Jaundice and Acute Liver Failure as the First Manifestation of Acute Myeloid Leukemia

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The liver is a common site for metastasis of solid tumors, yet hematological malignancies seldom cause clinically significant liver disease. Several case reports of cholestasis and of acute liver failure due to hematological malignancies have been described [2,3], secondary to lymphomas, lymphoid leukemias or acute myeloid leukemia. Cholestasis and acute liver failure as the initial manifestations of acute myeloid leukemia are rare and carry a poor prognosis [4]. Furthermore, a normal blood count in AML is rare: anemia is usually present at diagnosis, the median presenting leukocyte count is about 15,000/µl and platelet count < 100,000/µl appears in 75% of patients at diagnosis. In this report we describe a patient in whom the primary manifestations of AML were cholestasis and hepatocellular damage with a fairly normal complete blood count.

Patient Description

A 74 year old man presented with chest pain and abdominal discomfort. During the previous week this was accompanied by mild fatigue, decreased appetite and dark-colored urine. He reported no fever, dyspnea, nausea, vomiting or diarrhea. He had lost 6 kg in the preceding 6 months. The patient's history included coronary artery bypass graft 15 years earlier, hypertension and newly diagnosed diabetes mellitus type 2 six months prior to his admission. He had no risk factors for viral hepatitis nor a history of liver disease. His medications included aspirin, propanolol, felodipine, simvastatin and metformin. Physical examination upon admission revealed mild skin jaundice and icteral sclera. There was slight tenderness over his right upper quadrant. There was no organomegaly or peripheral signs of chronic liver disease. The rest of the examination was normal.

Laboratory results showed a hemoglobin level of 14.7 g/dl, white blood cell count of 8760/µl with no blasts (79% neutrophils, 6.5% lymphocytes and 12% monocytes), and platelet count of 138,000/µl. The serum bilirubin level was 8.4 mg/dl, of which 6.5 mg/dl was direct bilirubin; alkaline phosphatase was 622 U/L, aspartate aminotransferase 859 U/L, and alanine aminotransferase 443 U/L. Prothrombin time and albumin were normal (11.7 seconds and 3.7 g/dl respectively). Lactate dehydrogenase was 3357 U/L and D-dimer value 15,113 ng/ml. Serum electrolytes, renal function and blood gases were normal. A chest radiograph and electrocardiogram were normal at admission, as was a normal troponin T level. A lung scan indicated a low probabilty of pulmonary embolism. Ultrasound showed a normal sized liver of heterogenous texture and normal intrahepatic and extrahepatic bile ducts without calculi.

After 3 days his serum bilirubin concentration rose to 14.2 mg/dl and liver enzymes deteriorated. Computed tomography scan demonstrated an enlarged liver with hypodense areas and mild ascites with the absence of pancreatic lesions. Serological tests for infectious hepatitis and immunological hepatitis were taken and ascites paracentesis did not reveal any fluid. Furthermore, the patient became confused and disoriented. A brain CT was normal and blood amonia level was also normal. Treatment with neomycin and lactulose for hepatic encephalopathy was initiated. In the following 2 days, blood laboratory tests further deteriorated with emergence of leukocytosis, 14,600/µl (85% neutrophils, 5% lymphocytes), anemia (hemoglobin, 12.1 g/dl), electrolyte abnormalities and acute liver failure with albumin level of 3.0 g/dl, prothrombin time 26.2 seconds, and markedly elevated bilirubin and liver enzymes. Before a liver biopsy was performed the patient had expired.

On autopsy, the liver was enlarged with multiple white and red nodules and numerous cystic-like areas and necrosis. On frozen section, acute leukemia with multiple foci of necrosis were revealed. Bone marrow was infiltrated mainly by myeloid blast cells, positive to myeloperoxidase and vimentin. The urinary bladder and the prostate were also infiltrated by leukemic cells.

Comment

Obstructive jaundice with hepatocellular damage as the first manifestation of AML is rare and has been reported in several case studies [Table]. The obstructive jaundice is either secondary to a leukemic infiltration of the gallbladder or the bile

AML = acute myeloid leukemia

Table. Case reports of acute myeloid leukemia presenting with obstructive jaundice or acute liver failure

1	Abe Y, Takatsuki H, Okada Y, Saito A, Kimura T, Nishimura J. Mucosa-associated lymphoid tissue type lymphoma of the gallbladder associated with acute myeloid leukemia. *Intern Med* 1999;38:442-4.	A patient with mucosa-associated lymphoid tissue type lymphoma of the gall bladder who developed jaundice due to concurrent AML
2	Wandroo FA, Murray J, Mutimer D, Hubscher S. Acute myeloid leukaemia presenting as cholestatic hepatitis. *J Clin Pathol* 2004;57:544-5.	A 40 year old man who presented with cholestatic jaundice due to AML. Complete remission was achieved with chemotherapy.
3	Jaing TH, Yang CP, Chang KW, Wang CJ, Chiu CH, Luo CC. Extrahepatic obstruction of the biliary tract as the presenting feature of acute myeloid leukemia. *J Pediatr Gastroenterol Nutr* 2001;33:620-2.	A 4 year old boy presented with extrahepatic obstruction of the biliary tract as the presenting symptom of AML. He was treated successfully with chemotherapy and allogenic bone marrow transplantation.
4	Lillicrap DP, Ginsburg AD, Corbett WE. Relapse of acute myelogenous leukemia presenting with extrahepatic obstruction of the biliary tract. *Can Med Assoc J* 1982; 15: 1000-1.	A 51 year old woman with relapse of AML presenting with extrahepatic obstruction of the biliary tract. The patient expired thereafter.
5	Rajesh G, Sadasivan S, Hiran KR, Nandakumar R, Balakrishnan V. Acute myeloid leukemia presenting as obstructive jaundice. *Indian J Gastroenterol* 2006;25:93-4.	A 32 year old man with M4 subtype AML presenting as obstructive jaundice. The patient expired before chemotherapy was initiated.
6	Goor Y, Goor O, Michalewitcz R, Cabili S. Acute myeloid leukemia presenting as obstructive jaundice. *J Clin Gastroenterol* 2002;34:485-6.	A 36 year old man with obstructive jaundice. After remission-inducing chemotherapy, there was a complete regression of the jaundice
7	Anderson SH, Richardson P, Wendon J, Paqliuca A, Portmann B. Acute liver failure as the initial manifestation of acute leukaemia. *Liver* 2001;21:287-92.	A 30 year-old woman who presented with acute liver failure as the presenting sign of M5 subtype AML. The patient expired 8 days after admission.
8	Amitrano L, Guardascione MA, Schiavone EM, Brancaccio V, Antinolfi I, Iannaccone L et al. Hepatic vein thrombosis leading to fulminant hepatic failure in a case of acute non-promyelocytic myelogenous leukemia. *Blood Coagul Fibrinolysis* 2006;17:59-61.	A patient with Budd-Chiari syndrome complicating non-promyelocytic AML leading to fulminant hepatic failure.
9	Mano Y, Yokoyama K, Chen CK, Tsukada Y, Ikeda Y, Okamoto S. Acute myeloid leukemia presenting with obstructive jaundice and granulocytic sarcoma of the common bile duct. *Rinsho Ketsueki* 2004;45:1039-43.	A 54 year old man with AML presenting with obstructive jaundice and granulocytic sarcoma of the common bile duct.
10	Gonzales-Vela, Val-Bernal JF, Mayorga M, Cagigal ML, Fernandez F, Mazorra F. Myeloid sarcoma of the extrahepatic bile ducts presenting as obstructive jaundice. APMIS 2006;114:666-8.	A 75 year old woman who presented with jaundice due to myeloid sarcoma of the extrahepatic bile ducts. Eight months later she was diagnosed with AML.

ducts [4,5] or due to granulocytic sarcoma appearing with AML. Granulocytic sarcoma represents a mass lesion of leukemic cells that might lead to compression of the bile ducts. It can appear simultaneously with AML or prior to it. The diagnosis of leukemic infiltration of the liver and bile ducts is mainly established by liver biopsy or on autopsy, although in one case, Goor et al. [4] described a 34 year old man who presented with the simultaneous appearance of both blast cells in bone marrow and obstructive jaundice. In this case the patient underwent chemotherapy treatment without an invasive diagnostic liver investigation.

Acute liver failure, which developed rapidly in our patient, is associated with a poor prognosis and a high mortality rate. It is most commonly caused by viral infection and drug toxicity. Malignancy is an uncommon etiology of acute liver failure and it is typically diagnosed on autopsy [1]. Among the described malignancies that cause acute liver failure hematological neoplasms are the most common [1]. Case reports secondary to Hodgkin's and non-Hodgkin's lymphoma, chronic lymphoid leukemia, acute lymphoblastic leukemia, mostly in children, and AML have been described [2,3]. The proposed mechanism of acute liver failure is secondary to hepatic ischemia due to sinusoidal infiltration of tumor cells replacing the hepatic parenchyma. Acute liver failure as the initial manifestation of acute leukemia is extremely rare, it is difficult to diagnose due to the rapid progression of the disease and it usually carries a poor prognosis [3]. It has been described in acute lymphoblastic leukemia far more than in acute myeloid leukemia. In the cases described, it mostly presents with indicators of high cell turnover such as elevated lactate dehydrogenase and uric acid, an elevated white cell count and hyperlactatemia due to reduced hepatic clearance and regional ischemia in tumor tissue.

Patients with AML most often present with non-specific symptoms as fatigue, anorexia, weight loss, fever, bone pain, headaches, bleeding and easy bruising. Physical findings usually reveal fever, splenomegaly, hepatomegaly, lymphadenopathy, sternal tenderness and evidence of infection or hemorrhage. The median white blood count presented in AML is 15,000/μl, with 25–40% of patients having counts under 5000/μl and 20% above 100,000/μl. Anemia and thrombocytopenia are common at diagnosis. Our patient's initial diagnosis raised little suspicion of a hematological malignancy but rather an infection, immunological disease or solid tumor. Focusing on the white blood cell

differentiation, it is surprising that no blasts had been detected. Establishing AML diagnosis in this case was difficult and time consuming. The rapid deterioration due to acute liver failure preceded the diagnosis of AML and it was revealed only on autopsy.

Our report underlines the importance of considering AML as a rare cause of jaundice and acute liver failure. This etiology should be considered especially in those patients presenting with prodromal symptoms, an abnormal blood count, and elevated lactate dehydrogenase, uric acid and hyperlactatemia. In these cases, blood smear and bone marrow biopsy are required. Liver biopsy is important as well, although obtaining a tissue sample in a coagulopathic patient is a high risk procedure and in most cases contraindicated. The rapid diagnosis of the leukemia and the initiation of therapy are essential, although in most cases of acute liver failure and AML, the prognosis is poor.

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