Mandibular Mucormycosis in Immunocompromised Patients: Report of 2 Cases and Review of the Literature

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Mucormycosis, also known as *zygomycosis*, is an opportunistic fungal infection caused by a series of fungi in the Mucorales family in people with immune disorders. It is harmless to a healthy person, but when it has invaded the internal organs, it is frequently fatal in immunocompromised patients. It is known for having a very poor prognosis; however, with aggressive medical and surgical management, survival rates are currently thought to exceed 80%. It has 7 predominant clinical forms: rhinocerebral, pulmonary, cutaneous, gastrointestinal, central nervous system, disseminated, and, rarely, miscellaneous (ie, bone, kidney, cardiac, mediastinum, oral). Although oral involvement of this condition has been reported relatively frequently in the literature, mandibular involvement is a rarer condition than oral involvement. The purpose of this article is to report the treatment of isolated cases of mandibular mucormycosis and a review of the literature.
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Mucormycosis, also known as *zygomycosis*, is an opportunistic fungal infection caused by a series of fungi in the Mucorales family that affects people with immune disorders.[1] It was first described by Paltauf[2] in 1885. It is harmless to a healthy person, but when it has invaded the internal organs, it is frequently fatal in immunocompromised patients.[3] Immunocompromised patients, especially patients with poorly controlled diabetes mellitus, hematologic malignancy, organ transplants, chemotherapy, chronic renal insufficiency, malnutrition, deferoxamine therapy, and severe burns, are at risk of infection from mucormycosis. Because neutrophils play a crucial role in the protective host response, it follows that the immune impairments associated with hematologic malignancy may increase the risk for this opportunistic fungal infection.[4,5]

Absidia, Rhizopus, Rhizomucor, and Mucor are the most common pathogens of mucormycosis. After acquisition from the environment, these fungi have a tendency to erode and invade small blood vessels, a feature that leads to thrombosis, ischemia, and necrosis of surrounding tissues.[6] The mucormycosis infection occurs primarily in the sinuses, brain, or lungs. It has 7 predominant clinical forms: rhinocerebral, pulmonary, cutaneous, gastrointestinal, central nervous system, disseminated, and, rarely, miscellaneous (ie, bone, kidney, cardiac, mediastinum, oral).[7] The oral involvement of this condition has been reported relatively frequently in the literature. As in cutaneous mucormycosis, injured tissue in the oral cavity can be a suitable port of entry.[1]

Mucormycosis is known for having a very poor prognosis; however, with aggressive medical and surgical management, survival rates are currently thought to exceed 80%.[8] Early detection has been correlated with less tissue destruction and a better overall outcome. Even with successful treatment, Mucorales can become dormant and reappear during future courses of chemotherapy and neutropenia.[9] Although preservation of teeth adjacent to areas with lesions can be an option depending on the severity of

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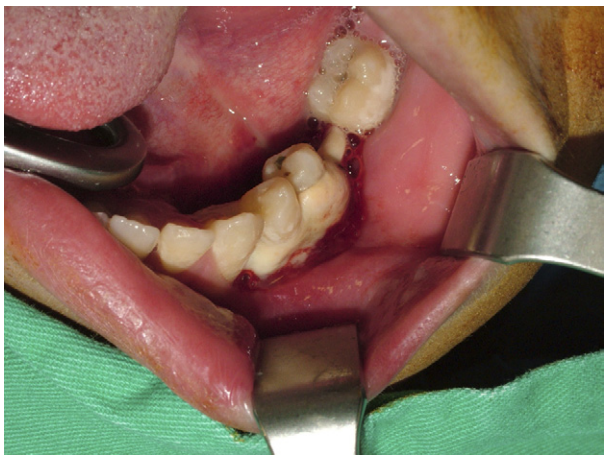

FIGURE 1. Case 1. Appearance of the lesion at the time of biopsy.

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necrosis,[10,11] the teeth affected directly by the mucormycosis should be extracted.

The purpose of this article is to report the treatment of isolated cases of mandibular mucormycosis and a review of the literature.

Report of Cases

CASE 1

A 15-year-old boy was referred to the maxillofacial clinic at Gaziantep University (Gaziantep, Turkey). Admission laboratory values of this patient showed a white blood cell count of 35.4×10^3 μL, an absolute neutrophil count of 8.67×10^3 μL, a hemoglobin level of 8.73 g/dL, a hematocrit level of 24.7%, and a platelet count of 33.3×10^3 μL. This patient originally visited a local dental clinic for a tooth extraction. After the extraction had been performed, the mucosa had not healed completely, and nausea, vomiting, exhaustion, and swelling on the neck and face had occurred during the postextraction period. At this time, the patient was diagnosed with acute myelogenous leukemia (AML). The patient was examined clinically and radiologically at the dispensary at Gaziantep University. The left mandibular premolar and molar region was encompassed by white necrotic-appearing tissue (Figs 1, 2). Swelling was noted in the adjacent buccal vestibule. Antifungal therapy was begun immediately with 80 mg/d amphotericin B. His creatinine levels had been fluctuating from 1.85 to 0.6 mg/dL during treatment, so his input and output levels were monitored much more closely. Because his output levels were decreasing, dopamine and dobutamine were started. Meropenem and vancomycin were also administered. The patient had received only 1 cycle of chemotherapy, 6 weeks before presentation at the clinic. Laboratory values before the first chemotherapy protocol showed a white blood cell count of 247×10^3 μL, an absolute neutrophil count of 57.4×10^3 μL, a hemoglobin level of 9.77 g/dL, a hematocrit level of 26.2%, and a platelet count of 109×10^3 μL.

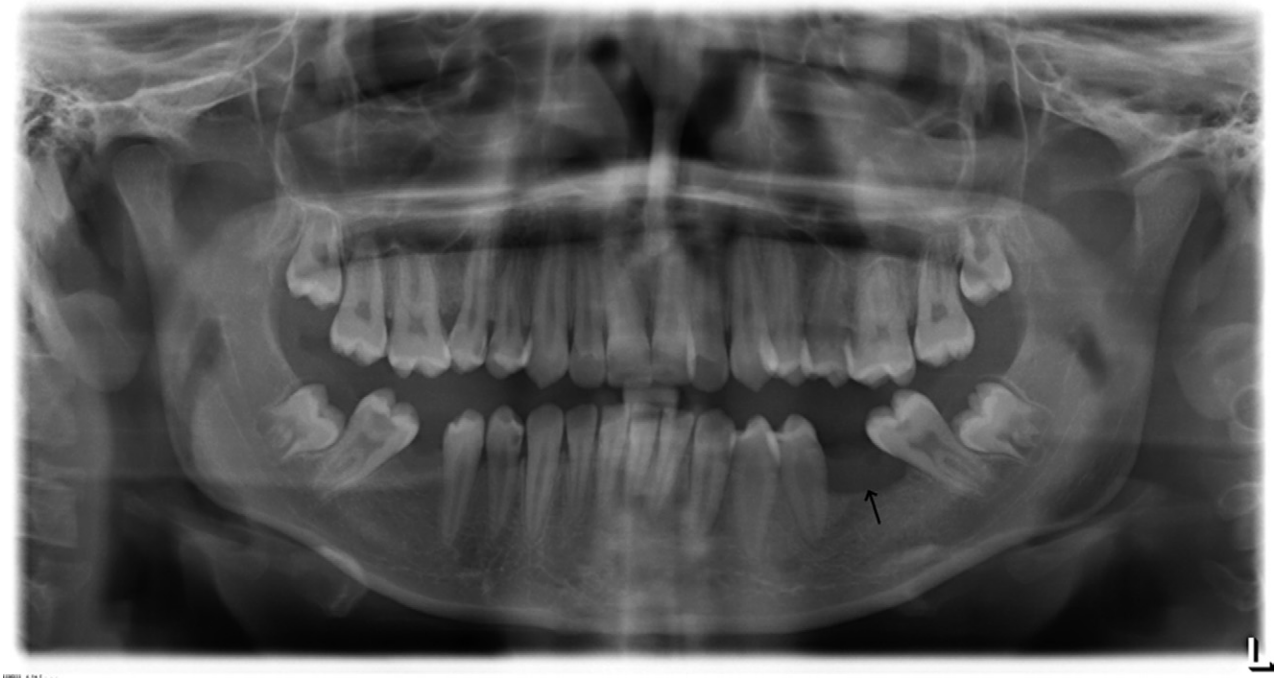

FIGURE 2. Case 1. Initial radiologic condition of the mandible. The mucosal lesion caused by mucormycosis causes minor resorption of the alveolar bone.

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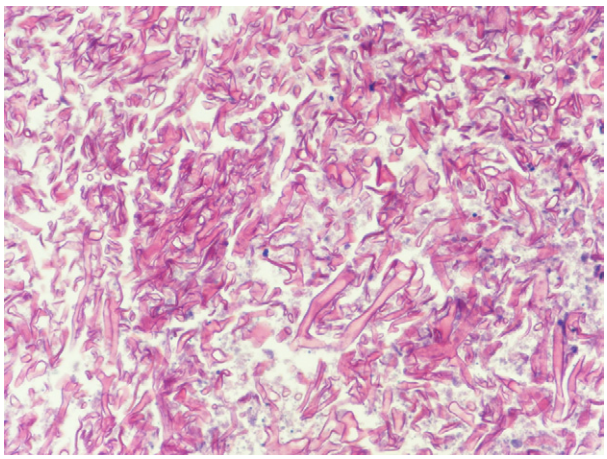

FIGURE 3. Case 1. Biopsy specimen showing broad nonseptate hyphae with 90° angle branching (hematoxylin and eosin stain; magnification, ×400).

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A soft tissue biopsy was taken from the necrotic area. Histologic sections of the specimens were stained with hematoxylin and eosin for routine histopathologic examination and with periodic-acid Schiff and Grocott's methenamine silver (GMS). Biopsy of the necrotic lesion showed fungal hyphae consistent with Mucorales invading the submucosal connective tissue and vasculature (Fig 3). Evaluation of the biopsy was consistent with the diagnosis of mucormycosis because of the broad nonseptate hyphae with 90° angle branching characteristic of Mucorales. Because biopsy of the lesion in the mandible confirmed the diagnosis of mucormycosis, the patient underwent surgery under general anesthesia to excise the necrotic lesion. Because of thrombocytopenia (platelet count, 33.3×10^3 μL) and prolonged prothrombin time (18.8 seconds), fresh-frozen plasma 4 U (2 × 2; 12 hours and 0.5 hour before) and platelet suspensions 2 U were administered to the patient just before surgery. The canine, first premolar, and first molar were extracted; underlying bone and a margin of normal-appearing soft tissue were removed. Then, the wound was closed primarily. A soft diet was maintained, and wound care included chlorhexidine rinses. Antibiotics were gradually tapered as the patient's clinical condition improved. Two months after surgery, there was no clinical evidence of mucormycosis, and the oral cavity showed no tissue breakdown in the area of previous infection (Figs 4, 5). However, the patient died of leukemia 7 months after the maxillofacial operation.

CASE 2

A 6-year-old boy who was diagnosed with neuroblastoma was referred to the maxillofacial clinic at Gaziantep University; admission laboratory values showed a white blood cell count of 2.95×10^3 μL, an absolute neutrophil count of 1.21×10^3 μL, a hemoglobin level of 9.0 g/dL, a hematocrit level of 26.8%, and a platelet count of 133×10^3 μL. He had complained of abdominal pain. The right mandibular second primary molar was encompassed by white necrotic-appearing tissue (Fig 6A, B). Swelling was also noted in the adjacent tissue. Laboratory values at the time the patient was diagnosed with neuroblastoma showed a white blood cell count of 5.84×10^3 μL, an absolute neutrophil count of 2.5×10^3 μL, a hemoglobin level of 9.6 g/dL, a hematocrit level of 31.4%, and a platelet count of 423×10^3 μL. Biopsy of the necrotic lesion showed fungal hyphae consistent with Mucorales invading the submucosal connective tissue and vasculature (Fig 7). After a biopsy was taken from the oral mucosa, the specimens were stained with periodic-acid Schiff and GMS for histochemistry. The biopsy confirmed the diagnosis of mucormycosis by showing broad nonseptate hyphae with 90° angle branching characteristic of Mucorales. Antifungal therapy (50 mg/d intravenous amphotericin B) was begun immediately after diagnosis of the lesion confirmed mucormycosis, and the patient underwent surgery under general anesthesia for excision of the necrotic lesion. The renal function of this patient was normal, and the creatinine level was only 0.5 mg/dL maximally during antifungal therapy. The second primary molar was extracted, underlying bone and a margin of normal-appearing soft tissue was curetted, and the wound was closed primarily. However, the permanent premolar tooth was left for spontaneous eruption. Ampicillin and sulbactam in combination were also prescribed to the patient for antibacterial

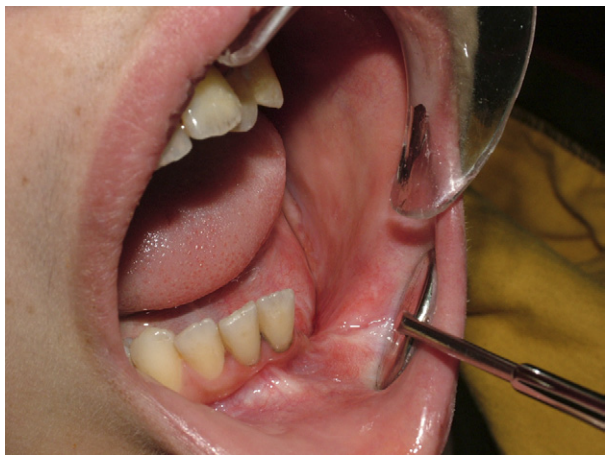

FIGURE 4. Case 1. Postoperative view of the left mandibular area shows well-healed mucosal tissue without evidence of recurrent mucormycosis.

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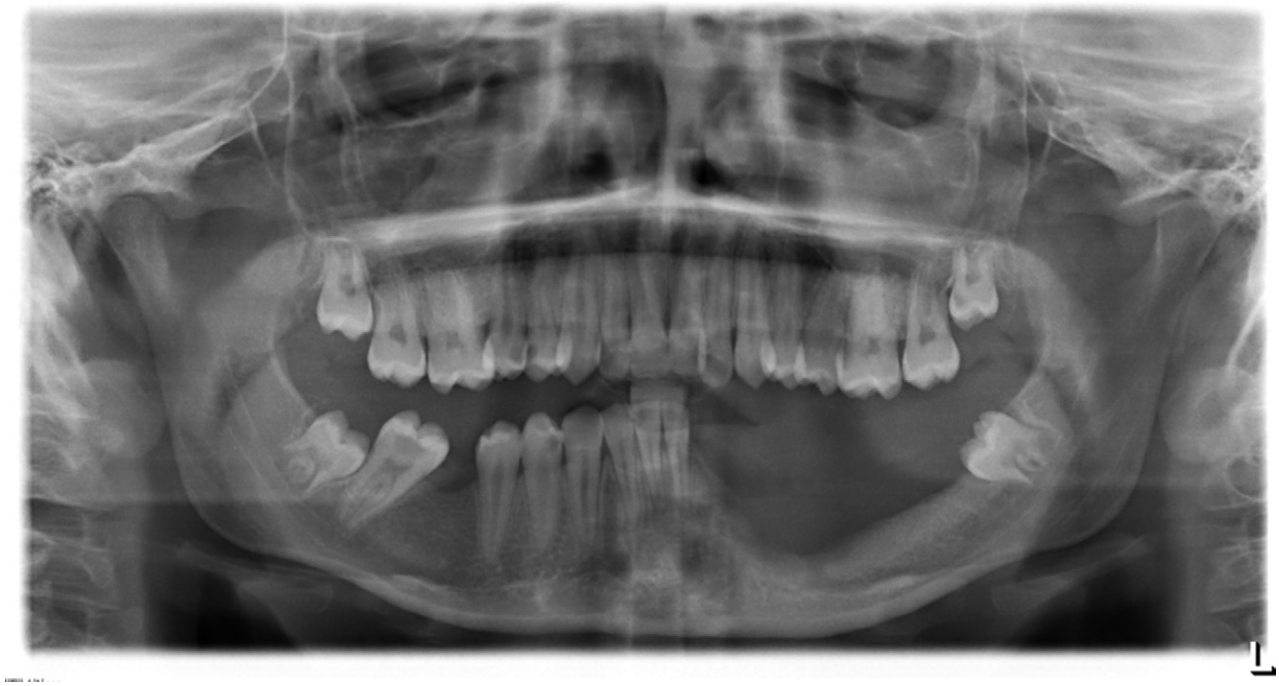

FIGURE 5. Case 1. Postoperative radiograph shows resected margin of the mandible.

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treatment. A soft diet was maintained, and wound care included chlorhexidine rinses. Antibiotics were gradually tapered as the clinical conditions improved. Two months after surgery, there was no clinical evidence of mucormycosis, and the oral cavity showed no tissue breakdown in the area of previous infection (Fig 8). However, the patient died of neuroblastoma 3 months after surgery.

Review of the Literature

The aim of this research was to identify mucormycosis cases that involved the mandibular region.

SELECTION CRITERIA

Articles that presented case reports or a review of the literature reporting mucormycosis cases were selected for this review.

The search was based on the foregoing "research topic." The database searched was the PubMed interface of MEDLINE (National Library of Medicine). The terms used were *mandibular mucormycosis*, *periodontal mucormycosis*, and *oral mucormycosis*. This strategy was augmented by reference to the bibliographies (or citation lists) of all reports identified by the databases (reference harvesting).

This research was exempt from review by the local institutional review board.

Results

The MEDLINE search results were as follows: #1 Search "mandibular mucormycosis" [Text word] 10#2 Search "periodontal mucormycosis" [Text word] 5#3 Search "oral mucormycosis" [Text word] 141#4 Search ((#1) or (#2)) or (#3) 151.

After reviewing all articles, 4 were selected because they reported mucormycosis cases that involved the mandible. Reference harvesting and hand searching produced 1 case report. When articles were considered using the selection criteria, 7 were selected for this review. These cases are presented in Table 1.

Discussion

In immunocompromised patients, mucormycosis infection usually involves the rhino-facial-cranial areas, the lungs, gastrointestinal tract, skin, or, less commonly, other organ systems, but may involve any area.[1,2] The oral involvement of Mucorales fungi has long been known. Bonifaz et al[1] reported that the oral involvement of this condition can occur at different levels. They suggested that the most frequent manifestations are palatal ulcers, which are almost always necrotic and well delimited with well-defined borders. They may be black or white, have a torpid course, and at times may form very rapidly, particularly when they are associated with various states of immunocompromising conditions.

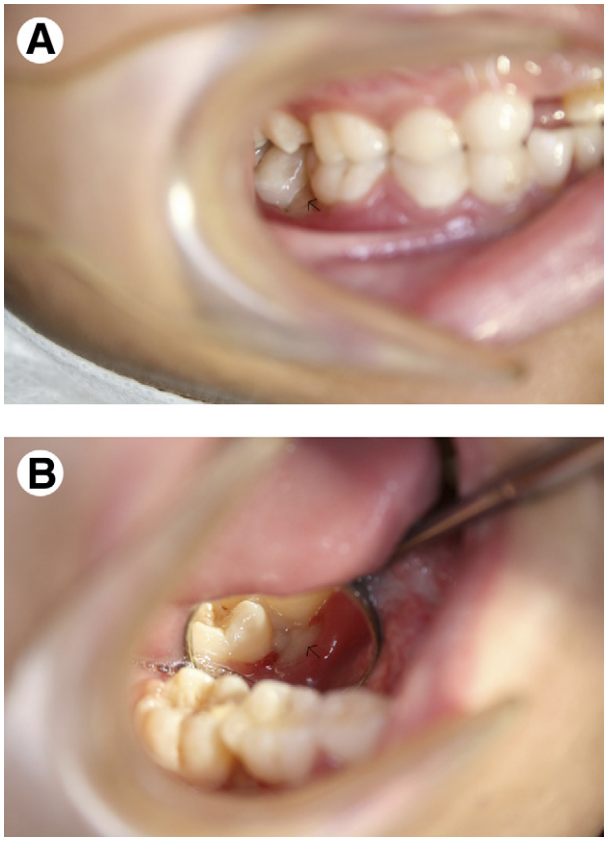

FIGURE 6. Case 2. *A, B,* Intraoral images at initial presentation, showing fibrotic gingiva adjacent to the right mandibular second primary molar.

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Oral zygomycosis may result from rapid lysis of the maxilla and other adjacent structures; it has been reported in the alveolar ridge, lips, cheeks, tongue, and mandible.[13-17] Although oral involvement of this condition has been reported relatively frequently in the literature, mandibular involvement is a rarer condition than oral involvement.[9,15,18-20] Mandibular involvement of mucormycosis was first reported by Eisenberg et al.[18] The present findings from a review of the literature showed that only 5 mucormycosis cases that involve the mandibular region have been reported previously. These cases are presented in Table 1.

Of the 3 patients with mucormycosis presented by Eisenberg et al,[18] only 1 patient had mandibular involvement. This 28-year-old female patient had been taking prednisone and azathioprine for treatment of a desquamative dermatologic condition. She had been admitted to the hospital with a diagnosis of acute pyelonephritis, at which time she was febrile to 38.7°C; urinalysis showed many bacteria and 50 to 60 white blood cells per high-power field. When the diagnosis of mucormycosis was

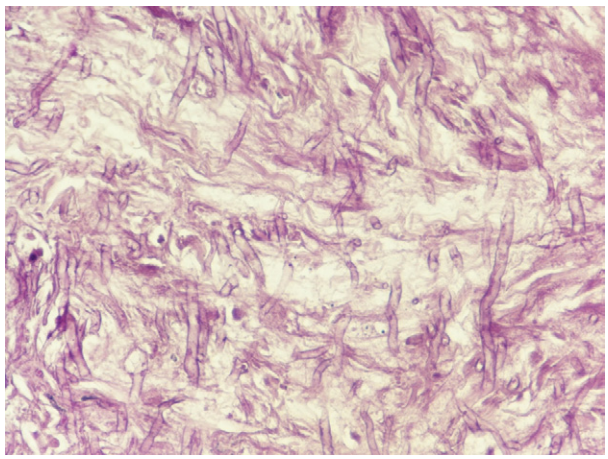

FIGURE 7. Case 2. Biopsy specimen shows the broad nonseptate hyphae characteristic of Mucorales (periodic-acid Schiff stain; magnification, ×400).

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made, steroid therapy was immediately tapered and daily amphotericin B therapy was started. Then, the patient underwent radical debridement of the mandible and other affected regions, and the lesions did not progress postoperatively. In another case, presented by Brown and Finn,[19] a 57-year-old man with diabetes mellitus and chronic renal failure requiring dialysis was admitted to their clinic with a "submental carbuncle." After biopsy of the lesion with a

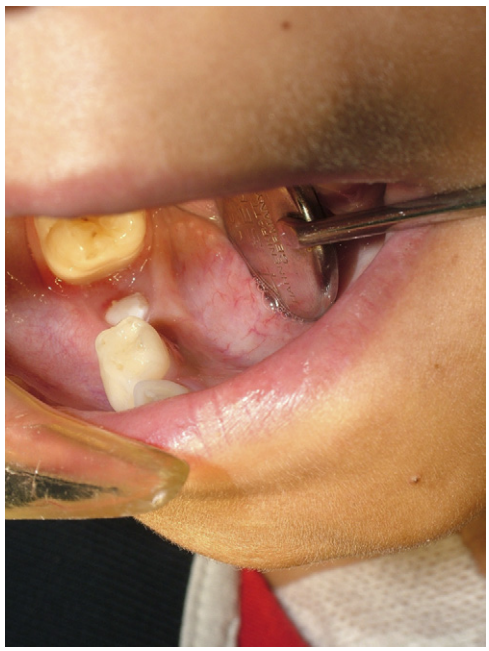

FIGURE 8. Case 2. Surgical site approximately 2 months after surgery, showing healing without evidence of recurrence. A permanent premolar tooth is visible in the healing region.

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Table 1. REPORTED CASES OF MUCORMYCOSIS THAT INVOLVE THE MANDIBLE

Study	Age (yrs)	Gender	Predisposing Diseases or Risk Factors	Treatment
Eisenberg et al[18] (1977)	28	F	Corticosteroid, acute renal failure, metabolic acidosis, hyperglycemia	AMB, surgical debridement
Brown and Finn[19] (1986)	57	M	Acute renal failure, diabetes mellitus	AMB, mandibulectomy
Jones et al[15] (1993)	43	M	AML, acute renal failure	AMB, surgical debridement
Salisbury et al[9] (1997)	60	M	AML, prostate cancer, heavy use of alcohol	AMB, surgical debridement
Lador et al[21] (2006)	42	F	ALL	AMB
Dogan et al[20] (2007)	7	M	AML	AMB, surgical debridement
Ojeda-Uribe et al[22] (2010)	55	F	AML	AMB, mandibulectomy
Present case 1	15	M	AML	AMB, surgical debridement
Present case 2	6	M	Neuroblastoma	AMB, surgical debridement

Abbreviations: ALL, acute lymphoblastic leukemia; AMB, amphotericin B; AML, acute myelogenous leukemia; F, female; M, male.

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diagnosis of mucormycosis, intravenous amphotericin B was begun, and the patient underwent wide debridement of the soft tissues and total mandibulectomy. Despite aggressive medical care, the patient died 2 months after treatment. Jones et al[15] reported 2 mucormycosis cases, 1 of which involved the mandible. The medical history of this 43-year-old male patient included AML, acute renal failure, and pancytopenia. After biopsy of the lesion with a diagnosis of mucormycosis, 80 mg/d intravenous amphotericin B was begun, and all necrotic tissue in the mandible was debrided. Clinical examination of the gingival tissue and gallium bone scan results of the mandible were within normal limits approximately 1 year after treatment. Salisbury et al[9] reported on another patient who was a 60-year-old man with prostate cancer, AML, and heavy use of alcohol. Because biopsy of the lesion in the mandible confirmed the diagnosis of mucormycosis, amphotericin B was immediately begun, and the patient was taken to the operating room for excision of the necrotic lesion. One year after discharge, the oral cavity showed no tissue breakdown in the area of previous infection, and there had not been any reappearance of mucormycosis. In a case reported by Lador et al,[21] a 42-year-old patient who had been diagnosed with acute lymphoblastic leukemia presented with mandibular mucormycosis. Treatment was limited to an intensive antifungal dosage (1.5 mg/kg amphotericin B) and to providing palliative care because the patient was at the terminal stage of the leukemia. The investigators reported that the patient died a few hours after these decisions were made. Dogan et al[20] reported on a 7-year-old boy with a diagnosis of AML. Because biopsy and histologic examination led to the diagnosis of mucormycosis, liposomal amphotericin B was started, and the lesion was debrided under general anesthesia. The investigators reported that after the fourth week of debridement, healing was incomplete at the site of the lesion. Ojeda-Uribe et al[22] presented a rare case of oromandibular *Rhizopus oryzae* infection in a 55-year-old woman with AML and decompensated diabetes mellitus. She was treated with a combination of an amphotericin B lipid formulation and caspofungin plus surgery. Reconstructive surgery was carried out, including insertion of a mandibular prosthesis, which showed excellent functionality after long-term follow-up. The investigators claimed that their case shows that a well-coordinated multidisciplinary approach is critical to increase the chances of clinical success in treating this life-threatening infection.

Pathologically, this disease involves thrombosis, vascular invasion, ischemia, and infarctions.[1] The fungi usually enter the body through the nasal mucosa, lungs, or skin. As in cutaneous mucormycosis, injured tissue in the oral cavity can be a suitable port of entry. For reasons that are unclear, the fungal hyphae preferentially invade the walls of blood vessels, producing thrombi and infarctions. Progressive tissue ischemia and necrosis are the inevitable result.[9] A high index of suspicion for tissue necrosis must be maintained, with early, definitive debridement of all involved tissues.[19] Because the initial signs and symptoms of the disease often involve the oral, facial, and cranial structures, it is critical that dentists, dental specialists, and otorhinolaryngologists be aware of this infection, especially in the diabetic or immunocompromised patient.[6]

Surviving this condition largely depends on early identification and treatment.[18] Treatment of mucormycosis requires several simultaneous approaches: surgical intervention, antifungal therapy, and correction of the underlying condition.[3] Antifungal treatment is based on systemic high-dose amphotericin B. Because amphotericin B has some serious side effects, in particular renal toxicity, careful monitoring of

serum urea nitrogen and creatinine and of creatinine clearance should be carried out during amphotericin B therapy. Despite aggressive management, the prognosis of the disease is generally poor in immunocompromised patients.[6] Although mucormycosis exhibits high mortality rates, which are influenced by the timeliness of the diagnosis and the patient's status,[1] mandibular involvement in this condition has a better prognosis than other types. In a multicenter retrospective study conducted by Pagano et al,[4] the investigators reported that 47 patients among the 59 infected with mucormycosis died within 3 months of the diagnosis of fungal infection. They suggested that mucormycosis was the main cause of death in 41 of these patients. In contrast, the present findings collected from the literature showed that infection of the mandibular region can be treated relatively easily. Among the 5 mandibular mucormycosis cases, 4 patients could have been treated successfully with just surgical debridement and amphotericin B combination treatment.[9,15,18-20] Brown and Finn[19] reported that mandibulectomy was performed for the treatment of the condition in their other case. In the present cases 1 and 2, treatment with a combination of surgical debridement and amphotericin B was successful. However, the first patient died of leukemia 7 months after the maxillofacial operation, and the other patient died of neuroblastoma 3 months after surgery.

Decisions related to the treatment planning of isolated mandibular mucormycosis may be difficult for clinicians because there are no controlled studies that identify when conservative or more aggressive treatment strategies should be used. Thus, clinicians must rely on case reports, personal experience, and clinical judgment.

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