

## Successful treatment of periodontal mucormycosis: report of a case and literature review

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Mucormycosis is an aggressive and potentially devastating fungal infection which typically manifests in pulmonary, rhinocerebral, or disseminated forms in patients with hematologic malignancy. Mucormycosis confined to the periodontium is uncommon, and to our knowledge only 6 cases have been reported in the English-language literature. This case report describes a patient with acute leukemia and periodontal mucormycosis. Calcofluor fluorescence microscopy is also proposed as a method for establishing a prompt diagnosis and guiding extent of intraoperative surgical debridement. (*Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010;109:e64-e69)

Mucormycosis is an aggressive, invasive, and potentially devastating opportunistic fungal infection first described by Paultauf in 1885.<sup>1</sup> The mucoraceae are a ubiquitous saprophytic group of fungi found in soil, dust, and decaying fruit and bread as well as in the nasal mucosa, oral cavity, and stool of healthy individuals. They belong to the class Zygomycetes, order Mucorales, and family Mucoraceae. The most common genera are *Absidia*, *Rhizomucor*, *Rhizopus*, and *Mucor*. The genus *Mucor* contains several species, including *ambiguum*, *circinelloides*, *hiemalis*, *indicus*, *racemosus*, and *ramosissimus*.<sup>2</sup>

Despite the widespread distribution of these organisms, infection due to mucormycosis is essentially limited to patients with poorly controlled diabetes mellitus, hematologic malignancy, organ transplant, chemotherapy, chronic renal insufficiency, malnutrition, deferox-

amine therapy, and severe burns. 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.<sup>3,4</sup>

Mucormycosis manifests in 7 predominant clinical forms: rhinocerebral, pulmonary, cutaneous, gastrointestinal, central nervous system, disseminated, and, rarely, miscellaneous (i.e., bone, kidney, cardiac, mediastinum, oral). In patients with hematologic malignancies, pulmonary and rhinocerebral manifestations are common.<sup>3</sup>

Mucormycosis is diagnosed histologically when broad, irregularly shaped, nonseptate hyphae with right-angle branching are seen invading tissue. If arterial invasion occurs, thrombosis and ischemic necrosis ensues. Identification of the fungal species requires culture, morphologic evaluation, and, where feasible, genetic analysis.

Herein, we present a patient with periodontal mucormycosis complicating her hematopoietic stem cell transplantation for acute leukemia. Using Calcofluor-guided fluorescence microscopy, we established a rapid and accurate diagnosis as well as the extent of surgical debridement. Prompt treatment of this infection was critical to preventing extension of this destructive process into the hard palate and maxillary sinus.

### CASE REPORT

The patient was a 47-year-old Vietnamese woman with myelodysplastic syndrome and acute myelogenous leukemia (AML) who was hospitalized for management of a neutropenic fever 5 days after completing cytoreductive chemotherapy with fludarabine, cytarabine, idarubicin, and filgrastim in preparation for allogeneic (sibling donor) stem cell transplant. Admission laboratory values showed: white blood cell count

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Fig. 1. Intraoral image of initial presentation, showing gray fibrotic gingiva adjacent to left maxillary second premolar and first molar.

(WBC) of 60 cells/ $\mu$ L (0.06 K/ $\mu$ L) and an absolute neutrophil count (ANC) undetected ( $<0.00$  K/ $\mu$ L) using electronic counting methods. Additional values included hemoglobin 10.8 g/dL, hematocrit 31.2%, and platelets 20 K/ $\mu$ L. Review of systems and physical exam were noncontributory. Pancultures and computerized tomography (CT) imaging were negative for infectious etiology. Empirical vancomycin, ceftazidime, and fluconazole were initiated. After 2 days, fluconazole was switched to caspofungin owing to persistent fever.

On hospital day 6, a conditioning regimen was started using fludarabine (25 mg/m<sup>2</sup> for 5 days) and total body irradiation (12 Gy in 8 fractions for 4 days), followed by cytoxan (60 mg/kg for 2 days). Laboratory values showed WBC 0.07 K/ $\mu$ L, ANC undetected ( $<0.00$  K/ $\mu$ L), and platelets 25 K/ $\mu$ L. By hospital day 8, the patient complained of pain in the left maxilla. Examination revealed gray fibrous gingiva involving the buccal, palatal, and interdental periodontal aspects of the left second premolar and first molar teeth with several pinpoint black foci (Fig. 1). The teeth were intact, nonmobile, and nontender. Maxillofacial CT showed a stable left maxillary retention cyst with no evidence of tissue or bone destruction. Nasal pharyngolaryngoscopy showed intact structures with no evidence of tissue breakdown. Laboratories showed WBC 0.04 K/ $\mu$ L, ANC undetected ( $<0.00$  K/ $\mu$ L), and platelets 52 K/ $\mu$ L. Gingival swabs of the region revealed broad, nondichotomous branching, nonseptate, ribbon-like hyphae which later grew *Mucor indicus* (Fig. 2). Liposomal amphotericin B (5 mg/kg IV daily), micafungin (1 mg/kg IV daily), metronidazole, and amphotericin B oral rinse were started. Caspofungin was discontinued.

Despite the patient's profound immunocompromise and the concern for fulminant infection and sepsis with an interventional procedure, it was decided that the benefit of conservative local debridement in conjunction with antifungal therapy outweighed the risks of antifungal therapy alone, given the

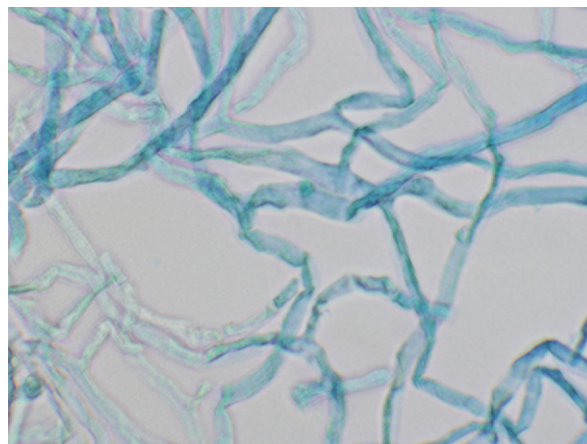


Fig. 2. Wet mount of gingival swab, showing broad, irregularly branching, ribbon-like, nonseptate hyphae (original magnification  $\times 400$ ).

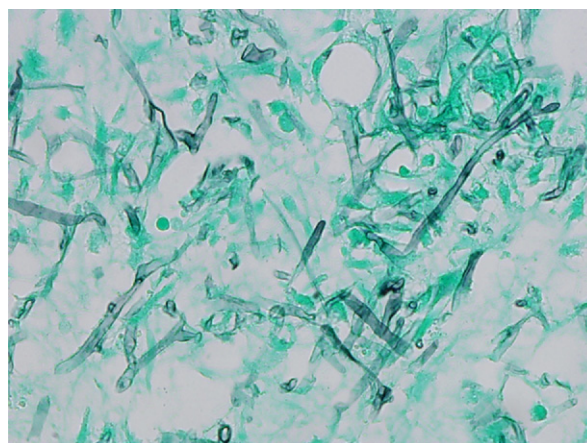


Fig. 3. Gingiva specimen, showing broad nonseptate hyphae with 90°-angle branching (Gomori methenamine silver stain; original magnification  $\times 400$ ).

potentially devastating outcome associated with inadequate treatment of this fungal infection. After platelet transfusion to the 50 K/ $\mu$ L range, the patient underwent urgent full-thickness debridement of the involved gingiva with a 0.5 mm surgical margin. The underlying bone appeared normal. Gomori methenamine silver (GMS) staining and Calcofluor fluorescence microscopy of the resected gingiva showed abundant broad, right-angle branching, nonseptate hyphae consistent with mucormycosis (Figs. 3 and 4).

The next morning,  $<12$  hours after debridement, gray fibrous boggy gingiva was noted in the surgical bed with several new pinpoint black foci along the buccal and lingual alveolar bone. Laboratory values showed WBC  $<0.01$  K/ $\mu$ L, ANC undetected ( $<0.00$  K/ $\mu$ L), and platelets 74 K/ $\mu$ L. At this point, there was renewed concern about the virulence of the infection and the decision was made to perform a second debridement consisting of wider gingival resection, extrac-



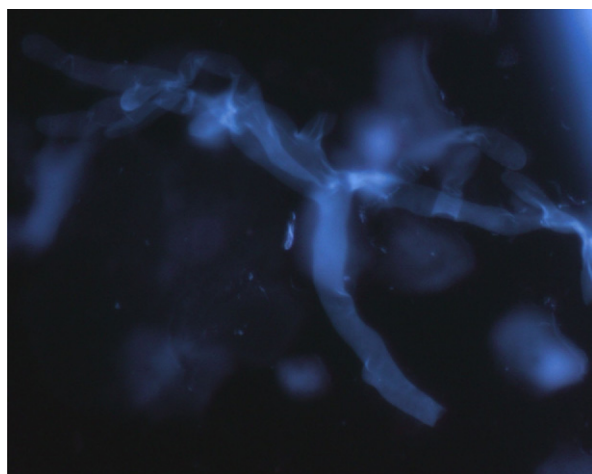


Fig. 4. Calcofluor fluorescence microscopy showing irregular nonseptate hyphae (original magnification  $\times 400$ ).

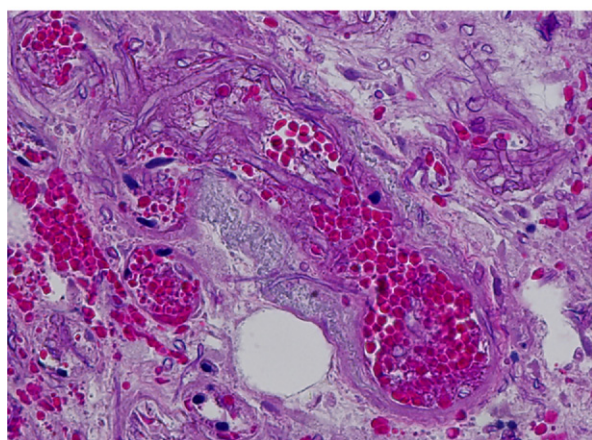
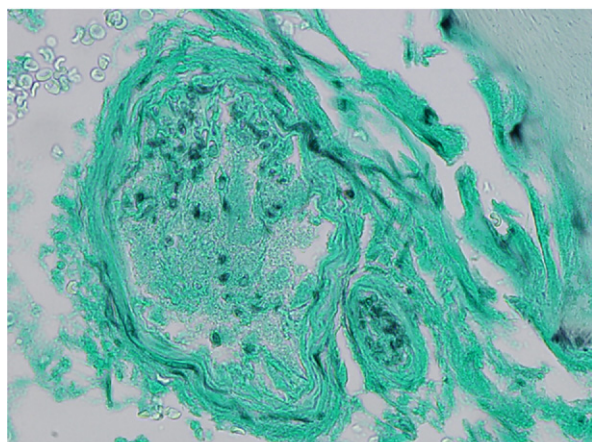


Fig. 5. Intravascular invasion by fungal hyphae (Gomori methenamine silver (**top**) and periodic acid-Schiff (**bottom**) stains; original magnification  $\times 400$ ).

tions of the second premolar and first molar and osteotomy of the associated alveolar bone up to the maxillary sinus membrane. The resection was performed with a 0.5 mm surgical

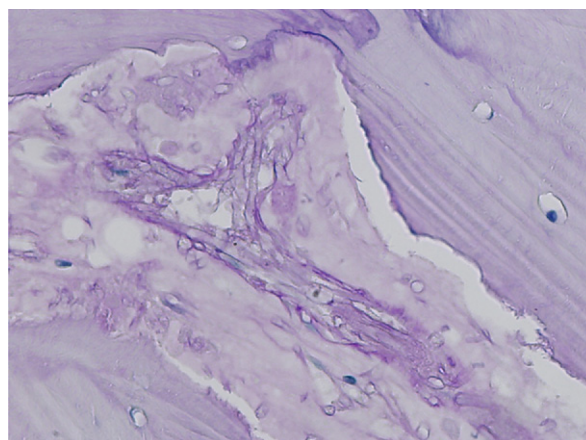


Fig. 6. Bone marrow invasion by fungal hyphae (periodic acid-Schiff stain; original magnification  $\times 400$ ).

margin and until healthy-appearing bleeding bone and soft tissue was encountered. The surgical site was left open to facilitate serial examinations. Periodic acid-Schiff (PAS) and GMS staining of the gingiva revealed intravascular hyphal infiltration (Fig. 5). PAS staining of the alveolar bone showed marrow infiltration by fungal hyphae (Fig. 6).

After surgery, vancomycin was discontinued and regular granulocyte infusions were started to maintain the WBC around 2-3 K/ $\mu$ L. Within 2 days after debridement, the ANC was 3.69 K/ $\mu$ L. The patient denied pain, nasal/sinus congestion, ocular abnormality, and headache. Over the next few days, healthy vascular granulation tissue was noted in the surgical bed with no evidence of tissue breakdown, discoloration, or sinus communication.

On day 4 after the second debridement, the patient received a T-cell-depleted allogeneic stem cell transplant. Maxillofacial CT showed no evidence of bone or soft tissue destruction. Laboratory values showed WBC 2.37 K/ $\mu$ L, ANC 2.34 K/ $\mu$ L, and platelets 83 K/ $\mu$ L.

On postoperative day #6, the patient developed tachypnea with transient oxygen desaturation. Three days later, she was transferred to the Intensive Care Unit for worsening respiratory distress, a left ventricular ejection fraction of 28%, lactic acidosis, acute renal failure with oliguria, and liver failure with rising transaminases and bilirubins. Laboratory values showed WBC 0.72 K/ $\mu$ L, ANC 0.71 K/ $\mu$ L, platelets 18 K/ $\mu$ L, creatinine 2.9 mg/dL, alanine aminotransferase 780 U/L, aspartate aminotransferase 6,114 U/L, lactate 13 mmol/L, lactate dehydrogenase 10,145 U/L, bilirubin<sub>T</sub> 2.6 mg/dL, and bilirubin<sub>D</sub> 1.7 mg/dL. Deferasirox iron chelation therapy, which had been administered for approximately 2 days, was stopped owing to its potential adverse effect on renal and hepatic function. Regular red blood cell and platelet infusions were continued. Given the concern that multiorgan failure in the context of profound immunosuppression was due to disseminated mucormycosis, the decision was made to take the patient to the operating room for exploratory laparotomy, esophagogastroduodenoscopy, and maxillary biop-



Fig. 7. Surgical site approximately 1 month after surgery, showing healing without evidence of recurrence.

sies with intraoperative Calcofluor analysis to rule out persistent oral mucormycosis.

Intraoperative findings showed no evidence of gastrointestinal mucormycosis. Ascites cultures and gastric biopsies were negative for fungus. Multiple oral biopsies of the resection bed, including the eschar and buccal and hard palate tissues, were negative for fungus on intraoperative Calcofluor analysis. Given these findings, further oral debridement was not performed and a working diagnosis of noninfectious toxic tissue injury following the conditioning regimen was made.

Within a few weeks the patient was extubated and her cardiac, hepatic, and renal function improved, and her laboratories trended into normal range. Approximately one month after debridement, her neutropenia was resolved and the oral surgical site was fully healed (Fig. 7). Liposomal amphotericin was discontinued after a 4 week course. She was discharged and she remains in remission and is doing well.

## DISCUSSION

Mucormycosis is an acute and rapidly progressing infection with a high mortality rate unless identified and treated promptly. It is the third most frequent fungal infection in patients with hematologic malignancies, with candida and aspergillosis being more common. In 1993, a 17-year consecutive series by Morrison and McGlave reported a 0.9% incidence (13 out of 1,500 patients) of mucormycosis in bone marrow transplant patients.<sup>5</sup> Ten of the transplants were allogeneic and 3 were autologous; six infections occurred within 90 days of the transplant; 54% of patients were neutropenic at the time of diagnosis; death from mucormycosis occurred in 77% (10 out of 13) of the patients. In a 2004 retrospective study, Pagano et al. described 59 patients with hematologic malignancy and mucormycosis. Pulmonary (64%) and rhinocerebral (24%) were the most

common manifestations.<sup>3</sup> Patients with acute leukemias (78%) had a higher incidence of infection compared with patients with other hematologic malignancies.

In 2002, a retrospective study by Marr et al. identified age >40 years, hematologic malignancy other than chronic myeloid leukemia, mismatched or unrelated donor, and graft-versus-host disease as risk factors for mucormycosis infection in hematopoietic stem cell transplant recipients.<sup>6</sup> Neutropenia is also a well recognized risk factor for infection in patients with hematologic malignancy, and several studies correlate the recovery from aplasia with granulocyte infusions or by enhancement of endogenous neutrophil production with a lower mortality rate.<sup>3,7-10</sup> Univariate analysis by Pagano et al. found that gender (male greater than female), amphotericin B, and neutrophil recovery from postchemotherapy aplasia were positively correlated with recovery from mucormycosis.<sup>3</sup> With multivariate analysis, however, only amphotericin B was significantly correlated with recovery. In that study, 47 out of 59 patients (79%) were neutropenic for a median 12 days before the diagnosis of mucormycosis, and 33 out of those 47 patients (70%) recovered from neutropenia within 7 days of diagnosis. Death from mucormycosis occurred in 41 out of 59 patients (69%). In this present report, the patient was neutropenic for 8 days before her diagnosis of mucormycosis. After diagnosis and debridement, she received regular granulocyte infusions to maintain the absolute neutrophil count in the 1,000-3,000 range.

To our knowledge, only 5 cases of human infection with *Mucor indicus* (previously known as *Mucor rouxii*) have been reported in the literature.<sup>11-15</sup> Four of those cases (80%) involved the gastrointestinal tract, and infection was thought to be the result of oral ingestion of the pathogen. Two cases (40%) involved hematologic malignancy, and 4 patients (80%) survived. In the present patient, the absence of gastrointestinal dissemination was surprising, given the oral location of her infection and her immunocompromised status.

Mucormycosis of the oral cavity is usually due to transpalatal extension of rhinocerebral infection, and mucormycosis localized to the periodontal tissues (i.e., gingiva and alveolar bone) is exceedingly rare; to our knowledge, only 6 cases have been reported in the English-language literature in the past 25 years.<sup>16-19</sup> The clinical features of these cases are summarized in Table I. Of note, all of the patients were neutropenic as a result of chemotherapy for hematologic malignancy or carried a diagnosis of diabetes mellitus. In 3 patients, mucormycosis arose at the site of recent dental extraction. Treatment involved amphotericin B with or with-



**Table 1.** Periodontal mucormycosis

Case source	Age(yr)/gender	Underlying condition	Location	Treatment	Outcome
Dogan et al. (2007) <sup>16</sup>	7/M	AML/neutropenia	Maxilla gingiva	Debridement, amphotericin B	Full recovery
	9/M	ALL/neutropenia	Maxilla gingiva	Amphotericin B	Full recovery
Auluck (2007) <sup>17</sup>	58/M	Diabetes	Maxilla extraction site	Debridement, amphotericin B	Full recovery
Salisbury et al. (1997) <sup>18</sup>	60/M	AML/neutropenia	Mandible extraction site	Debridement, amphotericin B	Full recovery
Jones et al. (1993) <sup>19</sup>	43/M	AML/neutropenia	Mandible gingiva	Debridement, amphotericin B	Full recovery
	68/M	Diabetes	Maxilla extraction site	Amphotericin B	Lost to follow-up

AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia.

out local debridement. Five patients made a full recovery, and 1 patient was lost to follow-up.

Mucormycosis has a very poor prognosis, with mortality rates of 80%-100%;<sup>20</sup> however, with early recognition and aggressive treatment, survival rates can exceed 80%.<sup>21</sup> Extensive surgical debridement to remove all devitalized tissue is generally believed to be the most important component of treatment. Concomitant correction of the predisposing condition and amphotericin B therapy are also critical.

Despite profound immunosuppression and infection with a virulent *Mucor* species, the present patient made a full recovery. This may have been due in part to early recognition and aggressive intervention. It is also possible that deferasirox chelation therapy, which the patient received briefly, provided adjunctive fungicidal therapy.<sup>22,23</sup>

A diagnosis of mucormycosis can be established by direct examination of a wet mount and touch prep of tissue by using Calcofluor, Fungifluor, or Blankofluor. Each of these reagents works on the principal of binding to the chitin and glucans of the fungal cell wall.<sup>24</sup> When treated specimens are evaluated by fluorescence microscopy, they have a distinct blue-white color. For cost-effectiveness, Calcofluor analysis is most commonly performed in a medical center setting owing to the need for fluorescence microscopy. It has been shown to be useful in the diagnosis of dermatophytosis, onychomycosis, ocular mycotic keratitis, and pulmonary fungal infections.<sup>25,26,29,30</sup> In the present case, we used Calcofluor fluorescent wet mounts of resected oral tissue to rapidly establish a diagnosis and to define clear surgical margins for invasive fungal infection.

Although not widely used in clinical practice, we believe that Calcofluor fluorescence may have a greater sensitivity compared with more traditional diagnostic methods (i.e., potassium hydroxide, PAS, and GMS stains), and this is supported by several studies.<sup>25-30</sup> Calcofluor fluorescence is also inexpensive and may be less costly compared with other detection methods. It can provide rapid results (30 seconds), which is conducive to timely treatment planning, intraoperative decision making, and optimal management of an aggres-

sive and potentially life-threatening infection. As such, we conclude that Calcofluor fluorescence provides a simple, rapid, and inexpensive method to detect fungal pathogens. This is especially important when early diagnosis and meticulous timely debridement is critical to optimizing outcome.

## REFERENCES

1. Paltauf A. Mycosis mucorina. Virchow Arch Pathol Anat 1885;102:543-64.
2. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis 2005;41:634-53.
3. Pagano L, Offidani M, Fianchi L, Nosari A, Candoni A, Piccardi M, et al. Mucormycosis in hematologic patients. Haematologica 2004;89:207-14.
4. Pizzo PA. Management of fever in patients with cancer and treatment induced neutropenia. N Engl J Med 1993;328:1323-32.
5. Morrison VA, McGlave PB. Mucormycosis in the BMT population. Bone Marrow Transplant 1993;11:383-8.
6. Marr KA, Carter RA, Crippa F, Wald A, Corey L. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. Clin Infect Dis 2002;34:909-17.
7. Gil-Lamagnere C, Simitsopoulou M, Roilides E, Maloukou A, Winn RM, Walsh TJ. Interferon-gamma and granulocyte-macrophage colony-stimulating factor augment the activity of polymorphonuclear leukocytes against medically important Zygomycetes. J Infect Dis 2005;191:1180-7.
8. Ryan ME, Ochs J. Primary cutaneous mucormycosis: superficial and gangrenous infections. Pediatr Infect Dis J 1982;1:110-4.
9. Leong KW, Crowley B, White B, Crotty GM, O'Brian DS, Keane C, et al. Cutaneous mucormycosis due to *Absidia corymbifera* occurring after bone marrow transplantation. Bone Marrow Transplant 1997;19:513-5.
10. Liles WC, Huang JE, Van Burik JH, Bowden RA, Dale DC. Granulocyte colony-stimulating factor administered in vivo augments neutrophil-mediated activity against opportunistic fungal pathogens. J Infect Dis 1997;175:1012-5.
11. Deja M, Wolf S, Weber-Carstens S, Lehmann TN, Adler A, Ruhnke M, Tintelnot K. Gastrointestinal zygomycosis caused by *Mucor indicus* in a patient with acute traumatic brain injury. Med Mycol 2006;44:683-7.
12. Ter Borg F, Kuijper EJ, van der Lelie H. Fatal mucormycosis presenting as an appendiceal mass with metastatic spread to the liver during chemotherapy-induced granulocytopenia. Scand J Infect Dis 1990;22:499-501.
13. Oliver MR, Van Voorhis WC, Boeckh M, Mattson D, Bowden, RA. Hepatic mucormycosis in a bone marrow transplant recipi-

- ent who ingested naturopathic medicine. Clin Infect Dis 1996;22:521-4.
14. Mata-Essayag S, Magaldi S, Hartung de Capriles C, Henao L, Garrido L, Pacillo V. Mucor indicus necrotizing fasciitis. Int J Dermatol 2001;40:406-8.
15. Aboltins CA, Pratt WA, Solano TR. Fungemia secondary to gastrointestinal Mucor indicus infection. Clin Infect Dis 2006;42:154-5.
16. Dogan MC, Leblebisatan G, Haytac MC, Antmen B, Surmego-zler O. Oral mucormycosis in children with leukemia: report of 2 cases. Quintessence Int 2007;38:515-20.
17. Auluck A. Maxillary necrosis by mucormycosis. A case report and literature review. Med Oral Patol Oral Cir Bucal 2007;12:E360-4.
18. Salisbury PL 3rd, Caloss R Jr, Cruz JM, Powell BL, Cole R, Kohut RI. Mucormycosis of the mandible after dental extractions in a patient with acute myelogenous leukemia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997;83:340-4.
19. Jones AC, Bentsen TY, Freedman PD. Mucormycosis of the oral cavity. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1993;75:455-60.
20. Kontoyiannis DP, Wessel VC, Bodey GP, Rolston KV. Zygomycosis in the 1990s in a tertiary-care cancer center. Clin Infect Dis 2000;30:851-6.
21. Sugar AM. Focus on fungal infections: an update on diagnosis and treatment. Clin Infect Dis 1992;14:S126-9.
22. Ibrahim AS. The iron chelator deferiasirox protects mice from mucormycosis through iron starvation. J Clin Invest 2007;117:2649-57.
23. Spellberg B, Andes D, Perez M, Anglim A, Bonilla H, Mathisen GE, et al. Safety and outcomes of open-label deferiasirox iron chelation therapy for mucormycosis. Antimicrob Agents Chemother 2009;53:3122-5.
24. Monheit JE, Cowan DF, Moore DG. Rapid detection of fungi in tissues using Calcofluor white and fluorescence microscopy. Arch Pathol Lab Med 1984;108:616-8.
25. Kim YK, Parulekar S, Yu PKW, Pisani RJ, Smith TF, Anhalt JP. Evaluation of Calcofluor white stain for detection of *Pneumocystis carinii*. Diagn Microbiol Infect Dis 1990;13:307-10.
26. Chander J, Chakrabarti A, Sharma A, Saini JS, Panigarhi D. Evaluation of Calcofluor staining in the diagnosis of fungal corneal ulcer. Mycoses 1993;36:243-5.
27. Monheit JG, Brown G, Kott MM, Schmidt WA, Moore DG. Calcofluor white detection of fungi in cytopathology. Am J Clin Pathol 1986;85:222-5.
28. Sautter RL, Kwee HG. Calcofluor white stain for fungi [Letter to the editor]. Am J Clin Pathol 1987;87:295-6.
29. Ruchel R, Margraf S. Rapid microscopical diagnosis of deep-seated mycoses following maceration of fresh specimens and staining with optical brighteners. Mycoses 1993;239-42.
30. Hamer EC, Moore CB, Denning DW. Comparison of two fluorescent whiteners, Calcofluor and Blankophor, for the detection of fungal elements in clinical specimens in the diagnostic laboratory. Clin Microbiol Infect 2006;12:181-4.

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