

Anaplastic large cell lymphoma presenting as acute liver failure: A report of two cases with review of literature

Uma Nahar Saikia, Nidhi Sharma, Ajay Duseja, Ashish Bhalla, Kusum Joshi

Departments of Histopathology, Hepatology and Internal Medicine.
Post Graduate Institute of Medical Education and Research, Chandigarh, India.

ABSTRACT

Primary hepatic anaplastic large cell lymphoma (ALCL) of the liver is a rare entity. We present here two cases of primary hepatic anaplastic large cell lymphoma (ALCL) of the null-cell type. Both the cases had jaundice with "B" symptoms and hepatomegaly. The serum bilirubin and liver enzymes were raised in both cases. The liver showed sinusoidal infiltration by atypical lymphoid cells with marked nuclear pleomorphism, dispersed chromatin and prominent nucleoli in both the cases. These cells were positive for CD30, negative for CD3, CD20 and EMA, and diagnosed as ALCL of the null-cell type. We hereby report these cases with the review of literature on primary hepatic ALCL with their possible etio-pathogenesis & diagnostic clues which may help in timely diagnosis & management in such cases.

Key words. Anaplastic large cell lymphoma, acute liver failure, case report.

INTRODUCTION

Anaplastic large cell lymphoma (ALCL), is a morphologically and immunologically distinct subtype of non-Hodgkin's lymphoma (NHL), accounting for 2-8% of all lymphomas.¹ ALCL occurs as two distinct forms, a cutaneous and a systemic variant.² There appears to be a male predominance, particularly in anaplastic lymphoma kinase (ALK) + cases, where the male/female ratio is approximately 3:1.³ Histomorphological features include proliferation of pleomorphic large atypical lymphoid cells with abundant amphophilic cytoplasm, often horseshoe or embryo shaped nuclei which are CD30-positive with frequent sinus involvement.⁴ Most cases exhibit a T cell phenotype whereas a very few cases are of B-cell origin.⁵ The cases which lack specific B- and T-cell markers are classified as null cell type. Dissemination to extra nodal regions such as skin, lung, pleura, pericardium, liver, and ovary is common in

ALCL especially in the T/null-cell phenotypes.⁶ Most cases of ALCL are associated with the characteristic chromosomal translocation t (2; 5), which results in up regulation of anaplastic lymphoma kinase (ALK) protein. The prognosis of ALCL depends on its phenotype. We report two cases of primary hepatic ALCL with clinical presentation as primarily liver related symptoms and acute liver failure.

CASE SUMMARY

Case 1

A 38 year-old male was admitted in the emergency ward at Post graduate institute of medical education and research (PGIMER), Chandigarh with history of fever & jaundice of one month duration. This was associated with dark colored urine due to jaundice and no other cholestatic features. He had drowsiness for four days with poor oral intake. There were no other prodromal symptoms. He was an alcoholic for last 18 years in non-cirrhotic doses and was also addicted to opium for the same duration. The clinical examination revealed a palpable liver 5 cm below right costal margin. Clinically there was no splenomegaly or free fluid in the abdomen.

The hemogram revealed anemia (52 g/L, normal 140-160 g/L) and thrombocytopenia ($80 \times 10^9/L$, normal $150-400 \times 10^9/L$) with normal differential count. There were no circulating atypical cells in

Correspondence and reprint request: Dr. Uma Nahar Saikia.
Department of Histopathology
Room No.507. Research Block A, 5th floor. Pgimer, Sector-12
Chandigarh, India
Tel.: 91-172-2755142. Fax: 91-172-2744401
E-mail: umasaikia@gmail.com

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the peripheral blood. The patient was positive for serum HBsAg, serology for anti HCV was negative and for HIV 1 & 2 was non reactive. His serum bilirubin was 23.3 mg/dL (normal 1 mg/dL) with direct bilirubin being 16.5 mg/dL. The serum aspartate transaminase AST was 97 IU/L (normal 10-40 IU/L), alanine transaminase (ALT) 70 IU/L (normal 0-60 IU/L) & alkaline phosphatase was raised i.e. 544 IU/L (normal 30-120 IU/L). Terminally the patient had raised serum urea/creatinine (132/1.8 mg/dL). The ultrasound abdomen revealed increased liver span with normal echotexture & no focal lesion, common bile duct and the gall bladder

was normal. There was no excess of free fluid in the peritoneal cavity.

The clinical possibilities kept were acute Hepatitis-HBV related versus acute on chronic liver disease with acute liver failure. The patient succumbed to his illness within 24 hrs of his hospital stay. An autopsy was performed to determine the cause of death.

Autopsy findings

A partial autopsy was performed and the brain was not examined. The liver was massively enlarged; bile stained and weighed 3,000 g. The outer and cut surface showed multiple whitish nodules measuring 2 mm-1cm D (Figure 1). Exaggerated mottling was also noted on serial slicing. There was portal vein & right hepatic vein thrombosis. On light microscopy normal lobular liver architecture was maintained, however there was infiltration of atypical lymphoid cells with prominent sinusoidal involvement and also forming nodules within portal tracts (Figure 2). These atypical cells were large, pleomorphic with prominent nuclear atypia. The nuclei showed varied profiles ranging from round to oval to kidney shaped with many bizarre and multinucleated cells & had dispersed nuclear chromatin and prominent nucleoli. Focally these cells showed spindling with frequent mitosis and apoptosis. Immunohistochemistry (IHC) revealed these cells to be negative for CD20, CD3, EMA and Alk-1 protein. The cells were positive for CD30 and CD68 was positive in the accompanying histiocytic cells. A diagnosis of hepatic ALCL, null cell type was thus made at autopsy. The immunohistochemistry for HBs Ag and HBcAg also showed cytoplasmic and nuclear positivity respectively.

The spleen weighed 1,000 g and was markedly enlarged with thickened capsule. The cut surface showed few lesions measuring 3-5 mm D. On light microscopy, there was diffuse sinusoidal infiltration by atypical lymphoid cells with nodule formation. The splenic vein showed thrombosis. The contiguous peripancreatic & periportal lymph nodes were enlarged (1-3 cm D) and showed infiltration by the lymphoma cells. Peridial extension was also noted.

The bone marrow and the kidney showed focal interstitial infiltration by the lymphoma cells. Microscopic sections from lungs showed evidence of aspiration with focal alveolar collapse. The rest of the organs were within normal limits on microscopic examination.

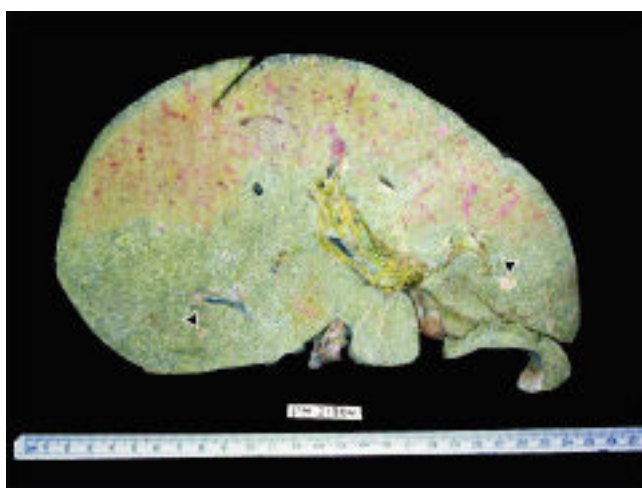


Figure 1. Case 1: Cut surface of enlarged liver showing exaggerated mottling with intervening grayish-white areas (arrows).

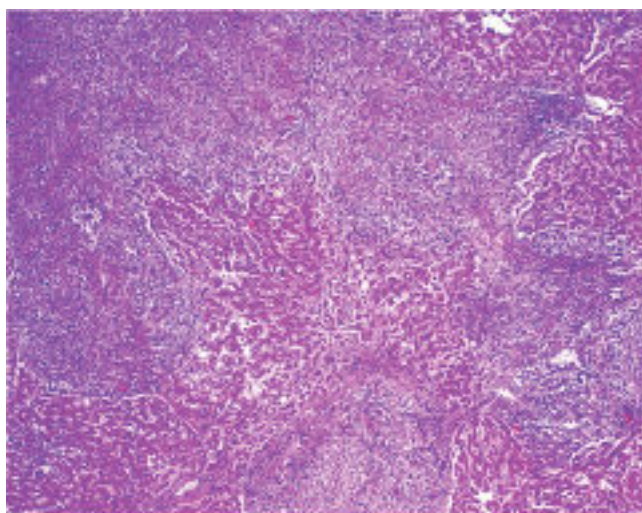


Figure 2. Case 1: Low power microphotograph of liver showing sinusoidal infiltrate by large atypical cells forming nodules (H & E, X280).

Case 2

A 30 year old female was admitted in the institute with eleven months history of jaundice, type 'B' symptoms and ascites. She had developed jaundice during the last trimester of pregnancy which was progressive in nature. She had mild splenomegaly and no lymphadenopathy. Her ultrasound abdomen revealed hepatic vein obstruction. She had raised alkaline phosphatase (ALP) 446 IU/L (normal 30-120 IU/L) and lactate dehydrogenase (LDH) 440 U/L (normal 100-190 U/L). The clinical possibilities kept were chronic Budd Chiari syndrome *vs.* overlap syndrome of autoimmune etiology. A liver biopsy was performed and subjected to histopathology. The

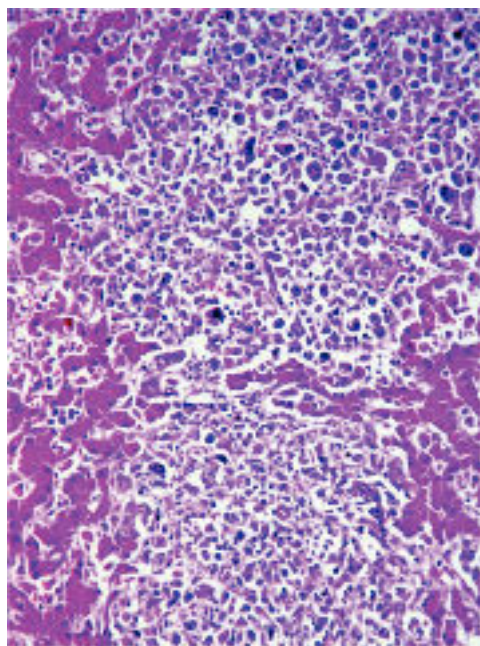


Figure 3. Case 2: High power microphotograph of liver showing large pleomorphic cells with dispersed chromatin and conspicuous nucleoli (H & E, X580).

patient died within few hours of her hospital stay. The cause of death could not be ascertained and an autopsy could not be performed due to lack of consent.

Biopsy findings

The liver biopsy showed preserved lobular architecture. However, the sinusoids were expanded with infiltration by atypical lymphoid cells (Figure 3). The cells were large, pleomorphic and had vesicular nuclei with prominent nucleoli. These atypical cells were positive for CD30, negative for CD3 and CD20. Thus a diagnosis of primary hepato-splenic lymphoma null cell type was suggested.

DISCUSSION

Primary hepato-splenic lymphoma is a rare clinical entity with only six cases reported in the literature to the best of our knowledge.^{7,8} Hepato-splenic involvement in any type of lymphoma as presenting feature is also quite rare,⁹ although hepatic involvement in advanced stages of lymphomas is encountered frequently. The terminology of primary hepatic lymphoma is used when the staging investigations fail to show extrahepatic disease or if the disease is predominant in the liver at presentation. However, infiltration can be identified at other sites, including the spleen, regional lymph nodes, and bone marrow.¹⁰ The first case fits into the second criterion as it showed predominant involvement by the lymphomatous infiltrate in the liver having symptoms related to acute on chronic liver failure at presentation with local spread.

The detailed data of all the six cases reported in literature is summarized in table 1. Of the six patients four were men and two women with the mean age of 44 years (range 33-60 yrs). Three of these pa-

Table 1. Data of all the six cases of primary hepatic anaplastic large cell lymphomas reported in literature.

Serial no	Age	Sex	HIV status	'B' symptoms	Hepatic enzymes	Reference
1	34	M	Positive	Fever	Elevated, mixed pattern*	17
2	51	F	Unknown	Fever	Normal	11
3	33	M	Positive	None	Elevated, mixed pattern*	12
4	60	M	Negative	Fever	Elevated, mixed pattern*	18
5	45	F	Negative	None	Unknown	15
6	43	M	Positive	Fever	Elevated, mixed pattern*	13
Case 1	38	M	Negative	Fever	Elevated, mixed pattern*	
Case 2	30	F	Negative	Fever	Elevated, mixed pattern*	

*Mixed pattern: Cholestatic and hepatic pattern of raised hepatic enzymes.

tients were positive for HIV serology. The commonest presenting feature was pain or discomfort in right hypochondrium with or without 'B' symptoms, such as weight loss and night sweats. Most of the patients (5/6, 83.3%) had multiple hepatic masses on radiological examination & had elevated liver enzymes (markedly raised alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) and moderately elevated transaminases). The first case described here presented with fever and history of jaundice for two months with raised hepatic enzymes. However, the second case had a long history of jaundice and raised enzymes for eleven months.

Lei KI reviewed 90 cases of primary hepatic lymphoma.¹¹ The cases were selected based on the following criteria:

- Clinical symptoms mainly caused by liver involvement at presentation.
- Absent distant lymphadenopathy.
- No leukemic involvement in the peripheral blood smear.

The lymphomas most commonly affected middle-aged individuals (median age 53 yr) with male: female ratio of 2.3:1. Pre-existing liver disease, such as cirrhosis secondary to hepatitis B or C virus, hemochromatosis, or cryptogenic cirrhosis, was present in 10 cases (11%). Grossly, a solitary liver tumor was present in 37 (41%) cases, and multiple nodular masses were identified in 27 (30%) cases. A diffuse pattern of hepatic involvement without a gross nodular lesion was seen in 17 (19%) cases. Most of the cases were classified as diffuse large-cell lymphoma (41 cases, 46%). Immunophenotyping was available in 53 cases. Most were of B-cell lineage (33 cases, 62%), 16 were T-cell (30%), and only 4 were null-cell type (8%).

Dmitry Y. Baschinsky, *et al.*, described a case of primary hepatic ALCL of T-cell phenotype in a patient with AIDS.¹² At autopsy it showed only hepatic involvement with lack of disease in other organs and hence suggested a primary ALCL which was confined to the liver. Both our cases were non-reactive for HIV.

There is only one case report of a Chinese patient with primary hepatic ALCL¹³ who presented with one month history of intermittent fever, epigastric pain, and hepatomegaly. The lymphoma was composed of cells with pleomorphic nuclei, coarse open chromatin, and prominent nucleoli. The tumor cells were positive for CD 30 and EMA, and the tumor was classified as anaplastic large-cell Ki-1 lympho-

ma. Stains for CD 20, CD 3 and CD 45RO showed no immunoreactivity in the neoplastic cells. The patient died of disseminated disease after 15.7 months, despite salvage chemotherapy. This case was similar to the case 1 in terms of clinical presentation, behavior and immunohistochemical profile; however we lost our case before any therapy could be instituted.

The etiology of ALCL is still unknown. However, higher prevalence of viral infections, such as human immunodeficiency virus (HIV) and hepatitis C virus, suggests that viral infection(s) have been implicated in the pathogenesis of ALCL. Epstein-Barr virus (EBV) has recently been identified in a significant proportion of ALCLs, in patients with or without underlying immune compromised state.¹⁴ An association with chronic hepatitis B virus infection has also been described.^{15,16} Some investigators speculate that chronic antigenic stimulation by hepatitis B virus might be involved in the pathogenesis of primary hepatic lymphoma, though this was not supported by others. Our case 1 was also seropositive for HBsAg however; it is difficult to prove it as an etiopathogenetic factor.

The other differential diagnosis of primary hepatic lymphomas include primary hepatic low grade B-cell lymphoma of mucosa-associated lymphoid tissue (MALT-lymphomas). Hepato-splenic T-cell lymphoma has been recently recognized and is characterized by predominantly sinusoidal infiltrates in the liver and diffuse involvement of the red pulp in the spleen. Primary hepatic involvement by mantle cell lymphoma and T-cell rich B-cell lymphoma has also been described. These have specific histopathologic features.

In conclusion these two cases highlight ACLF as a clinical presentation in primary Hepatic ALCL associated with type "B" symptoms. A diagnosis of primary hepatic ALCL must be clinically suspected especially with moderately elevated alkaline phosphatase and markedly increased LDH levels. An underlying immunocompromised state should further raise the suspicion of lymphomas. A liver biopsy/FNAC is mandatory with strong clinical suspicion and immunohistochemistry is essential for a definitive diagnosis and early institution of therapy.

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