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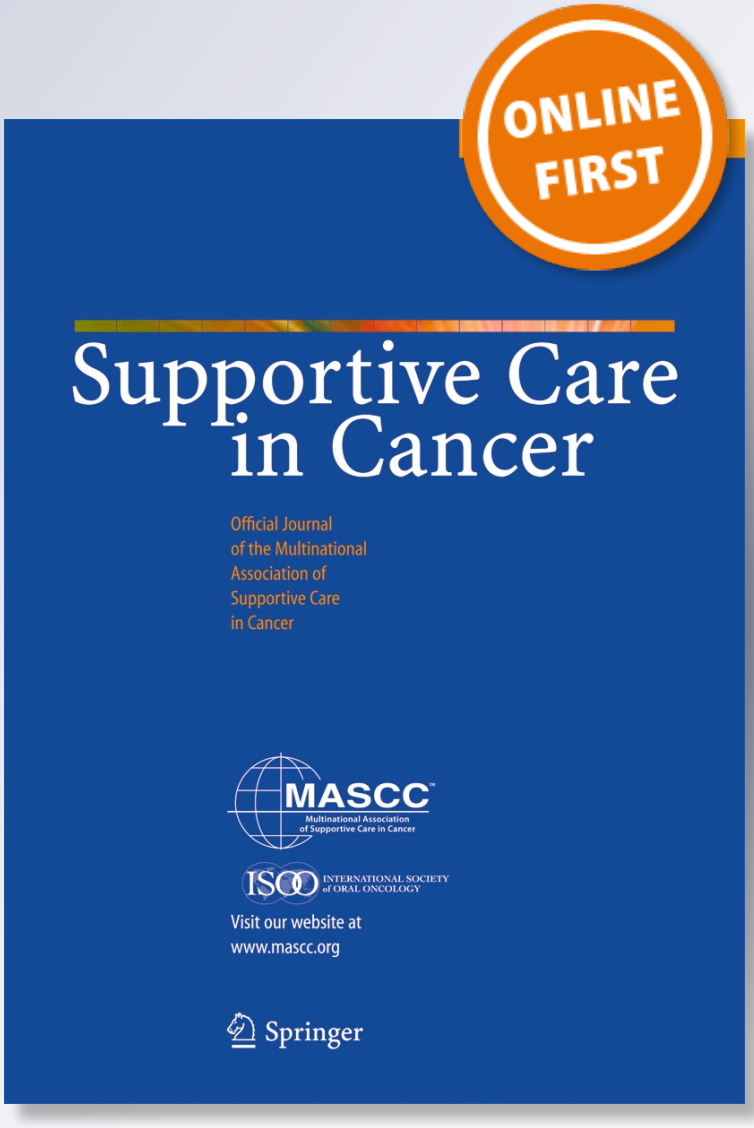

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ORIGINAL ARTICLE

Early diagnosis and successful management of oral mucormycosis in a hematopoietic stem cell transplant recipient: case report and literature review

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Abstract
Purpose Oral mucormycosis is a rare and high risk of infection in patients following hematopoietic cell transplantation few cases in the literature. We review the literature and present an additional case to emphasize the subtle changes that resulted in positive outcome when diagnosed and managed in a comprehensive transplant team.
Results A patient was diagnosed with gingival mucormycosis on day +25 following a hematopoietic stem cell transplant for lymphoblastic transformation of chronic myeloid leukemia. The patient was diagnosed with minor and nonspecific symptoms and was successfully treated with local dental extraction, a short course of liposomal amphotericin B and 4 months of oral posaconazole.
Conclusions The good outcome of this case highlights the subtle clinical changes that present early in mucormycosis and the importance of early detection and treatment of post-transplant oral infections by an experienced multidisciplinary team.

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Keywords Oral mucormycosis · Hematopoietic stem cell transplant

Introduction

Mucormycosis is a deep fungal infection due to fungi of the *Mucorales* species. These fungi are commonly nonpathogenic in the healthy person, but may become opportunistic pathogens in medically complex patients, and in this setting, infection is associated with high rates of morbidity and potential mortality [1]. The organisms may be recovered from the head and neck, nose, sinus, throat, and oral cavity, while most common forms of infection are pulmonary and sinus. Conditions that predispose to infection include diabetes, hematologic malignancies, solid organ, and hematologic stem cell transplantation (SCT) [2]. The infection may present as a local necrotic ulceration that can result in hematogenous spread leading to fulminant infection and death. The most common sites of mucormycosis are pulmonary, sinus, nasal, skin, and disseminated infections.

Mucormycosis is the third most common fungal disease in SCT and may have a rapidly progressive course with high mortality [3]. In a follow-up of 1500 SCT patients, mucormycosis was diagnosed in 0.9 % with mortality in 77 % of these cases [4]. The most common oral sign of mucormycosis is ulceration of the palate. The differential diagnosis may include odontogenic or periodontal infection and maxillary sinusitis [1]. Organisms may be identified on biopsy using periodic acid Schiff stain or methanamine silver stain.

We present a case of gingival mucormycosis diagnosed early following SCT and with good outcome. This case report was provided expedited review by the institutional IRB (Pro00041918).

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Case report

A 40-year-old male with chronic myeloid leukemia (CML), transformed to acute lymphoblastic leukemia (ALL), received a matched related donor allogeneic SCT in the second complete remission. The donor was his HLA-matched brother. He was conditioned with reduced intensity fludarabine/melphalan.

On day +10, he developed a fever, following which blood cultures recovered *Escherichia coli*. Cefipime was prescreibed and he became afebrile. There were no oral symptoms or clinical findings on day +10. Dental/mandibular discomfort of the lower left molar/bicuspid area developed on day +12. At that time, the patient reported constant aching pain that corresponded to an area of diffuse swelling of the left mandible in the tissue on the buccal of the lower left first molar (tooth no. 19) and the lower left second bicuspid (tooth no. 20). The area was tender on palpation. On day +13, metronidazole was added for improved oral coverage given the jaw discomfort and clinical findings and chlorhexidine rinse was prescribed. Examination revealed mild facial asymmetry due to minor diffuse swelling in the left lower jaw opposite to the molar area on the left, with mild local tenderness on palpation in the lower left buccal tissue extending to the vestibule. An adjacent tender left submandibular lymph node was noted. The adjacent teeth were not restored, and no clinical caries were seen. There was no TMJ or masticatory muscle tenderness. The gingival margin buccal of tooth no. 19 had a 2-mm collar of mucosal ulceration on the mesiobuccal aspect of the molar (Fig. 1). Due to discomfort, he was prescribed dilaudid and topical anesthetic applied to the area, with pain reduction. On the following day, examination revealed extension of the ulceration of the gingival margin to the mesiobuccal to the mesiolingual of the first molar. Tooth no. 19 and tooth no. 20 were mildly sensitive to percussion; however, the greatest tenderness was reported on palpation of the ulcerated gingival margin on the mesiobuccal of tooth no. 19. The gingival margin ulceration extended to the lingual of tooth no. 19 (Fig. 2). There was no mucositis seen, and no other sites of ulceration were noted. Oral hygiene was good.

Dental radiographs were completed, and no caries, restorations, periodontal bone loss, or periapical pathosis was seen in the left mandible. Minor interdental calculus was seen on the distal aspect of tooth no. 19. CT of mandible without contrast suggested mild ethmoid mucosal thickening, and the remaining sinuses were clear. No evidence of pathosis in the head/neck or jaw was noted.

The condition was clinically related to the gingival/perodontal findings. Due to recovery of counts and continuing symptoms and specifically the necrotic/gingival ulceration at a single site, dental extraction with biopsy of the marginal ulceration was suggested. The clinical differential diagnosis included herpes family viral infection, local trauma, and fungal infection.

He was provided platelet support, antibiotic cover of Augmentin and Flagyl, and chlorhexidine rinse. The procedure was completed on day +25 post-SCT with atraumatic extraction of no. 19 and no. 20 and gingival biopsy completed. The extraction sites were packed with Surgicel and 3–0 gut sutures placed. Hemorrhage was controlled with local pressure.

He was discharged on day +28 with no oral complications following dental extractions and biopsy and based upon his general and hematologic recovery. The day following discharge, pathology reported mucormycosis and he was then readmitted and begun on Ambisome 5 mg/kg IVPB daily. He had low-level discomfort in his left mandible, but was afebrile. He was evaluated by the oncology team including specialists in dental, ear, nose, and throat and infectious disease. The surgical wound appeared clean, and due to excellent wound healing, no additional surgical intervention was provided. No cervical lymphadenopathy was noted. Antibiotics for dental coverage were discontinued. He continued chlorhexidine rinses. He was discharged home with transition to oral

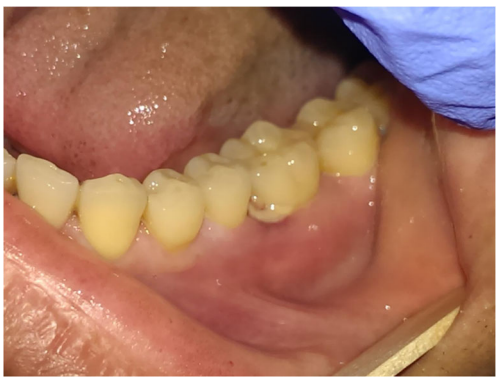

Fig. 1 Gingival ulceration. Localized ulceration limited to the interdental papilla, with minimal diffuse erythema extending into the buccal gingiva of the lower left first molar. Good oral hygiene without clinical gingivitis or plaque accumulations

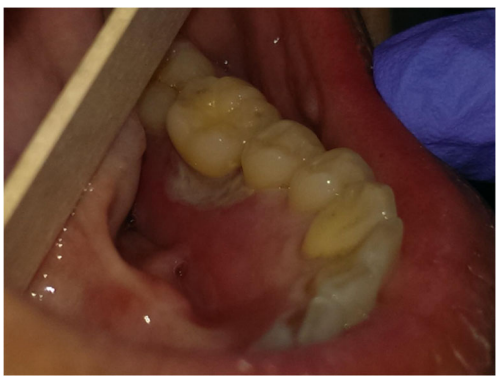

Fig. 2 Gingival ulceration. Gingival ulceration extending along the lingual margin of the first molar extending from the interdental papilla

posaconazole while continuing Ambisome IV until posaconazole level was adequate with daily visits to infusion center.

Post-transplant, he required a 3-week course of prednisone for possible acute GVHD of the liver. Unfortunately, his disease relapsed on day +100 and was started on ponatinib and taken off immunosuppression with good response. Posaconazole was discontinued after the development of transaminitis on day +140. The patient was doing well without any oral symptoms and with no evidence of mucormycosis or leukemia 10 months after his SCT.

Discussion

Oral mucormycosis is a rare infection primarily seen in immunocompromised patients and mostly presented in case reports. Intraoral presentation is most commonly reported on the hard palate leading to tissue necrosis. Gingival involvement is rare and potentially presents with ulceration and bone destruction leading to loosening of teeth [5]. In our case, the presence of low-grade discomfort and mild diffuse swelling was seen in a gingival site of intact teeth, later developing a linear ulceration at the gingival margin that extended from the buccal to the lingual of the lower left first molar, while no other oral lesions were present. Thus, mucositis was not suspected and local infection causing the nonspecific lesion was noted. The regional dental condition appeared noncontributory. Clinical experience and clinical suspicion were necessary to lead to dental intervention and to diagnosis on biopsy of the ulcerated gingival margin and early institution of antifungal therapy.

Cases of oral mucormycosis in the literature have been summarized recently [6]. In this report, palatal ulcerations were reported to require a high index of suspicion in order to lead to diagnosis.

A case of periodontal involvement due to mucormycosis and review of six cases in the literature were recently published [3]. The case presented with periodontal ulceration exposing bone on the buccal aspect of an upper molar in a patient following conditioning for SCT for AML. Diagnosis was made by culture, and treatment included local surgical debridement repeated twice with the second surgery involving extraction of adjacent teeth and bone resection and amphotericin B which lead to resolution. Six other cases were identified in the literature, three involving gingival sites and three developing following dental extraction. Treatment in these cases included loco-regional surgery and amphotericin B.

Invasive mycoses may result in significant morbidity and mortality in SCT [2–4]. Despite the high risk of mortality, particularly in cases with bone necrosis, successful management with surgical excision of necrotic tissue, amphotericin B, and posaconazole is reported [5, 7]. Amphotericin B and the second generation triazole posaconazole are the only currently available systemic antifungal with good activity against mucormycosis [8, 9], and prompt initiation of these agents is of paramount importance in the treatment of SCT patients with this infection.

Early detection of infection may be based on subtle signs and awareness of steps to achieve diagnosis. In the case presented here, extraction and tissue biopsy were recommended, leading to early diagnosis and appropriate treatment with good outcome. This was conducted prior to discharge from SCT despite limited clinical findings, but due to the unusual presentation of a single linear ulceration, with discomfort and mild nonspecific swelling at the time of engraftment. Based upon the clinical experience of the multi-disciplinary healthcare team that included dental, oral, and maxillofacial surgery, head and neck surgery, infectious disease, and bone marrow transplantation [9]. Our case presented with subtle signs not identified by routine medical or dental examination, but by an evaluation by an experienced provider that lead to surgical intervention and diagnosis.

Due to early detection, surgery to remove bone was avoided, as the organisms were confined to soft tissue, and surgical management of the teeth and gum margin proved adequate in conjunction with the appropriate systemic antifungal therapy. This case shows the importance of an integrated and experienced team in the management of complex oral condition in medically complex patients. In addition to improving patient outcomes, early detection and successful management are critical in reducing the cost of care, where complications can drive the cost of care but prevention and early stage diagnosis reduce cost of care and improve patient outcomes. The integrated team facilitated detection, diagnosis, and management of a potentially fatal fungal infection, with a good outcome.

Compliance with ethical standard

Conflict of interest The authors declare that they have no conflicts of interest.

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