Clonazepam is the first line treatment, having complete or partial success in 87% of patients. Amitriptyline, triazolam and clozapine have also been used.

The complete response to clonazepam in association with vivid and violent dreams meant that the differentials of sleep-walking, sleep terrors, nocturnal epilepsy and obstructive sleep apnoea were not pursued, though response to nocturnal epilepsy might also have occurred with clonazepam.

In patients with falls at night, particularly where there is co-existent neurological disease, direct questioning about vivid dreams should be undertaken and a description of violent attacks obtained from partner or spouse.

References

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its left lobe could be palpated 8 cm below the costal margin, there was no ascites nor signs of cirrhosis. Her spleen and lymph nodes were not enlarged. Laboratory results were normal apart from an erythrocyte sedimentation rate (ESR) of 89/mm (normal 1–20), mild anemia (Hb 11.6 g%, mean corpuscular volume 84), and elevated liver function tests: bilirubin 2.3 mg/dl (normal 0.3–1.1); aminotransferases: AST 89 u/l (normal <35), ALT 80 u/l (normal <35); lactate dehydrogenase (LDH) was mildly elevated: 923 u/l (normal 100–458); alkaline phosphatase 464 u/l (normal 38–126); and gamma glutamyl transferase (GGT) 1089 u/l (normal 7–50). Her calcium levels were normal. Serology tests for hepatitis A, B and C were negative, carcinoembryonic antigen (CEA) level was 1.8 mg/ml (normal <5), and alpha feto protein (AFP) was 2.3 ng/ml (normal <9). Immunoglobulin levels were normal without any monoclonal peak in the blood or urine.

Abdominal ultrasound and computed tomography (CT) scan revealed an enlarged liver with a huge single mass in its left lobe (Figure 1). There was no evidence of biliary or pancreatic disease, splenomegaly or abdominal lymphadenopathy. Chest X-ray and CT scan demonstrated normal-sized heart and normal lungs, with no enlargement of mediastinal lymph nodes. Gastroscopy showed normal upper GI tract with normal mucosa on biopsies; barium enema did not reveal any filling defects. Bone marrow biopsy demonstrated mild hypercellularity with normal maturation of all cell lines. There was no malignant infiltration nor B cell clonality determined by negative stains for CD20, therefore PCR, Fish or flow cytometry were not done. A core liver biopsy was performed, showing heavy infiltration composed mainly of large lymphoid cells. The cells were positive for CD20 and LCA, establishing a diagnosis of diffuse large B-cell lymphoma, according to the WHO classification. Proliferation index was very high with ki67 positive in 80% of the cells. Since there were no other foci of lymphoma the patient was diagnosed as suffering from extra-nodal lymphoma that originated in the liver.

Despite her age and after discussing treatment options and the risks of chemotherapy with the patient and her family, four courses of attenuated chemotherapy (miniCHOP): 5 days of cyclophosphamide 800 mg, adriamycin 30 mg and prednisone 60 mg were given (vincristine was not given due to the patient’s age). The courses were given every 2–3 weeks. Later the patient received three more courses with the addition of etoposide 100 mg per course (modified Pro-Mace).

There were no major complications during the treatment period (5 months) with the exception of a urinary tract infection treated with per-os antibiotic, which did not delay the administration of chemotherapy. The chemotherapy was given in an outpatient clinic. No blood transfusions or Neupogen were given. Within 4 months all liver function tests normalized, the tumour could not be palpated or visualized by ultrasound or CT, the patient’s condition improved, with resolution of the fever, nausea, lethargy and abdominal pain. The patient has been followed up for 2 years with no evidence for recurrence of the disease.

Discussion

Non-Hodgkin’s lymphoma is a common lympho-proliferative disease; liver involvement occurs in 10% of patients and defines advanced disease (stage 4).

Primary hepatic lymphoma (PHL) defines an extra-nodal lymphoma of the liver without involvement of any other organ (lymph node, spleen, etc). PHL is notably rare, representing <1% of all extra nodal lymphomas [1, 2]. The vast majority (67%) of PHL patients are middle-aged men (median age 50 years) that usually present with abdominal pain, nausea and constitutional symptoms [2]. Hepatomegaly is found in most patients (75–100%), B symptoms (fever, drenching sweats and weight loss) appear in 37–86%, weight loss in 57% and jaundice in 4% [1, 3]. PHL may present as a solitary liver mass (42%) or as multiple lesions (50%); diffuse infiltration of the liver is rare in Caucasians (8%) and more common in Chinese patients with PHL. The pattern of liver infiltration is not of prognostic value [1, 3, 4]. Patients with PHL have elevated liver function tests, mostly LDH and alkaline phosphatase, [3, 5]. Hypercalcaemia is found in 40% of the patients, for a reason yet unknown. Excess production of calcitriol by the malignant lymphoma cells is considered a possible cause [5–7].

Hepatitis C infection is found in 20–60% of patients with PHL. The frequent association with hepatitis C virus (HCV) suggests that this virus may play a role in the pathogenesis of PHL. Nevertheless the presence of HCV does not influence the response to chemotherapy or the patient’s outcome, unless liver disease is advanced [3, 8]. Our patient had neither HCV infection nor signs of chronic liver disease.

Diagnosis of PHL requires a liver biopsy compatible with lymphoma and the absence of lympho-proliferative disease outside the liver [3, 6]. A definite diagnosis of PHL is difficult to establish on clinical grounds. Hepatoma and metastasis from gastro-intestinal (mostly colon) carcinoma...
Present very similarly and are much more common. Normal levels of the tumour markers AFP and CEA are found in almost 100% of patients with PHL facilitating the differential diagnosis [1, 3]. However, examination of the colon to exclude primary colon carcinoma may be indicated. The predominant histology of PHL is diffuse large B-cell lymphoma (DLCL) [2–3], as was the case for our patient; a few cases of small lymphocytic [3], histiocytic, follicular [1, 9] T-cell [3, 10] and others were also described. Liver biopsy of PHL may mimic poorly differentiated carcinoma, especially when tissue is obtained by core needle biopsy; in these cases a high index of suspicion, immuno-histochemical typing and flow-cytometric studies are needed. In some cases a surgical biopsy might be required [6]. Our patient presented with clinical and laboratory features which were suggestive for PHL. Liver biopsy with specific immuno-histochemistry confirmed the diagnosis of primary hepatic lymphoma.

The optimal treatment of PHL is not yet defined. Surgical treatment, radiotherapy and chemotherapy were all reported as treatment modalities alone or in combination [10–15]. The prognosis of PHL was considered very poor with median survival as low as 6 months for patients treated with chemotherapy alone, and longer for patients treated with a combination of modalities [16, 17]. Massive liver infiltration, high index of proliferation, advanced age and elevated LDH levels, that were all present in our patient, as well as cirrhosis and elevated levels of β2-microglobulin are worse prognostic factors [3, 5]. Chemotherapy protocols for the treatment of lymphomas have changed in the last decade to multi-drug regimens such as CHOP, alternating triple combination therapy (ATT), IMVP-16, OAP (that include etoposide, cytosine arabinoside and others) [1, 3, 9]. Multi-drug protocols improve survival significantly for patients with PHL, and at least in one report almost 100% of patients reached complete remission and 83% reached 5 years survival with ATT chemotherapy [3]. Thus, the new aggressive multi-agent chemotherapy without the addition of surgery or radiation is probably the recommended optimal therapy [3]. Rituximab, a monoclonal chimeric antibody directed against CD20 B cell antigen, is now recommended as first line therapy together with CHOP for diffuse large cell lymphoma in the elderly. The addition of Rituximab to the CHOP regimen increased the complete-response rate and prolonged survival without an increase in toxicity (GELA study [18]). Unfortunately at the time our patient was treated Rituximab was approved in Israel only for relapsing indolent lymphoma.

In conclusion PHL, though a rare disease, should be considered in any patient at any age who presents with liver mass or infiltration. Although hepatoma or metastatic diseases are more common, the presence of B symptoms, and the absence of elevated levels of CEA and AFP should indicate a search for the presence of PHL. Establishing the diagnosis of PHL, even in elderly patients, is worthwhile, as it seems that the new multi-agent attenuated chemotherapy and the addition of Rituximab may offer an appropriate treatment with a very good response. The decision to treat an elderly patient is always difficult, and requires consideration of the patient’s performance status, general medical condition, the extent of the lympho-proliferative disease and the treatment options. Therefore this decision should always be made on an individual basis.

Key points

- PHL, though a rare disease, must be considered in any patient with liver mass or liver infiltration, especially if CEA and AFP levels are normal.
- High index of suspicion and special processing of the liver biopsy are needed for diagnosis.
- PHL is a treatable disease; best treatment is not defined but multi-agent chemotherapy seems to be an appropriate single therapy in many cases, as well as in elderly patients.
- The prognosis of patients with PHL is probably better than previously reported.

References


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