

# Liver injury and pancytopenia as initial symptoms of acute lymphoblastic leukaemia

## A case report

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**Abstract.** *Haematological malignancies commonly involve the liver, however, they rarely cause clinically significant hepatic disease. Hepatic involvement as the prodromal manifestation of acute leukaemia is exceptional. We describe a 54-year-old female who developed recurrent, symptomatic hepatitis and thrombocytopenia as initial features of acute lymphoblastic leukaemia. Transjugular hepatic biopsy revealed porto-sinusoidal infiltration with blast-cells. At immunohistochemistry the infiltrating cells shared the phenotypic characteristics of the medullary infiltrate. The patient was treated with a PALG 4-2002 chemotherapy regimen, which led to partial remission of haematological disease and normalization of hepatic laboratory tests.*

**Key words:** *liver injury, acute lymphoblastic leukaemia*

Neoplastic involvement of the liver in patients with haematological malignant diseases ranges from 32 % in multiple myeloma to 80 – 100 % in chronic leukaemias (9). In the majority of these cases a moderate accumulation of malignant cells in the liver does not produce clinical symptoms. Marked infiltration with cytokine producing blast cells may imitate viral or autoimmune hepatitis, and occasionally a massive collection of these cells in sinusoids results in ischaemic damage of hepatocytes with consecutive development of acute hepatic failure (1,7,10).

Hepatic infiltration by neoplastic cells in acute lymphoblastic leukaemia (ALL) is found in about 60 % of cases (9). In contrast to acute myeloid leukaemia, the blast cells in ALL patients accumulate in the liver mostly in portal triads, and to lesser degree within

sinusoidal vessels (1,9). Liver involvement in ALL is usually symptom-free, especially in the early stage of this disease. We report on an adult patient who developed symptomatic recurrent liver injury and pancytopenia as initial features of ALL.

### Case report

A 54-year-old female was admitted to city hospital because of sudden appearance of jaundice and fatigue. Hepatic laboratory tests were abnormal (serum total bilirubin 68  $\mu\text{mol/L}$ , serum ALT increased four-times, AST increased six-times over the upper normal limit; see Table) and there was pancytopenia characterized by low platelet, leukocyte and erythrocyte counts ( $44 \cdot 10^9/\text{L}$ ,  $2.2 \cdot 10^9/\text{L}$  and  $3.75 \cdot 10^{12}/\text{L}$ , respectively). White cell differential count revealed

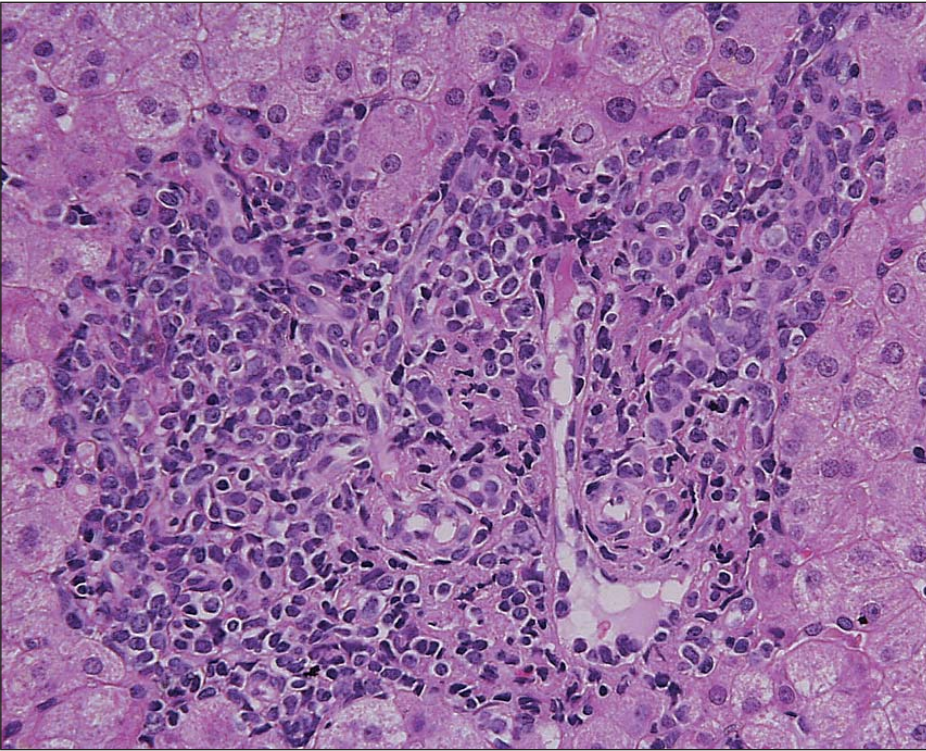


Figure 1  
Widespread portal infiltrate with large lymphoid cell population. Haematoxylin-eosin, magnification 250x.

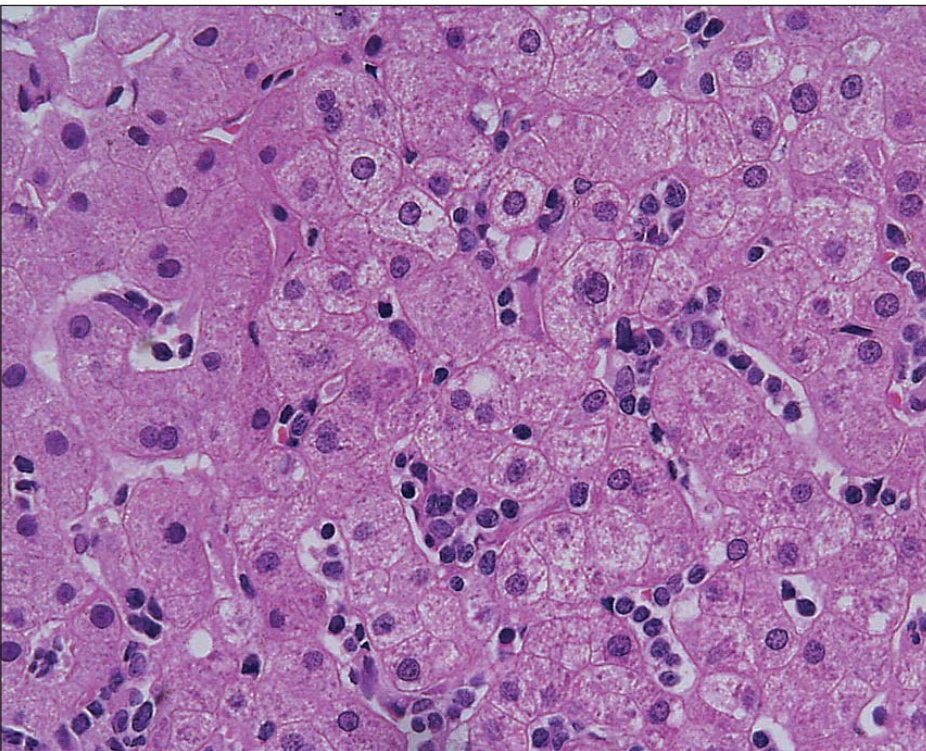


Figure 2  
Sinusoidal infiltrate with lymphoblasts. Haematoxylin-eosin, magnification 320x.

63 % of neutrophils and 35 % of lymphocytes. Abdominal ultrasound showed moderate enlargement of the liver and spleen. Serological tests for viral infections with HAV, HBV and HCV were negative and there was no alcohol abuse in the patient's history. Serum iron and transferrin concentrations, as well as ceruloplasminaemia were normal. The patient consumed a few potentially hepatotoxic drugs, i.e. non-steroidal anti-

inflammatory drugs for degenerative spine disease, a cholesterol-lowering drug belonging to statins and estrogens in the context of hormone replacement therapy. All these drugs were withdrawn and a hypothesis of drug-induced simultaneous liver and marrow injuries was put forward. Therapy with low-dose glucocorticosteroids was initiated and the patient was transferred to our department. On admission

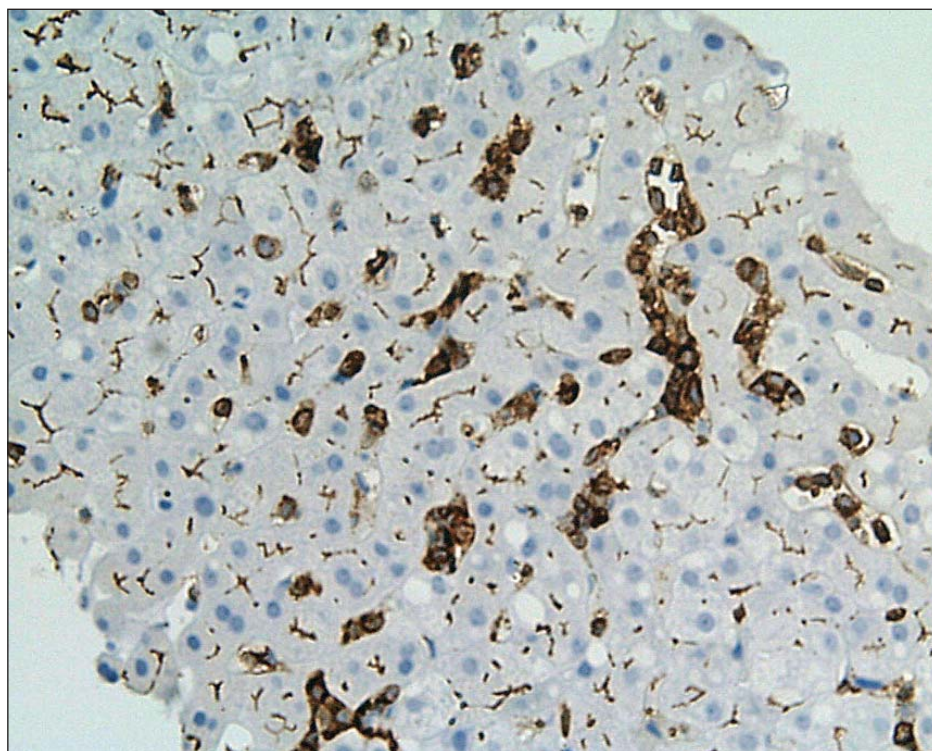


Figure 3  
CD20 membranous staining of the large atypical cells.

Table  
Laboratory serum liver tests

Date	Bilirubin $\mu\text{mol/L}$ (mg/dL)	ALT $\mu\text{kat/L}$ (U/L)	AST $\mu\text{kat/L}$ (U/L)	ALP $\mu\text{kat/L}$ (U/L)	GGT (GMT) $\mu\text{kat/L}$ (U/L)
Sep 29, 2004	68 (4)	8.20 (492)	3.10 (186)		
Oct 18, 2004	50 (2.9)	2.77 (166)	0.63 (38)	3.03 (182)	2.57 (154)
Oct 21, 2004	39 (2.3)	1.98 (119)		3.32 (199)	2.08 (125)
Dec 16, 2004	19 (1.1)	5.07 (304)	2.15 (129)	7.62 (457)	6.45 (387)
Jan 10, 2005	14 (0.8)	7.65 (459)	2.37 (142)	6.75 (405)	17.70 (1062)
Feb 14, 2005	9 (0.5)	0.80 (48)	0.62 (37)	3.20 (192)	3.00 (180)

she was pale without stigmata of chronic liver disease or peripheral lymphadenopathy. Liver synthetic capacity was intact as concluded from constantly normal INR and serum albumin level. During brief clinical observation the laboratory parameters either improved (see Table) or normalized (platelet and leukocyte counts), with persistence of anaemia (haemoglobin 85 g/L). Normal colonoscopy and gastroscopy excluded the digestive tract as a source of chronic loss of blood and magnetic resonance cholangiography ruled out any pathology within intrahepatic or extrahepatic biliary ducts. The patient was discharged with recommendation of haemato-

logical consultation and tapering glucocorticosteroids.

After 7 weeks the patient was readmitted because of fever and deterioration in laboratory liver tests (see Table), associated with high erythrocyte sedimentation rate (104 mm/hour) and serum C-reactive protein 242 mg/L (normal value < 5 mg/L). Liver function tests (INR 0.97, serum albumin concentration 38 g/L) and haemoglobin level were normal, but there was recurrence of thrombocytopenia ( $55 \cdot 10^9/\text{L}$ ) and leukopenia ( $2.5 \cdot 10^9/\text{L}$ ). Repeated blood cultures were negative. Direct immunofluorescence tests for antinuclear and anti-smooth muscle antibodies were positive (titres

unknown) with no elevation of gammaglobulin concentration. Although hepatic percutaneous biopsy could not be performed due to low platelet count, we proposed a diagnostic switch to autoimmune hepatitis and the patient was given an immunosuppressive treatment composed of glucocorticosteroids and azathioprine. This treatment was associated with immediate disappearance of fever, but had no definitive effect on laboratory data. Two weeks later the patient developed mucocutaneous haemorrhagic diathesis. Examination of peripheral blood revealed severe thrombocytopenia ( $16 - 19 \cdot 10^9/L$ ), leukopenia ( $1.8 - 2.5 \cdot 10^9/L$ ) and anaemia (erythrocytes  $3.86 \cdot 10^{12}/L$ , haemoglobin 98 g/L). Azathioprine was immediately taken off with no direct effect on haematological parameters. The patient required repeated transfusions of platelet and erythrocyte preparations. Concurrent liver tests are given in the Table. Bone marrow was hypocellular on aspiration biopsy and the consulting haematologist proposed the diagnosis of aplastic anaemia. Cytomegalovirus and HCV were not detected with the PCR method. Transjugular liver biopsy was performed and the histology disclosed portal and sinusoidal infiltration with lymphoblasts (Figs 1 – 2), which on immunochemistry showed characteristics of B-cells: CD20+ (Fig. 3), Tdt+, CD3-, CD30-, CD23-, CD43-, bcl6-, cyclin D1. A few days later the patient developed leukocytosis  $29 \cdot 10^9/L$  with 28 % of blasts and presence of Gumprecht shadows, with simultaneous normalization of aminotransferases and fall in ALP (see Table). The patient was transferred to the haematological department, where trephine biopsy demonstrated significant reticulin fibrosis in bone marrow and massive lymphoblastic infiltration (95 %). Flow cytometry revealed the same as in the liver phenotypic characteristics of infiltrate, showing positivity for CD20, CD79, Tdt, CD34, CD10, whereas testing for CD3 was negative. The final diagnosis was common bcr/abl(+) acute lymphoblastic leukaemia. Induction therapy according to the PALG 4-2002 scheme (fencort, farmorubicin, oncovin, kidrolase), with intraspinal infusion of methotrexate and fencort was administered. The treatment was followed by partial haematological response, but led to persistent normalization of hepatic laboratory tests.

## Discussion

Although haematological malignancies commonly involve the liver, they rarely cause clinically significant

hepatic disease. In acute leukaemias as well as in acute leukaemic episodes in non-Hodgkin lymphomas involvement of the liver is generally detectable clinically by the presence of hepatomegaly and subicterus. These abnormalities generally appear in later stages of haematological malignancies and usually have minor or no reference to the course of leukaemia or its therapy (1,7,8).

It is believed that clinical manifestation of liver disease is proportional to the density of porto-sinusoidal infiltrate. This suggestion is based on the knowledge that both proinflammatory/apoptotic cytokines produced by infiltrating cells and hepatic ischaemia evoked by sinusoidal blockade are major sources of liver injury in acute leukaemias (7,8). Hepatic involvement as the prodromal manifestation of acute leukaemia is exceptional and carries a poor prognosis with a considerable risk of rapidly fatal evolution, despite relevant chemotherapy (1,7,8). In such cases it is essential to recognize the neoplastic origin of liver failure, since hepatic transplantation is strongly contraindicated in these patients (7).

In the reported patient the liver injury was first manifestation of haematological malignancy. It preceded diagnosis of leukaemia by few months and presented itself as symptomatic hepatitis with uncompromised liver function. In the absence of peripheral stigmata of leukaemia this disease imitated a severe drug-induced or autoimmune liver damage. Mechanisms underlying trafficking the lymphoblasts to the liver and hepatic colonization by these cells are largely unknown. We presume that active entrapment of blast cells by the liver prevented their occurrence in peripheral blood, hence hepatic accumulation of these cells delayed the diagnosis of ALL. On the other hand, the sudden drop of aminotransferases activity concurrent with emergence of lymphoblasts in peripheral blood could be explained by loss of hepatic trapping capacity in the later stage of this disease.

Regarding the facts, that the liver disease in our patient was primarily associated with medullary hypoplasia with reticulin fibrosis and that we have no liver histopathology from this period of disease, a hypothesis alternative to blast cells hepatic infiltration should be proposed. In the available literature there are few reports of patients who developed hepatitis of unknown origin followed by bone marrow aplasia progressing to acute leukaemia (3-6). It is hypothesized that certain, and yet unrecognized

viruses or drugs are responsible for hepatic and medullary injury, probably resulting from immunomediated stem cell insult. In accordance with this theory there are data showing identical molecular disturbances in both the aplastic and leukaemic phase of disease (2,6). However, the latter hypothesis seems to be very unlikely as in our patient the liver disease had constantly the same character of mixed hepato-

cellular-cholestatic injury and thrombocytopenia appeared simultaneously with the first symptoms of liver disease.

In summary, our report shows that in case of hepatitis of unknown origin, especially accompanied by peripheral blood abnormalities, haematological malignancies should be considered as a possible cause of liver injury.

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