

Hepatosplenic Fungal Infection in Adult Patients with Acute Leukemia

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Background: Hepatosplenic fungal infection is an important infectious complication in adult patients with acute leukemia.

Methods: From 2001 to 2004, 163 adult patients were diagnosed with acute leukemia at our center: 41 patients had acute lymphoblastic leukemia (ALL) and 122 patients had acute myeloid leukemia (AML). Their charts were retrospectively reviewed.

Results: Of these 163 patients, 16 patients (9.8%) developed hepatosplenic fungal infection: three were ALL patients and 13 were AML patients. All of these patients suffered from febrile neutropenia after chemotherapy. Duration of agranulocytosis (absolute neutrophil count < 500/dl) was 10 to 36 days, with a median of 20 days. Clinical presentations in these patients were fever (94%), diarrhea (50%), abdominal pain (44%), oral mucositis (44%), papular skin lesions (31%) and lower back pain (7%). Fourteen patients (88%) had elevated alkaline phosphatase levels between 197 U/l to 1172 U/l (normal range: 28-94 U/l). The most common infection sites found by computed tomography were the spleen (94%) and the liver (88%). All patients were treated with antifungal agents. No patient died as a result of the fungal infection episode. Nine patients (56%) died due to uncontrolled underlying hematological malignancies. The median duration of follow-up was 15.2 months (range: 2.3~47.4 months).

Conclusion: Alkaline phosphatase level and computed tomography are useful tools for the diagnosis of hepatosplenic fungal infection. Infection-related mortality is very low with effective treatment. Treatment for underlying diseases should proceed as soon as possible if the infection has been controlled.
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Key words: hepatosplenic fungal infection, acute myeloid leukemia, acute lymphoblastic leukemia, chemotherapy

Infectious disease is one of the most important problems in patients with hematological malignancies, particularly in acute leukemia patients. Incidence of invasive fungal infections in patients

with malignancies has increased dramatically during recent decades.⁽¹⁻⁴⁾ The possible predisposing factors are decreased host defense immunity due to intensive cytotoxic chemotherapies and/or ablative radiation

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therapy, use of corticosteroids or cyclosporine, underlying hematological disease, environmental contamination, total parenteral nutrition, barrier disruption following cytotoxic chemotherapy, prolonged use and number of broad-spectrum antibiotics, and use of central venous catheters.⁽⁴⁾

METHODS

We retrospectively reviewed the charts of patients who were diagnosed with acute leukemia in 2001~2004 at our center and who were more than 17 years of age. We collected and analyzed the data of those who developed hepatosplenic fungal infections to evaluate incidence, patients' characteristics, clinical manifestations, laboratory, microbiology and image findings, antifungal treatment and outcome. The definition of acute leukemia was blast $\geq 20\%$ in bone marrow or peripheral blood according to the World Health Organization classification.⁽⁵⁾

The diagnosis of hepatosplenic fungal infection was made according to the criteria for chronic disseminated candidiasis established by 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 in 2002. The criteria were restricted to patients with cancer and recipients of hematopoietic stem cell transplants, and classed invasive fungal infections into proven, probable and possible groups. Three elements form the basis of the proposed definitions: host factors, clinical manifestations and mycological results. The host factors include neutropenia (less than 500 neutrophils/mm³ for more than 10 days), persistent fever for more than 96 hours refractory to appropriate broad-spectrum antibacterial treatment, body temperature above 38°C or below 36°C, and prolonged (more than 3 weeks) use of corticosteroids in the previous 60 days. Clinical features for chronic disseminated candidiasis are small, peripheral, target-like abscesses (bull's-eye lesions) in the liver and/or spleen demonstrated by computed tomography, magnetic resonance imaging or ultrasound, as well as elevated serum alkaline phosphatase levels. The proven category is the highest level of certainty and is attained by establishing the presence of fungal hyphae or yeast cells in tissue by biopsy or a needle aspirate, or a positive culture result from a sample

obtained from a normally sterile and clinically or radiologically abnormal site consistent with infection. For patients in the probable category, the elements of host factor and clinical features have to be present.⁽⁶⁾

RESULTS

There were 163 adult patients who were diagnosed with acute leukemia at our center in 2001 to 2004: 41 patients had acute lymphoblastic leukemia (ALL) and 122 patients had acute myeloid leukemia (AML). Of these 163 patients, 114 patients received chemotherapy: 79 patients (69%) were AML and 35 patients (31%) were ALL. Forty-nine patients did not receive chemotherapy due to old age, comorbidity or personal considerations. There were 16 patients (9.8%) who developed hepatosplenic fungal infections: three were ALL patients (3 of 41, 7.3%) and 13 were AML patients (13 of 122, 10.7%). All of these 16 patients had received chemotherapy. None of the 49 patients who did not receive chemotherapy developed hepatosplenic fungal infection ($p = 0.003$; evaluated by Fisher's exact test).

The characteristics of the patients with hepatosplenic fungal infections are shown in Table 1. The median age was 45.5 years (range from 17 to 58 years). The male to female ratio was 1:1. Five patients developed hepatosplenic fungal infection after just one course of induction chemotherapy, 8 patients developed an episode after post-remission chemotherapy, one after re-induction chemotherapy due to relapse of acute leukemia and 2 had non-

Table 1. Characteristics of Patients with Hepatosplenic Fungal Infections

Median age in years (range)	45.5 (17~58)
Male: Female ratio	1:1
Type of malignancy	No. of patients
Acute myeloid leukemia	13
Acute lymphoblastic leukemia	3
Disease status	No. of patients
Newly diagnosed	5
Complete remission	8
Relapse	1
Non-remission	2

remission of acute leukemia with salvage chemotherapy. All of these patients suffered from febrile neutropenia after chemotherapy. Duration of agranulocytosis (absolute neutrophil count < 500/dL) was 10 to 36 days, with a median of 20 days. Patients with ALL had received steroid treatment for more than three weeks.

Clinical presentations in these patients were fever (94%), diarrhea (50%), abdominal pain (44%), oral mucositis (44%), papular skin lesions (31%) and lower back pain (7%). Fourteen patients (88%) had elevated alkaline phosphatase levels between 197 U/L to 1172 U/L (normal range: 28-94 U/L). The median level was 444 U/L. Nine patients (56%) had elevated liver transaminase levels and 7 patients had elevated total bilirubin levels.

The infection sites detected by computed tomography are showed in Table 2 and Fig. 1 The most common areas were the spleen (94%) and the

Table 2. Infection Sites

Infection site	No. of patients (%)
Spleen	15 (94%)
Liver	14 (88%)
Spleen + Liver	13 (81%)
Spleen + Liver + Lung	3 (19%)
Spleen + Liver + Kidney	2 (13%)
Spleen + Liver + Infectious spondylitis with paraspinal abscess	1 (6%)

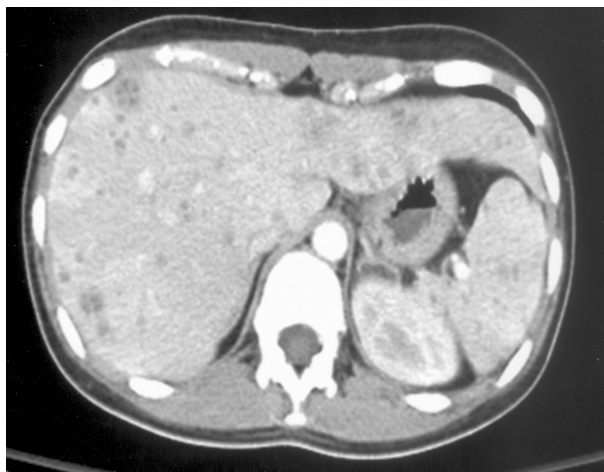


Fig. 1 Twenty-five-year-old woman with acute myeloid leukemia. Numerous small hypodense, hypoenhancing nodules in the liver and spleen.

liver (88%).

Blood cultures of these patients were negative for any organism, including bacteria and fungus. One patient had a permanent central catheter infection; the catheter was removed and the catheter tip culture was positive for *Candida tropicalis*. Seven patients had aspiration and/or biopsy of their lesions, 6 from liver lesions and one from a paraspinal abscess. The results of culture and pathology were negative from the liver specimens, and there was one positive result for *Candida albicans* from the paraspinal abscess. Fungal hyphae (mold) were seen on the smears of liver aspirates from one patient, as shown in Fig. 2 and Fig. 3. According to the criteria of the European Organization for Research and Treatment of

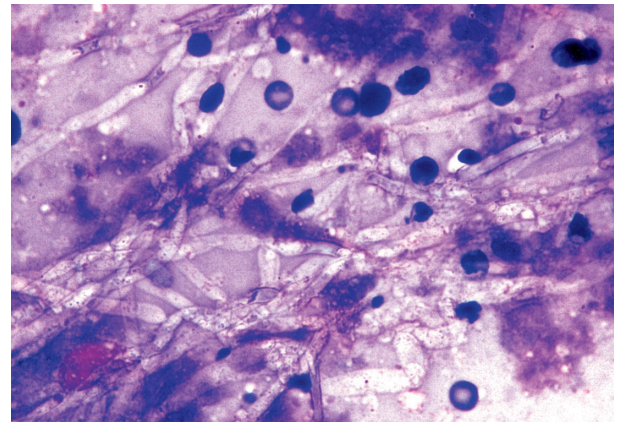


Fig. 2 (x 1000, Riu's stain). Fifty-year-old woman with acute myeloid leukemia. Direct microscopic examination of the liver aspirate. Numerous branched, septate hyphae and red blood cells.

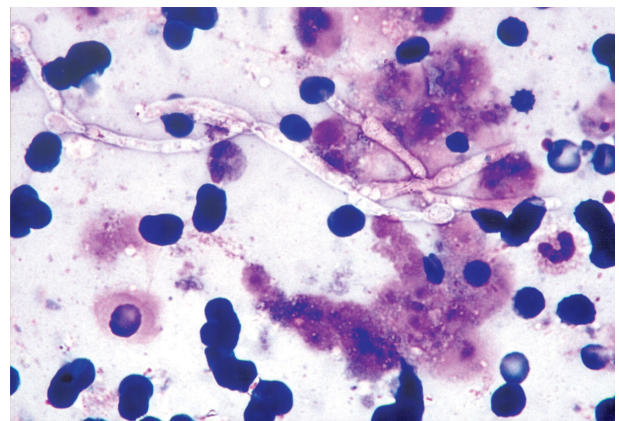


Fig. 3 (x 1000, Riu's stain). Dichotomously branched, septate hyphae and red blood cells.

Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group,⁽⁶⁾ there were 3 patients diagnosed with proven chronic disseminated candidiasis and 13 patients diagnosed with probable chronic disseminated candidiasis.

All patients were treated with antifungal agents. Treatment duration ranged from 6 to 12 months according to the patient's clinical presentation, infection sites, microbiology results and response to treatment (shown in Table 3). Nine patients initially received amphotericin B or liposomal amphotericin B (dosage from 930 to 4260 mg, median 1935 mg), then shifted to oral azole. Seven patients were treated with azole only (dosage of fluconazole was 8~10 mg/kg/day). Antifungal treatment was continued in patients with any of the following conditions: no regressive change shown on abdominal computed tomography, persist fever, further chemotherapy course given, incomplete remission of the acute leukemia.

Thirteen patients (81%) had regression of their hepatosplenic fungal infection, either improvement of fever or regression shown on image study. One patient did not show improvement after treatment and died of refractory acute leukemia. Two patients had early death due to uncontrolled acute leukemia complicated with other infections and it is difficult to evaluate their response to treatment of the hepatosplenic fungal infections.

Three patients had totally resolved fever, alkaline phosphatase levels and hepatosplenic microabscesses. Partial regression of hepatosplenic microabscesses on image findings and clinical manifestations was observed in 10 patients: 2 had regressive change but calcified lesions on images and 8 patients had

residual microabscess densities on images. No recurrence of hepatosplenic fungal infection was observed. The median duration of follow-up was 15.2 month (range: 2.3~47.4 month).

Twelve patients (75%) received further chemotherapy after the diagnosis of hepatosplenic fungal infection and the median duration from diagnosis of hepatosplenic fungal infection to the next chemotherapy was 3.3 month (range 1~7.3 month).

Nine patients (56%) died due to uncontrolled underlying hematological malignancies: 8 patients died of other infections and 1 died of leukemia. The median survival was 7.3 month (range: 2.3~15.6 month). No patients died as a result of the hepatosplenic fungal infection episode.

DISCUSSION

The incidence of chronic disseminated candidiasis or hepatosplenic fungal infection in patients with acute leukemia has been reported to range from 3% to 7%.^(7,8) From January 1995 through May 2002, hepatosplenic fungal infections were diagnosed in 37 (7.4%) of the 500 adult patients with acute leukemia who received chemotherapy at the National Taiwan University Hospital.⁽⁹⁾ In our study, the incidence (14.0%, 16 out of 114 adult patients who received chemotherapy from 2001 to 2004) was higher than previous reports.

In our series, patients with hepatosplenic fungal infections had all received chemotherapy: there was no hepatosplenic fungal infection in patients who did not receive chemotherapy treatment. The possible reasons for low fungal infection rate in untreated patients might be early mortality due to underlying acute leukemia, acute infections rather than chronic ones and less mucocutaneous barrier disruption due to chemotherapy in these patients.

Hepatosplenic fungal infection should be highly suspected in patients with prolonged and profound febrile neutropenia, especially if fever recurs after neutropenia recovers. In our study, 10 (63%) patients experienced persistent fever and 5 (31%) had recurrent fever after recovery from neutropenia.

Patients who had symptoms and signs of fungal infection over other areas also had a high possibility of hepatosplenic fungal infection, such as papular skin lesions, barrier disruption of the gut or oral mucositis, abdominal pain and diarrhea.⁽¹⁰⁾

Table 3. Antifungal Treatment and Response

	Total	Regression	No regression
AmB then fluconazole	7	6	1
Fluconazole alone	6	6	0
AmB then liposomal AmB then fluconazole	1	1	0
AmB then liposomal AmB then itraconazole	1	1	0
Voriconazole then fluconazole	1	1	0

Mean accumulative dose of amphotericin B (AmB) + liposomal AmB: 1935 mg (930~4260 mg); fluconazole dose: 8~10 mg/kg/day.

Elevated serum alkaline phosphatase levels can give physicians a hint of an infiltrative disorder of the liver and image studies should be performed. In our 16 patients, 14 patients (88%) had elevated serum alkaline phosphatase levels and the other 2 patients (12%) had microabscesses of the spleen without liver lesions. In our experience, computed tomography of the abdomen is a better tool for detection of hepatosplenic microabscesses than sonography. Computed tomography demonstrated multiple microabscesses in the liver and spleen, while sonography only revealed hepatosplenomegaly 2 days prior to the computed tomography in one of our patients.

The positive culture rate is low in such patients. Needle aspiration and/or biopsy of microabscesses for microbiology and pathology were relative high risk procedures due to thrombocytopenia or unstable clinical condition. Of our patients, six (38%) received liver aspiration and/or biopsy of their microabscesses, and the results of cultures and pathology were all negative. One patient with acute promyelocytic leukemia in complete remission presented with lower back pain 6 months after the last course of chemotherapy. Hepatosplenic microabscesses and paraspinal abscesses were demonstrated by computed tomography of the abdomen. Culture results from the paraspinal aspirate showed *Candida albicans*. This patient was a unique case among our patients in that there was a positive culture result.

Fluconazole is suggested as the first-line treatment according to the treatment guidelines because *Candida* species are the most common organisms in hepatosplenic microabscesses.^(11,12) Other choices of antifungal therapy have been reported as a result of weighing the greater activity of amphotericin B-based preparations and the echinocandin antifungal agents for some non-*albicans* species against the ready availability of oral and parenteral formulations of the azole antifungal agents.⁽¹²⁻¹⁷⁾ However, other rare conditions have been reported in patients with hepatosplenic microabscesses, such as leukemic infiltration, tuberculosis infection^(18,19) and coagulase-negative staphylococci.⁽²⁰⁾ So, it is important to perform microbiology and pathology examinations as soon as possible even though there is a low culture rate and relative high risk.

Hepatosplenic fungal infection is a chronic infection; fever may persist for more than one month

despite effective antifungal treatment, and persistent elevated alkaline phosphatase levels and abnormal image studies may last for several months even if antifungal treatment is discontinued.

Mortality from hepatosplenic fungal infection is low in our observation (0%) and other reports referenced (3%-19%).^(4,9,11,12) Chemotherapy for the underlying acute leukemia should not be postponed for a long period. Relapse of acute leukemia may occur if the intensity of treatment is inadequate. Treatment of hepatosplenic fungal infections requires a long period of time; it should be continued throughout all the chemotherapy courses.^(11,19,21)

In conclusion, hepatosplenic fungal infection should be considered when acute leukemia patients receiving chemotherapy have prolonged febrile neutropenia, especially if fever persists after recovery of the neutropenia. Alkaline phosphatase levels and computed tomography of the abdomen are useful tools for diagnosis. Microbiology study is crucial, even though the positive culture rate is low and it is a relatively high risk procedure to perform. The infection-related mortality is very low with effective treatment. Treatment for underlying diseases should proceed as soon as possible if the infection has been controlled.

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肝脾黴菌感染在成人急性白血病回溯性報告

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背景：肝脾黴菌感染是成人急性白血病重要的感染性併發症。

方法：自 2001 到 2004，有 163 位成人白血病在長庚醫院高雄院區診斷，41 位為急性淋巴性白血病，122 位為急性骨髓性白血病。我們將這些病歷回溯性整理予以報告。

結果：在這 163 位病人中，有 16 位 (9.8%) 發生肝脾黴菌感染，3 位為急性淋巴性白血病，13 位為急性骨髓性白血病。所有病人皆於化學治療後發生嗜中性球低下併發燒，嗜中性球低下之期間 (絕對嗜中性球數目小於 500/dl) 為 10 至 36 天，中位數為 20 天。臨床表現為：發燒 (94%)、下痢 (50%)、腹痛 (44%)、口腔黏膜炎 (44%)、表皮顆粒性紅疹 (31%)、以及下背痛 (7%)。14 位 (88%) 有血中鹼性磷酸酶上升，其值自 197 U/L 至 1172 U/L (正常值範圍為 28-94 U/L)。電腦斷層顯示最常見的感染部位為脾臟 (94%) 和肝臟 (88%)。所有病人皆有接受抗黴菌藥物之治療，且沒有任何病患死於當次肝脾黴菌感染。有 9 位病人 (56%) 於陸續追蹤中死亡，其主因為：其他感染有 8 位，無緩解的急性白血病有 1 位。追蹤期間為 2.3 至 47.4 個月 (中位數為 15.2 個月)。

結論：血中鹼性磷酸酶與電腦斷層是用來診斷肝脾黴菌感染的好工具。在有效的治療之下，死於肝脾黴菌感染之機率極低。在感染受到控制後，針對急性白血病的治療愈早執行愈好。
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關鍵詞：肝脾黴菌感染，急性骨髓性白血病，急性淋巴性白血病，化學治療

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