Primary hepatic lymphoma – favorable outcome with chemotherapy plus rituximab


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ABSTRACT

This article describes the case of a patient with a non-Hodgkin primary hepatic lymphoma who was successfully treated with chemotherapy combined with rituximab. Using the Medical Subject Headings the published reports of this rare entity were reviewed.

Key words: Primary hepatic lymphoma. Non-Hodgkin’s lymphomas. Rituximab.

RESUMEN

Comunicamos el caso de una paciente con un linfoma hepático primario tratado con éxito con quimioterapia combinada con rituximab. Utilizando los “encabezamientos estándar para búsquedas bibliográficas informatizadas” (Medical Subject Heading) revisamos los casos publicados hasta la fecha de esta infrecuente entidad.

Palabras clave: Linfoma primitivo de hígado. Linfomas no hodgkinianos. Rituximab.

INTRODUCTION

Primary hepatic lymphoma is a rare entity with non-specific clinical features that must be considered in the differential diagnosis of space-occupying lesions in the liver. Based on the review by Noronha et al. in 2005 (1), in which 251 cases reported until February 2003 were described, we made a research of all relevant cases of lymphoma and liver neoplasm published until July 2007 on Medline.

Because of its rarity and interest, we reviewed the characteristics of this entity based on the case of a patient who was hospitalized because of general malaise and alleged liver metastases on computerized tomography scans.

CASE REPORT

A 68 year-old woman with no relevant past medical history or toxic habits was admitted because of a one-month-long history of abdominal pain in the right upper quadrant, weakness, anorexia, and five-kilogram weight loss over the preceding month. She had no fever, respiratory, or digestive symptoms in the previous weeks.

Physical examination

General malaise; eupnea; normal color; no palpable goiter or nodules, and no laterocervical, supraclavicular or axillary adenopathies. Temperature was 37.0 °C, blood pressure was 130/90 mmHg, and cardiopulmonary auscultation was normal. Abdominal examination: firm and tender liver on palpation, 3 cm under right costal margin and 5 cm under the xiphoid process, crossing the midline; the spleen was not enlarged, and the extremities had no abnormalities.
Complementary examination

Blood test: hemoglobin 12 g/dl (normal range: 12-16); Hct 36% (36-48); mean corpuscular volume 86 µm³ (80-100); white blood cell count 7800/mm³; platelets: 228,000/mm³. Prothrombin time 12 seconds (11.5-13.5); kaolin cephalin clotting time 27 s (25-34 s); fibrinogen 506 mg/dl (200-400). Glucose 103 mg/dl (70-105); creatinine 0.79 mg/dl (0.7-1.10); AST 115 U/L (5-45); ALT 126 U/L (5-45); LDH 860 U/L (90-230); GGT 111 U/L (3-52); bilirubin 0.98 mg/dl (0.2-1.0); ALP 393 U/L (98-295); protein 6.2 g/dl (6.3-8.0); albumin 3.46 g/dl (3.2-5.5); and normal electrophoretic spectrum; calcium 9.6 mg/dl (8.4-10.2); phosphorous 3.4 mg/dl (2.3-4.6); uric acid 5 mg/dl (2.2-7.0); cholesterol 159 mg/dl (150-200); triglycerides 65 mg/dl (50-170); sodium 141 mEq/L; potassium 4.3 mEq/L (3.5-5.2); blood iron 45 µg/dl (60-120); ferritin 282 ng/ml (30-400); transferrin 185 ng/ml (200-360). Tumor markers: CA 15.3: 12 IU/ml (normal < 30); CA 54.9: 3 IU/ml (< 12); CA 125: 5 IU/ml (< 35); CA 19.9: 8 IU/ml (< 37); carcinoembryonic antigen (CEA): 3 UI/ml (< 5), and trypsin: 180 ng/ml (140-400); β₂-microglobulin: 4.2 mg/L (1.2-2.8). Serological tests for hepatitis B and C virus and HIV were negative. ECG: normal. Imaging: chest X-rays were normal; abdominal X-rays showed hepatomegaly; abdominal ultrasonography showed multiple solid lesions, about 1 to 3 cm, in the liver, suggestive of metastases; abdominal CT showed multiple solid hypodense lesions, 1-3 cm in size, occupying almost the whole liver, and there were no lymphadenopathies (Fig. 1). Colonoscopy was normal. A needle biopsy from one of the liver lesions was obtained under CT guidance; the histological analysis showed non-Hodgkin lymphoma. Liver biopsy confirmed a diffuse large B-cell lymphoma (Fig. 2). Immunostaining of tumoral cells demonstrated atypical cells with B phenotype (CD20 and CD79α positive); with reactivity for CD10 and bcl 6, but not for CD3, CD43, bcl 2 and keratins AE1-AE3 (Fig. 3). Tuberculosis skin test (Mantoux): 9 mm. The patient underwent a bone marrow biopsy, which was unrevealing. Polyclonality for the CD1 region of the IgH gene was found in the chromosomal analysis. The cerebrospinal fluid showed no pathological findings, and a head CT scan was normal. 67 Ga scintigraphy: normal.

Evolution

During admission the patient’s biochemical findings worsened, reaching the following values: bilirubin 2.8
mg/dl; AST 196 U/L, ALT 109 U/L, ALP 878 U/L, GGT 911 U/L and LDH 3,973 U/L.

She was treated with intravenous fluid therapy, prednisone, and low daily doses of cyclophosphamide (as prephase), together with antituberculous chemoprophylaxis with isoniazide. Six days after this treatment and with normalized bilirubin she received a first cycle of R-CHOP chemotherapy (rituximab 375 mg/m²; cyclophosphamide 750 mg/m²; doxorubicin 50 mg/m²; vincristine 1.4 mg/m² and prednisone 100 mg/day, for 5 days), plus triple intratecal chemotherapy and support with GM-CSF. Treatment was well tolerated by the patient, and at the end of the first course she showed the following biochemical values: bilirubin 1.3 mg/dl; GGT 337 U/l; LDH 397 U/l, and normal aminotransferases.

Because of the initially elevated International Prognostic Index (IPI), she received a second course of chemotherapy three weeks later with R-MegaCHOP (rituximab 360 mg/m², cyclophosphamide 1,500 mg/m², Adriamycin 65 mg/m², vincristine 1.4 mg/m² and prednisone 100 mg/day, for five days). Intratecal chemotherapy was again associated on this occasion, and was well tolerated.

After hospital discharge she received four more courses of chemotherapy according to the R-MegaCHOP protocol. However, after the third one she was readmitted to hospital because of neutropenic fever (leukocytes: 1,560/mm³ -1440 N, 90 L, 30 M-) and upper airway infection symptoms. We isolated RSV from her nasal exudate. She was successfully treated with inhaled ribavirin, and discharged in the seventh day after admission with the following white cell count: 2,490 leukocytes/mm³ (1490 N, 460L, 400M, 140E).

After six courses of chemotherapy, liver function tests and β₂ microglobulin were normal. Furthermore, on monitorization CT scans no lesions could be seen (Fig. 4). She achieved complete remission and for longer than two years remained stable and healthy with regular follow-up.

**DISCUSSION**

Malignant lesions found in the liver with imaging tests are not uncommon since the liver is, after lymph nodes, the most common tissue affected by metastasis. In most cases the primary neoplasm is known before the discovery of metastasis, or at least suspected from anamnesis and physical examination. In other cases there is a history of cirrhosis or B or C virus infection that suggests primary hepatocellular carcinoma. Finally, there are cases in which fine-needle aspiration or liver biopsy allows a primary hepatic lymphoma diagnosis (2,3).

We have described the case of a woman with no relevant past medical history who was admitted to hospital because of general malaise, painful hepatomegaly, abnormal liver function tests, and focal hepatic lesions on CT that histologically corresponded to diffuse large B-cell lymphoma.

A lymphoma is defined as a primary hepatic lymphoma (PHL) if symptoms are caused by liver involvement at presentation and there is no affectation of the spleen, lymph nodes, peripheral blood, bone marrow, or other tissues until at least six months after diagnosis. According to these stringent diagnostic criteria proposed by Caccamo (4), Li identified 90 cases between 1981 and 1993 (5), Noronha described 251 as published between 1981 and 2003, and we have found 17 more cases after 2003, most of them non-Hodgkin lymphomas (NHL) (6-12).

While the incidence of NHL has increased in the last three decades, and almost 30% appear as extranodal disease, with common liver involvement (16-26% of cases showed in the biopsy and around 56% in laparotomy), PHL is extremely unusual and represents 0.016% of all NHLs (1,13,14). An entity in itself are lymphoproliferative diseases in liver transplant recipients, with a prevalence of 2-4% in adults and up to 20% in children (15-17).

Although PHL can occur at any age, it is more frequently seen in the fifth decade of life, with a male/female ratio of 2-3/1 (1,5,10). The pathogenesis of PHL has not yet been well established, despite its association with several different disorders, including Epstein-Barr virus (EBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), liver cirrhosis, systemic lupus erythematos (SLE), and immunosuppressive therapy. Immunosuppressive states in general and viruses, particularly EBV, do have a significant role in PHL development (1,9,11,13,18-21). EBV induces a polyclonal proliferation of B cells, which in healthy individuals is limited by T cells. Since the regulatory function of T cells in immunosuppressed patients is deficient, B cells can proliferate and progress to lymphoma. HCV is a lymphotropic virus that produces a chronic stimulation of B cells with polyclonal and occasionally monoclonal expansion. As our patient had not suffered from any recent infec-

![Fig. 4. Computed tomography of the abdomen after six courses of chemotherapy. Hepatic lesions have dissapeared.](image-url)
tious disease, and serological tests were all negative, we could not establish a relationship between these viruses and PHL.

The most common symptoms of PHL at presentation are abdominal pain (39-70%) and general malaise, as in our case. However, it may present as low-grade fever, night sweats, and weight loss, more commonly known as B symptoms, or exceptionally as fulminant hepatic failure (1,4,8).

Liver function tests are abnormal in up to 70% of cases, LDH increases in 30-80%, and β2-microglobulin, a well-described prognostic marker, increases in 90% (1,5,18,22). A monoclonal paraprotein and hypercalcemia (almost always induced by calcitriol) have been described in a minority of cases (1,9,12,18,23).

Imaging tests show PHL as solitary lesions (39-60%), multifocal lesions (25-40%), or diffuse infiltration (1,18,21,25). Abdominal ultrasounds commonly reveal hypoechoic lesions, usually hypoechogenic in CT. Following the administration of an intravenous contrast, 50% of PHL lesions do not enhance, 33% show patchy enhancement, and 16% show a ring of enhancement. MRI findings in PHL are described as hypointense or isointense on T1-weighted images, and hyperintense on T2-weighted images (1,2,5,10,21,22,24,25).

Histologically, PHL can acquire three patterns: diffuse infiltrate of portal tracts (low-grade lymphoma); diffuse infiltrate along the sinusoid (hepatosplenic T-cell lymphoma); or nodular growth pattern in which lymphoma cells have a destructive growth pattern without detectable portal tracts (large cell lymphoma and high-grade lymphoma), which is the most frequent and the one observed in our case. Of the 121 cases described until 1997 an immunophenotype was obtained in 59-37 were B-cell, 15 T-cell, and 7 other types (1,19,21,22). Until 2005 only 16 mantle lymphomas were described, usually associated with primary biliary cirrhosis or infection by HBV and HCV (1,26,27).

As in other neoplasms, poor prognostic features include advanced age, constitutional symptoms, bulky disease, unfavorable histologic subtypes, elevated LDH and β2-microglobulin levels, high proliferation rate, cirrhosis, and comorbid conditions (1).

Treatment options for PHL include surgery, chemotherapy, radiation or varying combinations of these modalities. It has been suggested that, for low-volume localized PHL, surgical resection, alone or in combination with chemotherapy, might be a treatment option (1,5,22). But, as relapse after surgery is not unusual and PHL is chemosensitive, chemotherapy may be always employed. The study performed at the MD Anderson Cancer Center between 1974 and 1995 noted an overall complete remission rate of 83% and 5-year survival (17) results that were not corroborated by other groups (1,4,9).

Until 2001 the median survival for all patients was 15.3 months, but it varies depending on the pattern of liver involvement. Emile et al. observed that in patients with nodular hepatic involvement 1- and 3-year survival rates were 70 and 57%, respectively; but when the liver was diffusely involved, 1- and 3-year survival rates dropped to 38 and 18%, respectively (1,28).

The addition of rituximab to the treatment of B-cell non-Hodgkin lymphomas since 2002 has significantly increased complete responses, and patient survival (29,30). This chimeric monoclonal antibody, which binds to the cell surface CD20 antigen, has represented a new age in this field, and has led to revisit the International Prognostic Index (31). Rituximab is being experimentally used in the treatment of B-cell post-transplant lymphoproliferative disease, it is also an option as first-line monotherapy for follicular lymphoma, and added to CHOP therapy is recommended as the treatment of indolent, intermediate, and aggressive NHL (29-34). The development of humanized and radioimmunoconjugated derivatives of rituximab, and its possible association with other monoclonal antibodies, used alone or in combination with CHOP, will improve the prognosis of NHL resistant to current treatments.

In summary, although a rare entity, PHL should be considered in the differential diagnosis of space-occupying lesions in the liver. With a PHL diagnosis, our patient, who was admitted to hospital two years ago with the suspicion of liver metastasis from an unknown primary neoplasm, with a short-term poor prognosis, remains in complete remission and without symptoms after treatment with R-CHOP.

REFERENCES


