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Original Article

Mucormycosis in a pediatric population: a review of 20 cases from southern Turkey

Derya Alabaz[1], Gülsüm Yılmaz[1], Aysun Uğuz[2], Süleyman Özdemir[3], İlgen Şaşmaz[4], İbrahim Bayram[4]

Departments of [1]Pediatric Infectious Disease, [2]Pathology, [3]Otolaryngology-Head and Neck Surgery, and [4]Pediatric Hematology and Oncology, Çukurova University Faculty of Medicine, Adana, Turkey.

ABSTRACT

Background. Mucormycosis is a fatal invasive fungal infection seen most often in patients with compromised defense mechanisms. The aim of this article was to review the data of pediatric mucor in the South of Turkey.

Methods. Twenty pediatric cases with biopsy proven mucormycosis were reported, between January 2007 through January 2017. Data were extracted from the medical charts of patients retrospectively.

Results. Underlying conditions were hematological malignancy (75%), in whom 93% had acute leukemia, aplastic anemia (15%), diabetes mellitus (5%) and other malignancies (5%). The main sites of infection were sinus (85%); alone (29.4%) or with cerebral (17.6%), and orbital involvement (17.6%). Pulmonary involvement was reported in 11 patients (55%), two of them had the alone form and nine cases were associated with nasal sinus involvement. Disseminated mucormycosis was documented in 45%. Fever and pain/swelling of organs were the most commonly encountered signs and symptoms. Treatment compromised of am-photericin B monotherapy in five patients. All patients except one received liposomal formu-lations (LAmB). A combination of surgery and antifungal therapy was performed in 75%. Crude survival was 55%; among 15 cases treated with a combination of surgery and antifun-gal therapy, survival rate was 8/15 (53%). The overall mortality rate was high in patients diagnosed with disseminated infection (100%).

Conclusions. Mucormycosis in pediatric cases requires a high index of suspicion and urgent evaluation of clinical samples. Surgical debridement should be considered when feasible. Initial medical therapy should include an amphotericin preparation with or step-down to posaconazole.

Key words: mucormycosis, zygomycosis, children, immunosuppressive, amphotericin B.

Mucormycosis (zygomycosis) is the third emerging important invasive fungal infection dur-ing the past decade, it is associated with a worse outcome when compared to other invasive fungal infections such as candidiasis or aspergillosis.[1-4] The increase in the incidence may be attributed to a better outcome in the survival of immunocompromised patients.[5] Depending on the underlying condition, such as the withdrawal or reduction of corticosteroids, impair-ment of neutropenia, hematological malignancies, hematopoietic stem cell transplantation (HSCT), adequate control of glycemia in cases of diabetes, and the portal of entry, they can cause rhinocerebral, pulmonary, cutaneous, gastrointestinal or even disseminated infection.[6,7] The rapid initiation of antifungal therapy is the cornerstone due to the highly difficult treat-ment of this destructive infection.

We report retrospective results in the present study, where we reviewed clinical characteristics, risk factors, treatment and outcome of pediatric mucormycosis, diagnosed by histopathology at our center from 2007 until 2017, a University Hospital in Southern Turkey.

✉ Derya Alabaz
deryaalabaz@yahoo.com

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Material and Methods

The study was conducted in a tertiary medical college hospital (Çukurova University Faculty of Medicine). Our patients were managed by a multidisciplinary healthcare team comprised of oncologists, infectious disease specialists, surgeons, pathologists, radiologists and inten-sivists. The study was approved by the Institutional Ethics Committee (Approval number: 04-09-2019/91).

All pediatric patients (aged 0-18) that were diagnosed histologically as mucormycosis be-tween January 2007 through January 2017, were included in the study. All cases were proven as mucormycosis based on a histopathologic examination of a needle aspiration and/or a bi-opsy specimen which revealed hyphae and evidence of associated tissue damage from the nasal cavity and/or paranasal sinuses and/or palate, lung or dermis.

Histopathologic diagnosis: Mucor infections are one of the correctly detectable fungi by biopsy and they are determined as angioinvasive, broad, without septas and 90 degrees branching hyphae in tissue sections. Although routine hematoxylene-eosin tissue sections are generally sufficient some histochemical stains like PAS and GMS (Gomori's methanamine silver) can be used, its particularly predominant appearance is necrosis. Sometimes fungal hyphaes can be few, or degraded or folded in tissue sections.

All patients underwent computed tomography (CT) or magnetic resonance imaging (MRI) scans of paranasal sinuses, orbita, craniocerebrum and lungs.

The sites of infection were classified according to those utilized in the study of Roden et al.[4] Accordingly, sinusitis was defined as an infection involving the paranasal sinuses; those with disease in paranasal sinuses and orbital infiltration were defined as sino-orbital infec-tion; those with disease in the paranasal sinuses and the brain as rhinocerebral infection; those with disease in the paranasal sinuses and lungs were defined as having sinopulmonary infection; pulmonary infection was defined as infection confined to lung tissue and as deep extension when invading adjacent tissues, and dissemination was defined as two or more non-contiguous locations of Mucorales infection.

The demographic characteristics, type of underlying conditions, risk factors, the site of in-fection, clinical signs and symptoms of infection, radiological findings, treatments, and out-come were extracted from the medical charts of patients.

Results

The hospital pathology records identified 24 individual cases of mucormycosis in pediatric patients during 10 years. Of these, four cases were excluded from the database because they did not meet the stringent predefined inclusion criteria or the patient file could not be reached. During the study, 20 patients with proven mucormycosis (14 male, 6 female) were recorded. Demographic characteristics and clinical features are summarized in Tables I and II. The age at diagnosis ranged from 2 to 16 years (average age was 9 years) and 7 patients were aged ≤ 5 years. Two patients out of 20 were foreign (Syrian) nationals.

The patients' underlying conditions are listed in Table II. Fifteen patients (75%) with he-matological malignancy composed the largest group, in whom 93% had acute leukemia (one underwent HSCT). Three patients had aplastic anemia (2 were Fanconia anemia and one underwent HSCT). Eighteen patients were neutropenic and 8 patients were known as being on antifungal prophylaxis (5 patients with fluconazole and 3 patients with itroconazole) while 7 patients were receiving co-trimaxazole. Two patients had chronic renal failure and one patient had metabolic acidosis.

Nasal involvement was identified in a majority of the cases (17/20; 85%) patients, alone in 5/17, with cerebral involvement in 3/17, and with orbital involvement in 3/17 (Table III). Pulmonary involvement was reported in 11/20

Table I. Overview of our 20 pediatric mucormycosis cases (2007-2017).

Number	Age/sex/year City	Underlying medical problem predisposing factor	Prophylaxis	Symptoms and signs	Co-infection	Radiological findings	Clinical form	Surgical treatment (count)	First line antifungal therapy/duration (days, mg/kg)	Survival outcome (follow-up, cause of death)
1	13/F/2007 Osmaniye	AML(relapse)/ CHB Neutropenia	FLU (20 days)	Facial pain, blackish necrotic debris on nose	*Aspergillus*	CT: sinusitis, pneumonia, pericarditis	Sino-pulmonary, tracheitis, pericarditis/ deep extension/ dissemination	Only biopsy	LAmB (24 days, 10mg/kg)	Died (fungal infection)
2	3/F/2008 Maraş	ALL Neutropenia	FLU, KO	Fever, ulcerative palate lesion	*Aspergillus, Candida*	CT: sinusitis, sinus wall destruction,	Sinusitis	Surgery (1)	cAmB (90 days) then POS (7 months)	Cured
3	5/M/2008 Gaziantep	ALL (relapse) Neutropenia, hyperglycemia	?	Fever, nasal pain, facial swelling, epistaxis, cough	-	CT: sinusitis, air crescent sign (right)	Sino-pulmonary	Surgery (1)	LAmB	Cured (transferred to another center)
4	11/M/2008 Adana	AML(relapse) Neutropenia	?	Fever, voice loss, chest pain	-	CT: sinusitis, pulmonary nodule, consolidation	Sino-pulmonary tracheitis/ deep extension/ dissemination	Only biopsy	LAmB (31 days)	Died
5	3/M/2008 Urfa	ALL (refractory) Neutropenia, cerebral mucor history	?	Fever, facial pain and swelling, epistaxis, ulcerative palate lesion, cough	*Pseudomonas*	CT: sinusitis, sinus wall destruction, pneumonia MRI: cerebritis, leptomeningitis	Rhino-cerebral, pulmonary/ dissemination	Surgery (3)	LAmB (40 days)	Died (fungal infection)
6	8/M/2009 Adana	ALL (relapse) Neutropenia	I, KO	Fever, facial swelling	-	CT: sinusitis, pneumonia	Sino-pulmonary	Surgery (2)	LAmB (165 days, 10 mg/kg) +caspofungin, VOR, then POS	Cured (14 months)
7	8/M/2010 Urfa	ALL Neutropenia Mucor history (10 months)	FLU, KO	Fever, facial swelling, sepsis	-	CT: sinusitis, MRI: frontal lobe infiltration	Rhino-cerebral/ dissemination	Surgery (2)	LAmB (60 days, 7 mg/kg) POS (5 months)	Died (fungal infection)

ALL: acute lymphoblastic leukemia, AML: acute myeloid leukemia, cAmB: conventional amphotericin B, CHB: chronic hepatitis B, CRF: chronic renal failure, CT: computerized tomography, FAA: Fanconi aplastic anemia, FLU: fluconazole, HSCT: hematopoietic stem cell transplantation, I: itraconazole, KO: co-trimoxazole, LAmB: liposomal amphotericin B formulation, MRI: magnetic resonance imaging, PNET: primitive neuroectodermal tumor, POS: posaconazole, V: voriconazole.

Table I. Continued.

Number	Age/sex/year City	Underlying medical problem predisposing factor	Prophylaxis	Symptoms and signs	Co-infection	Radiological findings	Clinical form	Surgical treatment (count)	First line antifungal therapy/duration (days, mg/kg)	Survival outcome (follow-up, cause of death)
8	5/M/2010 Hatay	ALL (induction) Neutropenia	FLU	Fever, facial swelling, oral blackish necrotic debris, ulcerative palate lesion	-	CT: sinusitis, sinus wall destruction	Sinusitis	Surgery (2)	LAmB (163 days) POS (52 months)	Cured
9	12/M/2012 Osmaniye	ALL (induction) Neutropenia	-	Fever, blackish necrotic debris in nose, ulcerative palate lesion	-	CT: sinusitis, sinus wall destruction	Sinusitis	Only biopsy	LAmB (34 days) then itraconazole	Cured
10	2/M/2013 Urfa	ALL-HSCT Neutropenia	FLU, KO	Fever, cutaneous lesion	-	Ultrasound: cutaneous abscess	Cutaneous/deep extension	Surgery (1)	LAmB (22 days)	Cured
11	7/F/2013 Antakya	FAA and CRF Neutropenia, metabolic acidosis	KO	Fever, epistaxis, sepsis, periorbital swelling, sepsis	-	CT: sinusitis, periorbital cellulitis, hepatic calcification	Sino-orbital/ dissemination	Surgery (1)	LAmB (29 days) +VOR	Died (fungal infection)
12	16/M/2014 Urfa	PNET (metastatic) Neutropenia	I	Fever, mucositis, throat ache, nasal congestion headache, diarrhea	-	CT: sinusitis, sinus wall destruction, multiple pulmonary nodule (metastasis)	Sinusitis	Surgery (1)	LAmB (21 days) POS (5 months)	Cured
13	15/M/2014 Osmaniye	AML(relapse) Neutropenia	I	Fever, epistaxis	*Aspergillus*	CT: pansinusitis, air crescent sign (multiple, bilateral)	Sino-pulmonary/ dissemination	Surgery (1)	LAmB (28 days)	Died (fungal infection)
14	11/F/2014 Hatay	ALL(induction) Neutropenia	-	Facial swelling, palate lesion	*Candida*	CT: pansinusitis	Sinusitis	Surgery (1)	LAmB (60 days) POS	Cured

ALL: acute lymphoblastic leukemia, AML: acute myeloid leukemia, cAmB: conventional amphotericin B, CHB: chronic hepatitis B, CRF: chronic renal failure, CT: computerized tomography, FAA: Fanconi aplastic anemia, FLU: fluconazole, HSCT: hematopoietic stem cell transplantation, I: itraconazole, KO: co-trimoxazole, LAmB: liposomal amphotericin B formulation, MRI: magnetic resonance imaging, PNET: primitive neuroectodermal tumor, POS: posaconazole, V: voriconazole.

Table I. Continued.

Number	Age/sex/year City	Underlying medical problem predisposing factor	Prophylaxis	Symptoms and signs	Co-infection	Radiological findings	Clinical form	Surgical treatment (count)	First line antifungal therapy/duration (days, mg/kg)	Survival outcome (follow-up, cause of death)
15	5/F/2014 Adana	ALL(induction) Neutropenia	KO	Fever, cough	-	CT: air crescent sign (left)	Pulmonary	Surgery (lobectomy)	LAmB (75 days) +VOR POS (2 years)	Cured
16	11/M/2015 Adana	FAA-HSCT (1.5 years ago) and CRF	-	Cough	-	CT: air crescent sign (right)	Pulmonary	Surgery (lobectomy)	LAmB	Cured (transferred to another center)
17	16/F/2016 Adana	Diabetes mellitus Hyperglycemia	-	Pain of tooth and nose, nasal congestion, facial swelling, headache, vomiting	-	CT: sinusitis, MR: frontal lobe abscess (1 cm)	Rhino-cerebral	Only biopsy	LAmB (44 days) POS (43 day)	Cured
18	16/M/2016 Elazığ	Non-Hodgkin lymphoma (relapse)/ Neutropenia	KO	Fever, facial swelling, sepsis	*Aspergillus, Candida*	CT: pansinusitis, parotitis orbital cellulitis, pulmonary nodule and effusion	Sino-orbital, pulmonary, / dissemination	Surgery (2)	LAmB (15 day) +VOR	Died (fungal infection)
19	5/M/2016 Syrian	ALL(relapse) Neutropenia	-	Fever, facial swelling	-	CT: pansinusitis, periorbital cellulitis, pulmonary nodules (bilateral)	Sino-orbital, pulmonary/ dissemination	Surgery (4)	LAmB (60 days) / caspofungin (when LAmB not available)	Died (fungal infection)
20	107M/2016 Syrian	Aplastic anemia Neutropenia, hepatitis	-	Fever, facial and periorbital swelling, ulcerative palate lesion, tooth pain, sepsis	-	CT: pansinusitis, sinus wall destruction, tonsillar abscess, air crescent sign (right)	Sino-pulmonary, tonsillar abscess/ dissemination	Only biopsy	LAmB/ caspofungin (when LAmB not available) (105 days)	Died (fungal infection)

ALL: acute lymphoblastic leukemia, AML: acute myeloid leukemia, cAmB: conventional amphotericin B, CHB: chronic hepatitis B, CRF: chronic renal failure, CT: computerized tomography, FAA: Fanconi aplastic anemia, FLU: fluconazole, HSCT: hematopoietic stem cell transplantation, I: itraconazole, KO: co-trimoxazole, LAmB: liposomal amphotericin B formulation, MRI: magnetic resonance imaging, PNET: primitive neuroectodermal tumor, POS: posaconazole, V: voriconazole.

Table II. Patient demographics, predisposing factors, clinical findings and outcomes.

Clinical features	N (%)	Mortality, n/N (%)
Age		
<5 years	3 (15)	1/9 (11)
≥5-18 years	17 (85)	8/9 (89)
Male/Female	14/6	7/14; 2/6 (50; 33)
Co-morbidity		
Diabetes mellitus	1 (5)	-
Haematological malignancy	15 (75)	9/15 (60)
ALL	11 (55)	3/11 (27)
AML	3 (15)	3/3 (100)
Non-Hodgkin lymphoma	1 (5)	1/1 (100)
Other malignancies		
PNET	1 (5)	-
Haematological disease		
Aplastic anemia	3 (15)	2/3 (67)
Predisposing factor		
Neutropenia	18 (90)	9/18 (50)
Cancer chemotherapy	16 (80)	7/16 (44)
Co-infection with *Aspergillus*	5 (25)	2/5 (40)
Co-infection with *Candida*	3 (15)	2/3 (67)
Antifungal prophylaxis medication		
Fluconazole	5 (25)	2/5 (40)
Itraconazole	3 (15)	1/3 (33)
Co-Trimoxazole	7 (35)	
Signs and symptoms		
Fever	16 (80)	
Swelling of face/periorbital	12 (72)	
Blackish necrotic debris of nose/oral	8 (40)	
Ulcerative palate lession	6 (30)	
Facial/nasal/tooth/throat pain and tooth infection	6 (30)	
Bloody nasal discharge	4 (20)	
Cough	4 (20)	
Sepsis	4 (20)	
Headache	2 (10)	
Nasal congestion	2 (10)	
Voice loss	1 (5)	
Chest pain	1 (5)	
Surgery	15 (75)	
Outcomes		
Mortality	9 (45)	

(55%) patients, 2 of them had alone form and 9 associated with nasal sinus involvement. Disseminated mucormycosis was documented in 9/20 (45%) patients. There were unusual presentations, including 2 patients with parotitis and hepatitis.

Table III. Distribution of the sites of involvement.

Involvement	Sinusitis (%) [case no]		Dissemination (%) (case no)	Sex (M/F)	Malignancy	Aplastic anemia	Diabetes mellitus	Surgery	Mortality
	Yes	No							
Alone	5 (25%) [2, 8, 9, 12, 14]	-		3/2	5	-	-	4	0
Orbital	3 (15%) [11, 18, 19]	-	2 (10%) [11, 18]	2/1	2	1	-	3	3
Cerebral	3 (15%) [5, 7, 17]	-	2 (10%) [5, 7]	2/1	2	-	1		
Pulmonary	9 (45 %) [1*†, 3, 4*, 5, 6, 13, 18, 19, 20]	2 (10%) [15, 16]	7 (35%) [1, 4, 5, 13, 18, 19, 20]	7/2	9	2	-	8	8
Cutaneous	-	1 (5%) [10]	-	1/-	1	-	-	-	-
Total	17 (85%)	3 (15%)	9 (45%) #	14/6	16 (80%)	3 (15%)	1 (5%)	15 (75%)	9 (45%) #

*: tracheitis, †: tonsillar abscess, #: case 5 had cerebral and pulmonary involvement; case 18 had orbital and pulmonary involvement.

Generally, fever and pain/swelling of organs were the most commonly encountered signs and symptoms (Table II). None of the patients were culture positive. In cases accompanied by *Aspergillus*, 3 of the 4 cases showed death and worsened prognosis.

Treatment regimens prescribed for patients diagnosed with mucormycosis are shown in Table II. All patients were treated with a form of antifungal therapy, resulting in a survival of 55%. All patients except one (whom had conventional amphotericin B, cAmB) received lip-osomal formulations (LAmB). Fifteen of these cases were treated with a combination of sur-gery and antifungal therapy, resulting in a survival rate of 8/15 (53%) (Table II). Posaconazole has been used successfuly for step-down therapy in seven patients. The overall mortality rate of patients identified in this study was 45%, with a high mortality rate occur-ring in patients diagnosed with disseminated infection (100%).

Discussion

Mucormycosis is a life-threatening fungal infection characterized by a highly aggressive (angiotropic) progression that occurs mostly in immunocompromised patients.[8] Data concerning patient sex, age at onset of disease, symptoms and signs, radiological findings, treatment modalities, and outcome were analyzed retrospectively, for a 10-year period. To our knowledge, there have been a limited number of reports from Turkey in the pediatric population diagnosed with mucormycosis, therefore, our report is a large case series reported from our country.

In several studies, mucormycosis was reported primarily in males (65%). In case reports from Turkey, most of the patients were male (52%).[9] Although Pana et al.[1], in 63 children diagnosed with mucormycosis, reported the rate of girls as higher, in our study, a significant proportion of the patients were male. In our series, the majority of children (85%) were older than 5 years, with a mortality of 78%.

For older infants and children, Francis et al.[10] has recently reported that hematologic malignancy is a significant risk factor, as is being a hematopoietic stem cell transplant or solid organ transplant recipient, these were followed by diabetes. Kömür et al.[11] conducted a retrospective study evaluating 51 cases of mucormycosis in our city in adult patients and reported that malignancy was the most common co-morbidity affecting 59% of the subjects, followed by diabetes. In our series of 20 pediatric mucormycosis cases, the most prominent identified underlying conditions were hematological malignancies, especially acute leukemia (70%), and this was followed by aplastic anemia (15%). In patients with prolonged neutropenia, aggressive evaluation should be performed in case of fever.[12] The majority of patients in our series had neutropenia (90 %). Fever was observed in almost every neutropenic case. Although, we have a well working transplantation unit, only two (10%) of our pediatric mucor patients were transplant patients; the distribution of infection is different from the literature. In our experience, the mucor infection occurred in four patients in the early stage of chemotherapy, during induction, and that contrasts with the data in the literature of pediatric mucor cases in which this was reported to occur later on during chemotherapy.[13] Seven of the ALL cases were either relapsed or refractory and clinically unwell. In our study, in only one of 20 cases, the patient had uncontrolled diabetes mellitus.

Seasonal variation in atmospheric concentration of fungal spores has been documented for some molds in several geogaphical locations.[14,15] As reported in India and in Middle East countries such as Iran, events are reproduced in August and in tropical and subtropical sea-sons when spores are most intense in the air.[16] It is necessary to evaluate the contribution of this climate zone and the seasonal weather conditions we have in our city. The fact that our region is moist might be an effective risk factor for disease development.

The authors' prior and most recent experience with hematological malignancy patients suggests that mucormycosis is most likely in cases when the patient has been receiving As-pergillus-active antifungal (especially voriconazole) prophylaxis.[17-19] Although in our series, 8/20 patients who had received antifungal prophylaxis with fluconazole or itraconazole, did not have Mucorales activity.

For Mucorales the portals of entry in the human body are the respiratory tract through inhalation of fungal spores. In most series[20-25], such as the studies of Chakrabarti et al.[3] and Roden et al.[4], rhino-orbito-cerebral mucormycosis was reported as the most frequent clinical mani-festation and this can quickly progress to disseminated form with disastrous consequences if not diagnosed and treated early. This is consistent with the global trend, the most commonly identified condition was sinus involvement (75%) alone in 5/20 and with concomitant in-volvement in 12/20 in our study, followed by the pulmonary form, have been found to be the most prevalent in our study. Pulmonary mucormycosis has been reported at a frequency be-tween 44-64% in children.[26-29] Although rhinoorbitocerebral sinus disease is mostly common in diabetic patients, pulmonary disease predominates in pediatric patients with malignancy and hematopoietic cell transplantations (75%).[1] We detected that eleven cases (55%) had pulmonary involvement (9/11 had added involvement of other forms). Seven (7/11, 78%) with pulmonary involvement occurred as the disseminated form. From a recent review of Francis et al.[10] the dissemination form of the disease occurs in 32% to 38% of pediatric cas-es, which was 45% in our cases, higher than the literature. The patients with a single in-volvement form had a better outcome than those with dissemination.[30]

Histopathologic examination of clinical specimens and culture are recommended for the diagnosis of mucormycosis. Although tissues frequently are not available for biopsy, because of thrombocytopenia or hemodynamic instability, definitive diagnosis is made most frequently

on the basis of direct microscopic examination. However, tissue identification is a very important diagnostic tool, since it distinguishes the presence of the fungus as a pathogen in the specimen from a culture contaminant. Direct microscopy of clinical specimens allows a rapid presumptive diagnosis and differentiation of mucormycosis from aspergillosis and other hyalohyphomycoses and phaeohyphamycoses-and is strongly recommended for treatment decisions. In recent registries of mucormycosis, histopathology led to the diagnosis in 63% and 66% of cases.[31,32] The diagnosis of 75 cases from an Indian tertiary-care hospital was based on histopathology.[33]

Culture of a clinically relevant isolate enables identification and susceptibility testing of the pathogen. Culture is poorly sensitive because Mucorales hyphae are friable in nature, hence may be damaged easily during sample collection (avoidance of excessive tissue homogenization is recommended before culturing). Additionally, some species fall to sporulate in standard media, precluding a timely and easy morphological identification. Better recovery is seen if slices of minimally manipulated tissue are placed onto the culture medium or baited with bread to promote mycelial growth.[34,35] As a result, approximately only one-third of all histopatologically proven specimens result in a positive fungal culture.[36,37] Countless reports of negative culture results are scattered throughout the literature.

Imaging techniques are helpful; although they are non-specific and do not correlate well with surgical and pathological findings. According to the revised version of EORTC/MSG pub-lished in 2008[38], all of our patient's diagnosis were documented with proven mucormycosis by histopathology and none of them were culture positive. As our opinion, in our center neg-ative culture may be explained by various factors, such as aggressive processing of the spec-imen and inappropriate storage of samples before plating. Although the limitation in our study was biased by the selection of cases that were only proven by biopsy, the diagnosis of our patients was confirmed by histopathological and radiological examination in addition to clinical findings. Despite the limitations to the study, we retrospectively gave a good esti-mate for the burden of mucor infections in pediatric cases in Turkey, highlighting the index of clinical suspicion and the important role played by histology especially from suspected cases in the diagnosis that will be able to guide towards early surgery.

The mucormycosis treatment with antifungal medicine is an important factor affecting the outcome. According to the literature, the mainstay of therapy for treating mucor remains as amphotericin B, primarily in its liposomal formulation.[39] Furthermore, delayed antifungal therapy would increase mortality of mucormycosis among patients with neutropenia. In our series, the first line treatment was cAmB or LAmB in all patients, at different daily doses up to 10 mg/kg. In our experience, higher doses of LAmB were well tolerated. For combination therapy, Pagano et al.[41] reported the beneficial effect of posaconazole in addition to LAmB in hematological patients failing to response to LAmB monotherapy.[40-43] Though posaconazole was not available to give in the first years in our study. In recent years, 7 patients were given parenteral AmB followed by descalation to oral posaconazole. The optimal total duration of antifungal drug administration required for mucormycosis is controversial and varies depending on the extent of the disease.[44] In children successfully treated in our series, we discontinued antifungal therapy only when clinical resolution was evident and adequate im-mune recovery had occurred.

Because of the risk of rapid progression to dissemination of pediatric mucormycosis cases, when feasible, surgery should be considered as a treatment choice. Surgery and antifungal combination therapy are mostly the mainstays of management of invasive mucormyco-sis.[4,7,44] Children who received combined therapy had a mortality rate of 18.5% compared

with 60% for those who received antifungal therapy alone.[30] The majority of the patients suffered from serious underlying conditions (thrombocytopenia, pulmonary infection) limiting the possibility for surgery. Surgery was just performed on 15/20 patients in this study. Of these cases, there was a 60% response rate.

Despite aggressive surgical intervention and intensive antifungal treatment, mucormycosis is associated with a greater mortality rate (47-56%). It rises to range from 50-100% depending on the disease form, which is in agreement with our findings in the current study.[5,32,45,46] Our survival rate was 55%. Despite the fact that most of the disseminated cases received a combined treatment, the high mortality rate shows that this treatment is not sufficient.

Empirical treatment for mucormycosis is emergent if there are suspicions.The cases in our study were definitively diagnosed cases. In fact it is certain that the rate is higher than it is in this series, because we think most cases have not been appropriately diagnosed. Although surgery was performed in most of the cases, the mortality rate was high due to the severity of the disease. Perhaps an earlier intervention should be made. Unfortunately, we did not have a chance for postmortem examination to prove this claim.

In conclusion, a steady increase in the reports of mucormycosis during the last decades may be due to increased awareness of a fungal infection in risk groups, and early diagnosis and treatment of these invasive fungal infections can improve the outcomes of children. The recommended management for overall survival of invasive mucormycosis has been surgical debridement combined antifungal therapy and restoration of the underlying immune status should be considered a key factor for a better outcome of the disease. As can be seen from these, good management of risk factors, especially neutropenia and hyperglycemia, prevents this disease from occurring.

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