Primary Hepatic Lymphoma: A Diagnosis to Remember

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Abstract

We present 2 cases of PHL presenting to our hospital in the last 6 months. Both cases had similarities in that they had a rapidly progressive time course of less than 8 weeks and radiology failed to illustrate the normal disease pattern. Both were elderly men presenting with jaundice, rare presentations of PHL. One patient was interesting in that he had a bicytopenic blood picture, a common manifestation of PHL, whilst his lactate dehydrogenase was normal. The other had a past history of hepatitis B, interesting for its possible association with PHL. Whilst one patient died prior to treatment, the other was successfully treated with aggressive multi-drug chemotherapy. A liver biopsy is essential in any patient where there is a high index of suspicion for PHL based on a bicytopenic blood picture, abnormal liver function tests or radiology. If diagnosed early enough, chemotherapy has proven a successful treatment.

Keywords: Primary hepatic lymphoma; PHL; Hepatitis B

Introduction

Primary Hepatic Lymphoma (PHL) is a rare type of extranodal lymphoma accounting for less than one percent of all lymphomas [1]. It presents with a wide range of subtle manifestations and for this reason may be late or missed altogether. Diagnosis is confirmed only by liver biopsy and a review of the literature shows success with certain surgical and chemotherapeutic treatments. Late diagnosis, however, or failure to make the diagnosis can end in fulminant hepatic failure and ultimately death. We present 2 cases of PHL admitted to our district general hospital in the last 6 months and discuss the aetiology, presentations, investigations and treatments of this rare disease.

Case Report

Case 1

A 73 years old male presented with a 10 day history of jaundice, pale stools, dark urine and diarrhoea with some pain in the right upper quadrant. His past medical history included osteoarthritis, hypertension and hepatitis B from which he had recovered (HBsAg negative). His medications included lisinopril, spironolactone, omeprazole and ibuprofen. He denied drinking any alcohol or smoking. On examination, he was markedly jaundiced with tenderness in the right upper quadrant but had no organomegaly. Bloods tests on admission showed a bilirubin of 122 μmol/L (NR 2 - 17), alkaline phosphatase (ALP) 346 U/L (NR 35 - 104), aspartate transaminase (AST) 104 U/L (4 - 31), albumin 40 g/L (34 - 48), INR 1.1 (0.7 - 1.2), haemoglobin (Hb) 12.6 g/dL (11.5 - 16.5), white blood cell (WBC) 8.6 K/μL (3.4 - 11), platelets (Plts) 358 K/μL (140 - 450), Calcium (Ca) 3.52 mmol/L
An ultrasound of his liver revealed a course echotexture suggestive of cirrhosis with moderate ascites but no duct dilatation. Serology for Hepatitis B sAg, Hepatitis C, and Hepatitis A were negative and levels of Alphafetoprotein (AFP), Caeruloplasmin, and Copper were normal. Liver biopsy confirmed the patient to have Non-Hodgkins Lymphoma staining positive for CD20 lymphocytes (Fig. 1-4). He was commenced on a combination chemotherapy of Rituximab, Chlorambucil, Doxorubicin, Vincristine and Prednisolone (RCHOP) and went into tumor lysis syndrome with acute renal failure requiring admission to intensive care. However, he made a good recovery and within 4 months his liver function had normalized.

Case 2

An 80 years old male presented with a month’s history of diarrhoea 5 times daily with loose offensive stool. He had a week history of jaundice and was admitted urgently by his General Practitioner for investigation. His past medical history included chronic obstructive airways disease for which he took inhalers. He admitted to consuming 10 units of alcohol per week and was a non-smoker. On examination, he was jaundiced, cachectic with moderate ascites but with no organomegaly. Blood tests showed a bilirubin of 28 μmol/L, ALP 187 U/L, AST 113 U/L, alb 24 g/L, INR 1.6, Hb 12.4 g/dL, plts 91 K/μL and WBC 2.26 K/μL. A sigmoidoscopy showed an early diverticular stricture preventing further examination for the cause of his diarrhoea. A CT abdomen showed an enlarged liver edge, moderate ascites, 16 cm splenomegaly and some mildly enlarged nodes around the coeliac axis and porta hepatis measuring 15 mm. Autoimmune
and fevers (37-86%) are the most common. Jaundice is actual-
ly rare (4%) and symbolises diffuse hepatic involvement
[4]. Fulminant hepatic failure is very rare at first presenta-
tion. Liver function tests tend to be cholestatic in the absence
duct dilatation on ultrasound. LDH is raised in 85% of
cases [2]. A full blood count often demonstrates a pancy-
openic or bicytopenic picture, pancytopenia occurring most
likely in T cell lymphoma. AFP and CEA are both normal
distinguishing this from the other differential diagnoses of
HCC or metastatic Gastrointestinal cancer. A raised calcium
is seen in 40% [4] of cases and is put down to the production
of Calcitriol by malignant cells.

Both Ultrasound and CT help to diagnose the disease
with solitary tumors being seen in 42% of cases, multiple
lesions in 50% and diffuse disease in 8% [4] though the lat-
ter is commoner amongst Chinese. The pattern of infiltration
bears no prognostic value. Whereas Hepatocellular Carci-
noma (HCC) appears isodense on CT with rim enhancement
in the arterial phase, PHLs are hypodense and rarely enhance
and this allows distinction between these two types of pri-
mary liver cancers [5, 6].

Liver biopsy remains the mainstay of diagnosis.

Discussion

As stated already PHL is rare. PHL is different from other
lymphomas which involve the Liver in 50% of cases [2]
in that in order to make a diagnosis they must demon-
strate no nodal involvement, involve predominantly the liver and
must be in the absence of any evidence of leukaemia. Both
of our cases meet this definition.

Since clinical features and laboratory tests are wide
ranging liver biopsy is essential in confirming a suspected
diagnosis.

Diffuse large B cell is the most likely pathology fol-
lowed by Small cell lymphocytic, T cell (Fig. 5), follicular
and marginal zone lymphoma in decreasing prevalence [1,
3]. The majority of PHL patients (67%) are middle-aged men
(median age 50 years). Presentations vary significantly but
hepatomegally (80% of cases), weight loss (47% of cases),
and fevers (37-86%) are the most common. Jaundice is actu-
al liver cirrhosis.

Screen, hepatitis serology screen were all negative and Cae-
ruloplasmin, AFP, Immunoglobulins and Carcinoembryonic
Antigen (CEA) were all normal. Ferritin was 758 ng/mL.
Investigation of this patient’s bicytopenia showed a normal
blood film, reticulocyte count of 36 and a lactate dehydro-
gase (LDH) of 348 U/L. He underwent paracentesis, the fluid
protein content being 6 g/L, followed by a liver biopsy. He
was discharged on a salt restricted diet, diuretics and dietary
supplements with a view to follow-up. Unfortunately, he was
readmitted with sepsis and uncontrolled fast AF with respira-
tory compromise and died 2 weeks later. Liver biopsy result
showed him to have a low grade marginal zone lymphoma
staining positive for CD20+ lymphocytes.

Figure 6. Liver biopsy stained for Mib-1 (Ki 67), a prolifera-
tion marker which is positive in the nuclei of cells in the
mitotic cycle. In this case the proliferation index is nearly
100%, a finding associated with very aggressive lympho-
mas including Burkitts lymphoma and other diffuse large B
cell lymphomas.

In fact, these cases share very little in common other
than the presentation of jaundice and the speed at which
their disease progressed. Both patients had extensive disease
within 2 months of the first onset of symptoms. Neither pa-

tient had fulminant hepatic failure which is a hallmark of
other liver pathologies. Radiology demonstrated no single
or multiple lesions which would normally be expected. The
diagnosis was only made following a biopsy.

Hepatitis B has been speculated as playing a role in giving
rise to PHL [8] and it is interesting that one of our cases
had hepatitis B in the past. Although he was HbsAg nega-
tive his viral load was never checked and therefore we can
never be certain that he was without disease. Indeed, in the
case from Matano et al [9] immunohistochemical staining
demonstrated no replicating virus within the neoplastic cellls
although they hypothesised that chronic antigenic stimula-
tion by the virus could be associated with the development of
lymphoma rather like other immunological conditions such
as Hashimotos thyroiditis and Sjogrens syndrome [10] have
been linked to the development of extra nodal lymphomas
through the local proliferation of lymphoid tissues. Hepa-
titis B has a strong correlation with hepatocellular carci-
noma though no studies have provided a concrete link with
lymphoma. Cirrhosis itself has been linked to extra nodal

Primary Hepatic Lymphoma


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lymphoma in a number of cases [11-13]. Heimann et al [11] describe 49 patients with lymphoma, 8% of whom had cirrhosis. Hepatitis C and EBV have both been associated with the development of monoclonal B-lymphoproliferative disorders [14, 15]. Mixed cryoglobulinemia (MC) is seen by many as a variant of low grade B cell lymphoma [16] and antibodies to hepatitis C have been found in 98% of patients with type 2 MC. Bronowicki et al [17] explored further the relationship between PHL and hepatitis C and a retrospective study of 31 patients with PHL showed 6 (20%) were positive for the virus. Likewise Page et al [7] showed that 6 out of 10 of their 24 patients with PHL had hepatitis C.

Median survival has been reported as between 8 and 16 months with remission rates of less than 20% [1]. Poor prognostic factors include diffuse infiltration, high Ki index (Fig. 6), increased age, raised LDH, cirrhosis and presence of raised alpha-2 microglobulin.

To conclude with, there are few similarities between cases reported within the literature yet early detection of the disease yields successful results with standard chemotherapy regimes and therefore it is a disease for which we should have a high index of suspicion. Liver biopsy is suggested in any patient that presents with abnormal liver function tests, raised LDH and a bicytopenic/pancytopenic picture in the context of isolated hepatic disease radiologically. Hepatitis B and C may be an indirect aetiology through chronic antigen stimulation. The disease is aggressive with a short time course and RCHOP chemotherapy is the most suitable initial treatment although there is future hope with more aggressive regimes.

References