

Archives of Clinical Case Reports

Case Report

Cutaneous Mucormycosis of the Upper Extremity Affecting the Donor Site after Performing Radial Forearm Free Flap

Alejandro Thomas Santamaría^{1*}, Vicente Navarro², Laura García Monleón³, Carlos Navarro Vila⁴ and M. Empar Chenoll Cuadros⁵

¹Department of Oral and Maxillofacial Surgery, Hospital General de Elche, Alicante, Spain

²Department of infectious diseases, Hospital Vinalopo, Elche, Spain

³Department of Oral and Maxillofacial Surgery, Hospital San Juan de Alicante, Alicante, Spain

⁴Department of Oral and Maxillofacial Surgery, Hospital General Universitario, Gregorio Marañón, Madrid, Spain

⁵Biopolis-ADM Nutrition, Paterna, Valencia, Spain

***Address for Correspondence:** Alejandro Thomas Santamaria, Department of Oral and Maxillofacial Surgery, Hospital General Universitario de Elche, Alicante, Spain, Tel: +34 617 18 38 61; E-mail: alejthoms@gmail.com

Received: 31 May 2019; **Accepted:** 29 June 2019; **Published:** 30 June 2019

Citation of this article: Wang, ML., Chan, MP., Patel, RM., Lowe, L., Andea, AA., Fullen, DR. (2019) Novel Collision Tumor: Melanocytic Tumor of Uncertain Malignant Potential (MELTUMP) and Leiomyoma. Arch Clin Case Rep, 2(2): 017-020.

Copyright: © 2019 Wang ML, et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Mucormycosis is a severe infection that is commonly observed in diabetic patients with ketoacidosis. It has recently emerged in immunosuppressed patients such as transplant recipients or patients infected by the human immunodeficiency virus.

Cutaneous mucormycosis is relatively uncommon, representing less than 10% of reported cases. It occurs mainly in patients with superficial soft tissue trauma, and spores present in the skin are deposited in the wound.

We report two patients with mucormycosis and severe damage to the forearm after removal of a microsurgical flap performed in Hospital General Universitario Gregorio Marañón. Neither had suffered intravenous puncture of the affected limb. Both patients presented with characteristics of the superficial and gangrenous forms of the disease and in both cases the wound progressed from an enlarging eschar to ulcerated skin.

Antibiotic therapy with intravenous liposomal amphotericin B was administered, and infection was controlled using aggressive debridement. Neither of the patients underwent upper limb amputation. Case 1 died of multiorgan failure after rapid progression of infection and case 2 progressed well.

Keywords: Mucormycosis, Immunocompromised host, Antifungal agents, Surgical treatment, Microsurgical free flap

Introduction

Mucormycosis is an uncommon opportunistic infection caused by fungi of the class Zygomycetes, order Mucorales. It is the third most common invasive fungal infection after aspergillosis and candidiasis. The most commonly recovered microorganisms include *Mucor*, *Rhizopus*, *Rhizomucor*, *Absidia*, *Apophysomyces*, *Cunninghamella*, and *Saksenaea*. The most frequent clinical presentation is rhino-orbito-

cerebral infection followed by cutaneous, pulmonary, disseminated, and gastrointestinal infection. Cutaneous mucormycosis accounts for less than 10% of all cases [1].

Mucormycosis mainly affects immunocompromised patients [2] or patients with predisposing conditions, such as diabetes mellitus, intravenous drug use, malignancy, neutropenia, high-dose corticosteroid therapy, ketoacidosis, deferoxamine therapy, organ

transplantation, trauma, and burns. Immunocompetent patients rarely develop mucormycosis. However, when this infection does occur in the immunocompetent host, we must investigate any break in skin integrity or direct inoculation of mould spores into damaged skin [3].

Clinical forms of cutaneous mucormycosis vary and affect the upper layers of the skin in the form of plaques, pustules, nodules, blisters, ulcers, necrotizing fasciitis, osteomyelitis, and disseminated infection [4]. Multidisciplinary management is necessary to prevent dissemination and improve survival rates.

Case Report

We report two patients with mucormycosis and severe damage to the forearm after removal of a microsurgical flap performed in Hospital General Universitario Gregorio Marañón (Madrid).

Patient 1

A 79-year-old man was diagnosed with squamous cell carcinoma of the tongue. His clinical history included acute pancreatitis and cholelithiasis. He underwent surgery performing tracheostomy, bilateral functional neck dissection, resection of the tumor with safety margins, and reconstruction of the tongue with a microsurgical flap from the left forearm. A dermoepidermal graft was used to cover the bed of the donor site. At 38 days after surgery, he was admitted to the intensive care service with pneumonia requiring mechanical ventilation. Analysis of the bronchial aspirate revealed *Stenotrophomonas maltophilia* and *Pseudomonas aeruginosa*. He also presented a rapidly developing area of necrosis (3x4cm) surrounded by erythema on his left hand (Figure 1). There was no history of a peripheral catheter in this member. Mycologic culture identified *Rhizomucor* species and bacterial culture identified *Pseudomonas fluorescens*. Given the lack of significant clinical improvement, a skin biopsy was taken from the indurated border of the lesion. This revealed nonseptate hyphae consistent with a diagnosis of primary cutaneous mucormycosis (Figures 2 and 3). The patient received intravenous liposomal amphotericin B at 1.5µg/kg/d per day and underwent extensive surgical debridement. He died on the eighth day of admission in intensive care from multiorgan failure.



Figure 1: Case1. Donor site of the left hand and forearm. Area of necrosis (3x4cm) surrounded by erythema.



Figure 2: Skin biopsy: Arrow shows an area infiltrated by fungi. Inset: The fungi are often clearly visible after hematoxylin-eosin staining. The hyphae are very broad, non-septate, and bent at right angles.

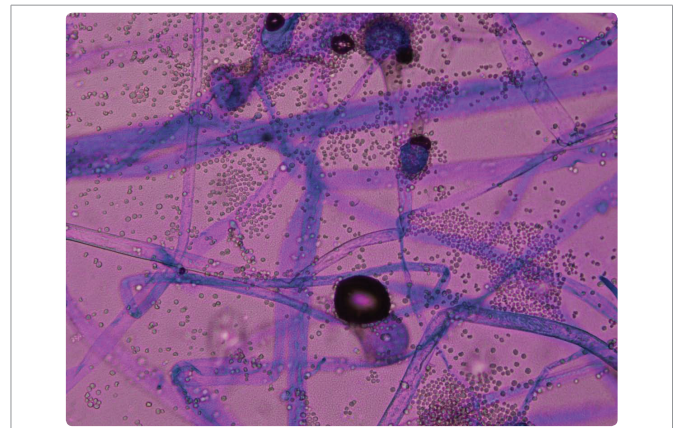


Figure 3: Direct fluorescent microscopic examination using calcofluor white stain. These photomicrographs reveal a mature sporangium of *Mucor* species. The mycelium is wide, aseptate, ribbon-like, and non-pigmented, with wide angle branching typical of the species. The spores are dark.

Patient 2

A 75-year-old man with a history of hypertension, hyperlipidemia, and chronic atrial fibrillation was diagnosed with squamous cell carcinoma of the floor of mouth and the right half of the tongue (T4N3Mo). He underwent tracheostomy, left functional neck dissection and right radical neck dissection. The tumor was resected with safety margins, and the procedure included a right marginal mandibulectomy and reconstruction with a microsurgical flap taken from the left forearm. We covered the flap donor site with a dermoepidermal graft from the anterolateral thigh. The patient had to undergo surgery immediately due to bleeding and was admitted to intensive care with aspiration pneumonia. On the eighth day in intensive care, hemorrhagic bullous lesions with surrounding erythema and an induration measuring 3x3 cm were observed on the donor forearm and the right hand (Figure 4), although there was no history of puncture. Culture of the area revealed growth of *Mucor* species and biopsies of the skin and dorsal interosseous muscle of the left hand confirmed the diagnosis of mucormycosis (Figures 5 and 6). Outcome was favorable following treatment with liposomal amphotericin B (1.5 mg/kg/d) during 8 weeks and extensive surgical debridement.



Figure 4: Case 2. Donor site of the right hand and forearm. Hemorrhagic bullous lesions with surrounding erythema and an induration measuring 2x3 cm.



Figure 5: Skin biopsy: Arrow shows an area infiltrated by fungi. Inset: The fungi are often clearly visible after hematoxylin-eosin staining. The hyphae are very broad, non-septate, and bent at right angles.

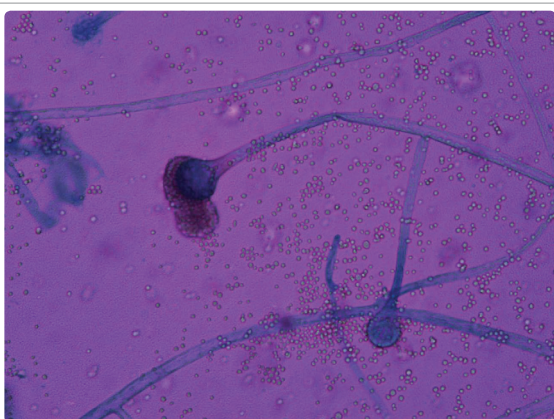


Figure 6: Direct fluorescent microscopic examination using calcofluor white stain. These photomicrographs reveal a mature sporangium of *Mucor* species. The mycelium is wide, aseptate, ribbon-like, and non-pigmented, with wide angle branching typical of the species. The spores are dark.

A review of operating room activity during the months of March and April revealed no other cases of surgical wound mucormycosis.

We also collected information on the dressings used on the surgical wounds of the forearm in the operating room and critical care unit. Environmental samples were taken from both areas and sent to the microbiology department for analysis. No growth of Mucorales was detected. Mucormycosis has not been observed in the hospital since these two patients were treated.

The coincidence in time and space of two cases of surgical wound infections by mucormycosis should be considered an outbreak. Both patients underwent surgery in the same service using the same technique, and infection by mucormycosis occurred at the same site (surgical wound on the forearm). These observations point to a possible origin in the surgical area. However, rapid progress of mucormycosis in the critical care unit also seems a plausible hypothesis.

Discussion

Mucormycosis is a severe infection that is commonly observed in diabetic patients with ketoacidosis. It has recently emerged in immunosuppressed patients such as transplant recipients or patients infected by the human immunodeficiency virus [5]. *Rhizopus* is the most common species, although several members of the order Mucorales can affect humans. These pathogens are commonly isolated from environmental sources, but rarely cause infection in the presence of normal immunity.

Cutaneous mucormycosis is relatively uncommon, representing less than 10% of reported cases. It occurs mainly in patients with superficial soft tissue trauma, and spores present in the skin are deposited in the wound.

The first cases of cutaneous mucormycosis to arouse medical attention were attributed to elastic adhesive tape in the late 1970s [6]. Injuries in immunosuppressed patients are a well-documented cause of cutaneous mucormycosis. In the setting of contaminated wounds, use of broad-spectrum antibiotics, shock/sepsis, and trauma in healthy patients are also sources of primary cutaneous mucormycosis.

Clinical presentation is often a hemorrhagic or necrotic lesion with indurated edges, edema, and erythema. However, clinical appearance alone cannot confirm the diagnosis, because the manifestations are usually no different from those of other soft tissue infections.

Histology reveals areas of necrosis with frequent mitotic figures that grow into non-septate hyphae (10-20 μ m) and thick spores that are visible with hematoxylin-eosin. The spores are bent at right angles and can be more easily visualized with PAS and Grocott staining. Invasion of blood vessels with occlusion causing ischemia can also be observed, as can thrombosis, infarction, necrosis, and hemorrhage in the affected area. Fluorescent microscopy and staining with calcofluor white can quickly identify fungi in frozen samples.

We describe two forms of cutaneous mucormycosis: a superficial form and a gangrenous form. Generally, the superficial form is painless and can occur in healthy individuals. Patients with superficial cutaneous mucormycosis usually recover with local surgical debridement, intravenous amphotericin B, or a combination of both. Gangrenous cutaneous mucormycosis is a more severe form, occurring only in immunocompromised patient. It manifests with signs of cellulitis and necrotizing fasciitis in the form of papules that progress rapidly to ulceration, vascular invasion, and thrombosis. Hematogenous spread is common and the mortality rate is high.

The literature describes survival rates of 33% after amputation of the affected limb and combination with intravenous amphotericin B [3].

Antibiotic therapy with intravenous liposomal amphotericin B was administered, and infection was controlled using aggressive debridement. Neither of the patients underwent upper limb amputation. The development of zygomycosis is not clearly understood, although it has been linked to factors such as cancer treatment, use of broad-spectrum antimicrobial agents, increasing use of immunosuppressive drugs, and environmental factors [7].

Few clinical trials analyze antifungal treatment in this condition, probably due to the rarity of the disease and the large number of variables. The choice of appropriate antifungal agent is based on the interpretation of *in vitro* antifungal activity, behavioral and experimental animal models, and experience. Liposomal amphotericin B is currently the drug of choice. It has demonstrated *in vitro* activity against causal microorganisms and is better tolerated due to its low toxicity [2].

The new third-generation triazoles, including posaconazole, have a broad spectrum of activity against Zygomycetes with less toxicity than amphotericin B [8]. Some studies suggest that the combination of posaconazole and other antifungals may be effective in the treatment of invasive zygomycosis. However, few studies demonstrate the effectiveness of combining antifungals [9].

Alternatives include iron chelator, whose activity differs from that of deferoxamine and could prove effective against zygomycosis [10]. Hyperbaric oxygen could also prove useful as adjunctive therapy in the treatment of mucormycosis, given that concentration of oxygen can slow fungal growth while enhancing the activity of phagocytes and tissue oxygenation [11]. The use of cytokines such as interferon gamma and granulocyte-stimulating factor and macrophages [12] have theoretical advantages in the treatment of mucormycosis, although no randomized clinical studies have clarified the role of these measures.

Conclusion

Mucormycosis typically affects immunocompromised patients. However, it can also affect healthy patients with trauma and a history of environmental exposure. Treatment of mucormycosis is based on four principles: early diagnosis, elimination of predisposing factors, extensive surgical debridement, and appropriate antifungal treatment.

Conflict of Interest

The authors declare to have no conflict of interests concerning the data published in this article.

References

1. Raizman, NM., Parisien, M., Grafe, MW., Gordon, RJ., Rosenwasser, MP. (2007) Mucormycosis of the upper extremity in a patient with alcoholic encephalopathy. J Hand Surg Am, 32(3): 384-388.
2. Moran, SL., Strickland, J., Shin, AY. (2006) Upper-extremity mucormycosis infections in immunocompetent Patients. J Hand Surg Am, 31(7): 1201-1205
3. Greenberg, RN., Scott, LJ., Vaughn, HH., Ribes, JA. (2004) Zygomycosis (mucormycosis): emerging clinical importance and new treatments. Curr Opin Infect Dis, 17(6): 517-525.
4. Prabhu, RM., Patel, R. (2004) Mucormycosis and entomophthoromycosis: a review of the clinical manifestations, diagnosis and treatment. Clin Microbiol Infect, 10(1): 31-47.
5. Arnáiz-García, ME., Alonso-Peña, D., González-Vela M del, C., García-Palomo, JD., Sanz-Giménez-Rico, JR., Arnáiz-García, AM. (2009) Cutaneous mucormycosis: report of five cases and review of the literature. J Plast Reconstr Aesthet Surg, 62(11): e434-441.
6. Gartenberg, G., Bottone, EJ., Keusch, GT., Weitzman, I. (1978) Hospital acquired mucormycosis of skin and subcutaneous tissue. N Engl J Med, 299(20): 1115-1118.
7. Chew, HH., Abuzeid, A., Singh, D., Tai, CC. (2008) Surgical wound mucormycosis necessitating hand amputation: a case report. J Orthop Surg (Hong Kong), 16(2): 267-269.
8. Sun, QN., Najvar, LK., Bocanegra, R., Loebenberg, D., Graybill, JR. (2002) In vivo activity of posaconazole against *Mucor* spp. in an immunosuppressed-mouse model. Antimicrob Agents Chemother, 46(7): 2310-2312.
9. Perkhofe, S., Locher, M., Cuenca-Estrella, M., Rüchel, R., Würzner, R., Dierich, MP., et al. Posaconazole enhances the activity of amphotericin B against hyphae of zygomycetes in vitro. Antimicrob Agents Chemother, 52(7): 2636-2638.
10. Lewis, RE., Pongas, GN., Albert, N., Ben-Ami, R., Walsh, TJ., Kontoyiannis, DP. (2011) Activity of deferasirox in Mucorales: influences of species and exogenous iron. Antimicrob Agents Chemother, 55(1): 411-413.
11. Bentur, Y., Shupak, A., Ramon, Y., Abramovich, A., Wolfen, G., Stein, H., et al. (1998) Hyperbaric oxygen therapy for cutaneous/soft-tissue zygomycosis complicating diabetes mellitus. Plast Reconstr Surg, 102(3): 822-824.
12. Abzug, MJ., Walsh, TJ. (2004) Interferon-gamma and colony-stimulating factors as adjuvant therapy for refractory fungal infections in children. Pediatr Infect Dis J, 23(8): 769-773.