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Case Report

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CYCLOSPORINE-INDUCED GINGIVAL HYPERPLASIA IN MYELODYSPLASTIC SYNDROMES

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ABSTRACT

Myelodysplastic syndromes (MDSs) comprise a group clonal hematopoietic stem cell disorders defined by dysregulated hematopoiesis, peripheral cytopenias, and a risk of leukemic progression. Is very difficult to diagnose the patients with MDSs because of the absence of symptoms in the early stage of the disease. Often it is accidentally discovered during a routine physical exam/blood test. Based on immune mechanisms that appear to play an important role in the pathophysiology of MDS particularly in refractory anemia (RA) and in refractory anemia with excess of blasts (AREB), cyclosporine has been used to treat those patients. Only a few cases of gingival enlargement associated with cyclosporine treatment of MDS are reported in the literature. We present here a remarkable case of gingival enlargement related to the use of cyclosporine used to treat MDS.

KEYWORDS: Myelodysplastic syndromes, cyclosporine, gingival enlargement, immunosuppressive therapy.

INTRODUCTION

Gingival hyperplasia is the overgrowth of gingiva characterized by the expansion and accumulation of connective tissue with the occasional presence of increased number of cells. There is a variety of causes generating a gingival hyperplasia, starting from a false enlargement to neoplastic, inflammatory, drug-induced, and associated with systemic diseases.[1] The clinical manifestation of gingival overgrowth can range in severity from minor variations to complete coverage of the teeth, creating subsequent functional and aesthetic problems for the patient.

Drug-induced gingival overgrowth is a noted disfiguring side effect of calcineurin inhibitors such as cyclosporine (CsA), of calcium channel blocking agents (CCBAs) such as amlodipine and nifedipine[2], and also of anti-convulsant/anti-seizure drugs such as phenytoin.[3]

Epidemiological studies have shown association between autoimmune diseases (AIDs) and MDS with both innate and adaptive immune systems overly active in the hematopoietic niche of MDS, therefore, use of immunosuppressive therapies would be an ideal treatment option for this group of malignant neoplasms. The use of cyclosporine was reported in several studies to be a very effective treatment in the patients with renal transplant where the prevalence of cyclosporine-induced gingival enlargement accounted for 25%-30%[4] but while the treatment efficacity for MDS patients with any marrow cellularity, especially for erythroid lineage and patients with good karyotype has been proved[5], the gingival overgrowth secondary to the treatment is rarely reported in the literature.

We present here the case of a generalized gingival overgrowth associated with the use of cyclosporine in MDSs, which is not a common encountered entity.

CASE REPORT

The patient, female, 56 years old, was hospitalized in our Service of Hematology in March 2015 complaining fatigue, respiratory difficulty during physical efforts and fever. On the physical examination she was pale and with ecchymosis in the arms and lower legs. No lesions in the mouth and throat, but she presented stained teeth and signs of bruxism, but no gingival problems. She presented severe anemia (Hgb 6,8 g/ dl, hct 19%), severe neutropenia (ANC 400/mm^3) and rare platelets on the peripheral blood smear. She underwent bone marrow aspiration resulting in trilineage dysplasia and 4% of blasts. Karyotype resulted 46, XX. The patient was so diagnosed with Refractory Cytopenia with Multilineage Dysplasia (RCMD), IPSS score 0.5, Intermediate -1 risk group. The patient has no other co-diseases so we decided to treat her with Cyclosporine 5mg/kg/ day.

To her was recommended to control the FBC and liver function tests and also renal function tests every other week and to do the consultations with the hematologist every 3 weeks.

She presented again in the consultation with the hematologist as recommended and the FBC was improving with the augmentation of the levels in FBC. After seven months of treatment with Cyclosporine she had Hgb levels of 8,3 g/dl, ANC 1100/mm^3 and platelets 40,000/mm^3. It was recommended to her to continue the treatment with cyclosporine.

One week after the consultation the patient came back in our Service complaining pain in the mouth and in the gingival mucosae.

On intraoral examination, there was generalized diffuse gingival enlargement, which was bulbous and lobulated near first and second upper right and left molars. There was generalized tendency of bleeding on probing. Hers oral hygiene was poor with generalized extrinsic stains and calculus.

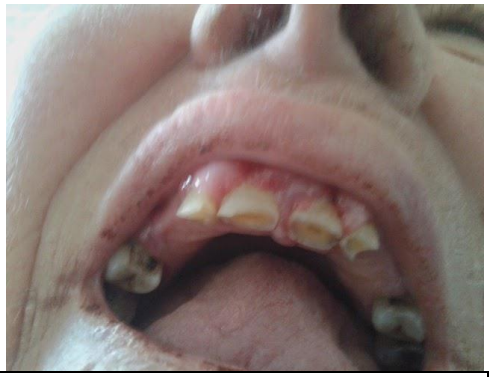

Figure 1. Generalised gingival enlargement.

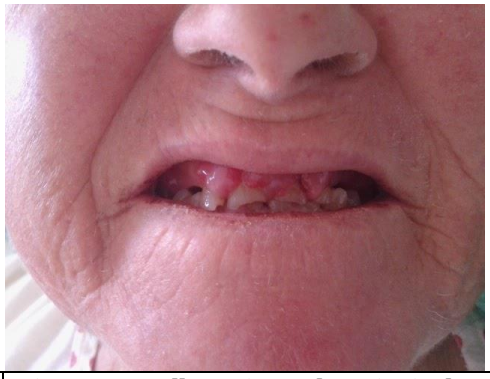

Figure 2. Bulbous irregular gingival enlargement in upper teeth region.

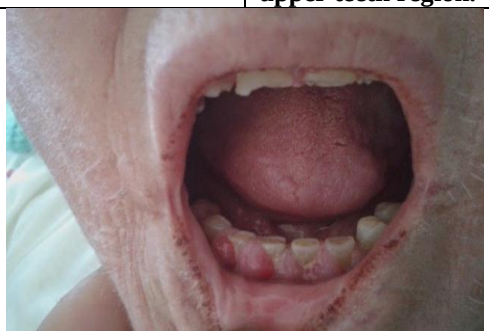

Figure 3: Bulbous and irregular gingival enlargement in lower teeth region.

The patient appeared very stressed, crying and complaining that all began with the use of cyclosporine. When we recommended a consultation with a dentist was uncooperative and irritated. In front of the possibility of transformation of RCMD in acute myeloblastic leukemia (AML) the patient underwent again the bonne marrow aspiration resulting with no specific changes for AML (Blasts 5%, trilineage dysplasia). We sent the patient to the maxillo-facial surgeon to judge the probability of gingival biopsy and he recommended to avoid cyclosporine The patient had PLT 40,000/mm^3 so the gingival biopsy has been postponed in order to avoid facing a high risk of bleeding in this case.

The patient interrupted the cyclosporine treatment and oral hygiene instruction was given to her, and also 0.2% chlorhexidine mouthwash combined with azithromycin was prescribed.

The patient came again in the consultation after 10 days of treatment and a gingival retraction was noted. The patient said that she has no further gingival bleedings and also no more pain in the oral cavity.

According to the medical diagnosis and the evolution of gingival findings even with the lack of gingival biopsy we made a provisional diagnosis of gingival overgrowth caused by the use of cyclosporine.

DISCUSSION

Myelodysplastic syndromes (MDS) comprise a group of bone marrow diseases characterized by profound heterogeneity in morphologic presentation, clinical course, and cytogenetic features. The diagnosis is made with three key elements: 1. The dysplasia ≧ 10% in one or three cell lines in the bone marrow; 2. The peripheral blood cytopenia; 3. The abnormalities in the karyotype. Epidemiologically, autoimmune diseases are common in patients with MDS, fueling hypotheses of common etiological mechanisms. Although supportive care, growth factors, and hypomethylating agents are the mainstay of MDS treatment, some patients demonstrate impressive response rates after immunosuppressive therapy. According to this cyclosporine is used to treat MDS patients.

While cyclosporine has been the drug of preference since the beginning of the transplant era, a number of longitudinal and crossover studies have reported an incidence of gingival problems associated with this drug in the range of 25% to 70%.[6] On the other side the incidence of oral complication in MDS ranges between 15% and 85%,[7] but usually from the infiltration by the leukemic cells. The cyclosporine-induced overgrowth is not so common, in fact is a rare complication that should be distinguished from the leukemic infiltration.

According to the 1999 reclassification of periodontal diseases, drug-induced gingival overgrowth is a dental plaque-induced gingival disease.[8]

A clear understanding of the etiology and pathogenesis of drug-induced gingival overgrowth has not been established.[9] There are three different classes of drugs that produce gingival overgrowth but they might share some common metabolic pathway, or they could produce a similarly appearing clinical condition from totally different mechanisms. There are different theories focusing on the direct effects of the drug or its metabolites on specific gingival cells of the periodontium, particularly on gingival fibroblasts, for example, Spoildorio et al. reported that as the severity of overgrowth increases, there are parallel increases in collagen and fibroblasts and a decrease in blood vessel content, possibly explaining the light pink appearance of the enlarged gingival tissue.[10]

Researchers have not yet determined how to prevent or eliminate drug-induced gingival overgrowth. The ideal approach would be the substitution of the causative drug that will result in a reversible gingival effect to the normality.

Some therapies may be effective in the immediate and short-term management of drug-induced gingival overgrowth. Non-surgical (i.e. periodontal debridement, local/systemic antimicrobial delivery) and surgical treatment options may be used individually or in combination to control this problem.

In front of all this the oral hygiene takes the first place.

CONCLUSION

The purpose of this case is to emphasize that the gingival-enlargement in MDS patients, induced by cyclosporine, can be possible during the course of the treatment of this disease. Dentists have the responsibility to provide the best possible care to all patients. They should be able to accurately diagnose and plan the appropriate therapy for the patients. The probability of dentists encountering patients with drug-induced gingival overgrowth exists, and for this reason, they should be prepared to offer maintenance and preventive therapies formulated specifically for the needs of these patients.

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