APLASTIC ANEMIA AND HEALTH OF THE ORAL CAVITY
CLINICAL CONSIDERATIONS

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Abstract: Aplastic anemia is a non-oncological haematological disease, which is a challenge for specialists due to the severity of the clinical symptoms. It is characterized by hypocellularity of the bone marrow and its secondary pancytopenia. The aim of this paper is to characterize the symptoms of the oral cavity and the associated risks in the context of aplastic anemia. A brief review of the literature was conducted that highlighted pathological changes in the oral cavity in patients with aplastic anemia, to which were added data from current clinical experience. The clinical picture varies depending on the predominantly affected cell line. In aplastic anemia, symptoms of the oral cavity are always present. Thus, pallor can be found in the oral cavity as a sign of severe anemia, infections secondary to severe neutropenia and secondary immune deficiency syndrome, spontaneous bleeding due to severe thrombocytopenia. In addition to the signs of damage to the oral cavity in the context of the disease, there are symptoms caused by the side effects of treatment specific to this haematological pathology. Of these, gingival hyperplasia secondary to cyclosporine treatment is the most constant. Often these symptoms are the initial manifestation of the disease, which requires special attention from the dentist. The prevention, diagnosis, and specific treatment of oral pathology in the context of aplastic anemia improves the quality of life of these patients.

Keywords: aplastic anemia, oral cavity, immunosuppressive treatment

INTRODUCTION

Aplastic anemia (AA) is a hematological disorder of the hematopoietic stem cells that results in a loss of the blood cell precursors and cytopenia in two or more cellular lines (red blood cells, white cells, platelets). The introduction of the concept of aplastic anaemia (AA) was by Paul Ehrlich in 1888 [1]. Normal haematopoiesis depends on a complex interaction between the hematopoietic stem cells and cells from the microenvironment [2].

An abnormal expansion of suppressor T cells may cause depletion and possibly also clonal abnormalities of the hematopoietic stem cells [3]. Another study suggests that
CD4⁺CD25⁺FOXP3⁺ regulatory T cells are deficient in these patients, like what is seen in other autoimmune diseases. The diagnosis of AA is based on the exclusion of other disorders that can cause pancytopenia. A bone marrow biopsy is mandatory and will confirm aplasia (the number of hematopoietic cells is decreased). It should also exclude a myelodysplastic syndrome or acute leukaemia, as well as bone marrow metastasis. Platelets count, haemoglobin, polymorphonuclears and reticulocytes are main parameters for diagnosis of severity of aplastic anemia. Severity of AA can be determined by neutrophil counts: patients with 0 to 0.2, 0.21 to 0.5, and >0.5 polymorphonuclear cells (PMNs) × 10⁹/L are classified, as very severe, severe, and moderate aplastic anemia [5,6]. Clinical symptoms of patients with aplastic anemia are results of peripheral pancytopenia and are represented by the anemia, bleedings, and infections. Anemia has fatigue as a common symptom, that occurs due to reduced oxygen to the cells or low haemoglobin. The oxygen carrying capacity is reduced ultimately. Dyspnea, dizziness, headache, pale skin, and chest pain are the other symptoms of anemia that have a negative impact on quality of life. The characteristic clinical indicators of thrombocytopenia include easy bruising of the skin, petechiae, ecchymosis, epistaxis, gastrointestinal bleeding, metorrhagia, haematuria, and bleeding from the gums. Infections remain the major cause of death in patients with aplastic anemia. Harrys et al reveal in their study that the bacterial infections, especially those caused by gram-positive cocci, constitute the main cause of infection episodes [7] and Lertpongpiroon et al report that the gram-negative bacteria are most frequent [8]. Splenomegal and adenopathies are not seen, and its presence suggests an alternative diagnosis.

**IMPACT OF THE APLASTIC ANEMIA ON THE ORAL CAVITY**

It is common for aplastic anemia patients to have symptoms of anemia or haemorrhage. Infection at presentation is not often, even with severe neutropenia. Oral symptoms are common in patients with aplastic anemia and are directly associated with severity of pancytopenia. Oral lesions of aplastic anemia can be first manifestation of aplastic anemia. So, dentists should be aware of these manifestations so that an early diagnosis of the disease can be made.

The anemia has an important impact on the anatomical structures of the oral cavity. It often described as a normocytic normochromic anaemia that determinates the pallor of the oral mucosa. The clinical cases from the literature didn’t show a specific sign of anemia in aplastic anemia. Sepuolveda at al. showed in their study that the most common oral manifestation of the aplastic anemia was haemorrhage, which developed most often in patients with platelet counts less than 25 × 10⁹ cells/liter [9]. The second and third most common oral manifestations were candidiasis and viral infection, respectively [9]. Another study that comprises 79 patients with aplastic anemia showed that patients with this disease presented most frequent oral petechiae, gingival hyperplasia, spontaneous gingival bleedings, and herpetic lesions [10]. Some studies add that melanin pigmentation on oral mucosa, traumatic lesions, dental biofilm, and gingival alterations through the main oral manifestations of AA patients [11]. Chronic periodontitis is a severe focal infection and considered a potential risk of systemic infection in patients with AA [12].

**IMPACT OF THE TREATMENT FOR THE APLASTIC ANEMIA ON THE ORAL CAVITY**

With a high mortality rate (80–90%), allogeneic hematopoietic stem cell transplantation from a matched related
donor is the initial treatment of choice for newly diagnosed young patients with severe aplastic anemia or very severe aplastic anemia [13]. According to current therapeutic algorithms, immunosuppressive therapy with a combination of horse antithymocyte globulin and cyclosporin A is the preferred first-line treatment for patients without a matched related donor and older patients [14]. A recent study concluded that the addition of eltrombopag to standard immunosuppressive therapy improved the rate of hematologic response, without additional toxic effects [15]. Gingival hyperplasia or gingival enlargement is a complication of cyclosporine therapy [10]. Cyclosporine A has been suggested to alter the function of gingival fibroblasts by increasing interleukin-6 secretion, which enhances collagen and glycosaminoglycan synthesis [16]. Gingival overgrowth normally begins at the interdental papillae and is more frequently found in the buccal surface of the anterior teeth [17,18]. This gingival enlargement is often associated with difficulties of plaque control and produces pain, discomfort, and aesthetic prejudice [19,20].

Oral mucositis is a frequent adverse effect of allogenic or autologous hematopoietic transplant and results from direct toxic injury to the mucosal epithelial cells by the immunosuppressive regimen [21]. Oral mucositis has different grades of severity according with World Health Organization [22]. The lesions of oral mucositis are represented by the oral erythema, ulcers, pain that can interfere with oral alimentation and life-threatening consequences [22]. Long-term corticosteroid therapy may produce the loss of bone density, which may affect alveolar bone and temporomandibular joints, and may be associated with an increased risk of avascular necrosis of bone [23].

The microbiome, composed of trillions of microorganisms, was studied to understand its function and role in health and disease. The oral cavity is colonized by a complex microbiota that grows and lives as diverse biofilms on all mucosal and dental surfaces [24]. Ames et al studied oral microbiome in patients with severe aplastic anemia during their therapeutic course. They found that there are differences between oral microbiome of AA patients with immunosuppressive therapy, cell stem transplant and health population. [25]

DENTAL MANAGEMENT IN PATIENTS WITH APLASTIC ANEMIA

Oral pathology is a major public health problem [26]. The oral cavity is a protentional site of complications in stem cell transplantation because it is the entrance for agents that can produce systemic infections. Patient undergoing immunosuppressive therapy are susceptible to develop opportunistic infections, mucositis, gingivitis, and ulcerations of the oral mucosa [23]. It has been shown that dental treatment prior to stem cell transplantation may prevent the additional death and reduce systemic infections by 20-25% [27]. The goal of dental treatment prior to stem cell transplant is to identify potential sources of infection and trauma, and to reduce the morbidity derived from oral complications [23]. Periapical lesions should be treated because they are a risk factor for acquisition of streptococcal viridians bacteremia after transplantation [28]. Assessment of periodontal and oral hygiene status should be performed in patients undergoing to the cell stem transplant [23]. For invasive procedures such as extraction and periodontal treatment that can cause bleeding and spread of bacteria in the blood, antibiotherapy must be performed [23]. To reduce the risk of uncontrolled bleeding during major dental treatments, the patients should be taking antifibrinolytics. There is
considerable debate and the interdisciplinary management is very important [29]. In cases with severe thrombocytopenia is important to receive platelets transfusion before de dental treatment. Agnihotri et al report the importance of nonsurgical therapy followed by electrosurgery for the management of residual gingival enlargement [30]. Combination of modalities such as platelet transfusion, oral hygiene instruction, and dental prophylaxis should be implemented for patients with aplastic anemia.

CONCLUSIONS

Aplastic anemia is a non-oncologic severe disease that can be a challenge for dentists and hematologists. It affects the anatomical structures of the oral cavity being implicate thrombocytopenia, anemia, and severe neutropenia. But at the same time the treatment for aplastic anemia adds another manifestation on the structures of the oral cavity like gingival enlargement, mucositis, osteoporosis. The oral microbiome must be study more to understand better the link between it and symptoms of aplastic anemia. For patients with aplastic anemia the dental management and oral hygiene are essential for therapeutic response and require an interdisciplinary approach.

REFERENCES