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Evaluation of patients with zygomycosis

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Aim: Zygomycosis is a severe angioinvasive infection caused by Zygomycetes. We retrospectively investigated 16 cases of zygomycosis.

Materials and methods: The data of patients, who had been followed between 2004 and 2010 in 8 tertiary-care teaching hospitals, were reviewed. Demographic characteristics, underlying diseases, and clinical signs and symptoms of the patients, as well as diagnostic methods, data obtained by radiological imaging methods, and the therapies, were recorded. Therapeutic approaches, antifungal agents and duration of use, and the characteristics of the cases were identified.

Results: The study included 11 female and 5 male subjects. The most common symptoms and clinical signs were fever (n = 9) and retro-orbital pain (n = 7). Rhinocerebral zygomycosis was the most common form. The mean time elapsed for diagnosis was 14.26 ± 13.96 (range: 2–52) days. Antifungal therapy was given to 15 patients (94%). In addition to antifungal therapy, 12 patients underwent surgical intervention 1 to 4 times. The mean duration of receiving antifungal therapy was 61.4 ± 58.02 (range: 1–180) days. The median duration of treatment was 62.5 (range: 42–180) days in survivors.

Conclusion: Zygomycosis is an infectious disease with high mortality despite antifungal therapy and surgical interventions.

Key words: Zygomycosis, predisposing factors, Zygomycetes

1. Introduction

The incidence of invasive fungal infections has increased in recent years. Reasons for this increment include increased numbers of cases with hematological malignancies, provisions of myelosuppression with higher doses of chemotherapy, increased numbers of patients that undergo organ transplantation, and increased use of corticosteroids. Therefore, zygomycosis is the other invasive fungal infection with increased incidence, in addition to aspergillosis and candidiasis (1,2). Zygomycosis usually occurs in patients with an underlying factor such as diabetes mellitus, immunosuppressive therapy, solid organ and hematopoietic cell transplantation, leukemia, lymphoma, burns, glomerulonephritis, gastroenteritis, broad-spectrum antibiotic use, hemodialysis, or deferoxamine therapy. Although zygomycosis is generally seen in immunocompromised subjects, it can also be seen in immunocompetent subjects. The causative pathogen is usually transported into the body via inhalation through the nasal sinuses. Moreover, direct spore inoculation or exposure of skin already compromised by burns or extensive trauma can lead to the cutaneous form of zygomycosis (2–8).

Zygomycosis is developed in 5 different clinical pictures: rhinocerebral, pulmonary, cutaneous, gastrointestinal, and disseminated. However, different clinical forms such as osteomyelitis and endocarditis have been rarely mentioned in the literature. Since the agent microorganism generally

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enters the body via the inhalation route, paranasal sinuses are the most commonly involved anatomical region in zygomycosis infection. Unfortunately, symptoms and signs of the sinusitis in this infection are not pathognomonic to be differentiated from the clinical picture of sinusitis caused by other pathogens. Nasal congestion, headache, maxillary pain, hyposmia, and anosmia may be seen. In addition, the presence of necrotic scarring in the nasal cavity and necrotic facial lesions indicate an angioinvasive infection (8–12).

Zygomycosis still has high mortality today, despite early diagnosis and treatment. Therefore, there is a need for new data about the treatment of this disease. The aim of this study was to analyze demographic characteristics, underlying diseases, and clinical and treatment results of patients diagnosed with zygomycosis in 8 tertiary-care teaching hospitals between 2004 and 2010.

2. Materials and methods

The data of patients who had been followed between 2004 and 2010 in 8 tertiary-care teaching hospitals were reviewed. Demographic characteristics, underlying diseases, and clinical signs and symptoms of the patients, as well as diagnostic methods, data obtained by radiological imaging methods, and the therapies, were recorded. Diagnosis of zygomycosis was made in accordance with the criteria issued by European Organization for Research and Treatment of Cancer/Mycoses Study Group (13). The clinical forms of zygomycosis have been defined based on the involved organ: rhinocerebral (rhino-orbito-cerebral, rhino-orbital), cutaneous, pulmonary, gastrointestinal, and disseminated (3,9). As well as the clinical findings, radiological imaging methods (computed tomography and magnetic resonance imaging) and endoscopic methods (rhinoscopy, gastrointestinal endoscopy) were used to detect the localization of the infections. Therapeutic approaches, antifungal agents and duration of use, and the characteristics of the cases were identified. The authors thought that ethical approval was not required for this retrospective study.

3. Results

The study included 11 female and 5 male subjects. The mean age was 52.50 ± 14.55 (range: 22–68) years. The majority of the patients (n = 15, 94%) were immunocompromised and most of them had type 2 diabetes mellitus (n = 10, 62.5%). Seven patients had received corticosteroid treatment. The most common symptoms and clinical signs were fever (n = 9) and retro-orbital pain (n = 7). Rhinocerebral zygomycosis was the most common form (Table 1). Mycological cultures were performed in 14 patients and half of them had a positive culture. Isolated pathogens included *Rhizopus* spp. (n = 4), *Mucor* spp. (n = 2), and *Rhizomucor* spp. (n = 1). Characteristics of underlying conditions, clinical forms, and management, as well as the data of the patients, are given in Table 2.

The diagnosis was made based on culture positivity alone in 2 (12.5%) of the cases, whereas it was made based on the histopathological findings in 9 (56.25%) and based on both culture positivity and histopathological findings in 5 (31.25%) cases. *Aspergillus flavus* was found as a second agent in 2 cases. The mean time elapsed for diagnosis was 14.26 ± 13.96 (range: 2–52) days.

The mean duration of receiving antifungal therapy was 61.4 ± 58.02 (range: 1–180) days. On the other hand, the median duration of treatment was 62.5 (range: 42–180) days in survivors. Overall, a favorable response was observed in 6 patients (37.5%). Antifungal therapy was given to 15 patients (94%) (Table 3). One patient (case 8) received voriconazole for aspergillosis. On the 25th day of treatment therapy was switched from voriconazole to liposomal amphotericin B (L-AmB) because the tissue samples were consistent with both zygomycosis and aspergillosis. In addition to antifungal therapy, 12 patients underwent surgical intervention 1 to 4 times. Local AmB irrigation was tried in 4 patients.

4. Discussion

Zygomycosis is associated with several risk factors. Diabetes mellitus is one of the most important risk factors for zygomycosis (5). Neutrophil dysfunction is a common condition in the diabetic patient, especially in the setting of diabetic ketoacidosis. In the current study, type 2 diabetes mellitus was present in 10 of 16 patients, 2 of which were steroid-induced, and it was the most common underlying disease (Table 2). Generally, the rhinocerebral form is seen in diabetic patients (14). In the present study, almost all diabetic patients showed sinus involvement, and 90% had the rhinocerebral form. The present study revealed that corticosteroid use was the most common comorbid condition that accompanied diabetes mellitus. Although mortality rates change in the presence of comorbid conditions that accompany diabetes mellitus, statistical analysis could not be done due to the limited number of patients. Roden et al. (5) found the mortality rate to be 44% among diabetic patients diagnosed with zygomycosis. In our study, the mortality rate was found to be 80% among diabetic patients regardless of comorbid disease. The difference might be explained by the higher mortality rates observed in rhinocerebral zygomycosis (62%) in the current study and the rate of disseminated disease (100%) in the current study, as well as other factors.

Another risk factor is renal failure. Deferoxamine use in such patients is likely an important risk factor for zygomycosis development. Deferoxamine binds to the host iron and is presented to the microorganism as

Table 1. Age, sex, predisposing conditions, symptoms and signs, clinical forms, cultures, pathology, and treatment managements of 16 cases of zygomycosis.

	Sex, age	Underlying conditions	Symptoms and signs	Clinical forms	Fungal cultures	Pathology (findings of zygomycosis)	Diagnosis	Management	Time elapsed for diagnosis (days)	Treatment duration (days)	Outcome
1	F, 34	DM	Headache, diplopia, dysphagia	ROC	Negative	+	Proven	Antifungal + surgery + AmB irrigation	52	92	Death
2	F, 64	DM, corticosteroid	Retro-orbital pain, facial palsy, orbital cellulitis	ROC	*Rhizopus* spp.	+	Proven	Antifungal + surgery + AmB irrigation	14	7	Death
3	F, 50	DM, corticosteroid	Retro-orbital pain, headache, unilateral facial swelling, necrotic scar in the nasal cavity	ROC	Negative	+	Proven	Antifungal + surgery	10	53	Death
4	M, 37	DM, corticosteroid, AML, neutropenia, broad spectrum antibiotic	Retro-orbital pain, fever, headache, unilateral facial swelling, orbital cellulitis	RO	Negative	+	Proven	Antifungal + surgery + AmB irrigation	8	36	Death
5	F, 27	None	2 × 2 cm diameter ulcer of the left thumb	Cutaneous	*Rhizopus* spp.	+	Proven	Antifungal + surgery	4 years	42	Alive
6	F, 62	DM*, corticosteroid, surgery	Purulent nasal discharge, orbital cellulitis, proptosis	ROC	*Mucor* spp.	+	Proven	Antifungal + surgery	12	180	Alive
7	F, 61	DM	Fever, diplopia, blurred vision, unilateral facial swelling, orbital cellulitis, proptosis	ROC	*Mucor* spp.	+	Proven	Antifungal + surgery	15	179	Alive
8	M, 60	DM*, corticosteroid, CRF	Ptosis, proptosis	ROC	*Aspergillus flavus*	**	Probable	Antifungal + surgery	33	1	Death
9	F, 61	Cirrhosis, corticosteroid, SOT	Melena	Gastrointestinal	Not performed	+	Proven	Antifungal	2	42	Alive
10	F, 63	Corticosteroid, MCL, broad spectrum antibiotic	Fever, abdominal pain	Disseminated	Not performed	+	Proven	–	12	–	Death
11	M, 63	Prostate cancer	Fever, cough, sputum	Pulmonary	*Rhizopus* spp.	+	Proven	Antifungal + surgery	3	68	Alive
12	F, 50	MDS, neutropenia	Fever, dyspnea, orbital cellulitis, proptosis, blurred vision, retro-orbital pain	Disseminated	*Rhizomucor* spp., *Aspergillus flavus*	–	Proven	Antifungal	5	7	Death
13	F, 22	Aplastic anemia, broad spectrum antibiotic, neutropenia	Fever, unilateral facial swelling	RO	Negative	+	Proven	Antifungal	21	57	Alive
14	M, 55	DM, cirrhosis, broad spectrum antibiotic	Retro-orbital pain, fever, unilateral facial swelling	ROC	*Rhizopus* spp.	+	Proven	Antifungal + surgery	7	12	Death
15	M, 63	DM, CRF	Retro-orbital pain, facial palsy, headache, unilateral facial swelling, orbital cellulitis, proptosis	RO	Negative	+	Proven	Antifungal + surgery + AmB irrigation	5	25	Death
16	F, 68	DM, CRF, surgery	Retro-orbital pain, fever, headache	Disseminated	Negative	+	Proven	Antifungal + surgery	15	120	Death

F: Female, M: male, DM: diabetes mellitus, DM*: corticosteroid-induced diabetes mellitus, CRF: chronic renal failure, AML: acute myeloid leukemia, MDS: myelodysplastic syndrome, MCL: mantle cell lymphoma, SOT: solid organ transplant, ROC: rhino-orbito-cerebral, RO: rhino-orbital, AmB: amphotericin B. **: Histologically, aspergillosis, and mucormycosis hyphae were detected in the specimen.

Table 2. Underlying conditions, clinical forms, and treatments of 16 patients, 10 of whom died.

	n (%)	Mortality n (%)
Underlying conditions*		
Diabetes mellitus	10 (62.5)	8 (80)
only	2 (20)**	1 (50)
and corticosteroid use	5 (50)**	4 (80)
and chronic renal failure	3 (30)**	3 (100)
and broad spectrum antibiotic use	2 (20)**	2 (100)
and surgery	2 (20)**	1 (50)
and cirrhosis	1 (10)**	1 (100)
Hematological disorders	4 (25)***	3 (75)
and neutropenia	3 (75)***	2 (66.7)
and broad spectrum antibiotic use	3 (75)***	2 (66.7)
and corticosteroid use	2 (50)***	2 (100)
Solid tumor	1 (6.3)	0 (0)
SOT*, corticosteroid use, cirrhosis	1 (6.3)	0 (0)
Clinical forms		
Rhino-orbito-cerebral	7 (43.75)	5 (71.4)
Rhino-orbital	3 (18.8)	2 (66.7)
Disseminated	3 (18.8)	3 (100)
Pulmonary	1 (6.3)	0 (0)
Cutaneous	1 (6.3)	0 (0)
Gastrointestinal	1 (6.3)	0 (0)
Treatment		
Antifungal therapy alone	3 (18.8)	1 (33.3)
Antifungal therapy + surgery	8 (50)	4 (50)
Antifungal therapy + surgery + irrigation with AmB	4 (25)	4 (100)
No therapy (postmortem diagnosis)	1 (6.3)	1 (100)

*: There were more than 2 conditions in some patients.
**: Calculated for 10 patients.
*** Calculated for 4 patients.
SOT: Solid organ transplant recipient, AmB: amphotericin B deoxycholate.

siderophores, inducing sporulation and development of zygomycosis (10,15). Pulmonary zygomycosis is seen in patients with renal failure (16). Chronic renal failure was present in 3 of the cases: 2 patients with the rhino-orbito-cerebral form and 1 patient with the disseminated form, all of whom died. The study conducted by Roden et al. (5) showed that 36 of 929 zygomycosis patients had renal failure and 89% died; multivariate analysis revealed that renal failure increased the mortality risk by 7 times.

Prolonged neutropenia is known to increase the risk for zygomycosis due to its reduced phagocytic characteristic. In the literature, more than 70% of zygomycosis patients have neutropenia, and the median neutropenia duration is between 12 and 16 days (17). Pulmonary zygomycosis

Table 3. Details of antifungal therapy.

Patient no.	Antifungal therapy	Total antifungal therapy duration (days)
1	AmB 1 mg kg^{-1} day^{-1} (8 days) then L-AmB 5–10 mg kg^{-1} day^{-1}	92
2	AmB 1 mg kg^{-1} day^{-1} (7 days) then L-AmB 5 mg kg^{-1} day^{-1}	7
3	AmB 1 mg kg^{-1} day^{-1} (23 days) then L-AmB 10 mg kg^{-1} day^{-1}	53
4	AmB 1 mg kg^{-1} day^{-1} (4 days) then L-AmB 5 mg kg^{-1} day^{-1}	36
5	AmB 1 mg kg^{-1} day^{-1}	42
6	AmB 1 mg kg^{-1} day^{-1} (1 day) then L-AmB 5 mg kg^{-1} day^{-1}	180
7	AmB 1 mg kg^{-1} day^{-1} (6 days) then L-AmB 5 mg kg^{-1} day^{-1} (93 days) then posaconazole 800 mg day^{-1}	179
8	Voriconazole (25 days, for aspergillosis) then L-AmB 5 mg kg^{-1} day^{-1}	2
9	L-AmB 5 mg kg^{-1} day^{-1}	42
10	–	–
11	AmB 1 mg kg^{-1} day^{-1} (1 day) then L-AmB 5 mg kg^{-1} day^{-1} (7 days) then posaconazole 800 mg day^{-1}	68
12	AmB 1 mg kg^{-1} day^{-1} (1 day) then L-AmB 5 mg kg^{-1} day^{-1}	7
13	AmB 1 mg kg^{-1} day^{-1} (8 days) then ABLC 5–9 mg kg^{-1} day^{-1}	57
14	L-AmB 3 mg kg^{-1} day^{-1}	12
15	AmB 1 mg kg^{-1} day^{-1} (1 day) then L-AmB 5 mg kg^{-1} day^{-1}	25
16	L-AmB 3 mg kg^{-1} day^{-1}	120

AmB: Amphotericin B deoxycholate, L-AmB: liposomal amphotericin B, ABLC: amphotericin B lipid complex.

is the most common clinical picture in neutropenic patients (18). In our study, neutropenia was found in 3 of the 4 patients with hematologic malignancy; 2 displayed the rhino-orbital form and 1 displayed the disseminated form. Neutrophils play a substantial role in preventing development of invasive fungal infection (17). Therefore, they form the most important part of the cellular host defense against zygomycosis (19).

Corticosteroid use is another risk factor for the development of zygomycosis. It has been shown in experimental models that corticosteroids suppress phagocytic activities of macrophages, leading to a tendency toward zygomycosis infection (20). Corticosteroids were used in 7 of 16 patients, 6 of whom died.

An association has been revealed between zygomycosis and the use of voriconazole, itraconazole, and caspofungin for treatment or prophylaxis (1,21). In the present study, none of the patients had used an antifungal agent within the last year, whereas 4 had received broad-spectrum antibiotic therapy. Liver cirrhosis and surgery also create a predisposition to the development of zygomycosis (5,22,23).

Rhinocerebral zygomycosis is characterized by nasal and paranasal sinus involvement as well as orbital, cavernous sinus, and cerebral involvement (9). In our study, the rhinocerebral form (including the rhino-orbital form) was identified in 10 patients, 7 of whom died. Concerning the remaining 3 cases, the time until diagnosis was 12, 15, and 21 days, respectively. Debridement was performed in 2 patients along with antifungal therapy; 1 patient received antifungal therapy alone. Various studies have mentioned high mortality rates concerning rhinocerebral involvement and the association between late diagnosis and mortality (9,24).

Pulmonary zygomycosis most commonly occurs in hematopoietic stem cell recipients and diabetic and leukemic patients who are receiving chemotherapy (19,25). Pulmonary zygomycosis usually presents as a rapidly progressing pneumonia. Nonetheless, symptoms and signs seen in early periods, such as fever, cough, thoracic pain, and dyspnea, are not specific. However, pulmonary zygomycosis should be considered in the case of prolonged fever and unresponsiveness to broad-spectrum antibiotics in the risk-group patients. Hemoptysis may also be seen and can even result in mortality if large vessel erosion has

occurred. In the present study, one patient had pulmonary zygomycosis with a solid tumor. The patient presented with fever, cough, and sputum; the thorax computed tomography showed a cavity of 6 × 6 cm in the upper lobe of the right lung. *Rhizopus* spp. was grown in the sample obtained and was consistent with zygomycosis upon histopathological examination. In addition to the surgical intervention, the patient received L-AmB at a dose of 5 mg/kg daily as antifungal therapy; however, the therapy was discontinued on the seventh day and posaconazole was commenced at a dose of 800 mg/day per os for 60 days.

The disseminated form is usually identified during postmortem evaluation of cases with deep immune suppression (9). In the present study, one patient was diagnosed with disseminated zygomycosis during postmortem evaluation. The patient had been diagnosed with mantle cell lymphoma and developed neutropenic fever on the 10th day of chemotherapy. She had abdominal pain and received broad-spectrum antibiotic therapy. The patient died before antifungal therapy could be started. However, postmortem examination revealed disseminated zygomycosis. The mortality rate is almost 100% in disseminated cases; in the present study, all of the 3 patients with the disseminated type died. Disseminated zygomycosis infection usually results from the extension of invasive pulmonary disease (19). In one of our cases, the clinical picture appeared as neutropenic fever and pneumonia with detection of necrotic tissues a few days later in the nasal region. *Rhizomucor* spp. were isolated from both the tissue sample from the nasal region and bronchoalveolar lavage fluid.

The incidence of the gastrointestinal form of zygomycosis is approximately 7%, with a mortality rate of 85% (5). The stomach, colon, and ileum are the most commonly involved sites. The symptoms vary depending on the involved site. Nonetheless, the most common symptoms include abdominal pain and distension accompanied by nausea and vomiting (19). The present study includes one patient with gastrointestinal zygomycosis. The initial complaint of the case was melena; a sample was obtained during endoscopic procedure from the black-red mottling around the ulcer, and hyphae consistent with zygomycosis were seen upon pathological evaluation of the material. Antifungal therapy was commenced for the patient. No other fungal infection focus was detected via other imaging methods. After 42 days of antifungal therapy, the patient underwent a control endoscopic evaluation, and it was observed that the lesion had disappeared.

Primary cutaneous zygomycosis can be developed even in immunocompetent subjects after traumas (motor vehicle accidents) and burns (9). The disease may present with slow or fulminant progress depending on the clinical condition. Cutaneous disease may lead to necrotizing fasciitis, which has a mortality rate of 80%. However, isolated cutaneous zygomycosis has a favorable prognosis and low mortality rate if surgical debridement is done (19,26). The present cutaneous case had no predisposing factors other than trauma. The clinical picture appeared as a cutaneous infection with a 4-year history. The patient was cured with antifungal therapy and surgery.

The zygomycosis case series showed that males are involved more than females. Various researchers attributed this discrepancy to the potential protective effect of estrogen (5). In the present study, 11 of 16 patients were female and 5 were male. This inconsistent finding with the literature can be attributed to the limited number of patients. Despite the availability of modern laboratory methods, the diagnosis of zygomycosis is difficult. Unfortunately, 4% of cases are diagnosed in the postmortem period; 6% can be diagnosed 24 h before death via culture and histological examination (25). In the present study, culture positivity may remain at a rate of 50% in the diagnosis of zygomycosis. The most commonly isolated agents include *Rhizopus* spp. and *Mucor* spp. (7). These were the most commonly isolated agents in the current study. *Aspergillus flavus* was isolated in the mycological cultures of 2 cases in addition to the zygomycosis agents. Previous literature has addressed the concomitance of these 2 microorganisms (27–29).

The mean time elapsed for the diagnosis was 14.26 ± 13.96 days. Since it could change the mean value, the 4-year duration of the cutaneous case was not included when the mean time was calculated. As mentioned, the mortality rate is low in early-diagnosed cases (24). In the present study, the time span from the onset of the symptoms to the diagnosis was between 2 and 21 days among survivors and between 5 and 52 days among those who died. When considered on a case-by-case basis, the time elapsed for the diagnosis was nearly the same in both groups.

The treatment of zygomycosis comprises 3 main factors: antifungal therapy, surgical debridement, and relieving underlying metabolic problems or improving immune status (19). Before the availability of AmB for the treatment of zygomycosis, the survival rate was less than 6%; today, it has reached 60% with the use of AmB lipid formulations in both experimental and clinical case series (30–33). In addition to AmB preparations, posaconazole is another agent that has shown in vitro efficacy against Zygomycetes and that has been successfully used in the treatment of zygomycosis cases in 2 clinical trials (34–36). The rates of improvement using 800 mg/day posaconazole were 60% and 79%, respectively, in the above-mentioned trials. Currently, it is recommended as salvage therapy. In the present study, posaconazole was used as salvage therapy in 2 cases, and successful outcomes were obtained. Although therapy duration in zygomycosis varies depending on the

case, it should continue for at least 6 to 8 weeks (18). In the present study, the mean therapy duration was 62.5 days (approximately 9 weeks) among survivors.

The success rate of antifungal therapy alone is low due to antifungal drugs passing into the tissue (37). In the present study, the success rate of antifungal therapy alone was 33%. The mortality rate decreases with appropriate surgical debridement; a systemic antifungal agent was used in the present study. Surgical intervention is an important factor in the treatment of zygomycosis. Aggressive surgical intervention of infected craniofacial tissues in the early period in cases of rhinocerebral zygomycosis is important for successful therapy (38).

Since there could be problems with antifungal agents passing into the related anatomical area due to massive amounts of necrotic tissue, local AmB application (in addition to surgical intervention and systemic antifungal therapy) was administered in 4 patients, all of whom died. Such a high mortality rate despite appropriate surgical debridement and appropriate antifungal therapy might have resulted from the limited number of cases. Therefore, more studies on AmB irrigation are needed.

In conclusion, diabetes mellitus and corticosteroid use are common underlying conditions in zygomycosis. Zygomycosis is an infectious disease with high mortality despite antifungal therapy and surgical interventions. A high degree of clinical suspicion in patients at risk of zygomycosis, together with aggressive diagnostic efforts as well as prompt initiation of medical and surgical therapy, are of utmost importance in order to improve outcomes.

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