Haematological malignancies presenting with acute liver injury: a single-centre experience

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Summary

Introduction: Early recognition and identification of the underlying cause of acute liver injury (ALI) is crucial in instituting medical treatment and assessing the need for liver transplantation. Haematological malignancies have been reported to present as ALI with progression to acute liver failure but experience is limited.

Aim: Review our experience of ALI secondary to haematological malignancies.

Patients and methods: Patients admitted to the liver unit with ALI secondary to a haematological malignancy between 1996 and 2006 were identified. A retrospective review was made of their case notes and our database.

Results: Of the 752 cases of ALI, six cases of ALI secondary to haematological malignancy were identified. Common features were a prodromal illness (median duration of 5 weeks; range 2–6 weeks) and jaundice (median bilirubin 208 μmol/l; range 112–238 μmol/l). The majority of patients (5/6) had hepatomegaly. Liver biopsy was performed in two patients and confirmed the diagnosis in both cases. In other cases, the diagnosis was made following lymph node biopsy (1), bone marrow examination (2) or from post-mortem examination (1). Median time from jaundice to encephalopathy was 12 days; range 1–22 days. A single patient underwent liver transplantation but died in the immediate post-operative period. All patients died soon after admission with a median survival of 8 days (range 3–26 days).

Conclusion: Haematological malignancy should be considered in ALI patients presenting with a prodromal illness, jaundice and hepatomegaly. Biopsy is essential to confirm the diagnosis but the benefit of definitive therapy such as chemotherapy and/or transplantation in this setting is unclear and survival is poor.

Introduction

Any cause of acute liver injury (ALI) can progress to liver failure characterized by the rapid deterioration of liver function in association with coagulopathy and altered mentation in a previously healthy person.1 Early recognition and identification of the underlying cause is important both in guiding medical treatment and in determining prognosis.

Unlike ALI due to acetaminophen overdose or viral hepatitis, haematological malignancies such as lymphomas are rare and often under-recognized causes of ALI.2 Lymphomas are now the fifth most common malignant neoplasm after cancers of the breast, prostate, lung and colon and their incidence is rising.3
The age-standardized incidence rate for non-Hodgkin’s lymphoma (NHL) in the United Kingdom increased by 6% in the 10-year period between 1995 and 2004. Systemic lymphomas can often affect the liver in a variety of different ways including biliary obstruction and focal or diffuse parenchymal infiltration. ALI is a rare complication of systemic lymphoproliferative disease and is more likely to occur as a result of diffuse infiltration than localized disease. Treatment options for these patients include chemotherapy and liver transplantation, although there is currently no consensus regarding therapy. Given the paucity of published data regarding treatment and outcome, we studied patients with haematological malignancy-related ALI admitted to a national liver centre in the United Kingdom. The clinical presentation and diagnostic work-up was reviewed and outcome and course of disease described.

Methodology

We defined ALI as a combination of abnormal liver biochemistry in association with decreased synthetic function in the form of coagulopathy, in the absence of previous symptomatic liver disease. In the study, we have included patients who progressed to develop acute liver failure defined by the onset of hepatic encephalopathy.

Between June 1996 and July 2006, 752 patients were admitted to the liver unit at the Queen Elizabeth Hospital in Birmingham with a diagnosis of ALI. In six patients (0.8%), ALI was secondary to infiltrative haematological malignancy.

Clinical analysis

A data set was developed using the Microsoft Excel programme (Part of Microsoft Office Professional Edition, 2003) to collect details of patients’ presenting symptoms, clinical features and laboratory investigations.

Stages of encephalopathy were determined by clinical examination in conjunction with numeric testing (Duphalac®, Solvay Pharmaceuticals B.V., Olst, Netherlands). Electro-encephalograms were performed to detect sub-clinical encephalopathy.

Haematological diagnosis

Histological and immunohistological assessment of formalin-fixed, paraffin-embedded sections of liver, lymph nodes and bone marrow was performed. Sections were stained with haematoxylin and eosin, liver biopsies were also stained with: reticulin, orcein, PASD, perls and haematoxylin van Gieson. Immunohistochemical stains for B and T lymphocytes including CD30, CD15, CD5, CD10, CD23, in addition to Epstein–Barr virus (EBV) latent membrane protein-1 (LMP-1) and Ki-67 as a proliferation marker were performed. For increased sensitivity of EBV detection, in situ hybridization for EBV-encoded RNA (EBERs) was performed in some cases. Thick paraffin sections were sent to the molecular laboratory at Southampton for analysis of T-cell receptor gene rearrangements in one patient (Patient 6).

Peripheral blood samples and bone marrow aspirates were assessed both morphologically and by flow cytometry (Patients 1, 2, 4, 5 and 6) to identify abnormal or clonal lymphocyte populations.

Liver screening tests and liver function

In all patients, acute viral serology (hepatitis A, B, C and E) and autoimmune (anti-smooth muscle antibody, anti-nuclear antibody, rheumatoid factor) and metabolic screens (serum caeruloplasmin and urinary copper excretion study) were normal. Blood acetaminophen levels and urine toxicology screens were performed. The international normalized ratio (INR; normal range: 1) and serum lactate (normal range: 0.9–1.1 mmol/l) were used as a measure of the liver synthetic function and marker of prognosis.

Routine biochemistry

Serial blood tests for liver biochemistry [serum bilirubin, aspartate transaminase (AST), alkaline phosphatase (ALP)] and renal function [serum urea, creatinine] were taken following admission to the liver unit. Normal ranges are: bilirubin: 1–22 μmol/l; AST: 5–43 U/l; ALP: 70–320 U/l; urea: 3.2–7.6 mmol/l; creatinine: 60–126 μmol/l.

Results

Patients

Six patients (three males and three females) were identified. Haematological malignancy subtypes comprised NHL (four patients), natural killer (NK) cell leukaemia (one patient) and adult T-cell leukaemia/lymphoma (ATLL; one patient). The median age of the patients at the time of presentation was 45 years (range 18–66 years).

All six patients died 8 days (median 8; range 3–26 days) following admission to the liver unit. Table 1 provides a summary of all six cases with associated clinical and biochemical features.
Clinical and laboratory features

Patients 1, 4 and 6 had been previously diagnosed with haematological malignancy. Patient 1’s complex past medical history included Hodgkin’s disease (Stage 1A) successfully treated 7 years previously with high-dose chemotherapy and radiotherapy. Four years prior to his admission with haematological malignancy-related ALI he underwent a liver transplant for seronegative fulminant hepatic failure. Two years after his transplant he developed cervical lymphadenopathy and was diagnosed with a high-grade B-cell NHL on a cervical lymph node biopsy; he was successfully treated with drug regimen comprising Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone (CHOP) chemotherapy. Patient 4 had been successfully treated with CHOP chemotherapy for NHL 13 years previously. Patient 6 had been found to be seropositive for human T-cell lymphotropic virus-1 (HTLV-1) and subsequently diagnosed with ATLL.

All six patients described a prodromal illness comprising malaise, fever and/or nausea, which predated the presentation by 5 weeks (median 5; range 2–6 weeks).

On presentation, all patients were icteric (median bilirubin at presentation 208 µmol/l; range 112–238 µmol/l). Five out of six patients had palpable hepatomegaly whilst two had peripheral lymphadenopathy. Total white cell count was elevated in one patient and 5/6 had a coagulopathy with abnormal renal and liver biochemistry (AST median 2219 U/l, range 161–10 000 U/l and creatinine median 153 µmol/l, range 106–244 µmol/l).

Imaging and tissue diagnosis

Ultrasound confirmed the presence of hepatomegaly in five out of six cases but focal lesions were only demonstrated in Patient 1. Transjugular liver biopsy was performed in two cases (Patients 2 and 6) and confirmed the presence of haematological malignancy in both patients. The biopsy specimen from Patient 6 is shown in Figure 1. In Patient 1, the diagnosis was made by lymph node biopsy. Bone marrow examination confirmed haematological malignancy in Patients 4 and 5 and haemophagocytosis was also demonstrated in Patient 5 (Figure 2). Tissue diagnosis and examination of the explanted liver in Patient 3 was made at post-mortem (Figure 3).

Treatment and outcome

Median interval between the onset of jaundice to encephalopathy was 12 days (range 1–22 days). Four patients (Patients 2, 3, 4 and 5) were managed on the intensive care unit, because of the requirement for renal and respiratory support. Patients 1 and 6 were not admitted to the intensive care unit as both patients had confirmed malignant processes prior to the development of multi-organ failure and
their clinical outcomes were deemed too poor to benefit from additional invasive therapy. Patient 1 was commenced on chemotherapy after biopsies confirmed the presence of a lymphoma. The 4-day regimen was stopped prematurely due to worsening renal failure. Patient 3 underwent a cadaveric liver transplant 48 h after presentation. Patient 5 was commenced on immunoglobulin therapy and methylprednisolone 3 days after admission for haemophagocytic syndrome associated with NK-cell leukaemia.

**Discussion**

In this case series, we have described six cases of ALI secondary to haematological malignancy. Whilst the incidence of lymphoma in developed countries continues to rise, haematological malignancies remain an unusual cause of ALI, responsible for <1% of referrals to our unit. This is somewhat surprising since the liver is involved in up to 25% of the patients with lymphoproliferative disease, particularly NHL.\(^7\)\(^-\)\(^9\) This suggests that the real incidence of ALI may be much higher as many of these patients are not referred to liver centres. Liver involvement in NHL has been characterized by hepatomegaly\(^10\) and increased serum levels of bilirubin and alkaline phosphatase.\(^8\)\(^,\)\(^11\) Importantly, it also represents an advanced stage of disease, conferring inferior disease-free and overall survival rates.\(^12\) This study serves as a reminder that haematological malignancies can present with acute liver dysfunction and can be difficult to distinguish from more common causes of ALI. Jaundice to encephalopathy times were very variable, ranging from 1 to 22 days and admission INRs ranged from 1.2 to above upper limit of our assay, although much of this reflects the lead time bias in referral to a liver unit. The presence of prodromal symptoms, jaundice, hepatomegaly (present in 5/6 cases) and lactic acidosis seem to be common characteristics of this group of patients, thus providing some distinction from other causes of ALI. Interestingly, three of the cases had previously been diagnosed with haematological malignancy while in the other cases ALI was the first manifestation of malignancy. Whilst clinical features such as an abnormal blood film, peripheral lymphadenopathy and previous history of haematological malignancy may raise suspicions of infiltrative disease, the absence of these features does not exclude the diagnosis. Hepatomegaly in any case of ALI should prompt urgent radiological imaging, but absence of focal lesions does not exclude an underlying malignancy, as only one of our patients had identifiable lesions on ultrasonography. A liver biopsy is recommended if there is any suspicion of a malignant cause. Our data suggest that a transjugular liver biopsy was as effective as a bone marrow aspirate in obtaining a tissue diagnosis. Urgent tissue biopsies and assessment of samples allowed appropriate management of patients and prevented 5/6 patients from having an inappropriate liver transplant. The only patient to undergo liver transplantation in our series was referred too late for a biopsy to be completed. Moreover, although the risks associated with percutaneous biopsies are increased in these patients by coagulopathy and/or thrombocytopenia, no additional mortality or morbidity was incurred in our series.

Primary hepatic lymphoma is a very rare cause of ALI\(^13\)\(^,\)\(^14\) and most cases of ALI secondary to lymphoproliferative disease are due to infiltrative NHL.\(^15\) Most of our cases had a high-grade T- or
B-cell lymphoproliferation rather than Hodgkin’s lymphoma or low-grade NHL. This is consistent with published experience. Another point of interest is the wide variation in peak AST levels and we noted possible variations in pathogenic mechanisms. Patient 1 appeared to have developed hepatocellular insufficiency due to malignant replacement, whilst Patient 3 had features of an ischaemic process and Patient 5 had a massive cytokine-induced form of hepatocyte injury.

Common to all patients with haematological malignancy-associated ALI has been the poor clinical outcome. Isolated case reports have described clinical responses or ‘rescues’ with chemotherapy, but it is likely that these patients have a more favourable biology in terms of disease grade and age. The vast majority of patients do not improve following chemotherapy or are too unwell to undergo treatment at the time of presentation, ensuring that the prognosis remains very poor. Delivering an effective chemotherapeutic regimen can be difficult in view of many of the drugs being metabolized in the liver, and therefore leading to increased toxicity from increased levels of primary drug/metabolites. None of the patients in our series survived supporting the view that patients with haematological malignancy-associated ALI should not be considered for liver transplantation because of their poor predicted 5-year survival.

Inevitably, some patients will undergo liver transplantation by virtue of the fact that in some cases the diagnosis will not be reached ante-mortem. We describe one such case, where a patient was transplanted before the diagnosis was disclosed, but who died of multi-organ failure in the immediate post-operative period. Only two patients in published case reports have had good outcomes after liver transplantation. In both instances, the diagnosis was not known prior to transplantation and the patients went into remission with courses of post-operative chemotherapy. In conclusion, haematological malignancies are an unusual cause of ALI but should be considered in all patients presenting with a prodromal illness, jaundice, early lactic acidosis and hepatomegaly. Tissue biopsy, either bone marrow, lymph node or liver should be undertaken as soon as possible to allow prompt administration of specific chemotherapy to patients who are fit enough to undergo treatment.

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References


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References