of life indicators [30].

Thus, in conclusion, complex problems like oral complications during antitumor treatment significantly affect quality of life of oncology patients, but this critically important topic remains understudied.

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