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ORIGINAL ARTICLE

Clinical characteristics of hepatosplenic fungal infection in pediatric patients

Ting-Yu Yen, Li Min Huang, Ping-Ing Lee, Chun-Yi Lu, Pei-Lan Shao, Luan-Yin Chang*

Department of Pediatric, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan

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Background: Hepatosplenic fungal infection (HSF) is a distinct form of invasive fungal infection with main involvement of the liver, spleen, and occasionally the kidney. In this study, we investigated the clinical characteristics and outcomes of patients with HSF in childhood.
Methods: We retrospectively reviewed pediatric patients with the diagnosis of HSF in a tertiary medical center in Taiwan between July 1999 and June 2009. The definition of HSF included imaging studies demonstrating multiple focal lesions in the liver and/or spleen with or without a microbiologic evidence for fungal infection. The clinical characteristics and outcomes were analyzed.
Results: We identified 15 pediatric patients with HSF. Eleven patients had diagnosis of hemato-oncologic malignancy, and two patients had severe aplastic anemia. All patients had fever, and most patients had abdominal pain, nausea, vomiting, and hepatosplenomegaly. The detection rate of computed tomography scan (15/15, 100%) was superior to abdominal sonography (10/15, 67%, $p = 0.01$). Ten (91%) of the 11 patients with microbiologic evidence were infected by *Candida* species. Neither recurrence nor breakthrough fungal infection was noted when the patients underwent further chemotherapy and stem cell transplantation. Six patients (40%) died before the end of the study, but no mortality was directly related to HSF.
Conclusion: Candida species was the major pathogen for HSF, and computed tomography scan was a good diagnostic tool to detect the multiple focal lesions. Under adequate antifungal treatment, HSF could be cured without recurrence in spite of further chemotherapy and stem cell transplantation.

* Corresponding author. Department of Pediatric, National Taiwan University Hospital, College of Medicine, National Taiwan University, No. 8, Chung-Shan South Rd, Taipei 10016, Taiwan.
E-mail addresses: ly7077@tpts6.seed.net.tw, lychang@ntu.edu.tw (L.-Y. Chang).

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Introduction

Hepatosplenic fungal infection (HSF) is recognized as a distinct form of chronic disseminated fungal infection with main involvement of the liver, spleen, and occasionally the kidneys. This condition was first reported by Bodey et al.[1] in 1969, and the incidence of HSF has significantly increased since 1980,[2] but it is still uncommon. It occurred almost exclusively in individuals with impaired host defense mechanisms, especially in patients with hemato-oncologic malignancy undergoing antineoplastic chemotherapy, and may occur in patients with chronic granulomatous diseases, Crohn's disease, diabetes mellitus, and patients receiving corticosteroid therapy.[3] The incidence of HSF ranged from 3% to 29.1% in patients with hematologic malignancy undergoing chemotherapy or hematopoietic stem cell transplantation.[2,4–7] Some cases had been reported in children since 1980s,[8–10] but the incidence of HSF in pediatric patient remained unclear.

Although laboratory tests usually showed increased level of serum C-reactive protein, elevated hepatic transaminase [aspartate transferase, alanine transferase], and alkaline phosphatase,[11] they were not diagnostic of HSF. As for imaging studies, computed tomography (CT) and magnetic resonance imaging (MRI) are superior to ultrasonography to detect hepatosplenic lesions.[11–13] Because blood culture was yielded in less than 50% of cases, deep-tissue specimen may not always demonstrate fungal infection[11,14,15] and the imaging studies usually revealed the lesions until the recovery of neutrophil counts,[16] early diagnosis of HSF was extremely difficult. In addition, the optimal treatment of HSF and the duration of treatment were still disputable.[6]

To clarify the uncertain conditions mentioned above, we retrospectively reviewed the pediatric patients with HSF in Taiwan to aim at the incidence for pediatric leukemia patients, clinical characteristics, and treatment outcome.

Methods

Patients

We retrospectively reviewed the pediatric patients who were admitted to National Taiwan University Hospital, a tertiary medical center from July 1999 to June 2009, in Taipei, Taiwan. We searched discharge diagnosis with implantable cardioverter-defibrillator code: 572.0 for liver abscess, 682.9 for abscess, and 117.0—117.8 for invasive fungal disease to identify the patients with HSF. The diagnosis of HSF was based on blood cultures, clinical studies, histological studies, and imaging studies. The demographic features, disease status before and after diagnosis of HSF, microbiological and radiological evidence of HSF, choice of antifungal therapy, and outcome were analyzed.

Definition for HSF

The definition of HSF was modified according to the criteria for invasive fungal infection established by the European Organization for Research and Treatment of Cancer/Mycoses Study Group in 2002 and the revised definitions in 2008.[17,18] The original criteria of HSF were limited to immunocompromised patients, and we modified the criteria to fit all pediatric groups as the following: the proven HSF was defined when there was radiologic evidence of fungal infection with multiple focal lesions in the liver and/or spleen and a specific diagnosis of fungal infection was established by the presence of fungi in deep-tissue biopsy, or aspiration specimens by culture, histological examination, or polymerase chain reaction (PCR) result, or blood culture; probable HSF was defined with typical imaging evidence and positive serum fungal antigen test (serum galactomannan test for *Aspergillus* spp); possible HSF was defined only with typical imaging study evidence. Patients who had invasive fungal infection (such as candidemia) without evidence of liver or spleen involvement were excluded from this study.

Laboratory data and imaging studies

Complete blood counts and a panel of blood chemistry, including hepatic transaminase, lactate dehydrogenase, alkaline phosphatase, blood urea nitrogen, creatinine, and electrolytes, were examined at least weekly during the hospital stay. At least one set of blood culture was done at the onset of fever and was frequently repeated if fever persisted. Liver tissue was obtained by blind needle aspiration or laparotomy biopsy on some patients. All biopsy specimens were submitted for cultures, pathological examinations, and some specimens were sent for fungal PCR assay if indicated. Serum galactomannan test was performed as indicated. Imaging studies including chest X-ray, CT scan, ultrasonography, MRI, and gallium scan were performed as needed in each patient.

Antineoplastic therapy

Patients in this study received antineoplastic therapy for acute lymphoblastic leukemia, acute myeloid leukemia, neuroblastoma, and hematopoietic stem cell transplantation for their underlying diseases. Antineoplastic chemotherapy was continued during the course of antifungal therapy to treat the primary neoplastic process on schedule, as aggressively as possible. Nine patients had attenuated modification of their antineoplastic therapy, consisting of a delay of a cycle in eight patients and modification of dosage in one patient.

Antifungal therapy

The initial antifungal regimen consisted of amphotericin B, 1.0 mg/kg/d or fluconazole 400 mg/d. Follow-up or salvage regimens included amphotericin B (1 mg/kg/d), fluconazole (6—12 mg/kg/d or 400—800 mg/d), liposomal amphotericin B (5 mg/kg/d), caspofungin (70 mg/m^2/d initially, then 50 mg/m^2/d), or voriconazole (4—8 mg/kg/d).

Response

Response to antifungal treatment was assessed mainly by serial imaging studies, clinical evaluation, and laboratory examination. Complete response was defined as resolution of all symptoms and signs attributable to HSF, negative blood culture for fungus, and disappearance of fungal

lesions in imaging studies. Partial response was defined as greater than 50% reduction of the number of lesions by imaging study. Stabilized HSF was defined as no further development of new lesions, no expansion of existing lesion size, and no clinical deterioration. Recurrent HSF was defined as development of new lesions after complete radiological resolution or calcification of lesions. Breakthrough fungemia was defined as blood culture proven invasive fungal infection.

Statistics

Comparisons of selected parameters were performed by χ^2 test. A p value <0.05 was considered statistically significant.

Results

Demography and diagnosis

From July 1999 to June 2009, HSF was diagnosed in 15 of the pediatric patients in National Taiwan University Hospital, and the characteristics were summarized in Table 1. During this period, we newly diagnosed 92 patients with acute myeloid leukemia and 252 patients with acute lymphoblastic leukemia undergoing antineoplastic chemotherapy in this period. The incidence of HSF was not significantly different between the patients with acute myeloid leukemia (AML, 5/92, 5.4%) and those with acute lymphoblastic leukemia (ALL, 5/252, 2.0%, $p = 0.09$). Two patients were diagnosed of very severe aplastic anemia; one was diagnosed simultaneously of HSF and aplastic anemia on his first time visit, and the other was just received peripheral blood stem cell transplant. Twelve (80%) patients ever had prior neutropenic episodes (absolute neutrophil count less than 500/mm^2) before the onset of HSF, and only four patients (27%) remained neutropenic on the time when an image study confirmed the diagnosis of HSF. Beside, the majority (87%) of patients had exposure to broad-spectrum antibiotics 2 weeks before the onset of HSF, and only three patients (20%) had the confirmed diagnosis of bacteremia (*Escherichia coli* in two and methicillin-sensitive *Staphylococcus aureus* in one). The blood cultures yielded positive bacterial results initially and then became sterile after antibiotic treatment. The therapeutic antibiotics for two patients with *E coli* bacteremia were piperacillin/tazobactam plus gentamicin initially, and then shifted to cefepime plus amikacin, and then vancomycin plus meropenem because of persistent fever. The patient with methicillin-sensitive *Staphylococcus aureus* bacteremia received oxacillin therapy for 14 days.

Table 1 Characteristics of 15 patients with hepatosplenic fungal infection

Characteristics	
Age in yr, mean (range)	9.4 (0.1–17.5)
Male:female	5:10
	No. of patients (%)
Clinical status ($n = 15$)	
Underlying disease:	
Acute lymphoblastic leukemia	5 (33)
Acute myeloid leukemia	5 (33)
Very severe aplastic anemia	2 (13)
Neuroblastoma	1 (7)
Biliary atresia with hepatic failure	1 (7)
Newborn	1 (7)
Prior neutropenia[a]	12 (80)
Prior bacteremia[b]	3 (20)
Recent broad-spectrum antibiotics[c]	13 (87)
Status of hemato-oncologic disease ($n = 13$)	
Newly diagnosed	7 (54)
Remission	3 (23)
Relapsed or refractory	2 (15)
Post-hematopoietic stem cell transplantation	1 (8)

[a] Neutropenia (absolute neutrophil count $<$ 500/mm^2) within 2 wk before the onset of hepatosplenic fungal infection.
[b] Bacteremia diagnosed within 2 wk before the onset of hepatosplenic fungal infection.
[c] Broad-spectrum antibiotics (third cephalosporin at least) used within 2 wk before the onset of hepatosplenic fungal infection.

Table 2 shows the clinical presentation and laboratory data. All patients had fever, and more than 70% of patients had abdominal pain, nausea, vomiting, and hepatosplenomegaly (Table 2). Six patients (40%) presented cutaneous lesions, which were important clinical signs for invasive fungal infection. The peak C-reactive protein concentration was moderately elevated [$>$5 mg/dL (normal, $<$0.8 mg/dL)] in 13 (87%) of the 15 patients. The peak serum levels of aspartate transferase, alanine transferase, alkaline phosphatase, γ-glutamyl transpeptidase, and total bilirubin were normal in 17%, 13%, 33%, 40%, and 27% of the patients, respectively.

Multifocal lesions were demonstrated in all patients by imaging studies. Both abdominal CT scan and ultrasonography were performed in all patients. CT scan had a significantly higher detection rate (15/15, 100%) than abdominal ultrasonography (10/15, 67%, $p = 0.01$). Only three patients received MRI study, and two of them revealed positive findings. The liver was the most commonly involved organ (15/15, 100%), followed by the spleen (10/15, 67%), the kidney (8/15, 53%) (Fig. 1), the lung, and the venous thrombosis (2/15, 13%) (Fig. 2).

Pathogens of HSF

Ten patients had proven HSF, one probable infection, and four possible infection (Table 3). All patients received blood cultures for fungus, and six patients (40%) had positive culture results, including *Candida tropicalis* in three, *Candida albicans* in two, and *Candida krusei* in one. A total of eight patients received liver biopsies after administration of antifungal therapy, and five patients had evidence of fungal infection by histopathologic examination of the liver biopsy specimens (four patients) or *Candida* PCR (one patient). Overall, among the 11 patients with definite pathogens, *Candida* species were the causative pathogen in 10 (91%) of them. Though the fungal infection was not confirmed by blood culture or examination of the tissue

Table 2 Clinical characteristics and laboratory data in patients with hepatosplenic fungal infection

Clinical characteristics	No. of patients (%)	Laboratory data	Mean (range)
Fever $>$ 38°C	15 (100)	Peak CRP (mg/dL)	18.7 (3.6—29.9)
Abdominal pain	12 (80)	Peak AST (U/L)	315.5 (20.0—2515.0)
Nausea and/or vomiting hepatosplenomegaly	12 (80)	Peak ALT (U/L)	275.7 (24.0—775.0)
Jaundice	11 (73)	Peak ALP (U/L)	815.7 (220.0—1989.0)
Cutaneous candidiasis	7 (47)	Peak GGT (U/L)	215.6 (12.0—823.0)
Respiratory tract symptoms	6 (40)	Peak total bilirubin (mg/dL)	9.6 (0.6—50.0)
	8 (53)		

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; CRP = C-reactive protein; GGT = γ-glutamyl transpeptidase.

biopsy specimens in four patients, they were considered to have possible HSF because of multifocal lesions in the liver and/or spleen without evidence of infection caused by other microorganisms.

Antifungal therapy and outcome

Table 3 shows the antifungal therapy, duration, and treatment outcome. One patient received fluconazole therapy empirically, but it was replaced by amphotericin B later because of unresponsiveness to the drug and persistent fever. Fourteen patients were treated with amphotericin B in the beginning. Five of these patients later received liposomal amphotericin B and two patients received caspofungin because of nephrotoxicity (impaired renal function greater than 50%). One patient was given caspofungin because of persistent fever and nephrotoxicity. Six patients (40%) died during a median follow-up of 5 months (range: 2—8 months) because of progression of underlying diseases. Ten patients received further chemotherapy after the diagnosis of HSF. Although repeated neutropenic status occurred after chemotherapy, there was no progression of fungal infection or recurrence of previous fungal infection. Among them, three patients underwent peripheral blood hematopoietic stem cell transplantation later (range from 26 to 255 days after diagnosis of HSF). Two of them were under amphotericin B prophylaxis, and another one was under fluconazole prophylaxis. All of them survived the first 100 days posttransplantation. One patient had positive findings on imaging before transplantation, but there was no evidence of recurrence of prior fungal infection in all patients. Because of progression of underlying diseases, two patients died on Day +123 and Day +158 post-transplantation, respectively.

Discussion

HSF is an uncommon but invasive infection, which has been attributed to prolonged neutropenia, presence of intravascular catheters, disruption of mucosal barriers, and administration of broad-spectrum antibiotics. Our patients mainly had hemato-oncologic malignancy undergoing chemotherapy or hematopoietic stem cell transplantation. Only two patients didn't have chemotherapy before, both of them have presence of intravascular catheters and disruption of mucosal barriers.

The incidence of HSF ranged from 3% to 29.1% in patients with hematologic malignancy undergoing chemotherapy or hematopoietic stem cell transplantation, depending on the diagnostic criteria used in adult patients.[2,4—7,15,19] Although there were several literatures discussing HSF in the pediatric group before, the incidence of HSF in pediatric patient was mentioned in three retrospective studies before. Verdeguer et al.[8] demonstrated the presence of hepatosplenic

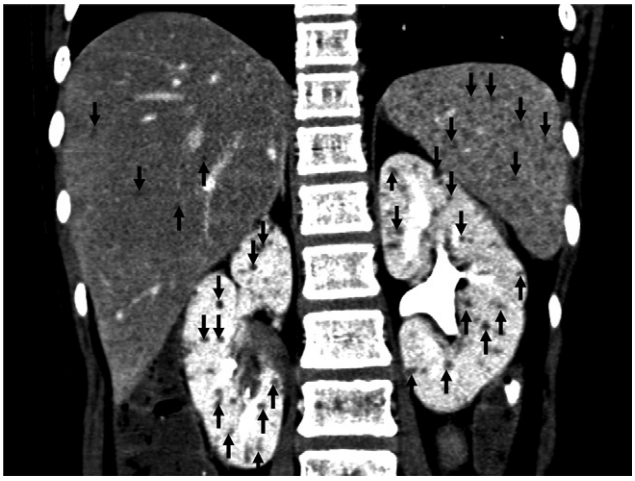

Figure 1. Computed tomography scan after recovery from nadir post-chemotherapy reveals radiological multiple hypodensities within the liver, spleen, and bilateral kidneys (arrows).

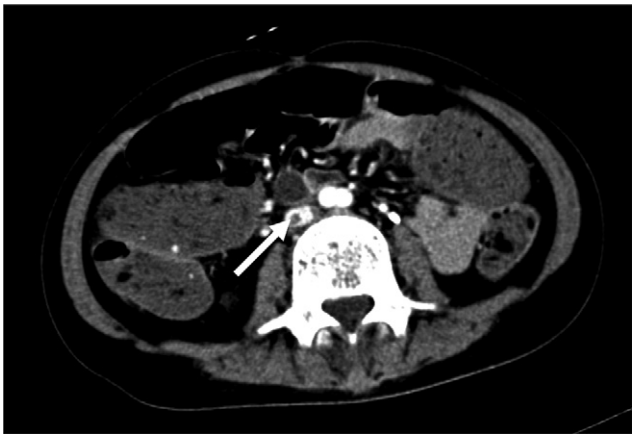

Figure 2. Computed tomography scan after recovery from nadir of neutropenia post-chemotherapy reveals a radiological single hypodense lesion within the inferior vena cava (arrow).

Table 3 Microbiologic evidence, treatment, and outcome of 15 patients with HSF

Patient	Age/sex	Pathogen	Microbiologic evidence	Initial AFT (d)	Salvage AFT (m)	Response	Further CT/HCT	Outcome
1	15/M	*Candida tropicalis*[a]	B/C	AMB (3)	L AMB/FCZ (11[d])	Partial	+/−	Alive
2	13/F	*C tropicalis*[a]	B/C	AMB (6)	Caspo/FCZ (9[d])	Partial	+/−	Alive
3	11/F	*C tropicalis*[a]	B/C	AMB (8)	Caspo/FCZ (2)	Complete	+/−	Alive
4	12/F	*Candida krusei*[a]	B/C	AMB (21)	L AMB/VRC (10[d])	Partial	−/−	Alive
5	0.1/F	*Candida albicans*[a]	B/C	AMB (69)	FCZ (4)	Complete	−/−	Alive
6	2/F	*C albicans*[a]	B/C	AMB (21)	L AMB/FCZ (5.5)	Stabilized	+/−	Died
7	6/F	*Candida* species[a]	Liver biopsy	AMB (45)	FCZ (6)	Stabilized	+/+	Died
8	1/M	*Candida* species[a]	Liver biopsy	AMB (7)	Caspo/VRC (33[d])	Complete	+/−	Alive
9	2/M	*Candida* species[a]	Liver biopsy	AMB (87)	FCZ (10)	Complete	+/+	Alive
10	8/F	*Candida* species[a]	Liver biopsy	AMB (12)	VRC (25)	Complete	−/−	Alive
11	6/F	*Aspergillus* spp[b]	GM test	AMB (51)	L AMB/VRC (2)	Persisted	+/−	Died
12	14/F	Unknown[c]	—	AMB (90)	L AMB/VRC (13)	Complete	+/−	Alive
13	16/M	Unknown[c]	—	AMB (60)	FCZ (2.5)	Stabilized	−/−	Died
14	17/M	Unknown[c]	—	FCZ (8)	AMB/FCZ (8)	Complete	+/+	Died
15	1/F	Unknown[c]	—	AMB (15)	FCZ (2)	Stabilized	−/−	Died

[a] Proven HSF.
[b] Probable HSF.
[c] Possible HSF.
[d] Still under antifungal therapy till the end of study.
AFT = antifungal treatment; AMB = conventional amphotericin B; Caspo = caspofungin; B/C = blood culture; CT = chemotherapy; F = female; FCZ = fluconazole; GM test = serum galactomannan test; HCT = hematopoietic stem cell transplantation; HSF = hepatosplenic fungal infection; L AMB = liposomal amphotericin B; M = male; VRC = voriconazole.

candidiasis in 3 (5%) of the 60 pediatric patients with acute leukemia. In the study conducted by Lai et al.,[10] the incidence of HSF in pediatric patient with persistent febrile neutropenia was 2.4%. Finally, HSFs were found in 2 (1.3%) of the 154 children with acute leukemia receiving long-term antifungal prophylaxis.[20] Our study reveals that the incidence of HSF is 2.0% in pediatric patients with acute lymphoblastic leukemia and 5.4% in patients with acute myeloid leukemia. However, only prospective multicenter trials with uniform definition of the term HSF will be able to provide accurate data that answer this question.

HSF should be highly suspected in patients with prolonged and profound febrile neutropenia, especially if fever recurs after recovery of neutropenia. In our study, seven (58%) patients experienced persistent fever and five (42%) had recurrent fever after recovery from neutropenia. In addition, 80% of the patients complained of abdominal pain, nausea, vomiting, and more than 70% of the patients had hepatosplenomegaly. In adult patients, elevated serum alkaline phosphatase levels can give a hint of an infiltrative disorder of the liver and image studies should be performed. However, the serum alkaline phosphatase level was interfered by several factors, such as bone growth and the normal range varied with different age group. Otherwise, its response delayed after clinical improvement. Therefore, it is difficult to make an early diagnosis of HSF only depending on the clinical manifestations.

Serum galactomannan test has been well studied in the detection of invasive aspergillosis in adult immunocompromised patients. The sensitivity was 78% (61%—89%) and the specificity was 81% (72%—88%) for an Optical Density Index (ODI) of 0.5. When the ODI cut-off value increased to 1.5, the sensitivity was 64% (50%—77%) and specificity was 95% (91%—97%).[21] Beside, Hayden et al.[22] demonstrated the presence of circulating galactomannan is a predictive of invasive aspergillosis in most pediatric oncology patients. One of our patients was diagnosed with probable HSF only by the serum ODI value 1.7 initially, and this value was highly specific to invasive *Aspergillus* infection. Therefore, the serum galactomannan test could precede clinical, microbiologic, or radiographic evidence of invasive aspergillosis.

Ultrasonography, CT scan, and MRI are clinically effective for evaluation and follow-up of HSF;[12,13,23] however, all imaging techniques have to be repeated in cases of suspected fungal infection. Although MRI achieved higher diagnostic accuracy of HSF than CT and ultrasonography in previous studies,[12,13,24] CT scan and ultrasonography are more widely used and more cost-effective in Taiwan. Karthaus et al.[25,26] reported serial ultrasonography up to twice a week had the same detection rate and reliability of hepatosplenic abscess compared with CT scan and MRI. However, we performed both CT scan and abdominal ultrasonography nearly at the same time in all of our patients to detect hepatosplenic abscess after the recovery of neutropenia, and the result revealed that CT scan had a better detection rate than ultrasonography (100% *vs.* 67%, $p = 0.01$). It is possibly because of the limitation of study frequency, tools, and expertise of operators in the latter examination. Beside, hepatic or splenic lesions may transiently disappear during neutropenia.[16] In the same way, Anttila et al.[11] analyzed the findings of ultrasonography and CT scan of 14 patients that were both performed within a 7-day period between Days 5 and 20 after each patient's recovery from neutropenia, and the detection rate for ultrasonography and CT scan were 43% and 93% respectively. Thus we suggested CT scan should be performed in pediatric patients who have suspected HSF after the recovery of neutropenia although the ultrasonography failed to reveal lesions.

Because yielding rate of positive blood cultures is less than 50%, deep-tissue specimen may not always demonstrate fungal infection, and obtained tissue specimen is associated with relative high risk of complications.[11,14,15] The confirmation of microbiology pathogen was difficult. In our study, we confirmed 11 patients with definite pathogen, *Candida* species were the most common causative pathogen (90.9%).

The optimal management of HSF and the antifungal therapy for choice are not well established. Because HSF was mainly caused by *Candida* species, fluconazole for stable or nonneutropenic patients, and liposomal amphotericin B or caspofungin for severely ill patients as the initial treatment were suggested by the Infectious Disease Society of America.[27–29] In our experience, aggressive antifungal therapy using conventional amphotericin B should initially be given for neutropenic or unstable patients and the cost was less expensive. If nephrotoxicity occurs, liposomal amphotericin B or caspofungin can be a good alternative drug for HSF. After the disease status gets stabilized, oral form fluconazole or voriconazole could be used as maintainable agent depending on the drug susceptible pattern of the pathogen. Hepatic or splenic lesions may transiently disappear during neutropenia,[16] thus antifungal therapy should not be discontinued on the basis of radiological findings alone.

Prior invasive fungal infection is a difficult problem for subsequent chemotherapies and hematopoietic stem cell transplantation. However, delaying the treatment schedule because of persistent radiological lesions may potentially have a negative impact on the underlying malignancy, resulting in disease progression or relapse[30] In this study, 10 patients received further chemotherapy with repeated neutropenic episodes after the diagnosis of HSF, and there was no progression of fungal infection or recurrence. Among them, three patients underwent peripheral blood hematopoietic stem cell transplantation later (26–255 days after diagnosis of the HSF) under amphotericin B or fluconazole prophylaxis. All of them survived the first 100 days posttransplantation without recurrence infection. Our data provide the evidence that HSF is not an absolute contraindication for subsequent chemotherapy and hematopoietic stem cell transplantation, if the infection can be controlled with antifungal therapy before transplant and continued until engraftment is established.[4,6,15,16,30–33]

In conclusion, HSF should be considered when hematooncologic patients receiving chemotherapy have prolonged neutropenic fever even after administration of broad-spectrum antibiotics, especially if fever persists or recurs after recovery of neutropenia. If abdominal pain, hepatosplenomegaly, nausea, and vomiting develop, CT rather than ultrasonography of the abdomen should be performed after recovery of the neutropenia. Under effective antifungal therapy and closely imaging monitor, the mortality directly caused by HSF was low in pediatric patients. Therefore, chemotherapy and hematopoietic stem cell transplantation for the underlying disease may be given to patients if the infection has been adequately controlled.

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