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SHORT REPORT

Acute Hepatic Failure in a Case of Acute Lymphoblastic Leukemia

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Hepatomegaly and mild elevation of serum transaminase values that might be caused by infiltration of leukemic cells are seen in some cases of leukemia. It may result from such conditions as viral hepatitis, liver toxicity due to chemotherapy and leukemic liver infiltration. However, severe jaundice is rarely observed, especially at the onset of leukemia and it greatly complicates initial therapy because most induction agents are metabolized primarily by the liver. Many authors have reported adult patients with malignancies presenting with fulminant hepatic failure (1-2). Zafrani et al. (3) reported 4 adults with acute monoblastic leukemia, acute phase of chronic myelogenous leukemia, or lymphoma presenting with fulminant hepatic failure. Harrison et al. (4) reported 3 patients with metastatic liver disease who presented with a clinical course compatible with fulminant hepatic failure. Severe hepatocellular dysfunction has also been reported in association with extensive metastatic liver disease. When publications were reviewed and analyzed from Pubmed, we found anectodal case reports presenting liver dysfunction and leukemia showing a spontaneous improvement. We report acute hepatic failure in a case of acute lymphoblastic leukemia.

Case

A 15 year-old boy presented at our clinic with a 2 weeks history of anorexia, malaise and jaundice in the sclera of the eye and skin, with darkened urine. The history revealed that one of his siblings had neurofibromatosis, the patient had not taken any toxic drug and no jaundice case was present in his family. The patient was generally well, alert and not confused. His temperature was 37.9 °C and pulse 88/min. There was a marked icterus in the sclera and the skin. He had no splenomegaly or hepatomegaly. Laboratory investigations showed that the leukocyte count was 2500/mm^3, Hb 14.1g/dl, platelet 80,000/mm^3 and erythrocyte sedimentation rate 10 mm/h. Biochemical analysis demonstrated that total bilirubin was 18.9 g/dl, direct bilirubin 10.3 g/dl, AST 350 U/L, ALT 1140 U/L and LDH 1789 U/L. Other biochemical tests were normal. The hepatitis markers anti-HBs and anti-HAVIgG were positive but HBsAg, anti-HCV and anti-HAVIgM were negative. Polymerase chain reaction showed that HBV-DNA and HCV-RNA were negative. Other viral markers including EBVIgM, CMVIgM , HSV-I and II IgM and HPV-B19 were negative but, EBVIgG, CMVIgG and HSV-I and II IgG were positive. Peripheral blood film showed atypical lymphocytes, blast cells and neutropenia (Figure 1). Because his body temperature exceeded 38.3 °C, an empiric double antibiotic combination consisting of sefepim and amicacine were initiated to treat him according to the febrile neutropenia protocol. To establish the etiology of the pancytopenia, the patient was referred to the department of hematology. The examinations of peripheral blood and bone marrow aspiration revealed a leukemic infiltration. *Escherichia coli*

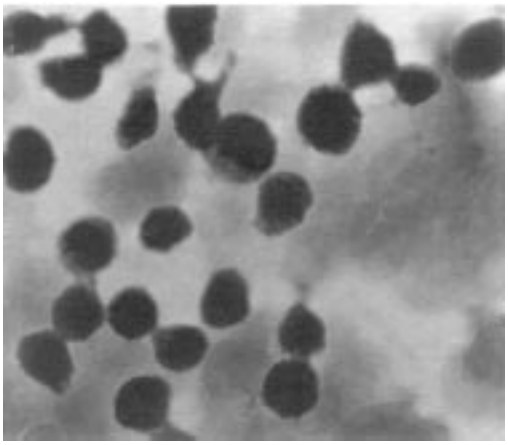

Figure 1. Patient's peripheral blood film shows atypical lymphocytes, blast cells and neutropenia.

was isolated in peripheral blood and bone marrow cultures. Jaundice was considered to be secondary to leukemic liver infiltration since other causes of hepatitis (i.e. viral hepatitis, toxic hepatitis, and metabolic liver disease) were ruled out. The patient's abdominal ultrasonographic imaging showed paranchymal echogenity, granulation patterns without mass and hepatosteatosis. At this time, we planned to perform a liver biopsy to clarify the cause of hepatic dysfunction. However, it was not performed due to the low level of platelets and coagulopathy. In addition, his family did not give permission for this procedure. The patient was definitely diagnosed with aberrant myeloid marker bearing pre-B ALL consequent to flow cytometry and immunohistochemical investigations. Cytogenetic analyses detected hypodiploidy and clonal deletion of chromosome 22. Remission induction chemotherapy for ALL was not initiated in the patient because of the risk of inducing massive liver necrosis and a worse outcome. Approximately 1 week later, his clinical and laboratory parameters such as fever, complete blood count, liver function tests and peripheral blood smear started to improve with supportive care and empirical antibiotherapy and he became almost normal. At this time, to clarify the unexpected improvement, it was decided to repeat the bone marrow examination but his family did not give permission for this repeat procedure. Because of this improvement in the clinical and laboratory picture, we decided to follow the patient without therapy. After several days, the fever rose together with severe jaundice in the patient. The laboratory parameters including liver function tests and complete blood count rapidly deteriorated (Figures 2-4). We observed leukemic cells in the peripheral blood smear again. Within several days, the clinical picture rapidly progressed to hepatic failure and encephalopathy. Finally, he died of multi-organ failure. No postmortem examination was performed since informed constent from the patient's family could not be obtained for autopsy.

Discussion

Hepatic involvement is most often moderate in patients with ALL, chronic lymphocytic leukemia (CLL),

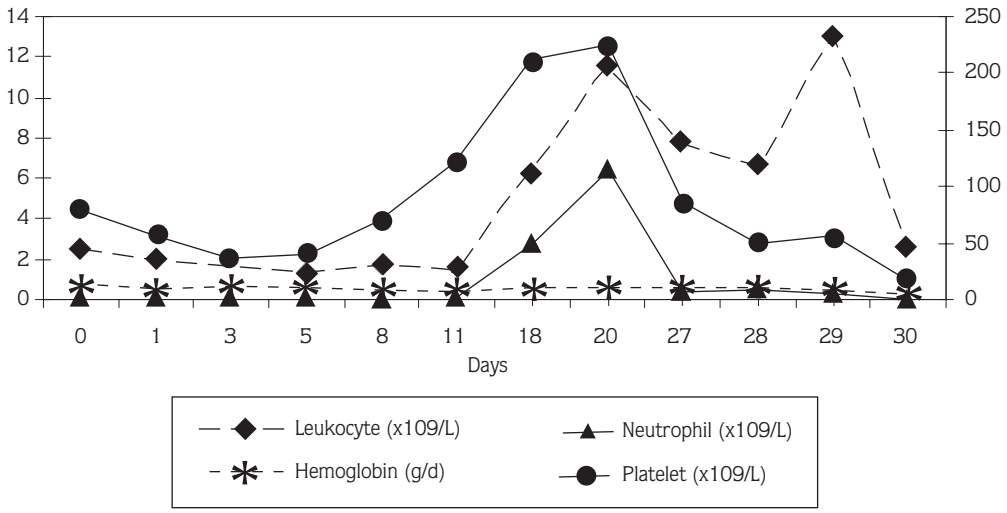

Figure 2. The course of complete blood count from initial presentation to death.

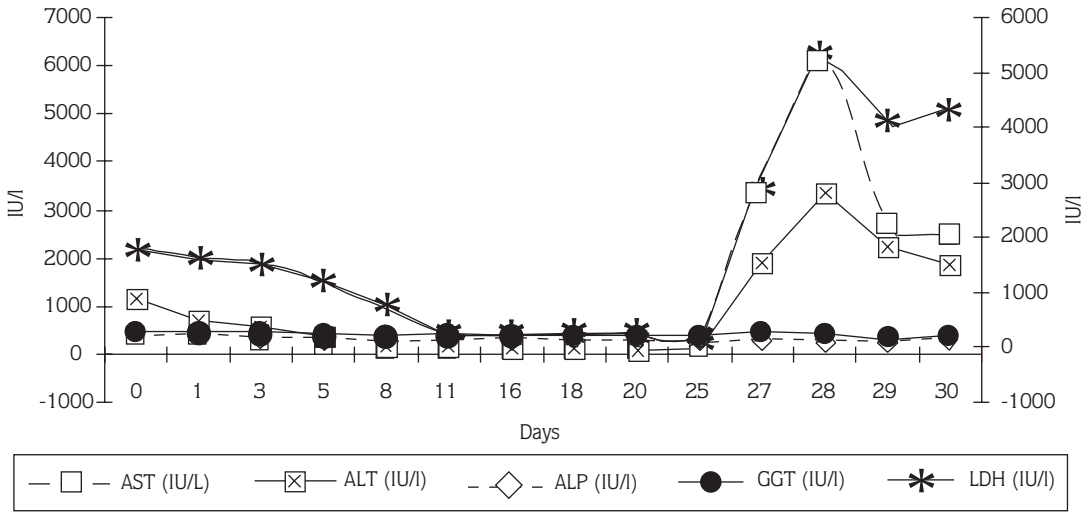

Figure 3. The course of liver enzymes from initial presentation to death.

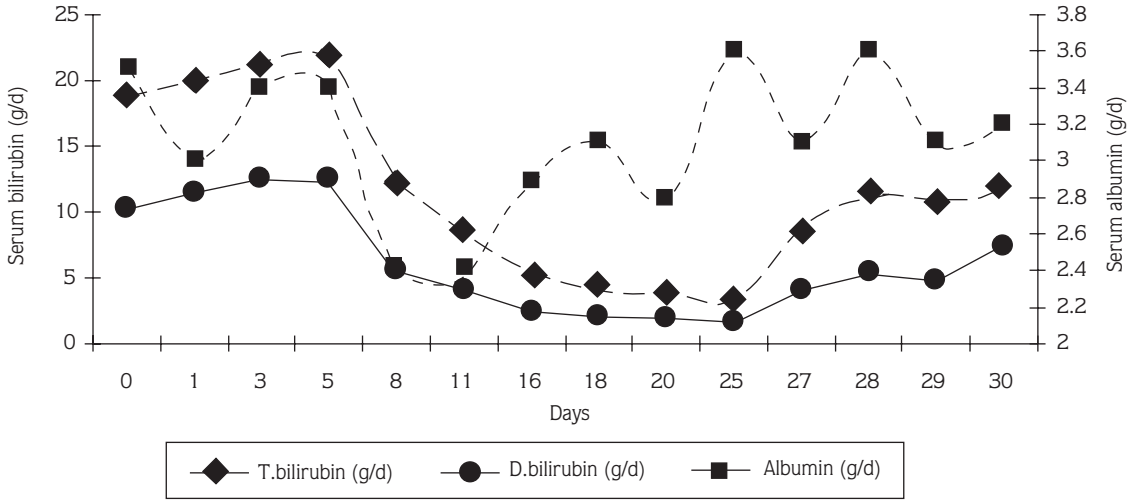

Figure 4. The course of the serum levels of bilirubin and albumin from initial presentation to death.

Hodgkin's disease (HD), non-Hodgkin's lymphomas (NHL) and the blastic crisis of chronic myeloid leukemia (CML), but it is unusual in multiple myeloma (MM) patients. Hepatomegaly may be present at the time of diagnosis but only rarely does liver dysfunction dominate (5). Pathologically, the liver shows diffuse enlargement secondary to infiltration by leukemic lymphoblasts. In ALL and CLL, the involvement of periportal spaces by neoplastic cells was common. Hepatomegaly may also be the result of hypertrophy of hepatocytes in the leukemias. In patients with ALL, significant enlargement of the liver was linked to a poor prognosis. Even in cases associated with marked hepatomegaly, liver function abnormalities are often mild. If any hepatic dysfunction does occur, it is usually accompanied by jaundice. While jaundice may be due to a variety or complications such as viral hepatitis, bacterial infection, or toxicity from anti-tumor therapy, it most often reflects infiltration of the liver by the tumor, at least in patients with HD. Accurate differentiation of the various causes of jaundice is important, but except for

distinguishing jaundice due to hemolysis from that due to liver disease, this is often a difficult task. Clinical features and liver function tests usually are of little help in differentiating liver disease due to tumor invasion from that due to other causes. Alkaline phosphatase and leucine aminopeptidase are often, but not invariably, elevated with tumor invasion. Liver biopsy can be helpful and is indicated unless coagulation is abnormal or posthepatic biliary obstruction is suspected (6). Scheimber et al. reported histopathological findings in the liver in a series of autopsies on 110 patients suffering from leukemia and lymphoma (7). They showed that 10 of 25 untreated patients had neoplastic infiltration. The clinical and pathological findings in 4 cases with fulminant hepatic failure due to massive infiltration of the liver by acute leukemia or lymphoma have been reported (6). Liver abnormalities were found simultaneously with, or led to the discovery of, hematologic malignancies and consisted of marked hepatomegaly and severe hepatocellular insufficiency. Immediate chemotherapy was instituted in these cases and complete remissions without hepatic complications were obtained. It is suggested that malignant hematological diseases with rapid cellular growth may present as fulminant hepatic failure. In order to avoid a rapidly fatal outcome secondary to liver failure and metabolic disorders, early recognition of these malignancies is necessary so as to assure prompt administration of appropriate chemotherapy (3). Systemic chemotherapy is the treatment of choice for hepatic infiltration with hepatic dysfunction. Irradiation, not exceeding 2000 rads, can be given to the entire liver (8). Aviles et al. (9) have carried out 29 liver biopsies in 25 patients with acute leukemia that presented with changes in liver functions tests. They have reported leukemic infiltration in 1 case, nonspecific lesions in 16 cases, 1 granulomatous hepatitis, 1 viral hepatitis; 1 did not show any change in the biopsy. Five patients (20%) showed drug-induced hepatitis; in these it was necessary to modify the chemotherapy. It is concluded that hepatic biopsy may be very useful in evaluating the undesirable effects of treatment of acute leukemia and in making therapeutic decisions. The risk of this procedure and the contraindications are similar in patients with acute leukemia and those with other diseases (5). In our patient, we thought that liver involvement by leukemic cell infiltration was due to marked liver dysfunction. This finding could not be supported by a pathological diagnosis since the liver biopsy could not be performed. Most ALL patients initially present with clinical symptoms resulting from bone marrow failure. One third have infection or fever at presentation. Approximately one half of the patients presented at diagnosis with lymphadenopathy, splenomegaly and hepatomegaly (6). There were rare reports of spontaneous remissions after viral or bacterial infections or transfusions in acute leukemia (10-12).

Cytogenetic analysis has become critical for the prediction of outcome and selection of therapy in ALL. Clonal chromosomal alterations are present in 75% of cases. The major cytogenetic abnormalities in ALL are clonal translocations (t[9;22], t[4;11], t[8;14], t[1;19] or t[10;14] and other structural abnormalities (9p, 6q, or 12p abnormalities) (6). There were hypodiploidy and clonal deletion of chromosome 22 in cytogenetical analysis of the bone marrow of our patient. Hypodiploidy was a sign of unfavorable prognosis. Although the importance of clonal deletion of chromosome 22 is unknown, this abnormality might be a part of t(9;22), with an unfavorable outcome, usually missed on standard cytogenetic analysis. We observed myeloid antigen expression on lymphoid blast cells by the flow cytometrical examination. This finding does not appear to have any independent prognostic significance but may be an adverse prognostic factor in adults (13).

In conclusion, our case illustrates that liver dysfunction may be the presenting feature of ALL. In this case temporary improvement in liver functions and complete blood counts was observed following an episode of septicemia and supportive care. However, this temporary advantage did not last long and he died of hepatic failure with ALL. Once the diagnosis of ALL was made definite, induction chemotherapy for leukemia should be immediately administered to patients not having other causes of hepatic dysfunction such as viral or toxic. This case was unique with regard to the spontaneous regression and progression of both leukemia and hepatic failure.

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