Open Journal of
Clinical & Medical
Case Reports

Volume 5 (2019)
Issue 7

ISSN: 2379-1039

Severe cunninghamella infection in an HIV patient: After cenotes exposure in Mexico

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Abstract

Mucormycosis is a highly lethal fungal infection characterized by tissue angioinvasion. The Cunninghamella genus is resistant to antifungals when compared to other Mucorales. It occurs more frequently in patients with diabetes and malignant hematological disease, and is less common in patients infected with HIV. Early diagnosis and antifungal therapy are the key to successful treatment. Traditional diagnostic methods, such as the identification of morphology, can be time consuming and require training and expertise. Thus, molecular methods provide an opportunity for the early, accurate, and differential diagnosis of Cunninghamella spp. and other Mucorales. This study presents a case of disseminated Cunninghamella bertholletiae infection in a patient with HIV-AIDS. The patient reported having visited caves with bats and swam in underground rivers called cenotes in Playa del Carmen, Mexico. The patient suffered from excoriations in the dorsal area. The primary lesion was cutaneous, which was later associated with a kidney abscess. Histopathology, microbiology and molecular studies showed the presence of Mucormycosis, identified as Cunninghamella bertholletiae. Following treatment with liposomal Amphotericin B and posaconazole, the patient had a favorable outcome.

Keywords

cunninghamella; HIV-AIDS; molecular diagnosis; mucorales; mucormycosis

Introduction

Mucormycosis is a high mortality fungal infection characterized by tissue angioinvasion. In terms of commonality, the Rhizopus genus causes disease most frequently in humans, followed by the Mucor and Lichtheimia genera [1]. Angioinvasion often occurs in infections caused by the Cunninghamella spp. genus. This is due to its virulence, as well as its resistance to antifungals when compared to other Mucorales [2]. It occurs most frequently in immunocompromised patients, including patients with diabetes or malignant hematological diseases. It is less common in patients infected with HIV who have received prophylaxis or

treatment with triazoles [3]. Early diagnosis and antifungal therapy are the key to successful treatment. Traditional diagnostic methods, such as the identification of morphology, are time consuming and require training and experience. Because of this, molecular methods provide an opportunity for the early, accurate, and differential diagnosis of Cunninghamella spp. and other Mucorales [4,5]. This research presents a case study of the Cunninghamella bertholletiae infection in a patient with HIV-AIDS.

Case Description

A 34-year-old man from Córdoba, Argentina, presented with dyspnea and fever. He had no past medical history, allergies, or toxic habits. The patient traveled to Playa del Carmen, Mexico, three weeks prior to his symptoms. He reported having visited caves with bats and swam in underground cenotes. Excoriations in the patient's dorsal area were presented. It began with respiratory failure and needed invasive mechanical ventilation. A computed tomography (CT) of the thorax was performed, which showed a bilateral interstitial alveolar infiltrates. Empirical antimicrobial therapy was initiated with cefepime 2 g twice a day, amphotericin B deoxycholate 0,5 mg/kg/day, and Trimethoprim/Sulfamethoxazole plus steroids. Serology was requested for examining the patient's HIV infection, revealing a positive TCD4 lymphocyte count of 57 C/uL 6%. A bronchoalveolar lavage was performed, resulting in a positive Pneumocystis j polymerase chain reaction. Antiretroviral therapy was started with atazanavir 400 mg/day plus ritonavir 100 mg/day plus abacavir 300 mg twice a day plus lamivudine 300 mg /day. The patient had favorable clinical outcome until day 30 of hospitalization, when the patient began to have daily febrile episodes in addition to a cutaneous erosion of 10 x 8 cm covered with hemorrhagic scabs in the interscapular region. These scabs progressed to become confluent ulcers with raised and elevated borders, perilesional erythema, and fundus with abundant fibrin (Figure 1). At that time, chest and abdominopelvic CT were performed, which showed the patient's right kidney to be enlarged, measuring 14.8 cm in longitudinal diameter. A hypodense area of 6 cm x 4.5 cm and 5.6 cm (volume of 85cc) at the cortical level showed in posterior mesorenal region, which was compatible with a renal abscess (Figure 2). A percutaneous biopsy was performed on both the renal lesion and a skin lesion. The histopathology, microbiology and molecular studies, all showed the presence of Mucormycosis, identifying Cunninghamella bertholletiae. After diagnosing the patient with Mucormycosis, treatment with liposomal Amphotericin b 3 mg/kg/day was administered. Following treatment, the patient was afebrile and hemodynamically stable without requiring invasive mechanical ventilation. In terms of skin lesions, there was a remission in diameter and depth with good tissue granulation (Figure 3). The patient's discharge from the hospital was decided, and posaconazole 300 mg/twice a day was prescribed for 24 hours. After that, the patient was instructed to continue with 300 mg/day and complete treatment until the lesion was completely resolved.

Mycological Studies: The result of the microbiology report presented the development of a filamentous fungi, non-septate hyphae, with 90° angulations (Figure 4). The histopathology report showed renal necrotic tissue, mixed infiltrate, formed by lymphocytes and neutrophils. Numerous elongated spherical and tubular structures with erratic angulation were reported, both PAS positive stain. Thrombosed vascular elements with the previous PAS positive elements in the vascular lumen were shown (Figure 5). There were hyperplastic epidermis replaced by fibrino leukocytic infiltrate where PAS positive spores and hyphae were

visualized, occupying vascular lumens (Figure 6).

Molecular Biology: The isolate was molecularly identified by sequencing the 5.8S RNA gene and its adjacent internal transcribed spacer 1 and 2 regions (ITS1 and ITS2). Genomic DNA was obtained by briefly using a phenol-chloroform based protocol [6]. PCR amplifications of the ITS regions were done in an Applied Biosystems thermos cycler (Tecnolab-AB, Buenos Aires, Argentina) in a 25 µl volume by using the PFU DNA polymerase (PBL, Buenos Aires) manufacturer's recommendations and universal ITS1 and ITS4 primers [7]. The cycling program included an initial 2 min step at 95ºC, followed by 30 cycles of 30 s at 95ºC, 30 s at 55ºC, and 2 min at 72ºC. The final step took 10 min at 72ºC. The PCR fragment obtained was purified and subsequently sequenced in an Applied Biosystems thermos cycler (Tecnolab-AB, Argentina). The sequence obtained was compared against the NCBI data base using the BLAST tool. It was in total agreement (100% homology) with the Cunningamhella bertholletiae strain CBS 182.84 ITS sequence deposited at GenBank under the number JN205877.1.

Discussion

Cunninghamhella spp. is a ubiquitous environmental fungus [8]. The infection is acquired through inhalation and is less frequently a direct inoculation of microsporangia [9]. C. bertholletiae infection rarely causes Mucormycosis. Mucormycosis generally corresponds to rhinocerebral, pulmonary, gastrointestinal, cutaneous, and disseminated infections. This type of infection has been found almost exclusively in patients with severe immunosuppression, much like the patient infected with HIV-AIDS in this case study [10]. Cutaneous involvement is relatively infrequent [11]. Infections occur less frequently in patients who are diabetic or those who have suffered burns or penetrating trauma. The disseminated form refers to a compromise of two or more non-contiguous organs or tissues, generally with retroperitoneal visceral involvement, among which is the renal form [12]. Diagnosis is usually made through morphological and physiological crop recognition [13]. In many cases, this does not allow the genus or species to be identified, despite being an important aspect of selecting the correct antifungal treatment. A study conducted by Kontoyiannis et al. compared the use of internal ribosomal transcribed spacer sequencing with classical morphological identification techniques. They found that upto 20% of Mucorales are misidentified [10]. Within this case study, genomic sequencing of the fungus was carried out, which allowed the treatment administered to be adjusted according to genus and species identification. The pathological anatomy confirms the diagnosis given, which positively demonstrates angioinvasion produced by Mucorales in the patient.

Figures

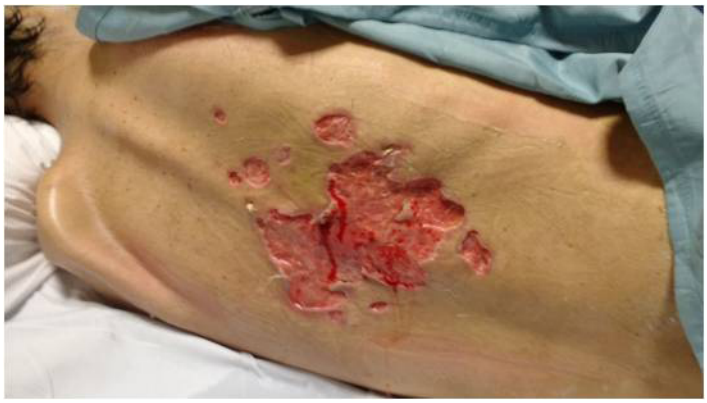

Figure 1: Cutaneous erosion of 10 x 8 cm covered with hemorrhagic scabs in the interscapular region that progressed to become confluent ulcers with raised and elevated borders, perilesional erythema, and fundus with abundant fibrin in HIV-AIDS patient with a Cunninghamella bertholletiae infection.

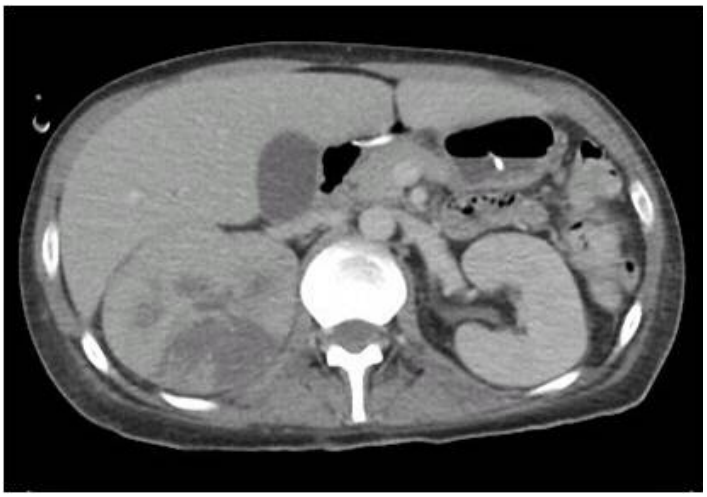

Figure 2: Abdominopelvic CT, which show the patient's right kidney to be enlarged, measuring 14.8 cm in longitudinal diameter. A hypodense area of 6 cm x 4.5 cm and 5.6 cm (volume of 85cc) at the cortical level present in posterior mesorenal region, which was compatible with a renal abscess.

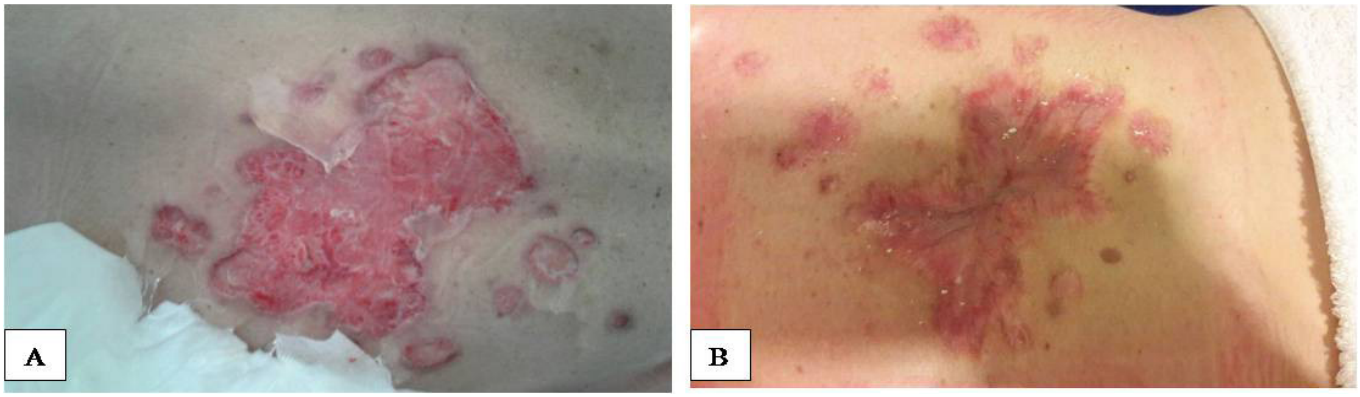

Figure 3: Dorsal ulcer after (A) 14 days of treatment and (B) 6 months of treatment with liposomal amphotericin B that show a remission in diameter and depth with good tissue granulation.

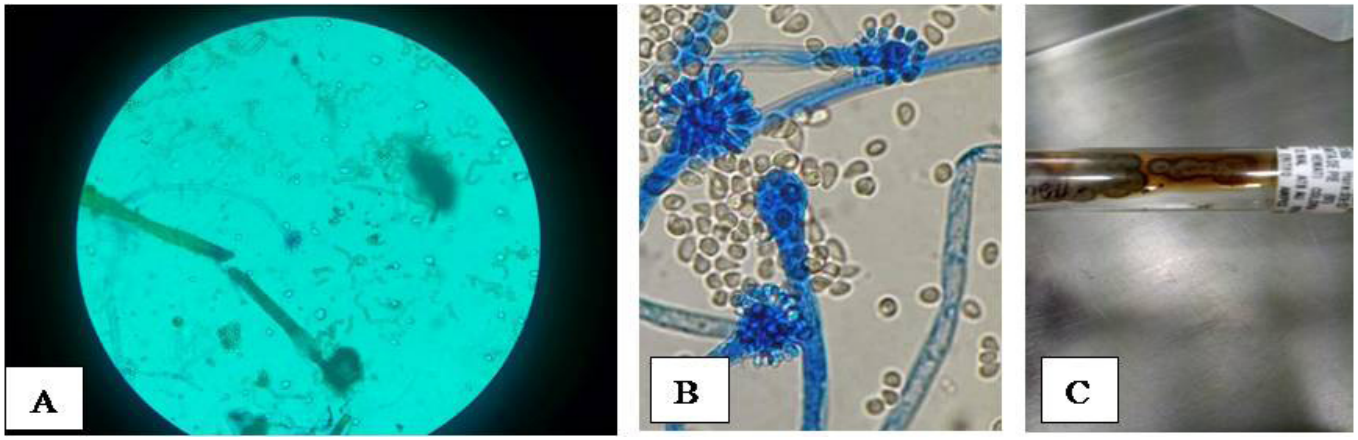

Figure 4: (A&B) The result of the microbiology report presented the development of a filamentous fungi, non-septate hyphae, with 90° angulations. Simple and branched sporangiophores in several maturation phases that are up to 20 µm wide, straight, with whorled or solitary branches. The vesicles are subglobose to pyriform, terminals are up to 40 µm and laterals are 10-30 µm in diameter. The sporangia are globose (7-11 µm in diameter), or ellipsoidal (9-13 x 6-10 µm), warty or short equine, and are hyaline alone but brown in mass. 40 x. (C) Dark gray colonies of C. bertholletiae, of fast growth, with a dusty aspect that produces sporangiophores, erect, straight, and branched, in medium Saboreau incubated at 37 ° C.

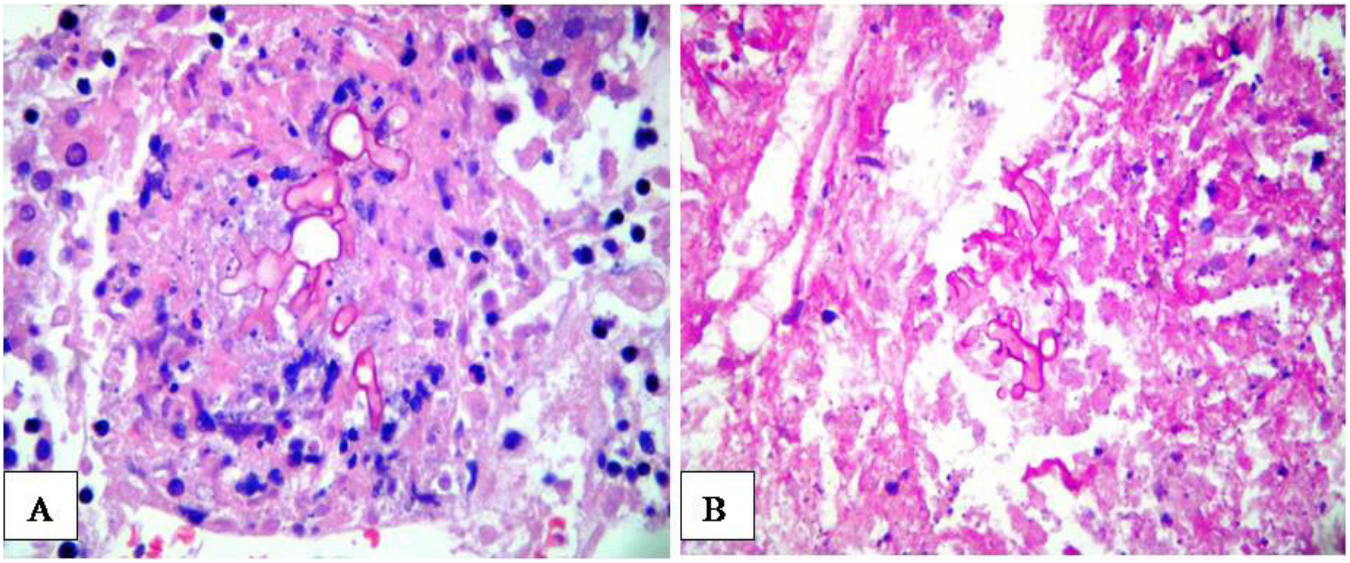

Figure 5: Kidney biopsy: (A) hematoxylin eosin 40x, and (B) PAS stain 40x.Renal necrotic tissue, mixed infiltrate, formed by lymphocytes and neutrophils. Numerous elongated spherical and tubular structures with erratic angulation were reported, both PAS positive stain. Thrombosed vascular elements with the previous PAS positive elements in the vascular lumen were shown.

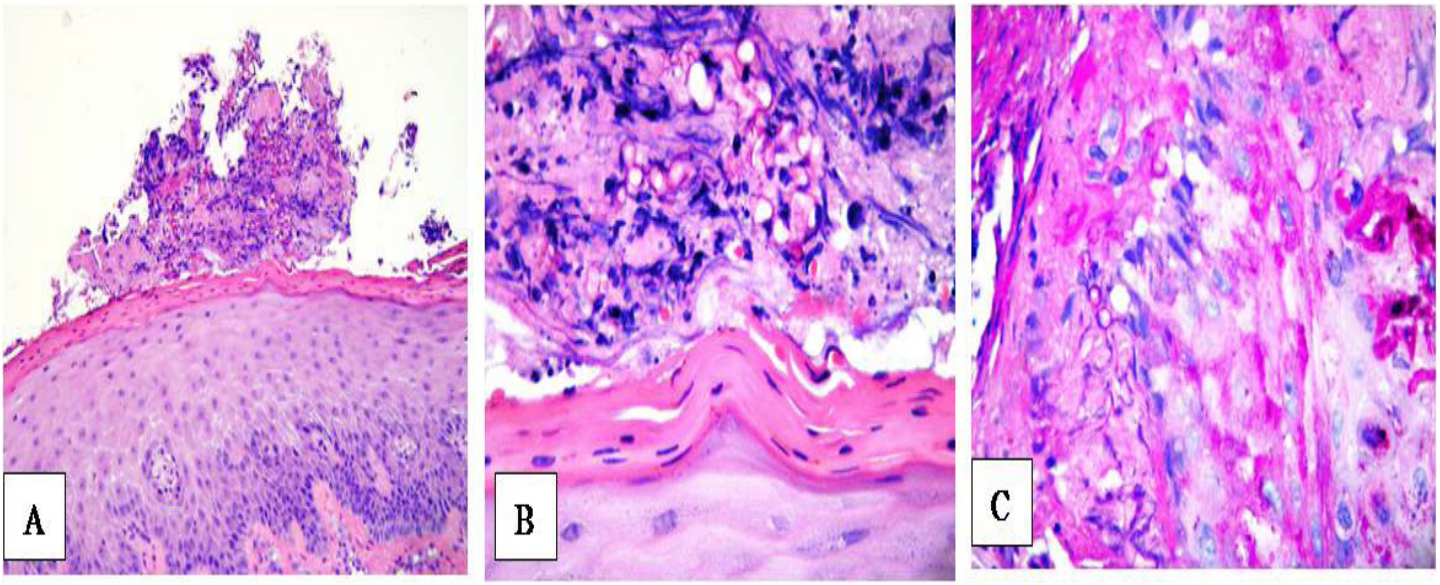

Figure 6: Skin biopsy: (A) hematoxylin eosin 10x, (B) hematoxylin eosin 40x, and (C) PAS 40x. Hyperplastic epidermis replaced by fibrino leukocytic infiltrate where PAS positive spores and hyphae were visualized, occupying vascular lumens.

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Manuscript Information: Received: March 20, 2019; Accepted: May 13, 2019; Published: May 15, 2019

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Citation: Giordano GN, Abiega C, Chipre E, Garcia-Effron G, Caeiro JP. Severe cunninghamella infection in an HIV patient: After cenotes exposure in Mexico. Open J Clin Med Case Rep. 2019; 1545.