RHINOCEREBRAL MUCORMYCOSIS IN A TRANSPLANTED PATIENT WITH RELAPSED ACUTE LYMPHOBLASTIC LEUKEMIA: A CASE REPORT

A. Ostojic[1], H. Minigo[1], D. Radic-Kristo[1], Nj. Gredelj[1], B. Jaksic[1, 2], R. Vrhovac[1,2]

[1]University Hospital Merkur, Zagreb, Croatia
[2]University of Zagreb School of Medicine, Zagreb, Croatia

correspodence to:
rvrhovac@mef.hr

BACKGROUND

Fungi of the order *Mucorales* are cause of mucormycosis (zygomycosis), a life-threatening fungal infection almost uniformly affecting immunocompromised hosts in either developing or industrialized countries. Mucormycosis is less common than other opportunistic fungal infections, such as those caused by *Candida* and *Aspergillus spp*.[1] Among the *Mucoraceae*, *Rhizopus oryzae* is by far the most common cause of infection.[2] Major risk factors for mucormycosis are: diabetes mellitus, neutropenia, steroid therapy, deferoxamine therapy, malnutrition and trauma. Based on clinical presentation and involvement of a particular body site, mucormycosis is divided into: rhinocerebral, pulmonary, cutaneous, gastrointestinal, central nervous system, and miscellaneous.[3] Rhinocerebral mucormycosis continues to be the most common form of the disease, accounting for between one-third and one-half of all cases of mucormycosis.[4] Four factors are critical for eradicating mucormycosis: timely diagnosis, reversal of the underlying predisposing factors (if possible), appropriate surgical debridement of infected tissue, and appropriate antifungal therapy.[1]
We present a patient with this rare fungal infection, previously treated with allogeneic hematopoietic stem cell transplantations.

CASE REPORT

A 37 year old woman was admitted in our center because of 4th relapse of her acute lymphoblastic leukemia (ALL) (Table 1). For this relapse she received combination chemotherapy and anti-infective prophylaxis tailored according to her risk (Table 2). Because of her steroide-induced diabetes, her blood glucose levels were closely monitored and she received insulin therapy according to them. Filgrastim (600 mcg sc qd) was introduced on day 15, when she became neutropenic and was continued throughout the period of neutropenia. When she developed severe mucositis (WHO grade 3-4) parenteral nutrition was started (day 10).

Ten days after beginning of chemotherapy she became febrile. Microbiological cultures, cytological smears and Galactomannan tests repeatedly did not point to cause of infection. She remained febrile despite several lines of empirical antimicrobial therapy (Table 2). On one occasion a multi-drug resistant *Enteroccocus faecium* was isolated from urine and vancomycin was added. After 48 hours without improvement on vancomycin and cefepime, CT-scan of lungs was done and it showed nodal lesion in lower right lobe that could point to aspergillosis, so voriconazole (6 mg/kg iv loading dose, 4 mg/kg iv maintenance dose) was applied. Two days after voriconazole was introduced, patient started to complain of nasal congestion, left upper jaw teeth-pain and left facial paresthesia, with physical finding of left facial edema. CT-scan of paranasal sinuses and brain showed hypertrophy of mucosa of left paranasal sinuses unilaterally without signs of intracranial progression (Fig 1A). Nasopharinx swab was done and *Rhizopus oryzae* sensitive to amphotericin B (amB) was isolated (Fig 2 and 3). Surgical treatment was contraindicated. She was treated with amB colloidal dispersion for 6 weeks (total dose 8610 mg) with premedication (chloropyramine, methylprednisolone and paracetamol). Patient clinically started to improve and became afebrile. After 16 days of amB treatment, patient was reevaluated with CT-scan (Fig 1B) and progression of mucosal hypertrophy was found, so amB was continued. After 6 weeks on amB, she was remarkably better, with radiological signs of improvement (Fig 1C). Posaconazole (200 mg q8h po) treatment was continued for 4 weeks after termination of AmB.

Currently, patient is in good clinical condition.

Table 1. Patient's medical history

2006		2007	2008	2009		2010
August	*August – December*	*January*	*January*	*September*	*October – November*	*End of January*
Dx: ALL -FAB : L2 -WHO: B-precursor	Induction: **Hyper-CVAD** (4 cycles)	**allo-HSCT (1)** MCR (Bu-Cy)	**allo-HSCT (2)** RIC (Flu/Mel/ATG)	**allo-HSCT (3)** RIC (Flu/Mel/Campath®)	**"Pulse" steroid therapy**	**4th relaps of ALL** -Extramedullar (without PB, BM or CSF involment)
				Probable IPA (treated with voriconazole)		
		Arterial hypertension (well controlled with antihypertensive therapy) →				
						Diabetes mellitus, steroid-induced (treated with insulin) →

ALL – acute lymphoblastic leukemia; allo-HSCT – allogeneic hematopoietic stem cell transplantation; MCR - myeloablative conditioning regimen; RIC – reduced intensity conditioning; IPA – invasive pulmonary aspergillosis; PB – peripheral blood; BM – bone marrow; CSF – cerebrospinal fluid

Table 2. Course of treatment

DRUG	DOSE	DAYS OF APPLICATION 1	2-3	4-5	10	11	20	24	28	30	37	78
clofarabine	20 mg/m²											
idarubicin	6 mg/m²											
methylprednisolone	1 mg/kg											
ciprofloxacin	500 mg bid											
acyclovir	400 mg q8h											
posaconazole	200 mg q8h											
co-trimoxazole	960 mg x2 weekly											
piperacillin/tazobactam	4.5 g q8h											
imipenem/cilastatin	1 g q8h											
cefepime	2 g q8h											
vankomycin	1 g q8h											
voriconazole	(1st day: 6) 4 mg/kg											
amphotericin B	"step-up" dosing regimen*											

*1st day: 60 mg| 2nd day: 100 mg| 3rd day: 150 mg| 4th day: 200 mg| 5th day untill end of treatment: 250 mg

Figure 1. Cranial CT (coronal sections) – slices at level of the ethmoid and maxillary sinuses: 1A - before amB therapy, 1B - After 16 days of amB therapy, 1C - At the end of amB therapy

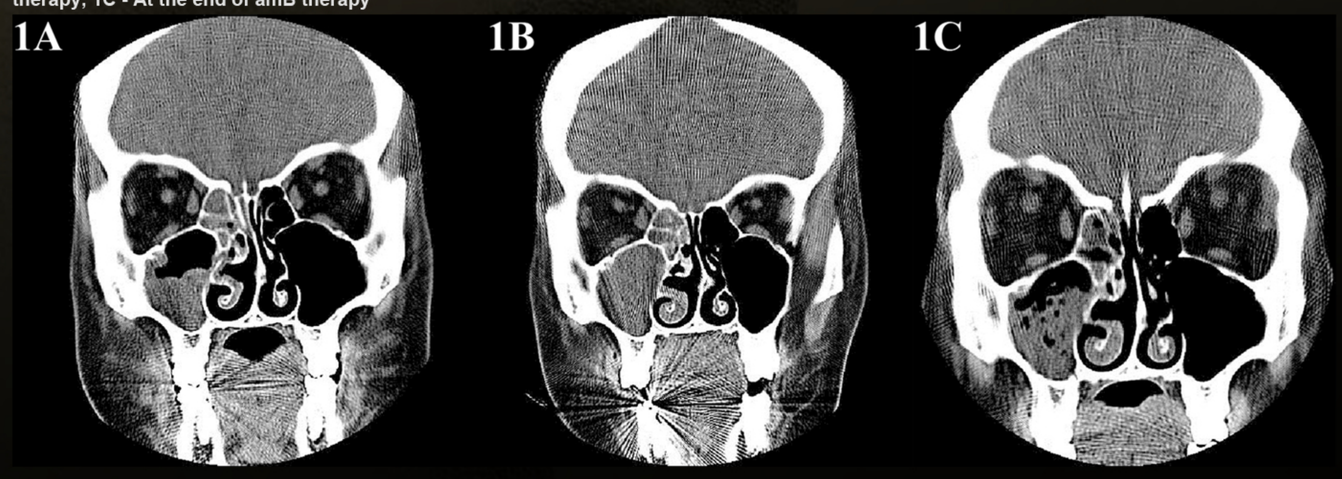


Figure 2. *Rhizopus oryzae* - culture from nasal swab (24h after cultivation).

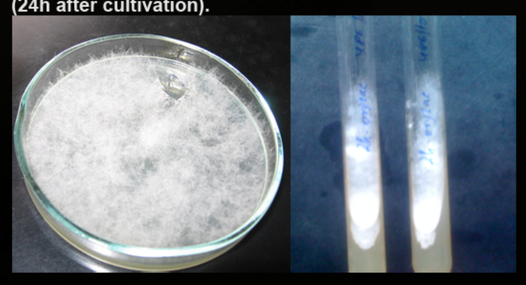
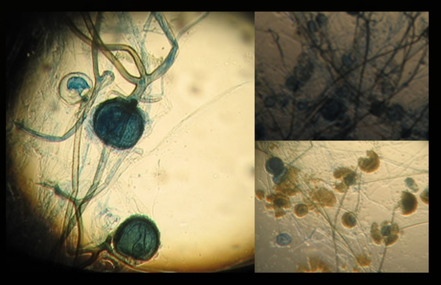


Figure 3 *Rhizopus oryzae* - light microscopy.



CONCLUSION

Mucormycosis is a very serious fungal infection that is, in the majority of cases clinically presented in its rhinocerebral form. The most common cause is *Rhizopus oryzae.* Pathogenesis of disease include susceptible host. After the fungus reaches paranasal sinuses, it invades mucosa blood vessels causing thrombi formation, consequently reduction of blood flow and, finally, tissue necrosis. Rapidly, it can penetrate to intracranial space or disseminate. If diagnosis is not prompt and treatment adequate, in most cases the outcome is death. Although it is a rare infective complication comparing to other fungal infections in patients with hematologic malignancies undergoing intensive chemotherapy, it should be always considered, especially in the subgroup of patients with high risk.
In spite a number of adverse factors the outcome of treatment in this case was favorable with a marked regression of rhinocerebral mucormycosis, without intracranial propagation or dissemination. We conclude that close clinical follow up, rapid and targeted diagnostic procedures followed by appropriate antifungal therapy can lead to good clinical responses, even in transplanted patients with poor prognosis.

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