Primary Hepatic Marginal Zone Lymphoma in a Patient with Chronic Hepatitis C

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ABSTRACT

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) is a low-grade malignant lymphoma that appears frequently in the stomach, but other sites can also be involved: the intestinal tract, lungs, head, neck, skin, thyroid, breasts and liver. Recently, epidemiological evidences support the idea that there is an association between hepatitis C and B-cell non-Hodgkin lymphomas (that include MALT as a subtype).

Primary non-Hodgkin lymphomas confined only to the liver are very rare (only 0.016\% of all cases of all non-Hodgkin’s lymphomas) and MALT is not the most frequent type.

We present the case of a male patient, age 62, known with chronic hepatitis C, previously relapsed after a 72 week treatment with peg-interferon alfa and ribavirin that was diagnosed at three years after the relapse with multiple focal liver lesions. One of the tumors was surgically removed and the histological exam performed demonstrated an extranodal marginal zone lymphoma with small B-cell with plasmacytoid differentiation confined only to the liver. Direct acting antiviral (DAA) therapy was started, but the virologic clearance was not obtained by week 10, leading to a change of DAA regimen at week 12. The antiviral therapy was continued until week 24. Imaging showed an increase in number and size of the focal lesions until week 12. At week 12 chemo- and immune-therapy was started with bendamustine and rituximab. Afterwards the evolution was favorable, the patient being now in complete remission and with undetectable viral load.

Keywords: Liver lymphoma, C hepatitis, extranodal marginal zone lymphoma, liver tumor
BACKGROUND

Primary hepatic lymphomas (PHL) are rare tumors, accounting for less than 1% of malignant lymphomas (1,2). The most common histological type is diffuse large B cell lymphoma (2,3). Other types are: extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT), follicular lymphoma, Burkitt lymphoma or Hodgkin lymphoma (4, 5). Primary hepatic lymphoma is confined to the liver with no evidence of lymphomatous involvement of the spleen, lymph nodes, bone marrow, or other lymphoid structures (2, 6). The etiology of PHL is not clearly established, but chronic inflammation seems to be involved (2, 4). Hepatitis, cirrhosis and immunosuppressive drugs have been proposed as possible causes.

MALT is a low-grade malignant lymphoma that was first described by Isaacson and Wright in 1983 (7). The stomach is one of the commonest sites of MALT development, but other sites can also be involved: the intestinal tract, lungs, head, neck, skin, thyroid, breasts and liver. Primary non Hodgkin liver lymphomas are very rare (only 0.016% of all cases of all non-Hodgkin’s lymphomas) and MALT is not the most frequent type (2,6). There are epidemiological evidences (accumulated mostly in the last two decades) for the association of chronic C infection with B-cell non Hodgkin lymphoma (B-NHL), the most frequently associated histologic types being diffuse large B-cell lymphoma, marginal zone lymphoma and lymphoplasmocytic lymphoma (8-10).

CASE REPORT

Our patient was diagnosed in 2009, at the age of 57 years with chronic C hepatitis. At that time his RNA HCV was 22,400,000 IU/ml, ALT 221 IU/l, AST 106 IU/l. HCV genotype 1b was demonstrated. Ultrasound examination: no significant findings and not consistent with cirrhosis. Fibrotest® (Biopredictive, Paris) score was A3F4. Fibroscan® (Echosens, Paris) was discordant with the result of Fibrotest® (Biopredictive, Paris) (8.2KPa = F2). A liver biopsy was performed that showed a possible transition to cirrhosis – Metavir F3. PEG-interferon alfa 2a (180 mcg/week) and Ribavirin (1000mg/day) was started in 2009 and continued for 72 weeks because of the slow virologic response. The relapse was noted in the first 6 months after the end of treatment.

Treatment with first generation of DAA’s was not available and the patient refused to participate in clinical trials. The patient remained in our surveillance and underwent periodic clinical, biological and imaging examinations (every 4 months).

In March 2014 the patient came to clinic for a routine examination. The blood tests showed ALT = 97 IU/l, AST = 67 IU/l, GGT = 193 IU/l, Alfa-fetoprotein (AFP) = 2.67 ng/ml, normal CBC, normal coagulation and protein electrophoresis. The patient had no complaints, his health was subjectively well. He did not consume alcohol or tobacco and had a healthy lifestyle. His BMI was 19 kg/m2. On abdominal ultrasound we found an aspect suggesting liver steatosis (to be mentioned that until this examination had no steatosis) with a hypoechoic area in the left lobe (which was interpreted as a possible fatty free area, but a tumoral process was not excluded). We asked the patient to come back 3 months later to reevaluate this finding.

The patient could not come for the reevaluation as asked and came back 8 months later. This time (November 2014), the ultrasound showed a clearly delimited hypoechoic round mass of 35 mm diameter in segment III of the liver. Spleen size was slightly increased (130 mm). ARFI® (Acoustic Radiation Force Impulse Imaging) (Siemens, Berlin) ultrasound of the liver was 1.82 m/s (F3/F4) and Fibroscan® (Echosens, Paris) 12 KPa (F3). Blood tests were similar with those performed in March, including normal AFP. The patient had still no complaints. On the abdominal CT scan with intravenous contrast in November 2014, the lesion in segment III is described as benign and the aspect is consistent with a hepatic adenoma (Figure 1). Contrast enhanced ultrasound raised the suspicion of a malignancy (Figure 2).

One month later, in December 3rd 2014, the ultrasound examination showed two more lesions (one in segment IV and the other in segment VI, both with the same characteristics as the first one). Colonoscopy showed no abnormal findings. Upper tract endoscopy showed grade I esophageal varices prominent only at Valsalva maneuver.

In December 08th 2014 the patient underwent surgery with the excision of the tumor in...
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Section III. The histopathological exam demonstrated malignant hepatic infiltration with small-sized lymphoid cells with plasmacytoid features (Figure 3A). Immunohistochemistry (IHC): the proliferation was with small B-cell CD20 positive (Figure 3B), with low proliferation index Ki67 (~20-25%), and kappa light chain restriction (kappa/lambda~20/1) (Figure 4A and B); the malignant cells were negative for CD5, CD10, BCL6 and Cyclin D1. A diagnosis of small B-cell marginal zone lymphoma with plasmacytoid differentiation, kappa chains restriction and follicular colonization was made. Hematological staging (including bone marrow trephine biopsy) confirmed liver confining of the disease. IRM (December 18th 2014) showed multiple pseudo-nodular lesions disseminated in both liver lobes (Figure 5).

AFP, CEA, CA 19-9 were normal. ALT was 78 IU/l, AST 67 IU/l, GGT 199 IU/l. CBC count was normal except platelet count (145,000/microliter). RNA HCV = 8,583,959 IU/ml.

On December 20th 2014 sofosbuvir/ledipasvir (Harvoni) therapy was started. The evolution of the viral load can be seen in figure 6. At week 10 RNA HCV was 435 IU/ml (2.63 log). At this point we decided to switch the therapy on ombitasvir/paritaprevir/ritonavir plus dasabuvir + ribavirin (Viekirax + Exviera + Copegus) suspecting resistance-associated variants. By week 12 RNA HCV became undetectable (under Harvoni) but we still changed the therapy. From week 15 we added sofosbuvir. Antiviral therapy ended on June 6th 2015.

Abdominal CT repeated in January 8th and March 10th 2015 showed the progression of the lesions which grew in dimensions and newly appeared lesions were identified.

Chemotherapy was started at week 12 of antiviral therapy (March 17th 2015) with Bendamustine (Levact) and Rituximab (MabThera) (preferred because of the lower hepatotoxicity) - 9 monthly cures (response – guided) that ended in November 2015. Chemotherapy and antiviral therapy went simultaneously for 3 months.

Seriated computer tomography showed the regression of the lesions under the above mentioned treatment. Last CT examination was done on April 9th 2016 and showed that some of the lesions completely disappeared and other have been replaced by fibroid scars. RNA HCV is negative 10 months after stopping antiviral therapy. Liver enzymes values are nor-
mal. Fibroscan® (Echosens, Paris) in April 2016 was 7.7 KPa (F2).

DISCUSSION

Primary hepatic lymphoma is a rare disease and a rare type of extranodal lymphoma. Although the diagnostic can be a real challenge, recognizing PHL is important because it responds favorably to chemotherapy and in many cases, in patients with chronic C virus infection, even to antiviral therapy alone (11, 12).

A recent literature review (13) identified 37 reports in PubMed and Ichushi Web by Japan Medical Abstracts Society, with 51 cases of primary hepatic MALT lymphoma. The radiological (CT, MRI and ultrasound) findings in these cases are inhomogeneous and do not permit to establish a clear pattern. The diagnostic is not possible until a biopsy is performed. The same review showed that in most of the cases, MALT lymphoma tends to be solitary and small. In our patient, multiple focal lesions were identified in the liver with quite large dimensions.

Until 2011, the combination of pegylated IFN-α and ribavirin (PR) was the only treatment for chronic hepatitis C. This regimen was the subject of the most studies that showed that HCV associated B-NHL has a good response to antiviral therapy. Arcaini et al (14) followed 100 patients with indolent HCV associated B-NHL (none of them primary hepatic) that received PR as first line therapy. In their study, the largest one to date on this subject, 80% of the patients achieved SVR, 44% complete remission of the B-NHL and 33% partial remission with only antiviral therapy. Another study, including 116 patients with HCV associated B-NHL of which 14 received antiviral therapy as first line therapy showed that 11 of these 14 patients achieved SVR and hematological remission (15).

There are only few reports on the use of DAA as first line therapy in HCV associated B-NHL. Rossotti et al (16) reported a rapid virologic and hematologic response with an all-oral regimen, based on faldaprevir and a deleobuvir in a patient with HCV associated splenic MALT. In their case report, Sultanik et al (17) showed that treatment with sofosbuvir plus ribavirin (changed at week 2 on sofosbuvir plus daclatasvir) obtained SVR and complete remission of a MALT located in the breast of a HCV infected woman.

Despite the significant drop in viral load and the normalization of ALT, in our patient the tumor size continued to increase and new nodules occurred in the liver by the week 12 of antiviral treatment. Starting the chemo-immune therapy was justified in this situation. After adding immune- and chemotherapy, the evolution was favorable.

CONCLUSION

Primary extranodal marginal lymphoma of the liver - a rare entity - should be suspected in patients with newly identified tumors of the liver and normal levels of alpha-fetoprotein especially if these patients have a chronic viral hepatitis. Making the right diagnostic is essential because primary extranodal marginal lymphoma of the liver is a potentially curable disease.

Treating first the infection and adding chemo- and/or immune therapy if necessary seems to be the right way of managing this form of lymphoma in patients with chronic C hepatitis.

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REFERENCES