Rhino-Orbital-Cerebral Zygomycosis in Solid Organ Transplant Recipients

Hsin-Yun Sun,[1,2] Graeme Forrest,[3] Krishan L. Gupta,[4] Jose M. Aguado,[5] Olivier Lortholary,[6,7] Marino Blanes Julia,[8] Nasia Safdar,[9] Robin Patel,[10] Shimon Kusne,[11] and Nina Singh[1,12,13]

Background. Rhino-orbital-cerebral disease is a significant manifestation of zygomycosis in solid organ transplant (SOT) recipients. However, its characteristics and outcome are not well addressed.
Methods. SOT recipients with zygomycosis as per the European Organization for Research and Treatment in Cancer and the Mycoses Study Group criteria in a cohort study at our centers published previously and those identified with a PubMed search from the 1950s to November 2009 were studied. Patients with mycosis involving the sinuses, orbits, or central nervous system (CNS) were included.
Results. Patients comprised a total of 90 SOT recipients with rhino-orbital-cerebral zygomycosis, including 13 in our cohort and 77 in the literature. CNS disease occurred in 57% (51 of 90). Overall mortality was 52.3% (46 of 88), and the mortality in patients with CNS disease was 73.5% (36 of 49). In logistic regression analysis, older age (odds ratio [OR] 1.12, 95% confidence interval [CI] 1.04–1.21, $P=0.002$) was associated with a higher mortality rate, whereas lipid formulations of amphotericin B compared with amphotericin B deoxycholate (OR 0.09, 95% CI 0.02–0.50, $P=0.006$) and surgery (OR 0.12, 95% CI 0.01–0.94, $P=0.043$) were independently associated with an improved survival even when controlled for CNS involvement and the era of diagnosis of disease.
Conclusions. Rhino-orbital-cerebral zygomycosis, particularly CNS disease, is associated with substantial mortality rate in SOT recipients. Older age is a significant risk factor for mortality, whereas lipid formulations of amphotericin B and surgery improved outcomes.

Keywords: Zygomycosis, Solid organ transplant, Rhino-orbital-cerebral.

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A growing population of immunocompromised hosts, effective treatment of more prevalent mycoses, and antimicrobial selection pressure have led to the emergence of zygomycosis as an important invasive fungal disease in the current era. An increased incidence of zygomycosis has been observed in diabetic patients, patients with hematologic malignancy, or hematologic stem-cell transplant recipients in whom prior voriconazole exposure has been identified as a risk factor (*1*, *2*). Data from the Transplant Associated Infection Surveillance Network showed that zygomycosis represented 2% of invasive fungal infections in solid organ transplant (SOT) population (*3*). Some but not all reports have also reported an increased frequency of zygomycosis in SOT recipients (*4*). Overall mortality rate in organ transplant recipients with zygomycosis is approximately 38% to 48% (*5*–*7*).

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[1] Division of Infectious Diseases, Department of Medicine, VA Pittsburgh Healthcare System, Pittsburgh, PA.
[2] Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan.
[3] Department of Medicine, Division of Infectious Diseases, University of Maryland, Baltimore, MD.
[4] Departments of Nephrology and Pathology, Postgraduate Institute of Medical Education and Research, Chandigarh, India.
[5] Unit of Infectious Diseases, Unidad de Enfermedades Infecciosas, Hospital de Octubre, Madrid, Spain.
[6] Department of Immunology, Infectious Diseases and Hematology, Universite Paris Descartes, Hopital Necker-Enfants Malades, Centre d'Infectiologie Necker-Pasteur, Paris, France.
[7] Centre National de Reference Mycologie et Antifongiques, Institut Pasteur, Paris, France.
[8] Infectious Diseases Unit, Hospital Universitario La Fe, Valencia, Spain.
[9] Department of Medicine, Section of Infectious Diseases, University of Wisconsin, Madison, WI.
[10] Divisions of Clinical Microbiology and Infectious Diseases, Mayo Clinic, Rochester, MN.
[11] Division of Infectious Diseases and of Transplantation Medicine, Mayo Clinic, Scottsdale, AZ.
[12] University of Pittsburgh, Pittsburgh, PA.
[13] Address correspondence to: Nina Singh, M.D., Infectious Diseases Section, VA Medical Center, University Drive C, Pittsburgh, PA 15240.
E-mail: nis5@pitt.edu
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Rhino-orbital-cerebral disease is among the most significant presentation of zygomycosis and develops in approximately 31% of the SOT recipients with zygomycosis (*5–7*). Mortality rate in SOT recipients with rhino-orbital-cerebral zygomycosis is 93% to 100% (*6*). Although it is well characterized in diabetic patients (*8*), published reports regarding rhino-orbital-cerebral zygomycosis in SOT recipients comprise largely case studies or descriptions of this entity as a part of disease presentation in case series (*6*, *7*). Preferred approach to antifungal therapy and whether lipid formulations of amphotericin B demonstrate an advantage over amphotericin B deoxycholate for the treatment of this entity in organ transplant recipients remain unknown. Herein, we present our cases with rhino-orbital-cerebral disease in a prospective multicenter study and review those published in the literature to summarize the clinical manifestations and outcomes of SOT recipients with rhino-orbital-cerebral zygomycosis (*5*).

PATIENTS AND METHODS

Patients comprised a multicenter cohort of SOT recipients with zygomycosis at the participating centers from 2003 to 2007. A detailed description of this cohort has been described elsewhere (*5*). Invasive zygomycosis was defined as per criteria proposed by the European Organization for Research and Treatment in Cancer and the Mycoses Study Group (*9*). Patients included in this study were those with proven or probable zygomycosis involving the sinuses, orbits, or central nervous system (CNS). Data collected included demographic characteristics, type of organ transplant, immunosuppressive regimen at the time of diagnosis of zygomycosis, rejection episodes occurring within 60 days before diagnosis, cytomegalovirus infection, use of antifungal agent within 6 months before the diagnosis, presentation, involved sites, microbiologic data, imaging characteristics, antifungal therapy employed, surgical resection, and mortality. Renal failure (defined as serum creatinine >2 mg/dL), requirement of dialysis, diabetes mellitus, neutropenia (defined as granulocyte count <1000 cells/μL), Acute Physiology and Chronic Health Evaluation II Score, and retransplantation were variables present at baseline (or diagnosis of disease). T-cell antibodies were categorized as nondepleting (interleukin-2 receptor antibodies such as basiliximab or daclizumab) or depleting (alemtuzumab or antithymocyte globulin) depending on whether they reduce responsiveness to T cells with or without depleting them (*10*). Disseminated zygomycosis was defined as CNS disease or more than or equal to two noncontiguous sites of involvement. An institutional review board approval was obtained as per local requirements (*4*).

In addition, SOT recipients with zygomycosis involving the sinuses, orbits, or CNS were identified with a PubMed search from 1950 to November 2009 by cross-referencing the keywords "zygomycosis" or "zygomycosis" and "sinusitis" or "rhinocerebral" or "rhino-orbital" or "rhino-orbital-cerebral" or "brain" or "central nervous system" and "transplantation" or "transplant." Reference lists of original articles were reviewed for additional cases. Data similar to those in the prospective cohort were collected. The denominators throughout reflect the number of patients for whom the particular data were available. For literature cases, zygomycosis reported since 2000 were considered to have occurred in the current era.

Statistical Analyses

Intercooled Stata version 9.2 (College Station, TX) was used for statistical analyses. Risk factors for mortality were evaluated using the maximum likelihood estimate of the odds ratio (OR). The variables found to be associated with mortality at *P* less than 0.10 in univariate analysis were entered into the logistic regression model.

RESULTS

The study population comprised a total of 90 SOT recipients with rhino-orbital-cerebral zygomycosis, including 13 in our cohort and 77 identified in the literature (*6*, *11–61*). The diagnosis was established by histopathology or cytopathology in 55.1% (49 of 89), culture in 7.9% (7 of 89), both in 37.1% (33 of 89), and unspecified in 1%. Detailed information on the 13 patients in the prospective cohort is summarized in Table 1, and demographics of the overall 90 patients are presented in Table 2. Immunosuppression used at diagnosis of zygomycosis included tacrolimus (32.8%, 21 of 64), cyclosporine A (25.8%, 16 of 62), azathioprine (45.9%, 28 of 61), and corticosteroids (97.3%, 73 of 75). At baseline, 46.1% (36 of 78) of the patients had diabetes, 67.7% (21 of 34) had renal failure, 13.9% (5 of 36) required dialysis, and 48.9% (23 of 47) had rejection before zygomycosis.

The median time to the onset of rhino-orbital-cerebral disease was 110 days posttransplant (interquartile range 30–540 days). Zygomycosis with an involvement of the CNS occurred in 56.7% (51 of 90) of the recipients. Of 49 patients with CNS disease in whom information regarding precise sites of involvement was available, rhinocerebral disease occurred in 57.1% (28 of 49), rhino-orbital-cerebral disease in 26.5% (13 of 49), cerebral involvement as a part of disseminated disease in 14.3% (7 of 49), and isolated CNS lesion in 2% (1 of 49; Table 3). In 26 patients with locations of brain lesions available, 50% (13 of 26) had lesions in the cerebrum, and frontal lobe (61.5%, 8 of 13) was most commonly involved followed by temporal (38.5%, 5 of 13), parietal (38.5%, 5 of 13), and occipital lobe (30.8%, 4 of 13). Disease involving the cerebellum, brain stem, and spinal cord was also reported. In 39 patients without an involvement of the CNS, 48.7% (19 of 39) had sinonasal disease, 46.2% (18 of 39) had rhino-orbital disease, and 5.1% (2 of 39) had zygomycosis involving both the sinuses and lung. Sinus disease developed most frequently in the maxillary sinuses (80.4%, 41 of 51), followed by the ethmoid (64.7%, 33 of 51), sphenoid (45.1%, 23 of 51), and frontal sinuses (21.6%, 11 of 51).

In 78 patients with clinical symptoms and signs reported, swelling, fever, and pain occurred most frequently (Table 4). In addition to headache, altered mental status, and seizure, CNS disease also presented with cranial nerve palsies, particularly the seventh cranial nerves, cavernous sinus syndrome, quadriplegia, and hemiplegia. Patients with sinonasal disease usually had pain, sometimes severe over the involved sites, nasal discharge, and necrotic lesions on the face, nasal cavities, or palates. Orbital manifestations included swelling or pain over the eye or periorbital region, diplopia, ophthalmoplegia, blurred vision, and blindness. Severe or uncommon complications often occurred as a result of disseminated disease with involvement of other organs, such as heart failure as a result of acute myocardial infarction or endocarditis, respiratory failure resulting from subglotitis or pulmonary disease, massive bleeding as a result of vascular erosion, intracranial aneurysm formation, brain herniation, and bowel perforation. *Rhizopus* species (65.7%, 23 of 35) was most common followed by *Mucor* species (17.1%, 6 of 35) and *Cunninghamella* species (8.6%, 3 of 35; Table 4).

Excluding one patient with sinonasal disease (1.1%, 1 of 90) who received only surgical debridement, six patients (6.6%, 6 of 90) in whom the diagnosis was established postmortem or who did not receive an antifungal agent as treatment, six patients (6.7%, 6 of 90) who received antifungal therapy for less than 5 days, and four patients (4.4%, 4 of 90) without data available, antifungal therapy was employed in

TABLE 1. Demographics, immunosuppressive agents, underlying medical conditions, clinical presentation, treatment, and outcome of zygomycosis in 13 solid organ transplant recipients in the prospective cohort

Patient	Age (yr)/ gender	Tx organ	IS	Other condition	Onset (d)	Sites of involvement	Presentation	Species	Antifungal agents	OP	Death
1	52/M	Renal	CsA, MMF, steroid	DM, RF	2446	RO	Facial pain and decreased sensation, decreased vision	NA	L-AmB	Yes	No
2	54/M	Renal	FK506, MMF, steroid	None	159	RO	Headache, eye pain	NA	AmBd	Yes	Yes
3	55/M	Renal	MMF, steroid	RF	3197	RO	Fever, cough	NA	AmBd	No	Yes
4	62/M	Liver	FK506, steroid	DM, dialysis	22	RO	Fever, necrotic lesions in nasopharynx, myositis of both thighs	*Rhizopus*	L-AmB	Yes	Yes
5	65/M	Liver	CsA, MMF, steroid	DM	26	RO	Fever, headache, ptosis	*Mucor*	L-AmB	Yes	Yes
6	59/M	Liver	FK506, steroid	DM, re-Tx	51	RO	Fever, facial pain	NA	AmBd	Yes	No
7	61/M	Renal	FK506, sirolimus, steroid	DM, RF	307	RO	Pain over right face, eye, and ear	NA	L-AmB	Yes	No
8	56/F	Renal	FK506, MMF, steroid	DM, RF	57	RO	Pain and swelling over left face, palatal mass	*Rhizopus*	L-AmB	Yes	No
9	57/F	SPK	Steroid	DM	3109	RO	Fever, orbital pain	*Rhizopus*	L-AmB	Yes	No
10	38/F	PK	FK506, MMF, steroid	DM, re-Tx	147	RO	Pain over right face, ear, and neck, fatigue	*Blakeslea*	L-AmB	Yes	No
11	23/F	Lung	FK506, steroid	DM	344	ROC	Orbitary cephalalgy	*Mycocladus*	L-AmB	Yes	No
12	29/M	Lung	FK506, steroid	DM, RF	2699	RO	Fever, facial pain	*Rhizopus*	L-AmB	No	No
13	65/M	Liver	FK506, MMF, steroid	Re-Tx	8	ROC	Coma	*Mucor*	L-AmB/posa	No	Yes

M, male; F, female; Tx, transplant; IS, immunosuppressants; OP, operation; CsA, cyclosporine A; MMF, mycophenolate mofetil; DM, diabetes mellitus; RF, renal failure (defined as serum creatinine >2 mg/dL at baseline); RO, rhino-orbital; NA, not available; L-AmB, liposomal amphotericin B; FK506, tacrolimus; AmBd, amphotericin B deoxycholate; Re-Tx, retransplant; SPK, simultaneous pancreas-kidney transplant; PK, sequential pancreas and kidney transplant; ROC, rhino-orbital-cerebral; Posa, posaconazole.

81.1% (73 of 90) of the recipients and included amphotericin B deoxycholate in 64.4% (47 of 73) and lipid formulations of amphotericin B in 35.6% (26 of 73; Table 5). Surgical debridement was performed in 67.5% (52 of 72) of the patients, and the majority was for sinonasal lesions (95.5%, 42 of 44) followed by orbital and brain lesions (Table 5). Several debridement or drainage procedures (ranging from 1 to 7) were required for patients with sinonasal disease. The interventions included Caldwell-Luc procedure, radical external or endoscopic debridement or excision of involved turbinates, soft or hard palate, and sinuses, sinosectomy of involved sinuses, and irrigation with amphotericin B deoxycholate or saline. Procedures for other lesions are described in Table 5.

Outcomes

Rejection occurred after the diagnosis of zygomycosis in 32.3% (10 of 31) of the patients (Table 5); reduction or discontinuation of the immunosuppression during treatment course of the mycosis was documented in 52.1% (25 of 48) and 33.3% (16 of 48) of the patients, respectively. Overall mortality was 52.3% (46 of 88); the mortality rate was 15.4% (4 of 26) in the recipients of lipid formulations of amphotericin B and 59.6% (28 of 47) in patients who received amphotericin B deoxycholate (Table 5). Recipients with zygomycosis diagnosed since 2000 had a mortality rate of 39.1% (9 of 23). In univariate analysis, disease involving the CNS (OR 8.03, 95% confidence interval [CI] 3.08–20.9, $P<0.001$) was associated with a higher mor-

TABLE 2. Demographics and clinical characteristics of 90 solid organ transplant recipients with zygomycosis involving the sinuses, orbits, or central nervous system

Variables	N=90
Era of diagnosis	
Since 2000, % (n)	30.3 (23/76)[a]
Age (yr), median (IQR)	48 (35–55)
Male, % (n)	72.2 (57/79)
Type of transplant, % (n)	
Kidney	70.0 (63)
Liver	12.2 (11)
Heart	7.8 (7)
Lung	6.7 (6)
Multiple visceral	3.3 (3)
Immunosuppression at diagnosis, % (n)	
Tacrolimus	32.8 (21/64)
Cyclosporine A	25.8 (16/62)
Azathioprine	45.9 (28/61)
Mycophenolate mofetil	25.0 (16/64)
Sirolimus	3.1 (2/64)
Corticosteroids, % (n)	97.3 (73/75)
Prednisone	76.2 (32/42)
Dose (mg/d), median (range)	25 (5–40)
Prednisolone	11.9 (5/42)
Dose (mg/d), median (range)	NA
Methylprednisolone	9.5 (4/42)
Dose (mg/d), median (range)	20 (20–30)
T-cell antibody, % (n)	5.5 (4/73)
Nondepleting (n)	1
Depleting (n)	3
Rejection before diagnosis of zygomycosis, % (n)[b]	48.9 (23/47)
Antifungal use before diagnosis of zygomycosis[c] (n)	
Voriconazole	1
Fluconazole	4
Itraconazole	1
Echinocandins	1
Retransplantation, % (n)	13.8 (8/58)
Renal failure at baseline, % (n)[d]	67.7 (21/34)
Dialysis at baseline, % (n)	13.9 (5/36)
Neutropenia, % (n)[e]	3.3 (1/30)
Cytomegalovirus infection, % (n)	18.2 (4/22)
Cytomegalovirus disease, % (n)	20.0 (4/20)
Diabetes mellitus, % (n)	46.1 (36/78)

[a] Denominator present the number of patients for whom the specified data were available.
[b] <60 d before diagnosis.
[c] <6 mo of diagnosis.
[d] Defined as serum creatinine >2 mg/dL at the time of diagnosis.
[e] Defined as granulocyte count <1000 cells/μL.
IQR, interquartile range; NA, not available.

TABLE 3. Infection sites of zygomycosis involving the sinuses, orbits, or central nervous system in 90 solid organ transplant recipients

Variables	Data (n=90)
Sites of involvement, % (n)	
Involvement of central nervous system	56.7 (51)
Rhino-cerebral	57.1 (28/49)[a]
Rhino-orbital-cerebral	26.5 (13/49)
Other sites of involvement[b]	14.3 (7/49)
Isolated involvement of central nervous system	2.0 (1/49)
No involvement of central nervous system	43.3 (39)
Only sinus involved	48.7 (19/39)
Rhino-orbital	46.2 (18/39)
Involvements of both sinus and lung	5.1 (2/39)
Distribution of brain and sinonasal lesions, % (n)	
Distribution of brain lesions	
Cerebrum	50.0 (13/26)
Frontal lobe	61.5 (8/13)
Temporal lobe	38.5 (5/13)
Parietal lobe	38.5 (5/13)
Occipital lobe	30.8 (4/13)
Cerebellum	15.4 (4/26)
Brain stem	11.5 (3/26)
Spinal cord[c]	7.7 (2/26)
Meninges	19.2 (5/26)
Other[d]	19.2 (5/26)
Distribution of sinus lesions	89.9 (80/88)
Right	48.7 (19/39)
Left	46.2 (18/39)
Bilateral	5.1 (2/39)
Maxillary	80.4 (41/51)
Ethmoid	64.7 (33/51)
Sphenoid	45.1 (23/51)
Frontal	21.6 (11/51)

[a] Of 51 patients with CNS disease, only 49 had information regarding other site involvement available.
[b] Other sites included the coronary artery, heart valves, myocardium, pericardium, thymus, thyroid gland, esophagus, stomach, small and large intestine, native or transplanted kidney, larynx, liver, spleen, pancreas, cutaneous tissue and lung.
[c] Spinal cord involvements included spinal meninges and cauda equine.
[d] Other brain lesions included amygdaloid nucleus, olfactory bulbs, fusiform basilar artery fungal aneurysms, and cranial base.

tality rate, whereas receipt of lipid formulations of amphotericin B compared with amphotericin B deoxycholate (OR 0.12, 95% CI 0.04–0.42, $P=0.001$) and surgical debridement (OR 0.11, 95% CI 0.03–0.35, $P<0.001$) were associated with a lower mortality rate (Table 6). Reduction or discontinuation of immunosuppression, renal failure at baseline, retransplant, and disease diagnoses since 2000 were not associated with mortality (Table 6).

In logistic regression analysis with age, CNS disease, receipt of lipid formulations of amphotericin B, and surgical debridement in the model, older age (OR 1.12, 95% CI 1.04–1.21, $P=0.002$) was independently associated with a higher mortality rate, whereas receipt of lipid formulations of amphotericin B versus amphotericin B deoxycholate (OR 0.09, 95% CI 0.02–0.50, $P=0.006$) and surgical debridement (OR 0.12, 95% CI 0.01–0.94, $P=0.043$) improved mortality. CNS disease per se was not independently associated with mortality. Receipt of lipid formulations of amphotericin B remained associated with better outcome even when adjusted for diagnoses in the current era.

Mortality was 73.5% (36 of 49) in patients with CNS disease and 25.6% (10 of 39) in those without it (Table 5). In uni-

TABLE 4. Clinical presentations and microbiology of zygomycosis involving the sinuses, orbits, or central nervous system in 90 solid organ transplant recipients

Variables	Data (n=90)
Reported clinical symptoms/signs, % (n)	
Swelling[a]	50.6 (39/77)
Fever	41.6 (32/77)
Pain[b]	41.6 (32/77)
Cranial nerves palsies[c]	29.9 (23/77)
Altered mental status	28.6 (22/77)
Headache	27.3 (21/77)
Necrotic lesions[d]	26.9 (21/77)
Nasal discharges[e]	24.7 (19/77)
Oral involvements[f]	19.5 (15/77)
Sensory change	16.9 (13/77)
Diplopia/ophthalmoplegia	16.9 (13/77)
Proptosis	16.9 (13/77)
Visual impairment[g]	14.3 (11/77)
Neurologic signs[h]	9.1 (7/77)
Other[i]	27.3 (21/77)
Complications/sequelae[j]	32.5 (25/77)
Microbiologic findings, % (n)	
Any	35
Rhizopus species	65.7 (23/35)
Mucor species	17.1 (6/35)
Cunninghamella species	8.6 (3/35)
*Mycocladus*species	5.7 (2/35)
Other genus[k]	2.9 (1/35)

[a] Swelling could involve the face, periorbital region, conjunctivae, and nose.
[b] Pain included facial pain, orbital/retro-orbital pain, toothache, pain over maxillary sinuses, mandible/jaw, cheek, ear, and neck.
[c] Involvements of cranial nerves included the second, third, fourth, fifth, sixth, and seventh cranial nerves.
[d] Necrotic lesions could be observed on the forehead, nose, cheek, conchae, sinus, gingiva, molars, and nasopharynx.
[e] Nasal discharges could be purulent, bloody, or blackish.
[f] Oral involvements included necrosis, ulcers, mass or whitish exudate containing black streaks on the soft or hard palate, and gingival swelling.
[g] Vision impairment included blurred or decreased vision and blindness.
[h] Neurologic signs included hemiplegia, quadriplegia, and pathogenic left plantar reflex.
[i] Other included dyspnea, sore throat, seizure, epiphora, hyperacusis, malaise/fatigue.
[j] Complications/sequelae included stroke, respiratory failure, heart failure, acute myocardial infarction, blindness, massive bleeding, bowel perforation, subglotitis, permanent nerve palsy, fecal incontinence, facial bone defect/sequestation, intracranial fungal aneurysms.

TABLE 5. Treatment and outcomes of 90 solid organ transplant recipients with zygomycosis involving the sinuses, orbits, or central nervous system

Treatment	Data
Percentage of patients receiving antifungal agents, % (n)	81.1 (73/90)
Lipid formulations of amphotericin B, % (n)	35.6 (26/73)
Liposomal amphotericin B (n)	18
Amphotericin B lipid complex (n)	6
Amphotericin B Colloidal Dispersion (n)	2
Amphotericin B deoxycholate, % (n)	64.4 (47/73)
Combination therapy, % (n)[a]	13.7 (10/73)
Surgical debridement, % (n)	67.5 (52/72)
Sinuses	95.5 (42/44)
Orbital[b]	9.1 (4/44)
Central nervous system[c]	6.8 (3/44)
Others[d]	6.8 (3/44)
Outcomes, % (n)	
Rejection after diagnosis of zygomycosis	32.3 (10/31)
Accessible response to therapy	60.0 (54)
Successful	68.5 (37/54)
Unsuccessful	31.5 (17/54)
Mortality	
Overall	52.3 (46/88)
Receipt of lipid formulations of amphotericin B	15.4 (4/26)
Receipt of amphotericin B deoxycholate	59.6 (28/47)
Involvement of central nervous system	73.5 (36/49)
Receipt of lipid formulations of amphotericin B	8.7 (2/7)
Receipt of amphotericin B deoxycholate	91.3 (21/29)
No involvement of central nervous system	25.6 (10/39)

[a] These included lipid formulations of amphotericin B in combination with itraconazole (one patient), posaconazole/deferaxirox (one patient), posaconazole/caspofungin/deferasirox (one patient), deferasirox (one patient), or posaconazole (one patient), and amphotericin B deoxycholate in combination with 5-fluorocytosine (four patients) or cycloheximide (one patient).
[b] The surgical intervention included orbital extenoration in three patients and orbital decompression in one patient.
[c] The operations included debridement of temporal abscess in one patient, burr holes in one patient, and dura mater resection in one patient.
[d] Other included abdominal exploration for bowel perforation in two patients and debridement for fasciitis in one patient.

variate analysis, older age (OR 1.07, 95% CI 1.01–1.13, $P=0.027$) was associated with a higher mortality rate in SOT recipients with CNS disease while receipt of lipid formulations of amphotericin B compared with amphotericin B deoxycholate (OR 0.15, 95% CI 0.02–0.95, $P=0.044$) was associated with a lower mortality rate. Renal failure, retransplant, and disease diagnosed since 2000 were not associated with mortality. In logistic regression analysis with age, use of lipid formulations of amphotericin B, and surgical debridement in the model, older age (OR 1.28, 95% CI 1.04–1.6, $P=0.015$) and receipt of lipid formulations of amphotericin B versus amphotericin B deoxycholate (OR 0.007, 95% CI 0.00–0.9, $P=0.043$), but not surgical debridement (OR 0.02, 95% CI 0.00–2.11, $P=0.101$), were independently associated with mortality.

DISCUSSION

This study focused on rhino-orbital-cerebral zygomycosis and systematically documents the clinical characteristics and outcomes of this entity exclusively in SOT recipients. Compared with diabetic patients with rhino-orbital-cerebral disease (*62*), SOT recipients in this report had a lower likelihood of orbital (80.0% vs. 34.8%) and sinonasal (100% vs. 89.9%) involvement, but a higher likelihood of CNS invasion (46.1% vs. 31.4%). Because disease manifestations depend on

TABLE 6. Variables associated with mortality in solid organ transplant recipients with zygomycosis involving the sinuses, orbits, or central nervous system

Variable	Reference	Univariate		Multivariate	
		OR (95% CI)	*P*	OR (95% CI)	*P*
Age	Continuous variable	1.03 (0.99–1.07)	0.10	1.12 (1.04–1.21)	0.002
CNS disease	No CNS disease	8.03 (3.08–20.9)	<0.001	2.48 (0.54–11.33)	0.240
Renal failure[a]	No renal failure	1.76 (0.43–7.19)	0.43		
Retransplant	No retransplant	0.40 (0.07–2.25)	0.30		
Disease since 2000	Disease before 2000	0.48 (0.18–1.33)	0.16		
Lipid formulations of amphotericin B	Amphotericin B deoxycholate	0.12 (0.04–0.42)	0.001	0.09 (0.02–0.50)	0.006
Surgical debridement	No surgical debridement	0.11 (0.03–0.35)	<0.001	0.12 (0.01–0.94)	0.043
Reduction or discontinuation of immunosuppression	No reduction or discontinuation of immunosuppression	2.18 (0.40–11.96)	0.36		

[a] Defined as serum creatinine >2 mg/dL at the time of diagnosis.
OR, odds ratio; CI, confidence interval; CNS, central nervous system.

the sites involved, a higher proportion of diabetic patients had ophthamologic symptoms and signs, whereas SOT recipients were more likely to have symptoms related to sinusitis or brain lesions. The maxillary and ethmoid sinuses were the most frequently involved in diabetic patients and SOT recipients. The frontal and temporal lobes were the most common brain lesions in both populations. Not surprisingly, however, diabetic patients with rhino-orbital-cerebral disease had a higher survival rate than SOT recipients (68% vs. 48%).

With the development of antimicrobial agents, our antifungal armamentarium has expanded in the current era. Although employment of antifungal prophylaxis with voriconazole, an agent to which zygomycosis is innately resistant, predisposes leukemic patients or hematopoietic stem-cell recipients to zygomycosis (*1*), multiple therapeutic options are available for the treatment of zygomycosis, and these include amphotericin B deoxycholate, lipid formulations of amphotericin B alone or in combination with echinocandins, iron chelating agents, or adjunctive therapies with interferon-γ and granulocyte macrophage colony-stimulating factor, and posaconazole as a salvage agent (*63*). Polyenes are regarded as the preferred therapeutic agents for zygomycosis; however, no randomized clinical trials have compared the efficacy of lipid formulations and amphotericin B deoxycholate for the treatment of zygomycosis. Nevertheless, some study results suggest that beyond their improved safety profile, lipid formulations of amphotericin B have better performance for the treatment of zygomycosis than amphotericin B deoxycholate, in particular liposomal amphotericin B.

In animal models with coccidioidal or cryptococcal meningitis, liposomal amphotericin B significantly reduced fungal burden in the brain and improved survival compared with amphotericin B deoxycholate (*64–66*). In addition, liposomal amphotericin B achieved a 5-fold higher concentrations in rabbit brain with *Candida* infection than amphotericin B lipid complex (*67*). Likewise, in a diabetic murine model of hematogenously disseminated *Rhizopus oryzae* infection, liposomal amphotericin B significantly improved overall survival than amphotericin B deoxycholate (*68*). Although liposomal amphotericin B and amphotericin B lipid complex were equally effective in the treatment of neutropenic mice with zygomycosis, liposomal amphotericin B was superior to amphotericin B lipid complex in the experimental model of diabetic mice with zygomycosis (*69*).

Data regarding direct comparison of efficacy of lipid formulations of amphotericin B and amphotericin B deoxycholate for treatment of zygomycosis are sparse (*70–79*). However, in hematologic patients or immunocompromised hosts receiving lipid formulations of amphotericin B, favorable responses rates were approximately 58% to 94.1% (*70–76*). A review of zygomycosis in patients with hematologic or oncologic disease showed that receipt of lipid formulations of amphotericin B achieved higher survival rates than that of amphotericin B deoxycholate (*77*). In addition, lipid formulations of amphotericin B were associated with improved survival in recent reports (*74*, *78*). Our study showed that receipt of lipid formulations of amphotericin B compared with receipt of amphotericin B deoxycholate was independently associated with improved survival in SOT recipients with rhino-orbital-cerebral zygomycosis (Table 6).

The combination of an echinocandin and lipid formulations of amphotericin B improved survival of zygomycosis in both murine model and in humans; immune stimulation by enhanced exposure of β-glucan as a result of the echinocandin has been proposed as the likely basis of the beneficial effect of the combination (*69*, *80–82*). It is plausible that this salutary effect also exists in organ transplant recipients; however, the number of patients who received this combination in our study was too small for meaningful assessment.

Although high-dose corticosteroid therapy has been proposed to be the risk factor for invasive zygomycosis (*83*), a previous case control study demonstrated that corticosteroid use or dose per se did not correlate significantly with the risk of zygomycosis in SOT recipients (*5*). In a published review of the literature of zygomycosis in all hosts (*7*), corticosteroid use alone was not specifically identified as a risk factor in any of the 929 cases. Thus, although corticosteroids contribute to the overall state of immunosuppression, these agents per se do not seem to be the primary or sole contributor to zygomycosis in SOT recipients.

Early diagnosis influences outcome in patients with rhino-orbital-cerebral zygomycosis. In a review of cases with heterogenous underlying diseases, the survival rate declined if amphotericin B was initiated 6 days after symptom onset, and

none of the nondiabetic patients survived if they did not receive antifungal agent within 12 days of onset of symptom (*56*). In SOT recipients with zygomycosis (*6*), a favorable outcome was associated with surgical intervention along with amphotericin B administration, whereas this study showed that lipid formulations of amphotericin B, but not surgical debridement, improved survival in recipients with rhino-orbital-cerebral disease with an involvement of CNS, whereas old age was an ominous predictor for poor outcome. It is possible that the brain lesions were not amenable to surgical intervention, or the outcome was dismal once the brain was involved regardless of whether surgery was performed.

Several weakness of our study should be acknowledged. Foremost among these is that our findings are limited by bias inherent to any review of existing literature. Nevertheless, this study offers detailed information about manifestations and outcomes of SOT recipients with one of the most significant types of zygomycosis, that is, patients with rhino-orbital-cerebral involvement, and identified prognostic factors to optimize the management of the disease in this population. We were not able to assess zygomycosis attributable mortality, and evolution of transplantation practices may also have played a role in patient outcomes. However, when adjusted for the disease diagnosis era, the advantage of lipid formulations of amphotericin B on mortality remained. Our findings should be interpreted with caution because this was not a randomized trial evaluating the therapeutic efficacy of antifungal regimens.

In conclusion, SOT recipients with rhino-orbital-cerebral zygomycosis are more likely to have brain involvement compared with diabetic patients with rhino-orbital-cerebral disease and carry a high-mortality rate, particularly when the brain is involved. Older age portended a poor outcome, whereas surgery was associated with a better prognosis. Lipid formulations of amphotericin B as therapy correlated with a lower mortality in SOT recipients with rhino-orbital-cerebral zygomycosis. Given their implications for optimizing outcomes, the latter findings warrant validation in future clinical trials.

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