GINGIVAL ULCERATIONS IN A PATIENT WITH ACUTE MYELOID LEUKEMIA: A CASE REPORT AND LITERATURE REVIEW

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SUMMARY – A 40-year-old female patient was admitted to the Department of Oral Medicine due to oral ulcerations. Oral ulcerations were present on vestibular mucosa above teeth 21, 22, 25 and 26 and were 1 cm in diameter, and also around teeth 45 and 46. The patient had prolonged neutropenia due to therapy-related myelodysplastic syndrome that progressed to therapy-related acute myeloid leukemia. Initially, the patient was successfully treated with polychemotherapy for non-Hodgkin lymphoma. Unfortunately, many toxic complications ensued, such as peripheral neuropathy, dilated cardiomyopathy and therapy-related myelodysplastic syndrome/therapy-related acute myeloid leukemia. The onset of therapy-related myelodysplastic syndrome was less than six months after initiation of chemotherapy treatment, which was rather early, but cytogenetic changes (monosomy 5 and 7) were consistent with the diagnosis. Upon admission to our Department, microbiological swabs were obtained and were all negative, while x-ray finding showed that ulcerations did not have dental cause. Biopsy was not obtained as the patient had severe neutropenia and thrombocytopenia. While viral and fungal swabs were negative, Stenotrophomonas maltophilia was cultured from the oral cavity. Thus, differential diagnoses are listed in this report. Neutropenic ulcerations did not heal albeit extensive medicamentous oral and systemic treatments were applied and the patient died.

Key words: Leukemia, myeloid, acute; Gingivitis, necrotizing, ulcerative; Case reports

Introduction

Oral neutropenic ulcerations have been so far described in patients suffering from neutropenia, multiple myeloma, and acute as well as T-large cell leukemia1-4. Barrett and Buckley2 report that neutropenic ulceration and herpes simplex infection were the major causes of morbidity in three patients following administration of high-dose melphalan for the treatment of multiple myeloma. In 2000, Copete and Sheridan3 concluded that it was still unclear whether ulcerations in the oral cavity of patients undergoing leukemia treatment were caused by infective etiology or they were manifestations of neutropenia. The same was concluded by Arvanitidou et al.4 in 2011. It seems that the degree of susceptibility to infection is roughly proportional to the blood neutrophil count.

However, it seems that oral ulcerations in leukemic patients might be a result of the following: 1) oral ulcerations might be induced by neutropenia in leukemic patients; 2) oral ulcerations may be a side effect of cytotoxic chemotherapy or develop as a consequence of direct toxicity of the medication itself.
known that chemotherapy agents such as methotrexate might induce oral ulcerations and that these might be dose dependent. It is well recognized that patients may benefit from temporary discontinuation of methotrexate; and 3) infectious etiology of oral ulcerations.

In the literature published so far, there have been few case reports on bacterial species such as oral *Fusarium moniliforme*, *Capnocytophaga ochracea* and *spitigend*, *Leptotrichia trevisanii*, and *Streptococcus mitis* infection which manifested as necrotic gingival ulceration in granulocytopenic patients. Furthermore, there also are case reports on viral infection such as herpes simplex virus, Epstein-Barr virus, cytomegalovirus in the oral cavity in patients undergoing chemotherapy for hematologic malignancies. The last but not the least, fungal infections such as candidiasis, aspergillosis, mucormycosis and histoplasmosis might be encountered in these patients.

Barrett et al. report that oral complications were detected in 89% of hospital admissions for treatment of acute leukemia in adults. Changes that reflected the underlying myelosuppression and general immunosuppression predominated. Hemorrhagic phenomena (77%), neutropenic ulceration (49%), and herpes simplex virus infections (39%) were the most common ones. Beattie et al. report that mouth ulcers are a frequent cause of morbidity in patients rendered neutropenic as a result of chemotherapy. The same authors report that herpes simplex virus (type I) was isolated in 13 patients and *Candida albicans* cultured in 17 patients. Both organisms were isolated in 9 patients. Their results suggest that both viral and fungal elements may be important in the etiology of oral ulceration and that antiviral and antifungal agents may each have a role in the prophylaxis and treatment of such patients.

**Case Report**

A 40-year-old female patient was referred to the Department of Oral Medicine due to painful oral lesions. Clinical examination revealed oral ulceration on the vestibular mucosa above teeth 21, 22, 25 and 26, which were 1 cm in diameter. There was also oral ulceration 3 mm in diameter behind tooth 46 in the retromolar area and on the tongue. Tooth 46 was implant supported crown. All ulcerations were covered with thick pseudomembranes and minimal surrounding inflammation. According to the orthopantomogram and vitality tests of the teeth, we concluded that ulcerations were of non-odontogenic origin. No plaque deposits on the teeth could be noticed.

Ten months before her referral to the specialist in oral medicine, the patient was diagnosed with diffuse large B-cell lymphoma, stage IVA. She received five cycles of chemotherapy according to the R-CHOEP protocol (rituximab, cyclophosphamide, doxorubicin, vincristine, methylprednisolone and etoposide), followed by three cycles of R-CHEVP (rituximab, cyclophosphamide, doxorubicin, etoposide, vinblastin and methylprednisolone) due to toxic neuropathy. Complete remission of lymphoma was achieved, but the clinical course was further complicated by the development of dilated cardiomyopathy two months after completion of hematologic treatment. In addition, prolonged thrombocytopenia was observed during the last two cycles of R-CHEVP and five months after
In our patient, oral fungal and viral swabs were all negative upon admission, therefore we concluded that ulcerations were exclusively due to neutropenia. Biopsy specimen was not obtained as the patient was severely thrombocytopenic and received blood transfusion almost every other day.

Several days before the patient died, oral microbial tests had shown the presence of *Stenotrophomonas maltophilia* and *Enterobacterium foecalis*. *Stenotrophomonas maltophilia* is an anaerobic gram-negative bacillus found in aquatic environments. It is an opportunistic microorganism of low virulence. *Stenotrophomonas maltophilia* causes infection in immunosuppressed hosts, especially those with neutropenia, on chemotherapy and broad-spectrum antibiotics. To our knowledge, there are only two case reports on exclusive *Stenotrophomonas maltophilia* infection in the oral cavity. Miyairi et al. described an immunocompromised patient with acute ulcerative necrotic gingivitis and bacteremia due to *Stenotrophomonas maltophilia*. Soga et al. described a patient with appearance of multidrug-resistant *Stenotrophomonas maltophilia* on the gingiva during leukemia treatment.

Based on our case, it seems that detection of *Stenotrophomonas maltophilia* and *Enterobacterium foecalis* was a concomitant finding in the oral cavity as neutropenic ulcers had been present for three months before these bacteria were found. However, we do agree with Teo et al. that the finding of mucocutaneous infections in neutropenic patients with malignancies seem to be a poor prognostic sign.

Differential diagnoses of ulcerations in neutropenic patients might be acute necrotizing ulcerative gingivitis, leukemic infiltrates, ulcers induced as a direct consequence of chemotherapy, bacterial, viral or fungal infection.

In patients undergoing leukemia treatment, gingiva acts as a site of proliferation and reservoir of multidrug-resistant opportunistic bacteria. To prevent abnormal increases in such bacteria on the gingiva, scaling and/or root planing together with local antiseptic and local/systemic antibiotic may contribute to infection control in such patients. This is sometimes impossible as patients may have severe neutropenia or thrombocytopenia, as seen in our case, as well as in cases reported by Arvanitidou et al.

In most cases, neutropenic ulcerations will clear up as the neutrophil count returns to normal values. However, it was not the case in our patient as the patient died.

Discussion

In our patient, oral fungal and viral swabs were all negative upon admission, therefore we concluded that
Conclusion

Prolonged neutropenia, as in this case of a patient with therapy-related myelodysplastic syndrome/therapy-related acute myeloid leukemia, was the underlying cause of oral ulcers rather than chemotherapy. In our patient, the presence of *Stenotrophomonas maltophilia* was considered as colonization. The last but not the least, all oral therapeutic procedures failed to improve oral ulcerations in our patient.

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Sažetak

ULCERACIJE GINGIVE U BOLESNICE S AKUTNOM MIJELOIDNOM LEUKEMIJOM: PRIKAZ SLUČAJA I PREGLED LITERATURE

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Bolesnica u dobi od 40 godina primljena je na Zavod za oralnu medicinu zbog oralnih ulceracija. Oralne ulceracije pro-
mjera 1 cm bile su prisutne na vestibularnoj sluznici iznad zuba 21, 22, 25 i 26, a također i oko zuba 45 i 46. Bolesnica je
imala produljenu neutropeniju uslijed mijelodisplastičnog sindroma povezanog s terapijom, koji je progredirao u akutnu
mijeloidnu leukemiju povezanu s terapijom. U početku je bolesnica uspješno liječena polikemoterapijom za non-Hodgkinov
limfom. Nažalost, uslijedile su mnoge toksične komplikacije poput periferne neuropatije, proširene kardiomiopatije i mijelo-
displastičnog sindroma povezanog s terapijom/akutne mijeloidne leukemije povezane s terapijom. Terapijski mijelodispla-
stični sindrom pojavio se u manje od šest mjeseci nakon započinjanja liječenja kemoterapijom, što je bilo prilično rano, ali su
citogenetske promjene (monosomija 5 i 7) bile u skladu s dijagnozom. Nakon dolaska na naš Zavod učinjeni su mikrobiološ-
ki brisevi i svi su bili negativni, a rendgenski nalaz je isključio odontogenu etiologiju ulceracija. Biopsija nije učinjena, jer je
bolesnica imala tešku neutropeniju i trombocitopeniju. Iako su virusni i gljivici brisevi bili negativni, Stenotrophomonas
maltophilia izolirana je iz usne šupljine. Stoga su u ovom prikazu navedene različite dijagnoze. Unatoč ekstenzivnim oralnim
i sistemskim tretmanima neutropenične ulceracije nisu zacijelile, a bolesnica je preminula.

Ključne riječi: Leukemija, mijeloidna, akutna; Gingivitis, ulcerativni; Prikazi slučaja