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DIAGNOSIS AND MANAGEMENT OF HYPERPLASTIC GINGIVITIS IN ACUTE LEUKEMIAS

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Objectives: The purposes of the study were to evaluate the diagnostic features and management of hyperplastic gingivitis (HG) in the acute leukemias (AL).

Methods: The study may be considered as analytical and descriptive. The following research modalities were used: epidemiological, analytical, data transfer, descriptive statistics. The AL patients have been followed up and treated at the Institute of Oncology between 2012-2020. The diagnosis was proved by the bone marrow aspiration (BMA) with cytochemical reactions, tissue biopsy or fine needle aspiration cytology. The immunotyping was performed in the selected cases. The type of myeloproliferative disorder was identified according to the Revised WHO classification of the myeloid neoplasms, approved in 2018. The review of the literature is based on a study of 17 references.

Results: Gingival tissues are considered more susceptible to leukemic cell infiltration because of their microanatomy and expression of endothelial adhesion molecules which boost infiltration by leukocytes. The HG may be observed in the non-lymphoblastic AL with a frequency of 3% to 5% of patients receiving anti-leukemia chemotherapy at the referral centers [Fatahzadeh M., Krakow A. M., *Spec. Care Dentist*, 2008]. We report a study of 5 cases with HG due to the myelo-monoblastic (M4) and monoblastic (M5) AL. The leukemia patients were admitted to the Institute of Oncology with a history of fatigue, anorexia, headache, gingival bleeding and enlargement initially identified by a family doctor from the consulting centers of the municipal hospitals. Clinical examination showed marked anemic syndrome, mild to moderate splenomegaly and slight hepatomegaly. ECOG-WHO performance status score was 2-3. The intra-oral examination revealed the generalized gingival hyperplasia. There was a fair amount of plaque and calculus, but did not justify the degree of enlargement. On palpation, the gingiva was spongy and painless, with solitary sectors of necrosis. Blood count: Hb 66-101 g/l, er. 2.3-3,7 x 10^{12}/l, leuk. 12,1-35.2 x 10^{9}/l, plt. 54.0-115.0 x 10^{9}/l, ESR 23-50 mm/h, blast cells 17-42%. The BMA detected hypercellularity, red cell line hypoplasia, the elevated rates of myeloid blast cells (31.0-48.0%) and monocytes (9.0-12.0%). HG regressed only in 3 of 5 patients after obtaining the complete hematologic response under the combined chemotherapy.

Conclusions: In AL the gingival hyperplasia is secondary to infiltration of the gingival tissue with blast cells, but may be mixed up with the benign conditions during the intra-oral examination. The HG may regress completely or at least partially under an efficient chemotherapy.

Keywords: hyperplastic gingivitis, acute leukemias, diagnosis, combined chemotherapy.

Background:

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Periodontal pathologies include a variety of conditions commonly affecting the health of the periodontium and may be considered as an actual issue of Public Health and Dentistry. Although the classification scheme defined at the 1989 World Workshop in Clinical Periodontics divided these pathologic conditions into a number of clinically defined subentities [1,14], the subsequent attempts to categorize patients according to the defined criteria have indicated the considerable overlap problem in the disease definitions [2]. In spite of the essential progress in defining both etiologic agents and pathways of pathogenesis in various forms of gingivitis, the lack of information exists to definitively recategorize these diseases. Acute leukemias (AL) are the hematologic malignancies resulting from a clonal proliferation and accumulation of the blast cells. AL affect persons of all ages and develop more frequently in males. The morbidity by AL correlates with the age. The incidence ranges worldwide between 1.6-3.6 cases per 100 000 population. The leukemic cell population may invade extramedullary tissues and its presence as leukemic infiltrates has been reported in the spleen, kidneys, lungs, bowels, breasts, testes, eyes, meninges, lymph nodes, liver, prostate, skin, and oral cavity [6]. Gingival hyperplasia is secondary to the infiltration of the gingival tissue with leukemia cells and is well described in the literature [4, 15, 16, 17]. Gingival enlargement is reported to be the most consistent symptom leading to a diagnosis of AL and directs the patient to seek early dental consultation [9, 15, 17].

Objectives:

The aims of the study were to evaluate the diagnostic features and management of hyperplastic gingivitis (HG) in AL.

Matherials and methods:

The analytical, descriptive and prospective study was performed. The following research modalities have been used: epidemiological, analytic, data transfer, descriptive statistics [13]. The AL patients have been followed up and treated at the Institute of Oncology between 2012-2020. The diagnosis was proved by the bone marrow aspiration with cytochemical reactions, tissue biopsy or fine needle aspiration cytology. The immunotyping was performed in selected cases. The type of myeloproliferative disorder was identified according to the Revised WHO classification of the Tumours of Haematopoietic and Lymphoid Tissues, approved in 2017 [12]. The review of the literature is based on a study of 17 references.

Results and discussion:

There are different types of periodontal diseases, one of which is “gingival overgrowth” or “gingival enlargement”. Gingival enlargement may be caused by a wide variety of etiologies and is classified according to the corresponding etiologic factors [10, 11]: 1. Inflammatory enlargement; 2. Drug-induced enlargement; 3. Enlargement associated with systemic diseases or conditions; 4. Neoplastic enlargement.

Gingival tissues are considered more susceptible to leukemic cell infiltration because of their microanatomy and expression of endothelial adhesion molecules which enhance infiltration of leukocytes [9]. In the most extensive review of the neoplastic enlargement, gingival hyperplasia was observed in myeloid AL with a frequency of 3% to 5% among 1,076 patients receiving anti-leukemia chemotherapy at a referral centre [5]. Gingival hyperplasia is commonly seen in myeloid AL subtypes, such as monoblastic AL (66.7%), myelo-monoblastic AL (18.5%), and myeloblastic

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AL (3.7%) [4]. Gingival hyperplasia is characterized by progressive enlargement of the interdental papillae as well as the marginal and attached gingiva. In the condition's severe forms, the crowns of the teeth may be covered. Gingiva appears swollen, devoid of stippling and pale red to deep purple in colour. Mucosal hemorrhages, ulcerative gingivitis, infectious gingivitis and odontalgia may be observed [3, 16]. Pallor, spontaneous hemorrhage, petechiae and ulceration have been described to occur more commonly in acute than chronic leukemia. Histologic characteristics are similar for each subtype of leukemia aside from the morphologic form of the invading cells. These cells are characterized by abundant mitotic figures. Typically, the lamina propria is densely packed with leukemia cells extending from the basal cell layer of the epithelium into the gingiva, thereby altering the normal anatomy. Regional blood vessels are compressed by the infiltrate.

The development of gingival infiltration is unpredictable in anyone patient. Gender has not been described as a risk factor for developing this manifestation. Leukemia cell gingival infiltrate is not observed in edentulous individuals, suggesting that local irritation and trauma associated with the presence of teeth may play a role in the pathogenesis of this abnormality. Dental caries and poor oral hygiene have not been described as risk factors for gingival hyperplasia. Additionally, an increased rate of dental caries as a complication of this abnormality has not been reported. However, poor oral hygiene and cavities predispose to super-infection, necrosis, pain and bleeding. The presence of caries in some patients may be likely incidental. In general, surgery should be avoided in leukemia-afflicted patients with gingival hyperplasia. Generally, gingival hyperplasia resolves completely or at least partly with effective leukemia chemotherapy. Of note, patients initially presenting with acute promyelocytic leukemia without gingival hyperplasia can develop this abnormality after all-trans-retinoic acid therapy. This manifestation is not considered to be predictive of poor outcome. New cutaneous lesions, oral or otherwise, are often the initial physical finding that leads to a diagnosis of leukemia [8].

In this manuscript, we report a study of 5 cases with HG due to myelo-monoblastic (M4) and monoblastic (M5) AL. The leukemia patients were admitted to the Institute of Oncology with a history of fatigue, anorexia, headache, gingival bleeding and enlargement initially identified by a family doctor from the consulting centers of the municipal hospitals. Clinical examination showed marked anemic syndrome, mild to moderate splenomegaly and slight hepatomegaly. The cardiovascular, respiratory and nephrourinary systems proved to be intact. ECOG-WHO performance status score was 2-3. The intra-oral examination and the subsequent evaluation of the medical and dental history were performed. The intra-oral examination revealed the generalized gingival hyperplasia. There were the fair amounts of plaque and calculus, but did not justify the degree of enlargement. On palpation, the gingiva was spongy and painless, with solitary sectors of necrosis. The tongue, palate, and temporo-mandibular joints were normal on examination. The following differential diagnoses were considered: inflammatory enlargement, drug-induced enlargement, conditioned enlargement, systemic enlargement, and neoplastic enlargement. Blood count: Hb 66-101 g/l, er. 2.3-3,7 x 10^{12}/l, leuk. 12,1-35.2 x 10^{9}/l, plt. 54.0-115.0 x 10^{9}/l, ESR 23-50 mm/h, blast cells 17-42%. Taken into consideration our concern about possible AL, which were suggested by the complete and differential blood counts, the bone marrow aspiration with cytochemical reactions and the gingival imprints were done. The bone marrow aspiration detected hypercellularity, red cell line hypoplasia, the elevated rates of myeloid blast cells (31.0-48.0%) and monocytes (9.0-12.0%). Both the bone marrow and the gingival morphology, thus, demonstrated

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leukemia cell infiltration, confirming the diagnosis of AL. The combined induction therapy with cytarabine and doxorubicin were performed. HG regressed only in 3 of 5 patients after obtaining the complete hematologic response under the combined chemotherapy. Oral hygiene instruction was given to the patient and 0.2% chlorhexidine was administered.

Conclusions :

- In AL the gingival hyperplasia is secondary to infiltration of the gingival tissue with blast cells, but may be mixed up with the benign conditions during the intra-oral examination.
- The gingival enlargement is more common in myelo-monoblastic and monoblastic AL.
- The HG may regress completely or at least partially under the efficient chemotherapy.
- Stomatologists should be aware of the periodontal manifestations and different complications of AL in order to enable the early diagnosis and timely referral to the comprehensive cancer centers or departments for subsequent proper management.

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