

Liver Cirrhosis and Rhino-Orbital Mucormycosis, a Possible But Rare Association: Description of a Clinical Case and Literature Review

Adriano M Pellicelli, Cecilia D'Ambrosio, Roberto Villani, Giuseppe Cerasari, Pasquale Ialongo, Andrea Cortese, Lucia Rosalba Grillo and Fabrizio Soccorsi

Liver Unit San Camillo Forlanini Hospital Rome Italy; Pathology, Histology and Diagnostic Cytology San Camillo Forlanini Hospital Rome Italy; Department of Radiology San Camillo Forlanini Hospital Rome Italy

Only few cases of rhino-orbital mucormycosis in patients with liver cirrhosis are described in the literature and most of these patients showed an associated diabetes mellitus. We describe a case of rhino-orbital mucormycosis in a patient with liver cirrhosis without other risk factors.

Key-Words: Liver cirrhosis, rhino-orbital mucormycosis, immunocompromised patients, mucor, surgical treatment.

Rhino-orbital mucormycosis has emerged in the last years as an increasingly important life-threatening infection. Since 1885 more than 929 cases were described in the literature [1]. In the cases reported, diabetes mellitus was the most common underlying condition but other predisposing conditions as haematological malignancy, bone marrow transplantation, solid organ transplantation, injection drug users, recipients of deferoxamine therapy and solid tumors were described in the literature [1]. In the case herein reported, we describe a case of rhino-orbital mucormycosis in a patient with liver cirrhosis due to Hepatitis C virus. At the present only other 9 cases of rhino-orbital mucormycosis in cirrhotic patients are reported in the literature. Liver cirrhosis seems to be a predisposing factor for rhino-orbital mucormycosis. We analyze the pathogenetic mechanism that could be at the basis of this fungal disease in cirrhotic patients and we review the literature.

Case Report

A 63 year old woman with a know history of Child-Pugh B class liver cirrhosis secondary to hepatitis C virus infection was admitted to our hospital for periorbital pain and swelling of two weeks of duration. At the time of the admission the patient was alert and oriented, her vital signs included a temperature of 36.9 C°, an heart rate of 90 bpm, and an arterial blood pressure of 135/85 mmHg. On physical examination, considerable hepato-splenomegaly and the presence of ascitic fluid was disclosed. Furthermore, a proptosis associated to red and swollen right eyes was present. There was also a pronounced right maxillary tenderness. One month prior, she was admitted to another hospital with headache and it was diagnosed a paranasal sinusitis. Results of laboratory examinations included white blood cell count of 2,000 cells/mm³ with 45% of neutrophils, hemoglobin level of 9.2 g/dL, and platelet count of 60,000/mm³, erythrocyte sedimentation time of 100 mm, reactive C protein of 6 mg/100 mL and normal plasmatic glucose level (85 mg/100mL). Urgent computed

tomography demonstrated right density-shadow of the soft tissue in the right maxillary sinus, ethmoid sinus, and sphenoid sinus (Figure 1 A). Biopsy of right maxillary sinus was performed and biopsy specimen revealed non-septate hyphae branching at right angles consistent with *Mucor* species (Figure 1 B-C). The patient underwent right orbital exenteration, right ethmoidectomy, maxillectomy and partial sphenoidectomy (Figure 2 A-B). She began receiving amphotericin B at a beginning dosage of 0.5 mg/Kg/day ev and subsequently at a dose of 1 mg/Kg/day. Her creatinine level increased to 2.5 mg/mL and amphotericin B treatment was stopped. The patient, after few days, had clinical improvement and recovery of renal function. A treatment with liposomal amphotericin B 5 mg/Kg/die was subsequently initiated. After one month of treatment, she was discharged from hospital. At eight months of follow up no evidence of recurrent infection was noted.

Discussion

Several infectious diseases are common among patients affected by liver cirrhosis [2]. Rhino-orbital mucormycosis is rare in cirrhotic patients. Risk factors that can contribute to development of this severe fungal disease are: diabetes mellitus, use of systemic steroid, immunodeficiency, neutropenia, haematological malignancies, bone marrow and solid organ transplantation. In the literature, only nine clinical cases of rhino-orbital mucormycosis in cirrhotic patients are described (Table 1). In the 10 cases reported in this article, diabetes was present in six patients (60%), while complications related to liver cirrhosis, as hepatocellular carcinoma, spontaneous bacterial peritonitis and portosystemic encephalopathy were present in 5 patients. A strict association between diabetes mellitus and liver cirrhosis exists, in particular an increased risk of developing diabetes mellitus is present in patients with liver cirrhosis due to hepatitis C and alcoholic liver disease while the risk is reduced in liver cirrhosis due to cholestatic liver disease [7]. Development of mucormycosis in cirrhotic patients with associated diabetes mellitus may reflect compromised immunity of the patient from diabetes mellitus more than liver disease. Diabetes mellitus represents the strongest risk factor to develop rhinocerebral mucormycosis. Chronic

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Address for correspondence: Dr. Adriano M Pellicelli Via Terni 97 00182. E-mail: HUadriano.pellicelli@tiscali.it UH apellicelli@scamilloforlanini.rm.it. Fax +39658704343 tel number +39658704369.

Figure 1. (A) Contrast enhanced computed tomography. Extensive soft tissue density was noted in right maxillary and sphenoid sinuses. The process shows an extension to into the ipsilateral ethmoidal air cells and to the maxillary bone. (B) Biopsy specimen of the maxillary sinus revealed non septate hyphae branching at right angles a finding consistent with *Mucor* species (Periodic acid Schiff stain x 250). (C) Biopsy specimen showing mucormycosis hyphae (haematoxylin and eosin stain original magnification, x 400).

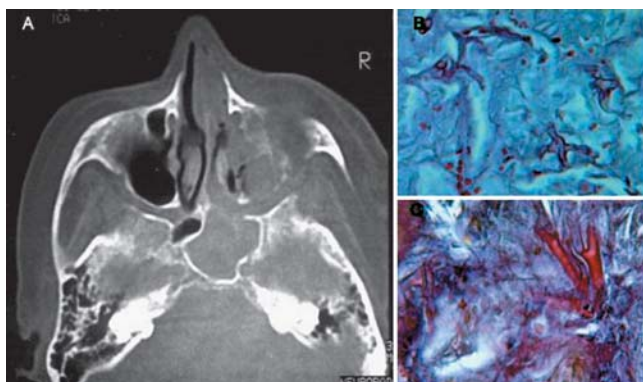


Figure 2. (A) Post surgical contrast enhanced computed tomography. Extensive surgical procedures with total enucleation of right eyeball and (B) a pansinusectomy was performed.



Table 1. In the table are reported all the cases of rhino-orbital mucormycosis reported in the literature.

Pts n°	Ref.	Age/ gender	Child Pugh class	Etiology	Cirrhosis	Comorbidity complication	CT	Treatment	Follow up
1	[3]	39/M	B	HCV	none	LC DM	Maxillary, ethmoid and sphenoid sinus, cerebral	Surgery/AmB	Died
2	[3]	57/M	C	HCV	PSE, SBP, HCC	LC	Not done	AmB	Died
3	[3]	55/M	C	HBV	PSE, SBP, HRS HCC	LC	Maxillary and ethmoid sinus	None	Died
4	[3]	15/F	C	Autoimm hepatitis	PSE, SBP	LC, DM, steroid therapy	Maxillary sinus	None	Died
5	[3]	53/M	C	HCV	none	LC, DM	Maxillary, ethmoid and sphenoid sinuses, orbit, cerebral	Surgery (Orbit enucleation and endoscopic debridement of sinuses) /AmB	Died
6	[3]	35/M	C	HCV	SBP, HRS	LC, DM	Maxillary ethmoid and sphenoid sinus, orbit	AmB	Died
7	[4]	44/F	B	Not reported	Not reported	LC	Ethmoid sinus, orbit	None	Died
8	[5]	58/F	C	Not reported	None	LC, DM, RI	Paranasal sinuses, orbit, cerebral	Liposomal AmB	Died
9	[6]	53/M	B	HCV	HCC	LC, DM	Not done	None	Died
10	Case reported	63/F	B	HCV	none	LC	Maxillary, ethmoid, sphenoid sinuses, orbitand	Surgery/AmB Liposomal AmB	Alive

Pts=patients Ref= references M=male, F=female, C= hepatitis C virus, B= hepatitis B virus, PSE=portosystemic encephalopathy, SBP=spontaneous bacterial peritonitis, HRS=hepatorenal syndrome, LC=Liver cirrhosis, RI=Renal insufficiency, HCC=hepatocellular carcinoma, DM=diabetes mellitus, HTN= arterial hypertension, CT=Computed tomography, AmB= amphotericin B.

hyperglycaemia impairs host defense mechanism such as cell mediated immunity, polymorphonuclear leukocyte function and antibody formation, in particular reduced leukocyte function predispose to fungal infection.

Rhino-orbital mucormycosis seems to affect patients with end stage liver disease, in fact all 10 patients herein reported, presented a functional Child-Pugh class B and C as observed in decompensated liver disease. In 4 cases out of 10, liver cirrhosis was not associated with other comorbidities. Furthermore in two of these four patients complications related to liver cirrhosis as hepatocellular carcinoma, portosystemic encephalopathy and spontaneous bacterial peritonitis, were present. Patients with decompensated liver cirrhosis have an increased susceptibility to develop opportunistic infections as rhinocerebral mucormycosis for an alteration of neutrophils chemotaxis and phagocytosis [8,9]. Neutrophil metabolic activity diminishes together with the intensification of liver failure and the metabolic potential of phagocytizing neutrophils is significantly lower in liver cirrhosis patients.

Neutropenia is frequently present in end stage liver disease as expression of hypersplenism and of an accelerated neutrophils apoptosis. In a study of Kusaba et al. it was demonstrated that, in cirrhotic patients, exist an altered neutrophil kinetic and that an accelerated apoptosis is at the basis of neutropenia [10]. All these alterations can predispose to a more frequent bacterial and fungal infections in these patients. Despite aggressive surgical and medical treatment the prognosis of rhino-orbital mucormycosis is poor and the presence of brain abscesses further reduce the survival [11]. The main stays of therapy are surgical intervention and treatment with high dose of amphotericin B. In advanced liver disease, deranged coagulation and thrombocytopenia make surgical intervention difficult to realize. The reported mortality rates in patients with cirrhosis undergoing various non transplant surgical interventions range from 8.3 to 25% and this wide range of mortality is related to severity of liver disease. Elective surgery is tolerated in Child-Pugh A and possible in Child -Pugh B cirrhosis while child-Pugh C is an absolute contraindication to surgical procedures [12]. In our case, a surgical intervention with removal of all involved tissues was performed with an important local control of fungal infection and without post operative complications. Furthermore, medical treatment with liposomal amphotericin B was started. Liposomal amphotericin B has the advantage to be utilized to an higher concentration and with a reduced incidence and severity of amphotericin B nephrotoxicity. In two studies, a small number of patients with mucormycosis infection were treated with either liposomal amphotericin B or amphotericin B lipid complex with minor collateral effects and a response rate of 75% [13-14] respect to conventional amphotericin B. In the clinical cases herein reported, only other two patients with associated diabetes mellitus were treated with a combined surgical and medical therapy. In one of these patients, only a palliative surgical treatment was allowed due to high surgical risk and in the other patient an extension of mucormycosis to the cerebral tissue was present. In our case, an adequate surgical and medical treatment was allowed due to less advanced liver

disease and to an high compliance of the patient to liposomal amphotericin B treatment.

In conclusion, this paper describes the clinical presentation and outcome of one case of rhino-orbital mucormycosis in a patient in which the only risk factor was represented by liver cirrhosis. Advanced liver cirrhosis could predispose to rhino-orbital mucormycosis through an altered function of white blood cells and in particular an alteration of neutrophils chemotaxis and phagocytosis. Despite aggressive surgical and medical treatment, the prognosis of rhino-orbital mucormycosis is poor. In selected patients, in which, a radical surgical approach and a good compliance to medical treatment with liposomal amphotericin B is achievable, the outcome was better respect to other patient with a more aggressive liver disease and with other comorbidity factors as diabetes mellitus and renal insufficiency.

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