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Pediatric Invasive Aspergillosis: A Retrospective Review of 59 Cases

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ABSTRACT

Invasive aspergillosis (IA) is an important cause of morbidity and mortality. In this study, we aimed to present our 10-year IA experience in a single center. Fifty-nine pediatric patients diagnosed with IA were included in the study. The male/female ratio of these patients was 42/17. The median age was 8.75 years. Hematologic malignancy was present in the majority of the patients (40/59, 68%). The mean duration of neutropenia was 18.5 days. Cytosine arabinoside was the most common immunosuppressive therapy directed at T-cells at the time of IA diagnosis. IA cases were categorized as proven (27%), probable (51%) and possible (22%) according to the 2008 EORTC/MSG criteria. The most common site of invasive aspergillosis was the lungs (78%) and nodules were the most frequent radiological finding (75.5%). In 38 (64.4%) patients receiving antifungal prophylaxis, prophylactic agents included fluconazole (30.5%), liposomal amphotericin B (23.7%), posaconazole (8.5%) and voriconazole (1.7%). Initial treatment was most commonly administered as monotherapy (69.5%). The median duration of antifungal treatment was 67 days. A total of 11 (18.6%) deaths occurred due to aspergillosis. We will probably continue to see IA frequently in pediatric patients with increased use of corticosteroids, biological agents, and intensive immunosuppressive chemotherapies.

INTRODUCTION

Invasive aspergillosis (IA) is an important cause of morbidity and mortality. Qualitative or quantitative deficiencies of neutrophils are the major risk factors to develop IA (1,2). A mortality rate of 52.5% was reported by a multicenter retrospective study (3).

Risk factors for IA include primary immunodeficiencies, chronic granulomatous disease (CGD) in particular, secondary immunodeficiencies, critical illness and chronic diseases of the respiratory tract in pediatric patients, and low birth weight and prematurity in neonates (2,4). Immunosuppressive therapies including corticosteroids at high doses and biologics interacting with the immune system (e.g., monoclonal antibodies that target tumor necrosis factor alpha) are also considered as risk factors for IA (5,6). Lastly, solid organ transplantation (SOT) is associated with IA especially in heart and/or lung recipients (7).

The incidence of IA in immunocompromised children is 0.4%, with reported incidences ranging from 0.1% to 30%. Highest incidences have been reported among allogeneic hematopoietic stem cell transplant (HSCT) recipients, lung transplant recipients, and patients with primary immunodeficiencies and acute myeloid leukemia (AML). The overall case fatality rates of IA range between 20% and 50% in children with cancer and those receiving a transplant but is highly dependent on the severity of immunosuppression and the extent of invasive disease. The incidence of IA ranges from 26% to 45% in children with CGD, and IA is the most common infectious cause of death. Neonatal IA is an infrequent infection with a favorable outcome in 73% of the patients (4,8-10).

Early diagnosis and treatment are major factors affecting the prognosis of IA and high mortality rate is largely due to delays in diagnosis. There are some practical issues related to histopathological and/or microbiological tissue culture method, which is required for definite diagnosis. Firstly, conditions such as thrombocytopenia, hypoxemia or hemodynamic instability of the patient may delay or even prevent implementation of invasive procedures. Secondly, fungal cultures require long incubation time. Finally, there is a risk of false negativity resulting from sampling errors. Clinical and radiological diagnosis of IA has limited sensitivity and specificity especially in children (8-11).

Invasive aspergillosis has been well characterized in adults; however, there are a limited number of studies that analyzed the IA incidence, risk factors, diagnostic methods, treatment and outcomes in pediatric patients. In this study, we aimed to present our 10-year IA experience in a single center.

MATERIALS AND METHODS

Subjects and Data Collection

For this study, medical records were retrospectively reviewed for 410 patients (aged 18 or younger) with risk factors for IA, including hematologic or oncologic malignancy, primary immunodeficiency, graft-versus host disease (GvHD), hematopoietic stem cell or solid organ transplant recipients, and neonates and children who were admitted to intensive care with suspected IA and followed at Ankara University Medical Faculty Children's Hospital between May 2010 and October 2019. Fifty-nine patients diagnosed with IA were included in the study. Demographic and clinical characteristics, underlying conditions and management, type and duration of antifungal prophylaxis and/or antifungal treatment, duration of fever and neutropenia, laboratory findings and survival status of these patients were retrieved from their medical files.

The group of patients with underlying conditions consisted of patients with hematologic malignancy, oncologic malignancy, primary immunodeficiency, HSCT, SOT, aplastic anemia, GVHD and neonates (prematurity and bronchopulmonary dysplasia). Patients with hematologic malignancy were divided into 4 subgroups: acute lymphoblastic leukemia (ALL), AML, relapsed leukemia and refractory leukemia. Relapsed leukemia was defined as the recurrence of ALL and AML; refractory leukemia was defined as leukemias without complete or partial remission (5% blast cells in bone marrow aspirate) after salvage chemotherapy, and post-HSCT relapses.

All IA cases were categorized into three groups according to the treatment stage of the underlying condition at the time of diagnosis: (i) those occurring during remission induction chemotherapy; (ii) those occurring after reinduction chemotherapy following relapse of underlying condition; and (iii) those occurring in patients with refractory leukemia or post-HCT relapse.

Patients were divided into two groups based on the activity of the underlying malignant disease at the time of IA diagnosis as those in complete remission and those with active disease (non-remission).

First-line therapy at the time of IA diagnosis was classified as monotherapy if a single systemic antifungal drug was used alone or sequentially and as combination therapy if two systemic antifungal drugs were administered concomitantly. Second-line or salvage therapy was defined as any treatment administered to patients who were unresponsive or intolerant to initial treatment.

The study was approved by the Institutional Review Board of Ankara University Faculty of Medicine (Approval date and number: 27-11-2019/ İ5-257-19).

IA Case Definitions

The diagnosis of IA was based on the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) 2008 criteria. According to EORTC/MSG, invasive fungal infections (IFD) are classified as proven, probable and possible (12).

For histopathologic diagnosis, Periodic Acid-Schiff (PAS) and Grocott methenamine silver (GMS) stains were used to detect *Aspergillus* hyphae in the tissue specimens. In biopsy specimens, thin (3 to 6 microns wide), septated hyaline hyphae with dichotomous acute angle (45°) branching were identified as *Aspergillus*. The specimens were cultured to identify the

genus and species. The specimens were immediately sent to the medical microbiology laboratory after collection. For each specimen, two Sabouraud dextrose agars (incubated both at 25°C and 37°C) and Potato dextrose agar (incubated at 25°C) (BD, USA) were used and incubated for 28 days for molds. Medical microbiology specialists performed both conventional microscopy and matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS, Bruker, Daltonics, Germany MBT - IVD Library v11) for the identification of fungal pathogens. Identification with MALDI-TOF MS was performed according to the manufacturer's instructions.

GM Antigen Assay

All galactomannan (GM) assays were performed using the Platelia *Aspergillus* EIA test (Bio-Rad Laboratories, Marnes, France). Patient specimens with a GM ≥ 0.5 were considered positive for galactomannan.

CT Evaluation

Chest CT reports of patients with IA were reviewed retrospectively at the time of diagnosis. The main CT findings were vascular invasion and airway invasion. Vascular invasion was determined based on the presence of at least two of the following characteristics: halo sign, infarcted consolidation or a central hypointense zone, cavity or air-crescent sign. Airway invasion was considered when at least two of the following features were present: small airway lesions, peribronchial consolidation or bronchiectasis. Dense/well-demarcated nodules were deemed typical signs of *Aspergillus*.

Statistical analysis

Descriptive statistics were reported as percentages of median for categorical variables and ranges for continuous variables. A p value less than 0.05 was considered statistically significant.

RESULTS

The male/female ratio of 59 patients diagnosed with IA was 42/17. The median age was 8.75 years (range, 10 days-17 years and 11 months).

Clinical characteristics of the patients diagnosed with invasive aspergillosis are shown in Table 1. Hematologic malignancy was present in the majority of the patients (40/59, 68%) including AML (n=14), high risk ALL (n=5), relapsed leukemia (n=9), refractory leukemia (n=12).

Among 59 patients, IA developed during remission induction chemotherapy in 5 (8.5%) ALL patients and 14 (23.7%) AML patients, during reinduction chemotherapy in 9 (15.3%) patients with relapsed leukemia, during salvage chemotherapy in 12 (20.3%) patients with refractory leukemia, and during HSCT in 7 (11.9%) patients.

Invasive aspergillosis developed in 1 (1.7%) patient with relapsed NHL while receiving ibrutinib in combination with RICE (rituximab, ifosfamide, carboplatin, etoposide). IA developed during tacrolimus therapy administered for treatment of chronic gastrointestinal GVHD following allogeneic HSCT in 1 (1.7%) patient with aplastic anemia. 1 (1.7%) patient developed IA while on treatment with steroids, tacrolimus and mycophenolate mofetil after heart transplantation. One other patient (1.7%) developed IA during treatment with steroids and tacrolimus after liver transplantation.

The median duration of neutropenia was 18.5 days (range, 2-310 days). Eight patients were not neutropenic. One patient was referred from an external center, and excluded from the statistical analysis since the mean duration of neutropenia was not known for that patient.

Cytosine arabinoside (n=28) was the most common immunosuppressive therapy directed at T-cells at the time of IA diagnosis, followed by fludarabine phosphate (n=8). Other chemotherapeutic agents used included cyclosporin (n=5), mycophenolate mofetil (n=4), tacrolimus (n=3), clofarabine (n=3), tioguanine (n=3), sorafenib (n=2), ATG (anti-thymocyte

globulin) (n=1), rituximab (n=1), interferon (n=1), and mercaptopurine (n=1). Use of steroids for longer than 14 days was present in 26 (44%) patients.

IA cases were categorized as proven (n=16; 27%), probable (n=30; 51%) and possible (n=13; 22%) according to the 2008 EORTC/MSG criteria. Of 16 proven cases, the diagnosis was confirmed with histopathology in 6 cases. *Aspergillus* growth was detected in the cultures of three of the patients. Detailed information on sampling sites and causative agents are shown in Table 2.

IA was localized in the lung in 46 (78%) patients, paranasal sinus in 5 (8.5%) patients, lung and sinus in 3 (5.1%) patients, skin in 2 (3.4%) patients, oral cavity and paranasal sinus in 1 (1.7%) patient, appendix in 1 (1.7%) patient, and peritoneum in 1 (1.7%) patient. The most common type of fungal infection was invasive pulmonary aspergillosis (IPA).

In 49 patients diagnosed with IPA, nodules surrounded with a halo sign or ground glass opacity were the most common findings on chest CT scans and detected in 37 (75.5%) patients (Figure 1).

In 11 patients with proven/probable IPA, nodules surrounded with a halo sign or ground glass opacity were the most common lesions on chest CT images, which were present in 6 (54.5%) patients. Other CT findings detected in these patients were segmental or lobar consolidation (n=4, 36.3%), pleural effusion (n=3, 27.2%), focal area of ground glass opacity (n=3, 27.2%), atelectasis (n=2, 18.1%), and thickening of septal and/or bronchial wall (n=2, 18.1%).

Seven patients with IPA underwent fiberoptic bronchoscopy. Bronchoscopy revealed ulceration/plaque suggestive of tracheobronchial aspergillosis in 3 patients. *Aspergillus* growth was observed in 5 BAL specimens, including *Aspergillus fumigatus* (n=2), *Aspergillus niger* (n=1) and *Aspergillus spp.* (n=2).

Five patients had invasive sinonasal aspergillosis and 3 patients had both invasive sinonasal aspergillosis and invasive pulmonary aspergillosis. Local pain was the most common finding in patients with invasive sinonasal aspergillosis (n=6). Additionally, eschar of the nasal mucosa (n=3), vegetation of nasal mucosa (n=1), and bone destruction extending from paranasal sinus to the orbit (n=4) were detected on paranasal CT scans.

Treatment and Survival

38 (64.4%) patients received antifungal prophylaxis and 21 (35.6%) patients did not receive antifungal prophylaxis.

Initial treatment was administered as monotherapy in 41 (69.5%) patients and combination therapy in 18 (30.5%) patients. Antifungal drugs used for monotherapy included liposomal amphotericin B in 32 patients (54.2%), voriconazole in 7 (11.9%) patients, caspofungin in 1 (1.7%) patient and micafungin in 1 (1.7%) patient. Combination therapies included liposomal amphotericin B plus voriconazole in 14 (23.7%) patients, liposomal amphotericin B plus caspofungin in 3 (5.1%) patients and voriconazole plus caspofungin in 1 (1.7%) patient.

Of 41 patients receiving monotherapy, 29 (70%) patients completed treatment on monotherapy, whereas 5 (12%) patients required switch to combination therapy. Voriconazole was added to liposomal amphotericin B therapy in 3 patients, posaconazole was added to liposomal amphotericin B therapy in 1 patient and amphotericin B was added to caspofungin treatment in 1 patient. Seven patients (17%) on monotherapy switched to salvage therapy. Various combinations of liposomal amphotericin B, caspofungin and voriconazole were used for these patients.

Of 18 patients who received combination therapy as initial treatment, 10 (55.5%) patients received salvage therapy, 2 (11%) patients received monotherapy and 6 (33%) patients received combination therapy as maintenance treatment. In these patients, liposomal

amphotericin B, caspofungin, itraconazole and voriconazole were used in various combinations.

The median duration of antifungal treatment was 67 days (range, 5-425). A total of 11 (18.6%) deaths occurred as a result of aspergillosis. These patients had leukemia (n = 4), refractory leukemia (n = 3), refractory HL (n = 1), aplastic anemia (n = 1), high risk ALL (n = 1) and SOT (n = 1). Among them, there were 5 patients in whom antifungal therapy was started as monotherapy and maintained as monotherapy, 4 patients who were started on monotherapy and switched to combination therapy and 2 patients who were started on monotherapy and switched to salvage therapy.

DISCUSSION

Over the past 50 years, survival and cure rates have significantly improved in children with leukemia with the use of multi-agent chemotherapy, better classification of disease subgroups, advances in supportive care and more effective prophylaxis and management of central nervous system disorders. With current chemotherapy regimens, approximately 15% of children with ALL and 45% of children with AML will have refractory disease or experience a relapse (13). Patients with relapsed or refractory leukemias accounted for 52% of our study population. Children with relapsed or refractory acute leukemia represent an extremely difficult population to treat. Several drug regimens exist for the management of relapses, most of which are based on the use of anthracyclines and cytarabine. Second-line chemotherapeutics include more intensive chemotherapy regimens (14). In a study by Harris et al. (15) twelve deaths from invasive fungal infections were reported after the use of high-dose cytarabine therapy in 52 patients with refractory acute lymphoblastic leukemia. In our study, cytarabine was used in 11 (11/21, 52%) of the patients with relapsed and refractory leukemia, 3 (3/11, 27%) of whom died.

New therapeutic approaches are more effective than previous treatments in controlling lymphoproliferative disease in patients receiving highly immunosuppressive drugs such as fludarabine, alemtuzumab (anti-CD52 monoclonal antibody) or rituximab (anti-CD20 monoclonal antibody), but they increase the risk of opportunistic infections (16-18). Herbrecht et al. (19) suggested that invasive aspergillosis should be included in the list of opportunistic infections occurring in this patient group. In the present study, 8 patients received fludarabine and 1 patient received rituximab.

In line with previous studies, *A. fumigatus* was the most commonly isolated causative agent was in our study (20).

Reports documenting the incidence of invasive fungal disease in pediatric SOT recipients are scarce. In a study by Saxena et al. (7) involving 584 pediatric patients undergoing solid organ transplantation, IA developed in 2 of 35 lung transplant recipients but in none of 172 recipients of liver transplants and 135 heart transplant recipients. Verma et al (21) reported fungal infection in 32 of 79 children who underwent liver transplantation, 3 of whom developed IA. In a separate study by Zaoutis et al. (22) in 1854 heart transplant recipients, IA was detected in 18 of 139 patients with proven invasive fungal infections. In our study, *A. flavus* growth was seen in the intra-abdominal abscess drainage fluid of a liver transplant recipient on the 70th day after transplantation. This patient also showed 2 cm nodules on chest CT images. Non-typeable *Aspergillus* spp. growth was present in the pericardial fluid culture obtained on 28th day after transplantation in one heart transplant recipient in the current study.

Typical CT findings of angioinvasive aspergillosis include macronodules larger than 1 cm in diameter which are surrounded by a halo sign. Additionally, pleura-based wedge-shaped areas of consolidation, alveolar consolidations, masses, reverse halo sign, cavities or air-crescent sign, ground glass opacities and pleural effusion may be present (23). In our study,

characteristic CT findings most commonly included well-defined nodules (75.5%) and 70% of these nodules (n=26) were surrounded by a halo sign. In Greene et al.'s study (24), a macronodule was detected in the vast majority of patients (94%) and halo sign in 61% of the patients. In a study by Kojima et al. (25), the most common radiological findings were nodule, halo, and consolidation. In Qiu et al.'s study (26), typical radiological findings inconsistent with the literature reports were the most common findings. However, as stated by ESCMID-ECMM guidelines, radiographic findings such as halo sign, air crescent sign and cavities, which are considered as typical hallmarks of pulmonary IA in adults, are not seen in most children with pulmonary IA, while nonspecific findings are more common in immunocompromised children with IPA (10). It seems likely that we will have more definite information when the centers share their radiological data in the future.

Antifungal monotherapy is the most common initial treatment of IA. The option to use combination therapy is acceptable and moderately recommended in patients with invasive fungal infection refractory to initial treatment. The reported response rates range between 42% and 60% in the largest series (27-30).

Voriconazole is now the guideline-recommended first-line treatment for all forms of invasive aspergillosis. Azole antifungal agents interact with chemotherapeutic drugs. Therapeutic drug monitoring (TDM) is required performed (1,10,31). However, at our center, Liposomal Amphotericin-B was primarily used because of the concern that drug interactions with voriconazole may not be detected with TDM. Our study was retrospective, and liposomal amphotericin-B was recommended as the first-line treatment in previous guidelines. Therefore, we preferred to use voriconazole, the first-choice antifungal therapy, in line with the updated guidelines.

In the context of salvage therapy, an additional antifungal agent may be added to current therapy, or combination antifungal drugs from different classes may be used other

than those used in the initial regimen (1,8,10). We used different antifungal therapies in salvage and combination therapy in our patients. A total of 11 (18.6%) deaths occurred as a result of aspergillosis. IA-related deaths occurred in the patient group who started their treatment on monotherapy. Since this study had a retrospective design and clinical comorbidities that previously existed in the study and patients could not be fully identified, prospective, large-scale, preferably multicenter studies comparing monotherapy with combination therapy in terms of mortality in children are warranted.

It seems likely that we will continue to see more cases of IA in pediatric patients in the future due to increased use of high-dose corticosteroids, biologics interacting with the immune system and intensive immunosuppressive chemotherapeutics. Sharing data on epidemiology, diagnosis and treatment of IA is vital for the management of this patient population.

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Figure legends. Chest CT findings of patients with IPA

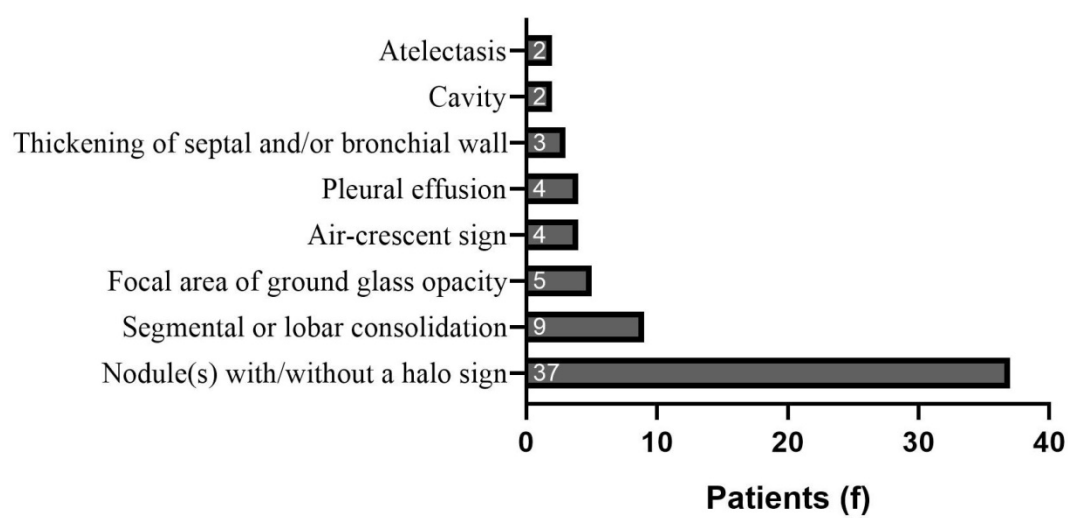
Table 1. Clinical characteristics of patients diagnosed with IA	
	IA (n=59)
Age, years, median (range)	8.75 (0.03-17.92)
Sex, male (n, %)	42 (72%)
Underlying condition	
Hematologic malignancy (n, %)	40 (68%)
Oncologic malignancy (n, %)	2 (3.4%)
HSCT (n, %)	7 (12%)
· Allogeneic HSCT (n, %)	5 (71.4%)
· Autologous HSCT (n, %)	2 (28.6%)
Aplastic anemia (n, %)	3 (5%)
Primary immunodeficiency (n, %)	3 (5%)
Solid organ transplantation	2 (3.4%)
GVHD (n, %)	1 (1.7%)
Prematurity (n, %)	1 (1.7%)
Neutropenia (n, %)	51 (86.4%)
Neutrophil count	
<500/mm ³	12 (20%)
<100/mm ³	38 (64.4%)
Duration of neutropenia (days, range)	18.5 (2-310)
Clinical IA manifestations	

Pulmonary aspergillosis (n, %)	46 (78%)
Aspergillus sinusitis (n, %)	5 (8.5%)
Pulmonary aspergillosis and aspergillus sinusitis (n, %)	3 (5.1%)
Aspergillus sinusitis and oral aspergillosis (n, %)	1 (1.7%)
Cutaneous aspergillosis (n, %)	2 (3.4 %)
Aspergillus peritonitis (n, %)	1 (1.7%)
Aspergillus appendicitis (n, %)	1 (1.7%)
Antifungal prophylaxis	
Fluconazole (n, %)	18 (30.5%)
Liposomal amphotericin-B (n, %)	14 (23.7%)
Posaconazole (n, %)	5 (8.5%)
Voriconazole (n, %)	1 (1.7%)
IA: Invasive aspergillosis, HSCT: Hematopoietic stem cell transplantation, GvHD: Graft- versus-host disease	

No	Sex/Age	Underlying disease	Clinical IA manifestations	Sampling sites	Diagnostic method	Culture result	GM	Antifungal prophylaxis	Initial treatment	Maintenance treatment	Treatment time (days)	IFA-related mortality
1	F/14 years	AML	Aspergillus sinusitis	Sinus	Histopathologic	–	Negative	Fluconazole	Liposomal amphotericin B + voriconazole	Monotherapy	200	–
2	F/16 years	Relapsed leukemia	Aspergillus sinusitis	Sinus	Histopathologic and culture	<i>Aspergillus fumigatus</i> + <i>Aspergillus niger</i>	Positive	No	Liposomal amphotericin B	Combined therapy	16	Died
3	M/13 years	Relapsed leukemia	Aspergillus sinusitis and oral aspergillosis	Buccal mucosa /palate	Histopathologic and culture	<i>Aspergillus fumigatus</i>	Positive	Liposomal amphotericin B	Liposomal amphotericin B + voriconazole	Monotherapy	161	–
4	M/14 years	Refractory leukemia	Pulmonary aspergillosis	Pleural fluid	Culture	<i>Aspergillus fumigatus</i>	Positive	Posaconazol	Liposomal amphotericin B + voriconazole	Monotherapy	67	–
5	M/9 years	Refractory leukemia	Aspergillus sinusitis	Sinus	Histopathologic and culture	<i>Aspergillus flavus</i>	Positive	No	Liposomal amphotericin B	Monotherapy	58	–
6	M/13 years	Refractory leukemia	Pulmonary aspergillosis and Aspergillus sinusitis	Sinus	Culture	<i>Aspergillus flavus</i>	Positive	Liposomal amphotericin B	Liposomal amphotericin B	Combined therapy	46	Died
7	F/8 years	AML	Cutaneous Aspergillosis	Skin	Culture	<i>Aspergillus spp.</i>	Negative	Fluconazole	Liposomal amphotericin B	Monotherapy	42	–
8	M/5 years	AML	Pulmonary Aspergillosis	Pleural fluid	Culture	<i>Aspergillus fumigatus</i>	Positive	Fluconazole	Liposomal amphotericin B	Monotherapy	235	–
9	M/7 years	Relapsed leukemia	Pulmonary Aspergillosis	Pleural fluid	Culture	<i>Aspergillus flavus</i>	Negative	Fluconazole	Liposomal amphotericin B	Monotherapy	59	Died
10	M/2 years	Refractory leukemia	Pulmonary Aspergillosis	Pleural fluid/lung	Culture	<i>Aspergillus spp.</i>	Positive	Liposomal amphotericin B	Liposomal amphotericin B	Monotherapy	30	Died
11	M/2 years	Refractory leukemia	Aspergillus Appendicitis	Appendix	Histopathologic	–	Positive	No	Liposomal amphotericin B	Combined therapy	69	Died
12	M/1 years	Relapsed leukemia	Pulmonary Aspergillosis	Lung	Histopathologic	–	Positive	Liposomal amphotericin B	Liposomal amphotericin B + caspofungin	Salvage therapy	190	–
13	F/10 months	SCID	Aspergillus Peritonitis	Peritoneum	Culture	<i>Aspergillus fumigatus</i>	Negative	No	Voriconazole	Monotherapy	56	–
14	M/10 days	Newborn (Prematurity)	Cutaneous Aspergillosis	Skin	Culture	<i>Aspergillus fumigatus</i>	Positive	No	Micafungin	Monotherapy	99	–
15	M/3 years	SOT (Liver)	Pulmonary Aspergillosis	Pleural fluid/lung	Culture	<i>Aspergillus flavus</i>	Negative	Fluconazole	Liposomal amphotericin B	Monotherapy	54	Died
16	M/17 years	SOT (Heart)	Pulmonary Aspergillosis	Pericardial fluid	Culture	<i>Aspergillus spp.</i>	Positive	Fluconazole	Liposomal amphotericin B	Salvage therapy	22	–

F, female; M, male; AML, acute myeloid leukemia; GM, galactomannan; IA, Invasive aspergillosis; SCID, severe combined immunodeficiency; SOT, solid organ transplantation;

Figure 1. Chest CT findings of patients with IPA



Note: Patients may have more than 1 lesion.