Splenic abscesses in therapy-resistant acute myeloblastic leukemia presenting as recurrent febrile neutropenia and unresolved splenomegaly

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A 14 7/12-year-old boy with acute myeloblastic leukemia M3v was admitted with disseminated intravascular coagulation, otitis media, lobar pneumonia, and splenomegaly. After induction therapy, M2 bone marrow was attained but splenomegaly persisted. Abdominal ultrasonography, which revealed diffuse splenomegaly at admission, showed splenic nodular lesions at the end of the induction therapy. The lesions persisted after M1 bone marrow was attained. He developed acute appendicitis and was operated. Ultrasonography-guided aspiration biopsy revealed nonspecific purulent abscess. Gram's stain and aerobic culture revealed no microorganism or fungi. Splenectomy was performed. The pathologic examination confirmed the diagnosis. He did not have an appropriate bone marrow donor, and developed bone marrow relapse and died.

Key words: splenic abscess, acute myeloblastic leukemia.

Isolated spleen abscess is rare and generally associated with immunosuppression[1]. Here, we present a boy with acute myeloid leukemia (AML) who was found to have splenic abscesses incidentally, while being investigated for incomplete regression of splenomegaly after induction therapy. Retrospective evaluation of the patient revealed that the only manifestation of splenic abscess that the patient displayed might have been the recurrent febrile neutropenia attacks, which were successfully treated by antimicrobial therapy.

Case Report

A 14 7/12-year-old boy was admitted to our hospital because of ear discharge, progressive restlessness, fever and cough. His physical examination revealed fever of 37°C, heart rate 116/min, blood pressure 60/40 mmHg, pallor, bilateral perforated tympanic membranes and mucopurulent discharge within the external ear canal. The spleen and liver were palpable 3 and 1 cm under the respective costal margins.

His hemoglobin was 3.9 g/dl, hematocrit 11.7%, white blood cell (WBC) 1.2 x 10^9/L, absolute neutrophil count (ANC) 0.072 x 10^9/L, platelet count 31 x 10^9/L, with 26% blasts, 6% polymorphonuclear leukocytes (PMNL), 64% lymphocytes and 4% monocytes in the peripheral blood. The bone marrow aspiration revealed 85% blasts, 2% myelocytes, 1% promyelocytes, 9% lymphocytes, 1% PMNL, 1% monocytes, and 1% eosinophils. The leukemic cells were characterized by nuclear folding or lobulation, overlapping of twinned nuclear lobes, occasional cytoplasmic granules, cytoplasmic protrusions or deeply basophilic cytoplasm. No Auer rod was visible. Cytogenetic investigation could not be done. Immunophenotyping revealed CD 34, CD13, CD33, and CD7 positivity by 63, 43, 80 and 81%, respectively. CD 14 was 3% and anti HLA-DR 4%. Prothrombin time was 19.3 sec (N: 10-14), partial thromboplastin time (PTT) 46.3 sec (N: 25-39), fibrinogen: 69 mg/dl (162-400), and D-dimer:

1236 ng/ml (N<250). Blood urea nitrogen (BUN) was 44 mg/dl, uric acid 6.2 mg/dl, calcium 8.1 mg/dl, total protein 5.5 mg/dl, albumin 2.5 g/dl, gamma-glutamyl transpeptidase (GGT) 87 U/L, lactate dehydrogenase (LDH) 330 U/L, and total and direct bilirubin 2.06 and 1.13 mg/dl, respectively; the rest of blood chemistry was normal. Chest X-ray revealed right lobar pneumonia. Abdominal ultrasonography (US) showed diffuse splenomegaly and mild hepatomegaly.

His condition improved and BUN, uric acid, GGT, and total and direct bilirubin normalized after replacement therapy of fluid, erythrocyte suspension and administration of regular fresh frozen plasma. Cefepime (100 mg/kg/d), amikacin (15 mg/kg/d), trimethoprim/sulfamethoxazole (trimethoprim 20 mg/kg), teicoplanin (10 mg/kg) and antiseptic ear drops were administered, with amikacin administered for 10 days and the others for 15 days. ANC reached 2.1 X 10^9/L on the 6th day. All-trans retinoic acid (ATRA, 15 mg/m^2 increased to 40 mg/m^2 gradually) was started on the 10th day and Hacettepe Acute Myeloblastic Leukemia (AML) 2000 protocol was started on the 15th day when all coagulation parameters and chest examination normalized. His central spinal fluid revealed normal protein and sugar levels and no blasts. On the 21st day of the induction therapy, he developed febrile neutropenia when his WBC and ANC were 1.8 x 10^9/L and 0.61 x 10^9/L, respectively, during which the cultures were negative. Cefepime (100 mg/kg) and amikacin (15 mg/kg) were started and trimethoprim/sulfamethoxazole, which had been administered for prophylaxis of *Pneumocystis carinii* (6 mg/kg trimethoprim), was continued. Because of the persistent fever, teicoplanin (10 mg/kg) was added after the 72nd hour. Fever normalized on the 5th day and antibiotic therapy was stopped on the 10th day.

At the end of the induction therapy, M2 bone marrow was attained, but the spleen was still palpable 1 cm under the left costal margin and the liver was nonpalpable. The abdominal US revealed five hypoechoic, nodular lesions with irregular contours in the spleen, the largest of which spanned 32 x 32 mm (Fig. 1). We decided to follow them until complete bone marrow remission was attained. After consolidation with high-dose cytosine

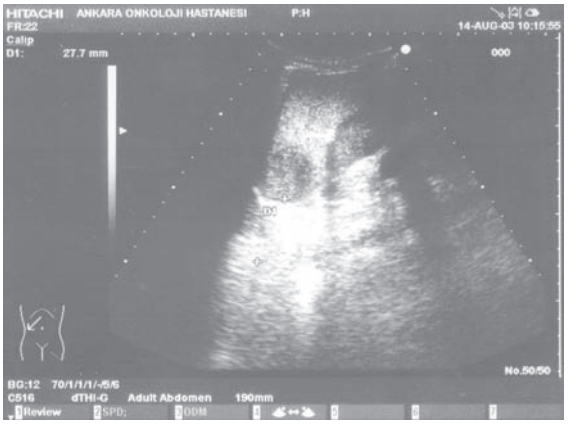

Fig. 1. Ultrasonographic appearance of the spleen with two hypoechoic nodular lesions with irregular contours.

arabinoside, he developed another febrile neutropenia when his WBC and ANC were 0.7 x 10^9/L and 0.01 x 10^9/L, respectively, and no culture could be tested. On the 2nd day of therapy with ceftazidime (150 mg/kg/d) and amikacin (15 mg/kg/d), his fever subsided and he was diagnosed with 'acute appendicitis' and was operated. Histopathologic examination revealed 'acute phlegmonous appendicitis'. Six days after the operation, two consecutive IDA-FLAG protocols were administered since blasts persisted in the peripheral blood. After each cure he developed febrile neutropenia. In the first attack, when his WBC and ANC were 0.4 x 10^9/L and 0.001x10^9/L, respectively, the cultures grew no bacteria. Ceftazidime (150 mg/kg/d) and amikacin (15 mg/kg/d) were started. Because of persistent fever, teicoplanin (10 mg/kg/d) was added after the 72nd hour. Fever subsided within 2 days. Ceftazidime and amikacin were administered for 10 days and teicoplanin for 7 days. The second attack developed when his WBC and ANC were 0.3 x 10^9/L and 0.001 x 109/L, respectively. The blood culture grew Pseudomonas aeruginosa, which was sensitive to cefepime and amikacin. Fever subsided on the 3rd day of therapy with cefepime (100 mg/kg/d) and amikacin (15 mg/kg/d), which were administered for 10 days. Fluconazole, which was administered in low dose[2] (1 mg/kg/day) as prophylaxis during both IDA-FLAG protocols, was continued during the following febrile neutropenia attacks. The patient attained complete bone marrow remission. However, the spleen was still palpable 1 cm under the left costal margin and

US revealed persistence of the focal lesions in the spleen. Computerized tomography (CT) revealed multiple splenic lesions with irregular contours, with peripheral contrast enhancement and decreased signal intensity of the liver and the spleen due to iron deposition.

The aspiration biopsy taken from the splenic nodular lesions was consistent with nonspecific purulent abscess. Giemsa stain revealed 90% PMNL and Gram's stain revealed no microorganism or fungi. Aerobic culture grew no microorganism. Anaerobic and fungal cultures were not available.

Chemotherapy was stopped and two weeks after pneumococcal and Haemophilus influenzae vaccinations, splenectomy was performed. Pathologic examination revealed multiple foci of microabscesses. No hypha, yeast or granuloma was evident. Gram's stain did not reveal any microorganism or fungi. After splenectomy, he did not develop any febrile neutropenia attack.

Since he did not have an HLA-matched sibling, bone marrow banks were being searched while he was receiving Hacettepe AML 2000 maintenance protocol and penicillin prophylaxis. Seventeen weeks later, isolated bone marrow relapse occurred. The parents gave consent for withdrawal of active treatment, and the patient died shortly afterwards.

Discussion

The incidence of splenic abscess in adult and childhood leukemia is 7.2% and 1.0%, respectively [3,4]. This is the first case of splenic abscess encountered in our clinic.

Although there is no specific symptom for splenic abscess[3], the patients generally present with fever, diffuse nonspecific abdominal pain, left upper quadrant pain, nausea/vomiting and weight loss[5]. The only symptom our patient displayed was fever, which manifested only when the patient had neutropenia. The febrile neutropenia attacks were considered as attacks with no detectable foci of infection, like in some other immunosuppressed patients with febrile neutropenia. Incomplete regression of splenomegaly was attributed to absence of complete remission of leukemia. The splenic nodular lesions of our patient were detected incidentally, when abdominal US was performed to evaluate unresolved splenomegaly. The US and CT appearances of the nodular lesions were consistent with neither typical candidal nor bacterial abscess[6], although there may be exceptions[3,6,7]. The first three febrile neutropenia attacks were successfully treated with empirical antibiotic therapy without necessitating antifungal therapy. Fluconazole (1 mg/kg/d), which had been administered during IDA-FLAG protocols just as prophylaxis and was continued during the two febrile neutropenia attacks preceding each protocol, was obviously ineffective in treating splenic fungal lesions in an immunocompromised patient. Therefore, we considered granulocytic sarcoma, nodules of infarct, extramedullary hematopoiesis[8,9] and metastasis of another tumor[10] in the differential diagnosis of the nodular lesions, rather than splenic abscess. The diagnosis was made by pathological examination of the lesions. During the time between the detection of the splenic lesions by US and their definite diagnosis by aspiration biopsy, the patient's chemotherapy proceeded, since we did not suspect splenic abscess. However, after the diagnosis of the nodules by aspiration biopsy, chemotherapy was stopped. Hence, whether patients with cancer and splenic microabscesses should continue ongoing cytotoxic therapy remains a dilemma[11]. Additionally, since the patient did not display any symptom of splenic abscess after the diagnosis by biopsy, we did not consider medical therapy until splenectomy.

The negative cultures and the clinical outcome of the patient suggest that the causative agent might have been a bacteria, but the broad spectrum antibiotics administered in the total five infection attacks before the aspiration might have prevented bacterial growth in culture, like in the previously reported cases[1,3]. Hence, the incidences of negative blood and pus cultures were reported as 51.8% and 27.1%, respectively, in the general population[1], and negative pus cultures were reported in 11 out of 11 AML patients[3].

Establishment of ideal criteria for selecting patients who require splenectomy necessitates awaiting further evaluation of more patients with this disease[7]. For fungal abscess, unless life-threatening systemic toxic effects of splenic fungal infection exist, splenectomy may be safely delayed, and response to therapy is evaluated over time[7]. However, splenectomy remains the definitive treatment for bacterial splenic abscesses[4,5], since there is a high

mortality without surgery[7] and symptoms of splenic abscess may subside with therapy but resume later[12]. Hence, we think that the abscesses in our patient might have been foci of reinfection during the proceeding three febrile neutropenia attacks, which he developed during the four months that elapsed from the diagnosis of splenic nodules to splenectomy. In conclusion, splenectomy not only provided the pathological diagnosis but allowed us to treat the patient appropriately.

Our patient developed splenic abscesses, obviously during the induction therapy, as reported by Grois et al.[3]. We do not precisely know in which time interval of induction our patient developed splenic abscesses. However, splenic abscesses in immunocompromised patients were reported to be detectable by US, after attainment of neutrophil recovery[6] and/or several weeks after establishment of splenomegaly[12].

The spleen's susceptibility to infarction in leukemia[7] probably increased because of the increased thrombogenic effect of M3 variant and this might have predisposed to abscess formation. We do not know if splenic abscesses were the predisposing factors for development of acute appendicitis.

In childhood, splenic abscesses were reported to be generally coexistent with or precedent to renal and/or hepatic abscesses and rarely alone[4]. It seems that our case is striking for involving the spleen alone.

We do not think asplenia affected the course of AML because splenectomy is a choice of treatment in some hematological malignant diseases[13,14], and the patient did not develop any febrile neutropenia after splenectomy.

We think that unresolved splenomegaly, even when hematological remission is not attained, and/or recurrent febrile neutropenia in a patient with leukemia should lead a physician to also consider splenic abscess in the differential diagnosis.

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