

Primary hepatic anaplastic large cell ki-1 lymphoma and celiac disease: a casual association?

Montiel Jiménez Fuertes¹, David Costa Navarro¹, Eva M^a Montalvá Orón², Rafael López-Andújar², Manuel de Juan Burgueño², José Mir Pallardó²

¹General and Digestive Surgery, Marina Baixa Hospital, Alicante, Spain; ²Hepatobiliopancreatic Surgery Unit, La Fe University Hospital, Valencia, Spain
Corresponding to: Montiel Jiménez Fuertes, MD. C. Convento Jerusalem 57, 17. Valencia, CP 46007, Spain. Email: montieljf@hotmail.com.



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Introduction

Although liver is one of the extranodal organs commonly involved in both Hodgkin and non-Hodgkin lymphoma, Primary Hepatic Lymphoma (PHL) is rare.

In non-immunocompromised patients, primary hepatic malignant non-hodgkin's lymphoma is a rare disease, with less than 100 cases reported (1).

Anaplastic large-cell lymphomas (ALCL) were first described by Stein *et al.* in 1985 (2) as large-cell neoplasms with a pleomorphic appearance, subtotal effacement of the lymph node structure and expression of the lymphoid activation antigen CD-30 (ki-1). ALCL frequently involves both lymph nodes and extranodal sites (3). The most common extra-nodal sites affected by ALCL include skin, bone, soft tissue, lung, and liver. However, is extremely rare for ALCL to present as a liver primary lymphoma, and only eight cases have been reported.

ALCL accounts for approximately 3% of adult non-Hodgkin lymphomas. The neoplastic cells consistently express CD30 molecule in all variants. 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.

We report a case of a primary hepatic anaplastic large T-cell ki-1 non-Hodgkin lymphoma in a 55-year-old patient with celiac disease.

Case report

A 55 year old man followed during one year because of adult celiac disease was hospitalized due to fever, right upper quadrant abdominal pain and itch. The patient had no complaints of weight loss or night sweats.

Physical examination was normal. Laboratory results were normal, apart from an increase in liver function tests.

Carcinoembryonic antigen (CEA) level and alpha feto protein (AFP) level were normal.

Epstein-Barr virus, hepatitis viruses and human immunodeficiency virus serologies were negative.

Abdominal ultrasound (*Figure 1*) and CT scan (*Figure 2*) showed an enlarged liver with a single mass in the right lobe (8.4 cm × 7.3 cm). No adenopathy was detected in the abdominal cavity, and there was a normal size and appearance spleen.

Percutaneous liver biopsy led the diagnosis of adenocarcinoma without differentiation.

Total body CT scan, PET-Scan (*Figure 3*), gastroscopy, colonoscopy and iliac crest bone marrow biopsy suggested a localized primary liver mass.

Because of the favourable anatomic location of the tumor and the absence of metastatic disease, a right hepatectomy was performed. The abdominal exploration revealed no evidence of extrahepatic tumor or adenopathy.

The postoperative course was favourable, and he was discharged from hospital on the 7th postoperative day.

The surgical specimen consisted of a right hepatic lobe of 1,500 g weight, with a neoplasm of 11 cm in segments 7 and 8. The tumor appearance was white, soft and homogeneous, without focal necrosis nor hemorrhage. It was well circumscribed and lobulated, and appeared to be completely within the limits of resection.

Microscopically, a population of lymphoid cells of large size with many mitotic figures was identified. The large neoplastic lymphoid cells immunostained positively for CD-30 (Ki-1), CD-3, ALC and CD-45, with an index of proliferation Ki 67 +++ (80%). The CD-20, CD-79a, CD-8, CD-4, CD-15, S-100, HMB45, AE1-3, CAM 5.2, actin/desmin tests were negative.

Therefore, the diagnosis of non-Hodgkin lymphoma, large-cell anaplastic type, Ki-1 lymphoma was given.

Postoperatively, the patient received systemic chemotherapy

with cyclophosphamide, vincristine, doxorubicin and prednisolone (CHOP) for four courses.

Twenty months after surgery the patient is disease free.

Discussion

Non-Hodgkin lymphoma is a common lympho-proliferative disease. Liver involvement occurs in 10% of the patients and it means advanced disease (stage 4).

The first report of primary hepatic lymphoma was by Ata and Kamal in 1965 (4). Primary hepatic lymphomas (PHL) are rare, with fewer than 100 cases reported in the world literature. PHL defines an extra-nodal lymphoma of the liver without involvement of any other organ. PHL is rare, representing <1% of all extra nodal lymphomas (5).

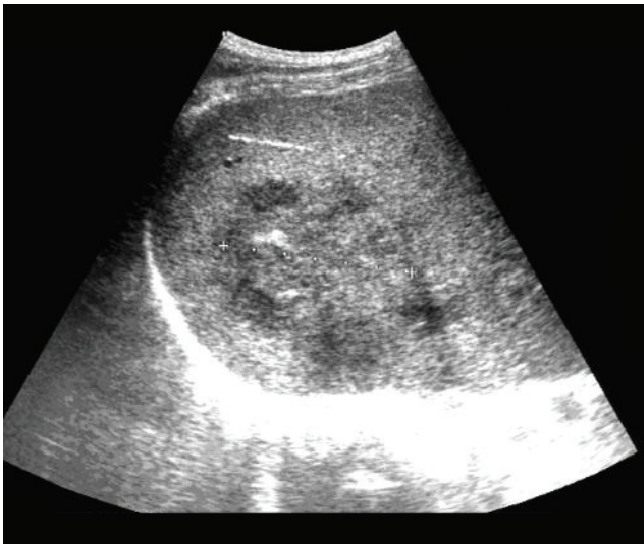


Figure 1 Abdominal US scan: large single mass in the right lobe, without splenomegaly and lymphadenopathies

Most cases of PHL tend to be of B-cell origin with only a minority of them of T-cell origin (6-11). The occurrence of primary hepatic anaplastic large cell lymphoma is extremely rare. In our review of the literature, we identified only eight other cases of primary hepatic ALCL (12-16) (Table 1).

The ALCL are a clinically heterogeneous group of T, B and indeterminate cell malignant lymphomas. In the general population, ALCL has T-cell phenotype in 50-70% of cases, and the remainders are mostly null (non-T, non-B) phenotype. Rare cases of ALCL with B-cell phenotype are currently separated from T-cell or null-cell ACLC.

ALCL is a subgroup of diffuse large-cell lymphoma with characteristic morphology and strong expression of CD-30 (Ki-1) antigen. The Ki-1 antibody is a monoclonal antibody against the Hodgkin cell line L428, and at first it was regarded as an antibody specific for Hodgkin and Reed-Sternberg cells of Hodgkin disease. However, the Ki-1 antigen was also discovered later in patients with diffuse large cell-type non-Hodgkin lymphoma. The most frequently involved extranodal sites are skin, bone, soft tissue, GI tract and lung (6).

Most patients with PHL are middle-aged. Patients usually present with abdominal pain and constitutional symptoms. Hepatomegaly is found in the majority of patients (75-100%) and B symptoms (fever, drenching sweats and weight loss) appear in 37-86% of them (7). Less common presentations include ascites, hepatic failure, thrombocytopenia and hypercalcaemia.

PHL may present as a solitary liver mass (42%) or as multiple lesions (50%); diffuse infiltration of the liver is rare in Caucasians and more common in Chinese patients, but the pattern of the liver infiltration has no prognostic value (8).

The pathogenesis of PHL has not been established. An increasing number of cases are now being diagnosed in

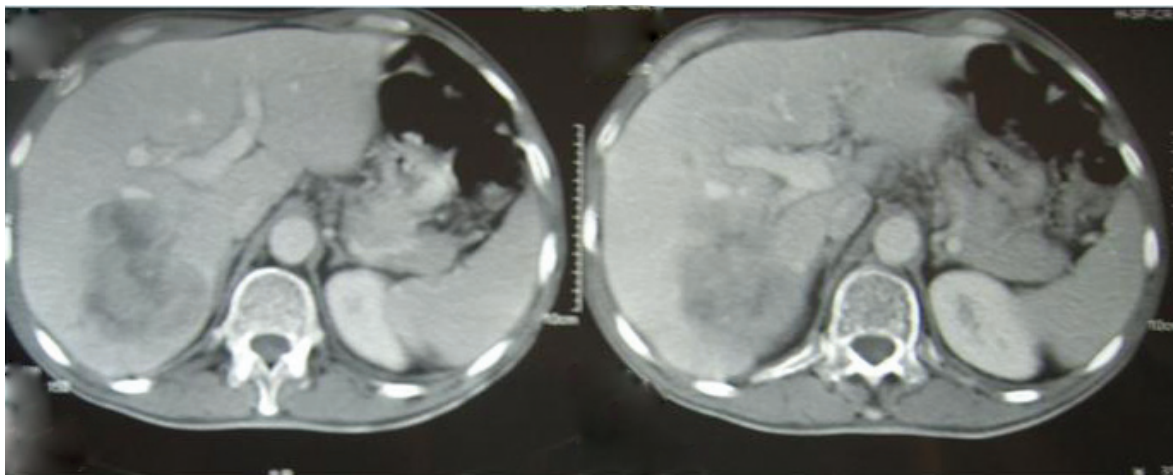


Figure 2 Abdominal CT scan: large single mass in the right lobe, without splenomegaly and lymphadenopathies

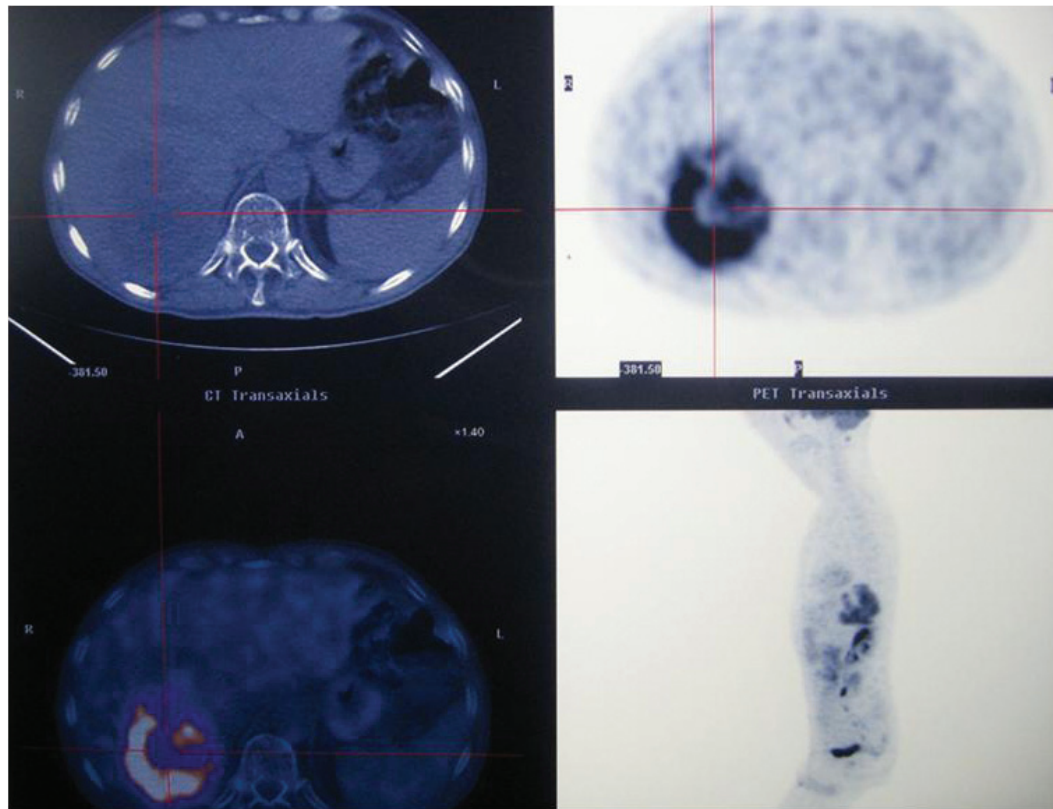


Figure 3 PET-Scan revealing only the tumor of the right liver

Table 1 Clinical features of primary hepatic ALCL

Case	Age	Sex	HIV status	B symptoms	Hepatic mass
Chadburn 1993	34	M	+	present	multiple
Lei 1995	51	F	?	fever	solitary
Baschinsky 2001	33	M	+	none	multiple
Andrés 2003	60	M	-	present	multiple
Bronowicki 2003	45	F	-	none	multiple
Cai 2005	43	M	+	present	multiple
Saikia 2010-1	38	M	-	fever	multiple
Saikia 2010-2	30	F	-	fever	multiple
Our case	55	M	-	none	solitary

immuno-compromised patients, particularly patients with Human Immunodeficiency Virus. There is an association with hepatitis C (Hepatitis C infection is found in 60% of patients), which suggests that this virus may play a role in the pathogenesis of PHL, Epstein-Barr virus infection, immuno-suppression, organ transplantation, primary biliary cirrhosis and systemic lupus erythematosus.

Our patient neither virus infection nor signs of chronic liver disease were found.

Diagnosis of PHL requires the absence of lymphoproliferative disease outside the liver.

Liver biopsy of PHL may mimic poorly differentiated

carcinoma, and in these cases, a high index of suspicion is needed. In our patient, liver biopsy did not confirm the diagnosis, and only the study of the surgical specimen gave the diagnosis of PHL.

Immuno-histochemical studies are required in order to distinguish between these tumours and poorly differentiated carcinomas. Sometimes further tests including cytogenetic studies, flow cytometry and gene rearrangement are necessary. However, detection of lymphomas by cytometry analysis is dependent of adequate sampling of the tissue, specimen viability and the ability of tumor cells to survive processing, and false negative results are common in large

cell lymphomas (25% of large cell lymphomas are not detected by cytometry analysis). The main advantage of cytometry over immunohistochemical analysis in the initial diagnosis is speed, and may be helpful when the material for immunohistochemical analysis is not available, such as in the case of fine-needle aspiration (9).

ALCL is a T-cell lymphoma immunophenotypically characterized by positive CD30 staining in a membranous and Golgi zone pattern. Approximately 60-85% ALCL cases are positive for ALK protein. The translocation [2;5] between the ALK gene on chromosome 5 is the most common cytogenetic abnormality that leads to upregulation of ALK protein. The majority of ALC cases will show one or more T-cell-associated antigens. However, there are cases of ALCL that are negative for all T-cell markers and they are known as null-cell type.

The optimal treatment is not yet defined due to the low incidence of this disease. Surgery, radiotherapy and chemotherapy were all reported as treatment modalities alone or in combination (11). Only 17 patients, including our case, have been surgically treated. The importance of surgical resection for a cure or for a reduction of tumor burden cannot be assessed by this limited series. Whether or not systemic treatment with chemotherapy will give comparable results to surgery in resectable cases is also not currently known. Pescovitz *et al.* (10) noted that the disease-free survival rate for 5 patients treated with resection and combined chemotherapy was 80%, compared with 54% survival for chemotherapy alone. But Page *et al.* (7) reported complete remission in 83.3% of 24 cases evaluated with combination chemotherapy. Five year cause specific and failure free survival rates were 87.1% and 70.1% respectively. Outcomes are poorer in patients with AIDS, and in those with coexisting liver disease.

Currently, the most common treatment of PHL involves combination chemotherapy CHOP. Rituximab, an anti CD 20 monoclonal antibody, is added to this chemotherapy regimen if the histology confirms that the lymphoma is CD 20 antigen positive.

Massive liver infiltration, high index of proliferation, advanced age, elevated LDH levels, cirrhosis and increased levels of β 2-microglobulin are the worst prognosis factors (12).

This is, to our knowledge, the first reported case of primary hepatic anaplastic large cell Ki-1 non-hodgkin lymphoma in a setting of adult celiac disease. The only link between both diseases is a markedly increased incidence of gastrointestinal T-cell lymphoma in celiac disease.

In conclusion, PHL is a rare disease, but it should be considered in any patient at any age who presents liver mass or infiltration, and, although hepatoma or metastatic diseases are more common, the absence of elevated levels of

CEA and AFP should indicate a search for PHL.

Our patient had none of the classic predisposing factors for hepatic lymphocytic proliferation, such as chronic viral hepatitis, HIV, EBV or autoimmune hepatic disease.

However, other mechanisms for the development of NHL in celiac disease may be implicated. It is also possible that this may be an entirely fortuitous association.

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