CASE REPORT

A tip from the nose: rhinocerebral mucormycosis in a patient with alcoholic liver cirrhosis and cocaine abuse, an uncommon association

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SUMMARY

We present the case of a 28-year-old man with a long-standing history of cocaine abuse and Child-Pugh class C alcoholic liver cirrhosis who developed severe lower respiratory tract infection complicated with septic shock and multiple organ dysfunction. He was managed in the intensive care unit. On the eighth day after admission, he developed a nose discolouration, which was initially thought to be associated with high-dose vasopressors. Despite the reduction of vasopressors, the lesion progressed rapidly. It was later diagnosed as rhinocerebral mucormycosis. Amphotericin B was administered, but unfortunately the patient succumbed to the complications postinfection. The association between alcoholic liver cirrhosis and rhinocerebral mucormycosis should be known and prompt recognition warrants immediate treatment.

BACKGROUND

Alcohol abuse is the most common cause of liver cirrhosis, but now the less common aetiologies are increasingly being recognised. Hepatic steatosis develops in 90%–95% of heavy drinkers, which subsequently progresses to steatohepatitis, liver cirrhosis and hepatocellular carcinoma in some cases. Alcohol-induced liver damage is caused by several mechanisms, mainly by altered oxidative stress and mitochondrial dysfunction. Patients with advanced liver disease frequently have neutropenia, caused by splenic sequestration and increased neutrophil apoptosis, which poses a higher risk for bacterial and fungal infections.^{1 2} Rhinocerebral mucormycosis is an angioinvasive fungal infection caused by the ubiquitous fungi of the family Mucoraceae, order Mucorales and class Zygomycetes, with the *Rhizopus* species being the most common. These fungi are usually found in decaying organic matter and are acquired by inhalation of the airborne spores. Mucormycosis is classified based on the affected anatomic as rhinocerebral, pulmonary, cutaneous, gastrointestinal and disseminated mucormycosis. The infection propagates rapidly by direct extension to the vessels causing thrombosis and subsequent necrosis of the adjacent tissue. The primary risk factors for the development of rhinocerebral mucormycosis include immunocompromised states such as poorly controlled diabetes mellitus with or without ketoacidosis, malignant haematological diseases with or without bone marrow

transplantation, solid organ transplant, major trauma, extensive burns, iron overload, and intravenous drug use among others. The cardinal sign of rhinocerebral mucormycosis is a black eschar on the face caused by necrosis of the subjacent tissue, although not all patients develop it. Patients may also have fever, headache, chills, lethargy, visual loss, proptosis, unilateral facial pain, ophthalmoplegia and cranial nerve palsies in the advanced stages. The diagnosis is usually made by visualising the tissue biopsy under the microscope. The biopsy reveals the presence of broad, irregularly branching aseptate hyphae forming 90° angles, arising from the main body. Amphotericin B alone or in combination with surgery are the most frequently used treatment regimens and has demonstrated better outcomes.^{3–7} The correlation between alcoholic liver cirrhosis and rhinocerebral mucormycosis is not widely known. Although this infection is uncommon, rapid recognition and appropriate treatment can result in better outcomes. The scope of this case report is to make healthcare providers aware of this association.

CASE PRESENTATION

A 28-year-old man with a long-standing history of cocaine abuse and alcoholic liver cirrhosis presented with a 2-week history of a lower respiratory tract infection. He had been on oral prednisone for alcoholic hepatitis for the previous 3 months. On examination, the patient appeared wasted and lethargic with the presence of moderate respiratory distress, jaundice, nosebleed and flapping tremor. The temperature was 36.4°C and the blood pressure 96/70 mm Hg, the pulse measured 102 beats per min and the respiratory rate 23 breaths per min. Lung auscultation revealed diminished breath sounds with coarse crackle in both lung bases, predominately on the left. Abdominal distension was noted with the presence of ascites without organomegaly. No focal neurological signs were observed. Initial laboratory studies revealed leucocytosis with neutrophilia and lymphopaenia, mild anaemia, moderate thrombocytopenia at $52.91 \times 10^3/\mu\text{L}$, hypoalbuminaemia at 3.30 g/dL, total proteins 5.2 g/dL, hyperbilirubinaemia at 14.80 mg/dL with a direct bilirubin of 9.10 mg/dL, lactate dehydrogenase elevated at 904 U/L and aspartate aminotransferase slightly elevated at 75 U/L. Alanine aminotransferase, alkaline

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Table 1 Medications used during hospital stay

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
Total parenteral nutrition	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Rifaximin 400mg PO	✓									
Lactulax 20mg PO	✓									
Vitamin K 10 mg IV	✓									
TMP/SMX 800/100mg IV*	✓									
Albumin 20% IV		✓								
Terlipressin 2 mg IV			✓	✓	✓	✓	✓	✓	✓	✓
Furosemide 20 mg IV	✓	✓	✓			✓				
Meropenem 1 g IV	✓	✓	✓	✓	✓	✓	✓	✓		
Ceftazoline 600 mg IV	✓	✓	✓	✓	✓	✓	✓	✓		
Romiplostim 300 mg SC	✓	✓	✓	✓	✓	✓				
Clindamycin 900mg IV		✓	✓	✓		✓				
Anidulafungin 200 mg IV		✓	✓	✓	✓	✓	✓	✓	✓	✓
Hydrocortisone 100 mg IV		✓	✓	✓	✓	✓	✓ 50 mg	✓ 50 mg	✓ 50 mg	✓ 50 mg
Norepinephrine 16 mg IV		✓ 8 mg	✓	✓	✓	✓	✓	✓	✓	✓
Dexmedetomidine 400 mg IV	✓	✓	✓	✓	✓	✓				
Vancomycin 1 g IV				✓						✓
Pooled human plasma		✓		✓	✓	✓	✓	✓	✓	
Human prothrombin complex				✓						
Fresh frozen plasma				✓						
Platelet transfusions				✓	✓	✓	✓	✓	✓	
Packed red blood cells				✓	✓	✓	✓	✓		
Colistin 150 mg IV								✓		
Ciprofloxacin 400 mg IV								✓	✓	✓
Colistimethate 150 mg IV									✓	✓
Levetiracetam 500 mg IV									✓	✓
Metronidazole 250 mg IV									✓	✓
Amphotericin B 200 mg IV†									✓	✓

*Trimethoprim/sulfamethoxazole.

†3 mg/kg (70 kg).

✓, administered; IV, intravenously; PO, per os; SC, subcutaneous.

phosphatase, gamma glutamyl transferase, glucose and electrolytes were normal. Blood urea nitrogen was elevated at 116.2mg/dL, with a normal creatinine levels at 0.6mg/dL. Prothrombin time and activated partial thromboplastin were elevated at 40 and 63.1 s, respectively, INR was 3.44. The initial chest and abdominal CT scan revealed bilateral pneumonia and ascites. The patient was diagnosed with Child-Pugh class C liver cirrhosis, MELD score of 30 points with a predicted 3-month mortality of 52.6%, grade II hepatic encephalopathy, septic shock, acute renal dysfunction and moderate thrombocytopenia with bleeding coagulopathy. Due to the patient's clinical status, he was admitted to the intensive care unit for appropriate management. The initial treatment included respiratory and cardiovascular monitoring with fluid resuscitation for septic shock, early total parenteral nutrition and a stress-dose hydrocortisone due to the history of prednisone use in the previous 3 months. Broad spectrum antibiotics were administered along with the management for hepatic encephalopathy and thrombocytopenia, respectively. The medications are indicated in table 1. The patient was initially managed with high-flow oxygen nasal cannula. However, rapid deterioration of the cardiorespiratory function on the second day required endotracheal intubation and mechanical ventilation, as well as vasopressors, including norepinephrine and the addition of vasopressin on the next day. Bronchoscopy was performed with

bronchioalveolar lavage. Fungal, viral and bacterial causes were investigated. The patient was positive for *Candida glabrata*, negative for acid-fast bacilli and *Mycobacterium tuberculosis* PCR. Grocott methenamine silver stain was negative for *Pneumocystis jirovecii* while viral PCR for enterovirus and rhinovirus were positive. Blood cultures remained negative. On the sixth day, the patient was found to have melanic stools and the patient underwent an upper gastrointestinal endoscopy, revealing small oesophageal varices and a bleeding gastric ulcer. Mechanical haemostasis was accomplished. On the seventh day, a disseminated intravascular coagulation was diagnosed due to blood oozing from the central venous catheter site and generalised petechial rash. The patient had a Sequential Organ Failure Assessment score of 22, indicating a high risk of mortality. He remained in a critically ill state throughout the stay, requiring multiple blood product transfusions as well as slow continuous renal replacement therapy. On the eighth day, the patient developed focal seizure noted by involuntary contractions of the left eyelid and lip, which was thought to be caused by a haemorrhagic stroke, given the high propensity of bleeding. At that time, the pupils were equal in size and corneal reflex and pupillary light reflex were present bilaterally. An electroencephalogram indicated epileptiform activity in the left frontotemporal lobe. Cranial ultrasound and a head CT did not reveal any signs of bleeding or other abnormalities. On the same day,

Figure 1 A and B show a large area of an ecchymotic skin lesion on the nose and the perinasal area, a black eschar on the nasal bridge and scleral icterus can also be noted.

Figure 2 A and B show mucosal friability with bleeding and the presence of white hyphae.

a dark discolouration on the tip of the nose was noted and skin necrosis secondary to high-dose vasopressors was suspected ([figure 1A,B](#)). Despite reduction in vasopressor infusion, rapid progression of the lesion was evidenced over a 3-hour period. A nasal endoscopy indicated mucosal friability with bleeding and the presence of white hyphae ([figure 2A,B](#)). Mucormycosis seemed likely and a punch biopsy was obtained from the upper lip. Liposomal amphotericin B was then initiated. The diagnosis of rhinocerebral mucormycosis was made by microscopic histopathology; confirmatory culture was not performed ([figure 3](#), [figure 4A,B](#)). The patient was deemed unfit for surgery given the poor prognosis and imminent death.

DIFFERENTIAL DIAGNOSIS

Based on the clinical findings of dark discolouration on nose tip, its rapid progression, the patient's immunocompromised state, focal neurological signs and the positive histopathology findings, rhinocerebral mucormycosis was a straightforward diagnosis. Skin necrosis secondary to vasopressors was first thought to be the cause of the nose lesion, however, when the histological findings were reported this diagnosis was clearly ruled out. Medical literature reports norepinephrine-induced skin necrosis usually occurs on the fingers and toes, which may be related to the distribution of its receptors.⁸ To our knowledge, there are no reported cases of norepinephrine-induced skin necrosis of the nose.

Figure 3 Mucormycosis fungi can be seen with H&E staining as a non-septated, broad (10 µm thick), ribbon-like, grey-blue, pauciseptate hyphae, with a branching pattern of 45°–90°.

TREATMENT

The patient received intravenous liposomal amphotericin B at 3 mg/kg.

Figure 4 (A) Histologically, this is a destructive and invasive organism that produces poorly defined areas of ischaemia with necrosis. Brisk neutrophilic infiltrate and areas of necrosis are common. (B) Gomori methenamine silver staining highlights the previously described morphology.

OUTCOME AND FOLLOW-UP

On the 10th day after admission, the patient died from multiple organ failure despite all efforts made.

DISCUSSION

As per the medical literature, the most common aetiologies of liver cirrhosis on patients with rhinocerebral mucormycosis were HCV and HBV infections, autoimmune hepatitis and a few cases of alcoholic hepatitis. All patients reported in had Child-Pugh classes B and C, as in the case of our patient. Most patients died despite antifungal therapy and surgery.^{6,9–11} The survival rate of mucormycosis infection in patients with liver cirrhosis has been reported to be as low as 11.7%.¹⁰ Patients with advanced liver disease frequently have neutropaenia caused by splenic sequestration and increased neutrophil apoptosis, which poses a higher risk of bacterial and fungal infections. Our patient's neutrophil count remained in a normal-to-high value throughout his stay, which can be explained by glucocorticoid-induced neutrophilia.^{2,6} The presence of protein malnutrition and multiple vitamin and mineral deficiencies is a common finding in alcoholic patients, which may also play a role in the immunosuppression.¹ Stress-dose hydrocortisone also potentially contributed to the immunosuppression. However, it was necessary due to the history of prednisone use in the previous months. Patients with liver cirrhosis who develop rhinocerebral mucormycosis also commonly have diabetes mellitus, which worsens the immunosuppression. Some authors report a 60% prevalence of diabetes mellitus.⁶ Several factors contribute to the higher risk of performing surgery in cirrhotic patients, including reduced blood flow, hypoxaemia and altered drug metabolism during surgery; also the type of surgery and individual risk assessment play an important role in the presurgical and postsurgical risk stratification. The Child-Pugh score and MELD score correlate well with the operative risk and postsurgical mortality. Some authors consider alcoholic hepatitis as a contraindication for elective surgery, however, these studies only included abdominal surgeries.¹² A study done in cirrhotic patients with a Child-Pugh class C liver cirrhosis who underwent head and neck surgery for cancer affecting these sites showed a postoperative mortality rate of 66.7%.¹³ Therefore, performing face debridement surgery in patients with alcoholic liver cirrhosis who develop rhinocerebral mucormycosis should be individualised, and one should consider the overall summative scores like the Child-Pugh score and MELD score, as well as the patient's overall clinical status. The association of alcoholic liver cirrhosis and rhinocerebral mucormycosis in the setting of a lower respiratory tract infection and intensive care unit admission has been reported in another case report, with a similar presentation, hospital course and outcome.⁹ Recent guidelines for the diagnosis and treatment of mucormycosis recommend making a presumptive diagnosis by a direct microscopy of the biopsy, followed by a confirmatory test by culture.¹⁴ In our case, the diagnosis of rhinocerebral mucormycosis was made based on the clinical presentation and direct microscopy of the biopsy. Although the head CT did not show any signs of brain mucormycosis, we based the diagnosis on focal seizures. The head magnetic resonance was not performed, given the patient's haemodynamic instability. Amphotericin B alone has been the most commonly used antifungal medication for the treatment of rhinocerebral mucormycosis, some authors have used micafungin in combination with amphotericin B with good outcomes.¹⁵ In our case, we

initiated the prophylaxis with anidulafungin as per our institution's protocol, and continued it throughout in combination with amphotericin B. However, this did not seem to help the patient.

Learning points

- ▶ The association between alcoholic liver cirrhosis and rhinocerebral mucormycosis in critically ill patients should be identified promptly.
- ▶ Rapid recognition of early signs of rhinocerebral mucormycosis warrants immediate administration of amphotericin B and assessment for surgery.
- ▶ In critically ill patients with alcoholic liver cirrhosis, nose discolouration should not be attributed to other factors such as high-dose vasopressors.
- ▶ Use of broad spectrum antibiotics does not seem to protect the patient.
- ▶ Mucormycosis infection spreads extremely fast and aggressive infection can result in mortality.

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