

Severe acute liver failure as the initial manifestation of haematological malignancy

Paulo Souto¹, José Manuel Romãozinho¹, Pedro Figueiredo¹,
Manuela Ferreira¹, Isabel Sousa², Ernestina Camacho¹,
António Donato¹ and Diniz Freitas¹

Acute liver failure is rarely secondary to lymphoma or leukaemia and it is extremely uncommon as the initial presentation of malignancy. We report a case of a young adult patient with severe acute liver failure referred for liver transplant, in which a Burkitt acute lymphoblastic leukaemia was diagnosed by bone marrow examination. A complete recovery and long remission were obtained with chemotherapy.

European Journal of Gastroenterology & Hepatology 1997, 9:1113-1115

Keywords: acute liver failure, malignancy, Burkitt's lymphoma, liver transplantation

Introduction

Liver is commonly affected by primary and metastatic malignancies, usually in the context of well established disease. Gastrointestinal tumours are the most common tumours which metastasize to the liver. Hepatic failure may be present in some patients with extensive metastasis. Breast tumours, melanomas, lymphomas and oat cell carcinomas of the lung are the most common malignancies implicated [1]. Acute liver failure is a rare complication of lymphoma or leukaemia, but its presentation as the first manifestation of the haematological malignancy is extremely uncommon [2-6]. The prognosis is poor. Early diagnosis is imperative, not only because it represents an absolute contraindication to liver transplantation but also because it is a potentially treatable medical condition.

We report a case of a young adult patient referred for liver transplant, in which it was possible to obtain a complete recovery from severe acute liver failure and a long remission of a Burkitt acute lymphoblastic leukaemia with chemotherapy.

Case report

A 20-year-old Portuguese white female, previously healthy, complained of abdominal pain, fever and vomiting for 6 days. She was admitted to a hospital in Zurich, where she was living. Examination revealed jaundice and painful hepatomegaly. Neither spleen nor lymph nodes were palpable. Laboratory tests revealed a total bilirubin of 4

mg/dl, alkaline phosphatase of 635 units/l, aspartate aminotransferase 155 units/l and alanine aminotransferase 179 units/l. Full blood count revealed 24 900 leucocytes/mm³ (lymphocytes 23%, neutrophils 67%, monocytes 8% and eosinophils 2%) with normal haemoglobin, haematocrit and platelets. Albumin and creatinine were also normal. Prothrombin rate was 76%. Abdominal ultrasonography showed hepatomegaly with multiple solid tumours, suggesting lymphoma or metastatic malignancy, but no lymphadenopathies or splenomegaly were detected. There was no history of medication, alcohol or drug abuse.

As the patient refused to stay in Switzerland, she was referred to an Oporto hospital where she was admitted the next day. Chest x-ray was normal. Pelvic and abdominal computed tomography (CT) revealed minor ascites and a heterogeneous enlarged liver with areas of hypodensity (Fig. 1). Tumour aetiology was regarded as improbable because CT scan suggested steatotic areas in preserved parenchyma. Spleen and lymph nodes were normal. Hepatic biopsy was deferred due to the sudden development of coagulopathy (prothrombin time 23 s above normal value) on the fourth day in hospital. Simultaneously, she developed prostration and severe metabolic acidosis with increased anion gap (pH 7.15; PCO₂ 17.7 mmHg; bicarbonate 6 mmol/l; anion gap 30 mEq/l). Total bilirubin increased to 12 mg/dl, alkaline phosphatase to 929 units/l, aspartate aminotransferase to 166 units/l and alanine aminotransferase to 235 units/l. Lactate dehydrogenase (LDH) was 2059 units/l and gamma-glutamyltranspeptidase 658 units/l. The uric acid level was 12 mg/dl (normal <7 mg/dl). HIV and hepatitis

From the ¹Department of Gastroenterology and ²Department of Haematology, Coimbra University Hospital, Coimbra, Portugal. Requests for reprints to Paulo Souto MD, Department of Gastroenterology, Coimbra University Hospital, 3049 Coimbra Codex, Portugal.

Date received: 28 April 1997; revised: 6 June 1997; accepted: 22 July 1997.

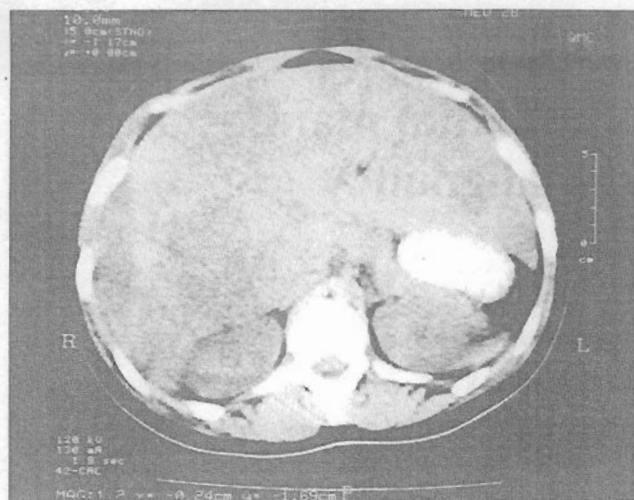


Fig. 1. Abdominal CT scan: heterogeneous enlarged liver with areas of hypodensity.

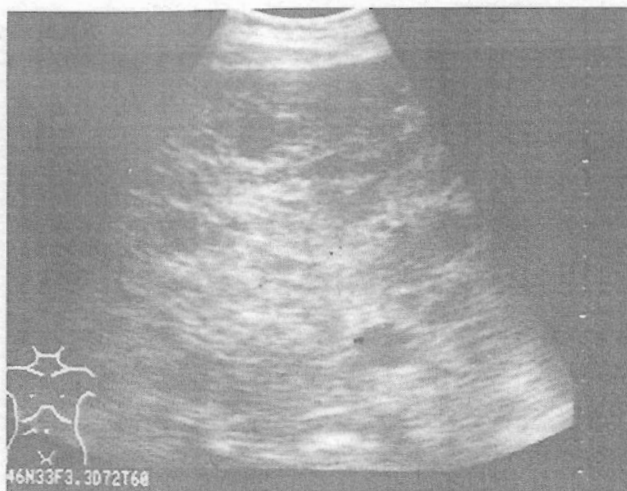


Fig. 2. Abdominal ultrasonography: hypoechoic areas in a heterogeneous hepatomegaly.

A, B and C virus serology were negative. She was admitted to an intensive care unit, and at that same day (less than 2 weeks after the onset of symptoms) she was transferred to the Gastroenterological Intensive Care Unit (GICU) of Coimbra University Hospital for 'management of severe acute liver failure and evaluation for liver transplant'.

Just after admission in GICU, abdominal ultrasonography was repeated, showing heterogeneous hepatomegaly with hypoechoic areas (Fig. 2) and ascites. Papilloedema was suspected on fundoscopy. A cerebral CT scan was performed, excluding focal masses, but suggesting some degree of cerebral oedema. The prothrombin rate was 27%, factor V level 35% and factor VII level 27%. Fibrinogen degradation products were absent. Leucocytosis persisted and platelet count was down to $92\,000/\text{mm}^3$. For operational reasons, transjugular liver biopsy was not immediately possible. Bone marrow aspiration, promptly executed, revealed B-type blast cells with vacuoles and hyperbasophilic cytoplasm, consistent with Burkitt cells (Fig. 3). Peripheral blood smear showed a leucoerythroblastic non-leukaemic pattern.

Chemotherapy was started 8 h after admission in GICU, with a COP course consisting of a small dose of cyclophosphamide ($300\text{ mg}/\text{m}^2$), vincristine ($1\text{ mg}/\text{m}^2$) and 7 days of prednisone ($60\text{ mg}/\text{m}^2$ per day). This initial phase was followed by two consecutive COPADM courses, each of them with high dose methotrexate ($3\text{ g}/\text{m}^2$), vincristine ($1\text{ mg}/\text{m}^2$) doxorubicin ($60\text{ mg}/\text{m}^2$), prednisone ($60\text{ mg}/\text{m}^2/\text{day}$) and 3 days of cyclophosphamide ($500\text{ mg}/\text{m}^2/\text{day}$ in the first course and $1\text{ g}/\text{m}^2/\text{day}$ in the second course). Tumour lysis and aplastic phase were handled with minor complications. Rapid clinical improvement occurred, with regression of hepatomegaly and normalization of liver function tests. Malignant cells were not detected in cerebrospinal fluid. Cranial irradiation (18 Gy) and intrathecal methotrexate (12.5 mg) were applied as central nervous system prophylaxis. Almost 3 years later the patient is still in remission, having completed 2 years of maintenance therapy as an out-patient, consisting of daily 6-mercaptopurine ($75\text{ mg}/\text{m}^2$), weekly methotrexate ($20\text{ mg}/\text{m}^2$) and monthly

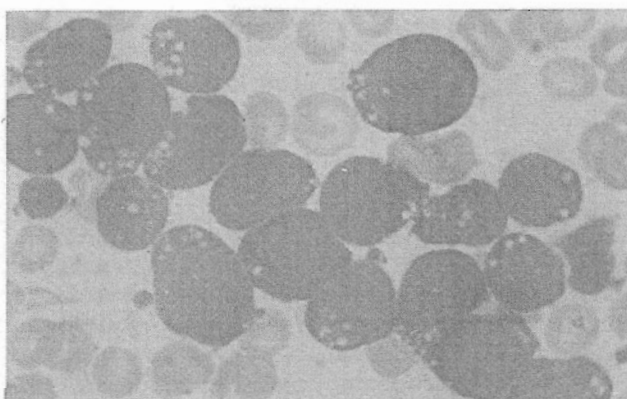


Fig. 3. Bone marrow aspiration: infiltration by blast cells with hyperbasophilic vacuolated cytoplasm (May-Grünwald-Giemsa, $\times 1000$).

consolidation pulses of vincristine (2 mg) and prednisone ($40\text{ mg}/\text{m}^2/\text{day}$ for 7 days).

Discussion

Acute liver failure is rarely secondary to haematological malignancies. Cases of Hodgkin's and non-Hodgkin's lymphoma [2–6], acute leukaemia [5] and malignant histiocytosis [7] have been reported. Without specific treatment a fatal outcome is rapidly inevitable [1]. Urgent diagnosis is required so that chemotherapy can be promptly started and acute liver failure reversed [2–5].

Our patient fulfils the definition criteria for severe acute liver failure [8], and when referred to GICU our first concern was to detect or to exclude malignancy. The presence of a large heterogeneous liver with hypoechoic areas, a disproportionate elevation of LDH and lactic acidosis, despite the absence of splenomegaly or lymphadenopathy, led to the suspicion of malignancy. As reported by other authors [3,4], these aspects should be considered suspicious of underlying lymphoma. LDH and uric acid levels may be related to tumour burden [9]. The presence of lactic acidosis carries a poor prognosis [4]. Bone marrow aspiration promptly allowed the diagnosis and the beginning of

chemotherapy for a Burkitt acute lymphoblastic leukaemia. The initial small doses induced a good tumour reduction, allowing management of metabolic complications [10].

Burkitt's lymphoma, frequently extranodal, progresses rapidly with a potential doubling time of about 24 h [9]. Treatment is an oncological emergency [10]. Prognosis is worse in adults, as well as in advanced stages, in patients with central nervous system involvement and in Burkitt acute lymphoblastic leukaemia [10]. In adults, an overall cure rate of 71% and a 5-year relapse-free survival rate of 42% can be achieved with intensive chemotherapy [10,11].

Although uncommon, lymphoma and leukaemia should be considered in the differential diagnosis of acute liver failure. Unequivocal diagnosis is required. An aggressive approach to obtain histological or cytological specimens from liver, lymph nodes, bone marrow or effusions [12] should be pursued, taking into account the condition of the patient, the hospital facilities and the urgency of the diagnosis and treatment.

References

1. Uhl MD, Riely A: Unusual causes of acute liver failure. In *Acute Liver Failure*. Edited by Lee WM, Williams R. Cambridge: Cambridge University Press; 1997:43-52.
2. Saló J, Nomdedeu B, Bruguera M, et al.: Acute liver failure due to non-Hodgkin's lymphoma. *Am J Gastroenterol* 1993, 88:774-776.
3. Woolf GM, Petrovic LM, Rojter SE, et al.: Acute liver failure due to lymphoma: a diagnostic concern when considering liver transplantation. *Dig Dis Sci* 1994, 39:1351-1358.
4. Ghosh P, Fox IJ, Rader AM, et al.: Fulminant hepatic failure as initial manifestation of non-Hodgkins lymphoma. *Am J Gastroenterol* 1995, 90:2207-2209.
5. Zafrani ES, Leclercq B, Vernant JP, et al.: Massive blastic infiltration of the liver: a cause of fulminant hepatic failure. *Hepatology* 1983, 3:428-432.
6. Braude S, Gimson AES, Portmann B, et al.: Fulminant hepatic failure in non-Hodgkin's lymphoma. *Postgrad Med J* 1982, 58:301-304.
7. Colby TV, LaBrecque DR: Lymphoreticular malignancy presenting as fulminant hepatic disease. *Gastroenterology* 1982, 82:339-345.
8. Bernuau J, Rueff B, Benhamou JP: Fulminant and subfulminant liver failure: definitions and causes. *Semin Liver Dis* 1986, 6:97-106.
9. Ziegler JL: Burkitt's lymphoma. *N Engl J Med* 1981, 305:735-745.
10. Patte C, Michon J, Frappaz D, et al.: Therapy of Burkitt and other B-cell acute lymphoblastic leukaemia and lymphoma: experience with the LMB protocols of the SFOP (French Paediatric Oncology Society) in children and adults. *Baillière's Clin Haematol* 1994, 7:339-348.
11. Ostronoff M, Soussain C, Zambon E, et al.: Burkitt's lymphoma: a retrospective study of 46 cases. *Nouv Rev Fr Hematol* 1992, 34:389-397.
12. Haddad MG, Silverman JF, Joshi VV, et al.: Effusion cytology in Burkitt's lymphoma. *Diagn Cytopathol* 1995, 12:3-7.