

Primary Non-Hodgkin's Lymphoma of the Liver

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The clinicopathological features of a rare case of primary non-Hodgkin's hepatic lymphoma (PHL) are described and compared to those of the other 76 cases reported in the world literature. PHL is mainly a disease of Caucasian, middle-aged males and, in approximately half of the reported cases, was associated with other diseases involving depression or chronic stimulation of the immune system. Right upper abdominal and epigastric pain with loss of weight are the most common presenting symptoms. The tumour is usually a single large mass involving both hepatic lobes and is almost invariably composed of lymphocytes reacting with B-cell markers. Most tumours are of intermediate or high grade according to the classification of the Working Formulation for Clinical Usage. No correlation is apparent between gross appearance of PHL (massive or nodular) and grade of severity. Chemotherapy or radiotherapy alone appears to be ineffective, while relatively good results can be obtained with combination modalities.

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Although primary non-Hodgkin's hepatic lymphoma (PHL) is rather uncommon, it is an accepted entity with 77 unequivocal cases being described in the literature from 1965 (1–31).

In this article a further case of PHL is reported and the literature is reviewed, with particular attention to the natural history of the disease.

CASE REPORT

A 38-year-old Caucasian male presented in 1986 complaining of upper abdominal pain, fatigue, and generalized itching. A 12.5 × 12 × 10-cm liver mass was detected by abdominal ultrasonography and the patient underwent laparotomy with needle core biopsy. A histological diagnosis of inflammatory pseudotumour was made and no further therapy was deemed necessary.

Follow-up ultrasound scans showed no enlargement of the mass until 1990, when a sudden increase in size of the lesion was detected. The patient was referred to our Institution for further evaluation. At this time the patient was again complaining of excruciating pain in the upper right abdominal quadrant, fatigue, weakness, oedema of the lower extremities, itching and loss of weight. On examination, a large mass was felt in the right upper abdominal quadrant and mesogastrium. Abnormal laboratory values included ALT 160 u/l and total bilirubin 2.6 mg/dl. Serologic tests for cytomegalovirus, Epstein-Barr virus and

HIV-1 were all negative. A CT scan confirmed the presence of a hypodense, heterogeneous mass involving almost completely the right lobe and segment 4, with focal, small, central calcifications. The spleen was mildly enlarged and no other extrahepatic masses or adenopathy were found. A CT-guided biopsy of the hepatic mass yielded only necrotic tissue. Selective arteriography of the coeliac axis and an inferior vena cavogram showed extrinsic compression of the right hepatic artery branches and stretching of the retrohepatic vena cava, respectively. On exploratory laparotomy no other intra-abdominal pathology was found and the tumour was removed by an extended right lobectomy. The resected right lobe of the liver weighed 5200 g and measured 15 × 15 × 27 cm. Almost the entire specimen was replaced by a yellow-white, lobulated, firm tumour, with central calcification (Fig. 1). A thin rim of residual hepatic parenchyma surrounded the tumour. Lymph nodes from the porta hepatis appeared normal. The tumour approached the resection margin, but there was no capsular invasion. Microscopically, the tumour was composed of diffuse sheets of loosely aggregated, large malignant cells with pleomorphic nuclei, containing prominent eosinophilic nucleoli. Cytoplasm was generally scanty. Scattered large, bizarre tumour giant cells with polylobated vesicular nuclei and multiple eosinophilic nucleoli were also observed. There were extensive areas of necrosis throughout. Immunoperoxidase studies revealed

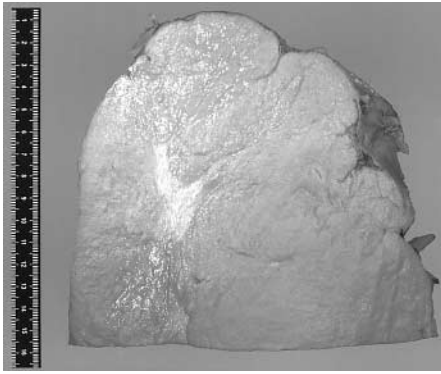


Fig. 1. Gross appearance of the resected right lobe of the liver. Hepatic parenchyma is almost totally replaced by a firm whitish tumour with central calcification.

strong tumour cell reactivity for leukocyte common antigen and B-cell markers (4KB5, L26). Tumour cells did not stain with pancytokeratin, histiocyte (3MA) and T-cell (UCHL-1) markers. The histological features were those of a diffuse, large cell, polymorphous B-cell lymphoma. No lymphoma was found in a subsequent bone marrow biopsy.

Four months after discharge the patient developed a biopsy-proven local recurrence of lymphoma. On CT scan the mass was found to have invaded the right kidney and renal artery and the inferior vena cava. In spite of multiple courses of chemotherapy, the patient developed bone metastases and died 17 months after surgery.

DISCUSSION

The first unequivocal case of PHL was reported by Ata & Kamel in 1965 (3). To date, 77 cases, including the present case, have been described (1–31); other 26 articles in the literature report tumours that also involved adjacent organs, regional lymph nodes or the bone marrow, so that their origin from the liver could not be established with certainty. PHL is, therefore, a rare disease if only tumours confined to the liver at initial presentation are considered. In 1986, Caccamo et al. (7) proposed strict criteria to define PHL. According to these authors, the disease should be confined to the liver on necroscopy or, in a clinical

setting, it should be proven with a biopsy. No palpable superficial lymphadenopathy or splenomegaly should be present. Normal thoracic CT scans, normal bone marrow, and blood counts should be recorded for at least six months after the time the biopsy is performed. The case herein presented appears to fulfil all of these criteria.

The clinical presentation of PHL, as extrapolated from the articles in the literature, is fairly uniform. Sixty-three of the reported patients were Caucasian (81%), and 14 were Chinese (19%), with a slight prevalence of the male gender (69%). The ages at diagnosis ranged from 8 to 78 years (mean 48 years). The most frequent initial complaints were right upper abdominal or epigastric pain (43%) and loss of weight (35%). Fever was also common (22%), most often without night sweat. Other symptoms included anorexia, nausea, vomiting, astenia and itching. The duration of symptoms ranged from one week to one year (mean 3.5 months), with the exception of our patient whose hepatic inflammatory pseudotumour was diagnosed 4.5 years before the actual development of PHL. The right hepatic lobe was invaded in 34.6% of the cases and both lobes were invaded in 62%; the lesion usually presented as a discrete, large solitary mass (71.2%); multiple white nodules, occasionally confluent and variable in size, were also common (25%). Less frequently (3.8%) diffuse hepatomegaly was observed, a pattern of infiltration more common to Hodgkin’s disease. Grading of lymphomas, according to the Working Formulation for Clinical Usage, was: intermediate grade in 51.9% of cases, high grade in 29.8% of cases and low grade in 10.3% of cases. In four instances the histology of the tumour was not reported, and in the other two old cases the tumour was classified as reticulum cell sarcoma (Table 1). When tested, the immunophenotype was B, with the only exceptions of two T-cell lymphomas (13, 22).

The observation of Kim et al. (12) that ‘small nodular deposits in extranodal lymphomas are associated with the well-differentiated lymphomas and a better prognosis, whereas the massive pattern of the less well-differentiated lymphomas has the same poor outlook as metastatic carcinoma’, could not be confirmed from our review of PHL. Although most of the massive PHL were of intermediate (69.5%) or high (25%) grade, nodular lymphomas were equally distributed among the three grades of severity.

Table 1

Classification of all reported PHL cases according to the Working Formulation for Clinical Usage

Low grade	n	Intermediate grade	n	High grade	n
Nodular small cleaved	6	Nodular large	1	Diffuse immunoblastic	6
Small lymphocytic	1	Diffuse small cleaved	1	Diffuse polymorphous large	16
Nodular small non-cleaved	1	Diffuse mixed small and large	4	Lymphoblastic	1
		Diffuse large	34		
Total	8		40		23

Histology not stated: 6 patients. Two further cases classified as reticulum cell sarcoma.

Furthermore, 50% of the low-grade PHL were of the massive type.

Associated diseases involving depression or chronic stimulation of the immune system were present in 32 patients, but no concomitant pathology was evidenced in the remaining 45 cases (Table 2). Therefore, the roles of immune disturbances in the development of PHL still await clarification.

Diagnosis was made on autopsy in the 11 oldest cases, while recent cases were usually diagnosed from the resected specimen or a biopsy, either percutaneous or taken at laparoscopy. Fine-needle aspiration biopsy has occasionally been employed (5, 16).

Initial treatment for PHL consisted of surgery, chemotherapy or radiation therapy alone, or combinations of these modalities. Withdrawal from Cyclosporine A (CyA) therapy was used for two grafted patients, but no information is given on their outcome (10). The longest mean period of disease-free (NED = no evidence of disease) survival was obtained with surgery alone (54 months in 72% of patients treated with partial hepatectomy). With the addition of chemotherapy, the percentage of NED patients was 77% after an average follow-up period of 44 months. The highest percentage of relapses was observed with chemotherapy alone (19% of 21 patients), after a mean period of 24.7 months. The only patient treated with radiotherapy alone died of the primary disease after 3 months.

Table 2

PHL and associated diseases

References	Patients (n)	Disease
25	1	Chronic hepatitis C
6, 7, 21, 23	6	AIDS
10	2	Cyclosporine A therapy in allograft recipients
8	1	Paraproteinemia
3, 16	2	Cirrhosis
31	1	Autoimmune haemolytic anaemia + SLE
11	1	Gallbladder stones
11	1	Liver abscess
4	1	HBV + HCV + HIV infection
14, 15	2	Hepatitis C and cirrhosis
13, 24, 28	7	Hepatitis B
30	1	Active tuberculosis
1	1	Immune thrombocytopenic purpura
20	1	EBV infection
24	2	Other neoplasms
29	1	Hepatocellular carcinoma + post-hepatic HBV cirrhosis
9	1	Treated malaria

SLE = systemic lupus erythematosus; HBV = Hepatitis B virus; HCV = Hepatitis C virus; HIV = Human immunodeficiency virus; EBV = Epstein-Barr virus.

Considering the relatively favourable results obtained with the combination of surgery and chemotherapy, the fatal outcome of our patient is frustrating. However, it must be noted that his hepatic disease was rather advanced when he underwent surgery and the tumour was found close to the resection line. The average greatest size of the hepatic masses in the 13 cases of the literature treated by combination of surgery and chemotherapy was 12 cm, compared to the 15 cm of the present case.

In conclusion, PHL is still an uncommon disease; however, comparatively more case reports have recently appeared in the literature (56 out of 77 after 1985). This may be due to an increasing awareness of this condition, rather than to its higher incidence. Treatment modalities have so far been tentative and further examination of similar cases is required to establish the best therapy.

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