



Invasive rhinocerebral mucormycosis in a patient with liver cirrhosis leading to fatal massive stroke



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ABSTRACT

Immunocompromised status is associated with invasive fungal infections including mucormycosis. These infections are challenging to treat and associated with high overall mortality.

Here we report a fatal case of invasive mucormycosis in a cirrhotic, diabetic patient. Despite the swift diagnosis and management; the fungal invasion of the right internal carotid artery lead to massive ischemic stroke.

Timely diagnosis and management is crucial for management but it seems not always enough and new approaches for treatment must be sought.

1. Introduction

Mucormycosis is a spectrum of invasive fungal infections that is caused by Mucorales order that belongs to the subphylum Mucoromycotina, with the genera most involved in humans include: Rhizopus, Mucor, Rhizomucor and Lichtheimia. These fungi may present in a vast range of clinical syndromes with sinus, cerebral, pulmonary and cutaneous involvement. The angioinvasive capability of these organisms can lead to direct infiltration to blood vessels and thrombosis or emboli thus presenting as acute ischemic stroke.

Several risk factors are described including diabetes mellitus, malignancies, solid and bone marrow transplantation and iron overload status. Diabetes mellitus stands as the strongest risk factor giving that 36% of patients with invasive mucormycosis were diabetic in a previous review of 929 cases [1]. Association with liver cirrhosis is rare and previous literature reviews revealed only few cases [2].

We describe a case of rhinocerebral mucormycosis in a Child B liver cirrhosis patient due to chronic hepatitis C infection, who is also diabetic. He presented initially with right facial swelling. The patient later developed acute massive right ischemic stroke from direct fungal invasion to the right internal carotid artery and passed away from sepsis.

Despite prompt diagnosis and treatment with surgical debridement and IV amphotericin the patient developed the stroke while on treatment. Thus new approaches for treatment and extending antifungal coverage must be considered.

2. Case

A 54-year-old man previously diagnosed to have Insulin dependent diabetes mellitus, hepatitis C chronic infection with established liver cirrhosis child B complicated by esophageal varices, presented to the emergency department of Hamad General Hospital, Doha, State of Qatar; which is a tertiary hospital; with the complaint of right sided facial weakness, right sided headache, blocked right nostril and a fever of 7 days, he was on the treatment for presumed bell's palsy with a short course of steroids.

Initial vital signs in the emergency department showed a BP 140/70 mmHG, Pulse of 92 beat per minute, oxygen saturation on an ambient air of 99% and a Temperature of 38.2 Celsius.

On examination the patient was conscious, alert and oriented, in no apparent distress. Swelling of the right side of the face at the upper part involving the upper lid was observed. Right eye complete ptosis, chemosis and injection, with mid dilated fixed pupil, resembling a right frozen globe was noticed.

Neurological examination revealed multiple cranial nerves palsies: II, III, IV, V1, VI, VII palsy on right side with no other focal neurological deficits. Ophthalmoscopy showed right central retinal artery occlusion with edematous retina. Fiberoptic nasoscope revealed right side black discoloration in the roof of the nasal cavity with pale mucosa.

Initial labs (at day 0 – day of admission) as illustrated in the table [Table 1] showed high WBC count, hyperglycemia and abnormal kidney function. Non contrast head CT showed pansinusitis. The patient was started on IV fluids and insulin along with IV liposomal amphotericin, Linezolid and ceftazidime for suspected complicated fungal

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Table 1
Initial laboratory values.

WBC	17.4 × 10 ³ /uL
HB	11.7 gm/dL
PLT	147 × 10 ³ /uL
Urea	15.6 mmol/L
Serum Creatinine	141 μmol/L
Sodium	124 mmol/L
Potassium	5.3 mmol/L
Chloride	99 mmol/L
Bicarbonate	20.3 mmol/L
Random blood sugar	31.8 mmol/L
CRP	200 mg/L
PH (VBG)	7.36 mmHg

infection.

Right radical endoscopic sinus surgery was done at day +1 with wide debridement and the patient was extubated and stayed in the surgical intensive care for 3 days. CT head with Iodine based IV injection of medium contrast at day +1 post surgery showed pansinusitis with inflammatory changes of the optic nerve and adjacent muscles, and a bony defect in the right lamina papyracea [Fig. 1].

The nasal swab by microscopy returned positive for *Mucor* species (Day +1). Later the histopathology confirmed the diagnosis of invasive mucormycosis (Day +4) [Figs. 2–4]. Further identification of the exact species was not done at the time of diagnosis as it was beyond our laboratory's capabilities; the isolate is also no longer available for further analysis and further examination of the tissue was not possible due to legal constraints.

The patient became afebrile, his blood sugar improved on basal-bolus insulin and his kidney function improved on IV fluids however rose again on Day +4 (serum creatinine 260 μmol/L). This rise was attributed either to amphotericin toxicity or to contrast induced nephropathy. IV fluids support was continued along with the IV amphotericin as benefit outweighs risk.

Patient deteriorated at day +8 manifesting decreased level of consciousness, confusion with a drop of GCS to 9/15 with the vital signs being stable. Non contrast head CT (day +8) didn't show any new changes; he was started on management for presumed hepatic encephalopathy with lactulose, broad spectrum antibacterial agents and monitoring of mental status.



Fig. 1. Post surgery Contrast CT showing pansinusitis with no obvious significant ischemic changes.

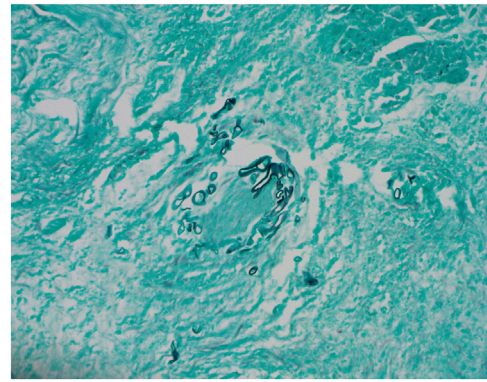


Fig. 2. Photomicrograph of nasal polyp stained with Grocott's methenamine silver stain.

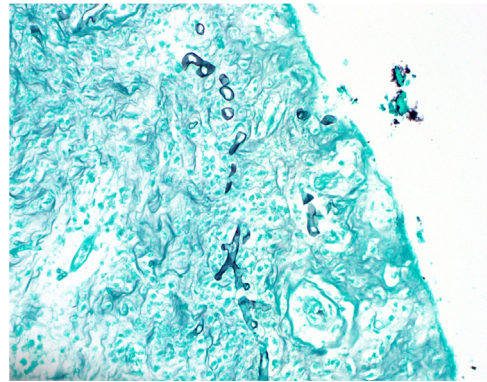


Fig. 3. Grocott's methenamine silver stain showing delicate ribbon like non septate hyphae.

His level of consciousness didn't improve on management thus brain MRI was considered and performed on day +15 which showed: Total occlusion of the right internal carotid artery, right anterior and middle cerebral arteries causing edema effect and compression of the right posterior cerebral artery, secondary massive infarction along the whole right cerebral hemisphere, the upper brain stem, the left frontal and

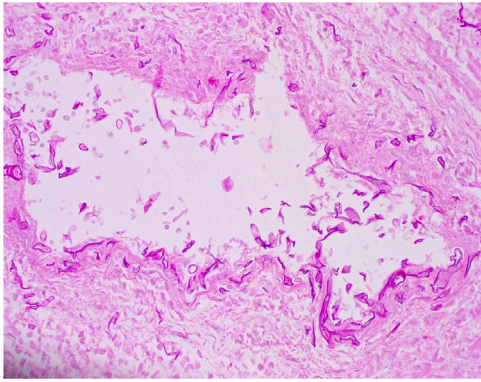


Fig. 4. PAS stained slide showing large blood vessel infiltrated by non-septate hyphae, characteristic of Mucor.

basal ganglia regions as well as the right cerebellar hemisphere with evidence of hemorrhagic change and secondary mass effect and

significant midline shift [Figs. 5 and 6].

Patient was declared brain dead on day +17 after apnea test was positive. Thorough discussion with the family for withdraw of care was conducted, however the family objected. The patient passed away later on day +21 after refractory septic shock.

3. Discussion

Invasive mucormycosis is invasive fungal infection that affects immunocompromised individuals. Well - established risk factors include: Diabetes, hematologic malignancies, hematopoietic cell and solid organs transplant, iron overload status including treatment with iron chelation therapy and steroids use. Diabetes stands as the strongest risk factor with a previous review of 929 patients found that 36% of the patients were diabetic [1]. Other rare association is liver cirrhosis as we found only 24 previous cases in literature [2].

These fungi present with a wide variety of clinical syndromes thus can be missed and have delayed diagnosis and treatment. Rhino- orbital- cerebral involvement is the most common [1]; with the disease starting as inhalation of the spores into the sinuses; the fungi flourish if

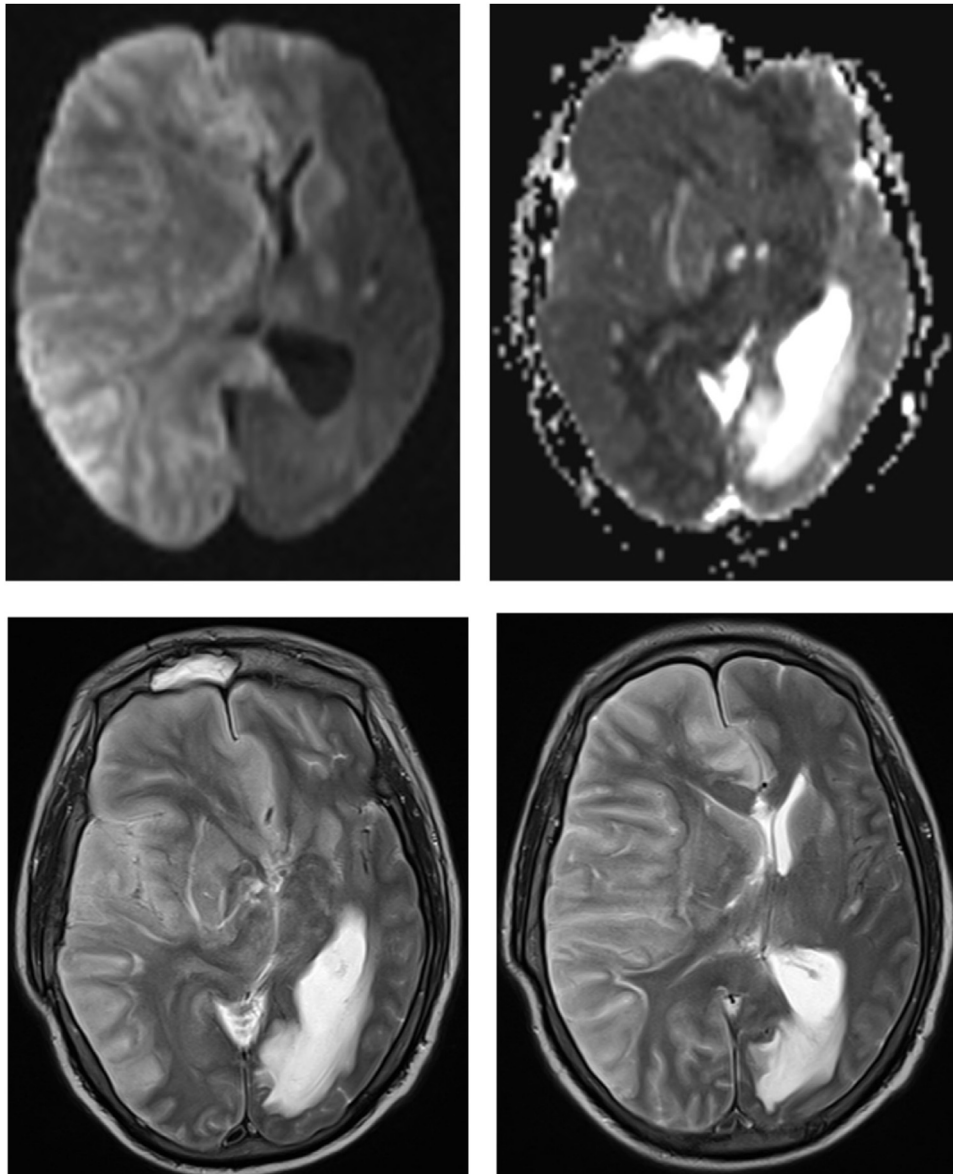


Fig. 5. Diffusion, ADC and T2 weighted images showing diffusion restriction of the right cerebral hemisphere denoting massive ischemia with secondary mass effect compressing the right lateral ventricle.

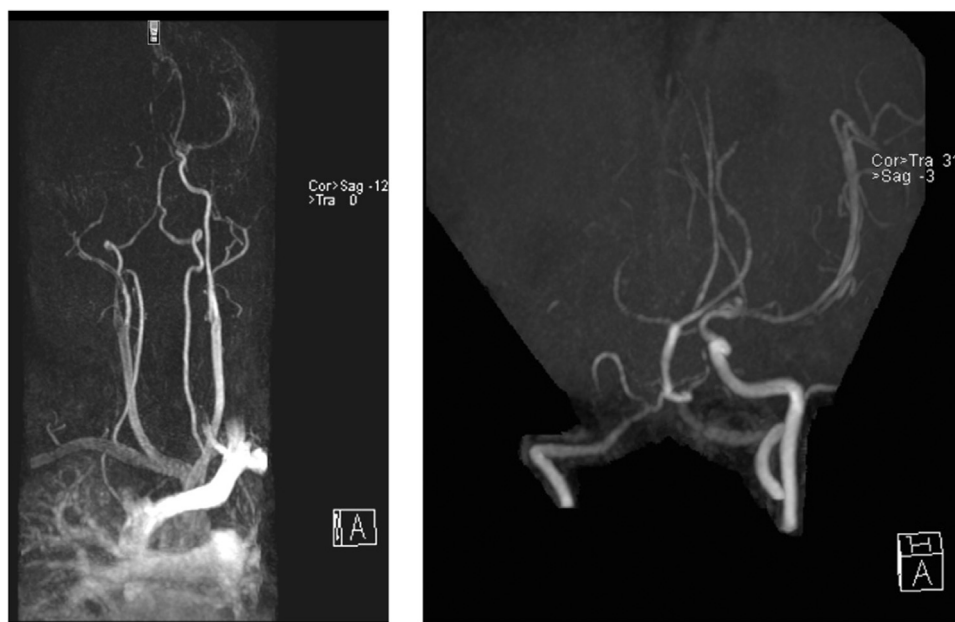


Fig. 6. MR angiography of the neck and intracranial arteries showing marked tapering of the proximal portion of the right internal carotid artery ending with total occlusion, absent flow in right anterior and middle cerebral arteries, reduction in caliber of right posterior cerebral artery.

Table 2

Demographics and clinical characteristics of reported cases of invasive rhino - cerebral mucormycosis in patients with liver cirrhosis.

Case	Age	Gender	Cause of liver disease	Child score	Other risk factors	Cerebral involvement	Treatment	Outcome	References
1	39	Male	HCV	B	DM	Basal ganglia stroke	Surgery + antifungals*	Died	[8]
2	53	Male	HCV	C	DM	Brain direct extension	Surgery + amphotericin B	Died	[8]
3	28	Male	Alcoholic	C	None	Brain direct extension	Amphotericin B	Died	[9]
4	59	Female	Alcoholic	NA	None	Brain direct extension	NA	Died	[10]
5	63	Female	NA	NA	DM	Cerebral aneurysm rupture	None	Died	[11]
6	54	Male	HCV	B	DM	Internal carotid artery occlusion	Surgery + amphotericin B	Died	This case

the host had impaired defense systems. Uncontrolled diabetes and ketoacidosis create a suitable environment by impairing phagocytic activity through unclear mechanisms. It is still also unclear why liver cirrhosis patients may be prone to invasive fungal infections and studies are ongoing to investigate the relation between liver cirrhosis and neutrophils dysfunction. One theory that advanced cirrhosis patients who have hypersplenism might develop neutropenia. Higher ammonia levels also correlated with reduced neutrophils phagocytic activity even in normal counts in one study [3].

There are several mechanisms which mucormycosis may involve the brain, with direct extension being the most encountered. *Mucor* species have also angioinvasive capability and can invade major vessels leading to ischemic stroke [4]. Other rare presentations include fungal emboli and mycotic aneurysm formation [11]. Mortality remains high with cerebral mucormycosis reaching 62% compared with localized rhino – orbital disease (24%) [1].

We reviewed multiple databases looking for case reports describing patients who have liver cirrhosis who developed rhino - cerebral mucormycosis. We only found 5 previous cases that described this association. Including our case, 4/6 patients (67%) were also diabetic, 2 had child B score, 2 had child C score, 6/6 died (100% mortality) [Table 2].

Despite starting antifungal from the first encounter along with surgical debridement a day later in our case, it was not enough. We attributed the altered mental status in our patient to hepatic encephalopathy, but after declining mental function despite treatment MRI was done which showed the findings of internal carotid artery occlusion and a massive stroke.

The suggested standard treatment includes surgical debridement with IV amphotericin B. Some studies proposed amphotericin combined

with either echinocandins or azoles but were not encouraging [5,6]. Other suggested modalities include hyperbaric oxygen use. Prophylaxis against these molds in high risk patients could be considered. However, one previous study showed that prophylactic azoles use in patients with hematological malignancies increased the risk of invasive mucormycosis, although result could be biased, more studies are needed to test the efficacy [7].

In conclusion, invasive mucormycosis is a devastating disease that associates with diabetes and rarely liver cirrhosis. It must be always kept in mind in high risk individuals. Even with standard early therapy it remains associated with high mortality rates in cerebral involvement. Newer treatment regimens or preventive measures should be considered.

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Conflict of interest

There are none.

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