Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

Primary spleen lymphoma associated with hepatitis C virus infection

Ricardo Cotta-Pereira,¹ Roberta Acar,² Carlos Eduardo Brandão Mello,³ Antonio Carlos Iglesias,¹ Carlos Alberto Basílio-de-Oliveira²

¹Department of Surgery, Gaffrée & Guinle University Hospital, Rio de Janeiro, Brazil;

²Department of Pathology, Gaffrée & Guinle University Hospital, Rio de Janeiro, Brazil;

³Department of Internal Medicine, Gaffrée & Guinle University Hospital, Rio de Janeiro, Brazil

Correspondence to Ricardo Cotta-Pereira, rc@rtcp.com.br

Summary

Lymphoproliferative disorders associated with hepatitis C virus (HCV) make up a heterogeneous group of diseases, including lymphomas. It was only recently that HCV was recognised as being a potential cause for the development of non-Hodgkin's lymphoma. The authors report a case of an older woman with chronic hepatitis C who developed primary spleen lymphoma. This case report points out the pathophysiological mechanisms of this disease and the importance of considering this disease in the differential diagnosis of patients with chronic HCV infection.

BACKGROUND

The aim of this report was to suggest a possible aetiological role of hepatitis C virus (HCV) in the development of lymphomas in the hepatosplenic region, including an unusual presentation of this disease (primary mass of the spleen).

CASE PRESENTATION

A Caucasian woman, 59 years of age, was brought to the surgery department with a history of anorexia and pain in the left scapular waist that radiated to the upper quadrant of the abdomen. She had suffered a weight loss of 3 kg in a 1-month period. She was using propranolol and chlorthalidone to treat systemic arterial hypertension. Abdominal examination revealed hepatomegaly, splenomegaly, an epigastric mass and pain in the right and left hypochondrium.

INVESTIGATIONS

Several blood tests were performed with normal results, except for a thrombocytopenia (119 000/ml) and positive anti-HCV antibodies. The diagnosis of hepatitis C was confirmed by PCR.

Abdominal images were performed. The ultrasonography showed a normal liver volume with a heterogeneous parenchyma and a central hypoechogenic and heterogeneous nodular lesion in the spleen with solid features measuring 56×49 mm (figure 1). An abdominal CT confirmed the ultrasound findings and also showed an expansive formation, with low attenuation, measuring 3.3×3.2 cm and situated behind the left lobe of the liver (figure 2).

After surgery, the macroscopic examination of the spleen revealed an irregularly lobulated white mass of hard consistency. After it was sliced, it appeared lobulated, firm and whitish with well-defined borders and measuring 7.0 cm across its largest axis (figure 3). The microscopic

examination showed a diffuse proliferation of lymphoid cells with large vesicular nuclei that were toothed or highly lobulated with one or more prominent nucleoli and amphophilic cytoplasm (figure 4). Regarding the subhepatic mass, the histopathological findings showed the same morphological and immunohistochemical characteristics as for the splenic lesion (figure 5). The histological findings of the liver biopsy were compatible with chronic hepatitis and micronodular hepatic cirrhosis.

DIFFERENTIAL DIAGNOSIS

Primary spleen lymphoma (PSL); spleen metastasis.

TREATMENT

The patient underwent laparotomy that revealed an exofitic firm mass of the spleen invading the hilum and the presence of a subhepatic mass under the left lobe. Splenectomy with biopsies of the liver and the subhepatic mass was performed.

OUTCOME AND FOLLOW-UP

The patient was discharged and oncologic treatment started with the following chemotherapeutic agents: cyclophosphamide, adriamycin, vincristine and prednisone. After 8 months of post-surgery follow-up, the patient was asymptomatic with no evidence of disease on ultrasonographic and tomographic examinations.

DISCUSSION

Lymphoproliferative disorders associated with HCV make up a heterogeneous group of diseases, including lymphomas.¹ It was only recently that HCV was recognised as being a potential cause for the development of non-Hodgkin's lymphoma (NHL). This association was

Figure 1 Hypoecogenic splenic nodule, solid and heterogeneous, measuring 4.8×5.6 cm (see arrow).

first suggested during studies of essential mixed cryoglobulinaemia (EMC)—an auto-immune chronic lymphoproliferative disease with subacute clonal proliferation of B cells in the bone marrow.²

Chronic hepatitis C has only been indicated as the main cause for EMC in the past 10 years with anti-HCV antibodies present in 84–98% of the patients with EMC. This pathological condition causes a predisposition for developing malignant B cell NHL.² This condition was proposed in a retrospective study involving 31 patients with EMC and detectable HCV-RNA in the serum; bone marrow biopsy confirmed low-grade NHL in 12 patients (39%) and monoclonal reactive infiltration in 11 patients (36%).³ Nevertheless, cases of NHL associated with HCV infection without cryoglobulinaemia have also been reported.⁴

Although HCV's lymphotropism plays an important aetiopathogenic role, the precise mechanism through which a malignant lymphoma develops is still unclear.⁴ PSL is a relatively rare pathological condition, comprising only 1–2% of the patients with this malignancy, although secondary spleen involvement by NHL is becoming more common.⁵

The number of PSL cases in the literature is increasing as a result of its wide definition in the medical literature. The definition for PSLs, as established by Das Gupta *et al* and reinforced by many recognised authors, is an NHL subtype in which the disease involves the spleen or hilar lymph nodes with no evidence of recurrence for a minimum period of 6 months after splenectomy.^{4–6}

A variety of lymphotropic viruses (eg, Epstein–Barr virus, herpes virus type 619 and HIV type 120) have been suggested as being the causative agents for malignant lymphoma. More recently, HCV has been described to have an important role in NHL.

Nearly 50 cases of B cell NHL associated with HCV infection have been reported in the past few decades. Most cases were associated with a nodal distribution.³ Extranodal lymphomas (primary hepatic lymphoma and PSL) have also been reported, as have cases of NHL that were associated or not with cryoglobulinaemic complications. Such findings suggest the existence of heterogeneous neoplastic processes in NHL associated with HCV.

The prevalence of PSL remains unknown probably because of the lack of well-defined criteria for its diagnosis among different authors.^{6–8} PSL is quite rare using the criterion suggested by Das Gupta *et al*, which establishes the involvement of only the spleen and hilar splenic lymph nodes with a minimum disease-free period of 6 months after splenectomy.⁶

The aetiology of PSL remains unclear. Recently, some reports have demonstrated a high incidence of hepatitis C viral infection in NHL cases suggesting an important role for this virus in the pathogenesis of the disease.⁴ It is known that HCV cannot encode a reverse transcriptase; consequently, the RNA-HCV sequences do not integrate into the host genome. Thus, HCV cannot be directly involved with the transformation of B lymphocytes and must have an indirect role in the development of NHL.

Figure 2 CT of abdomen demonstrating spleen with augmented volume and large hypodense area (yellow arrow), in addition to an expansive formation of soft parts measuring approximately 3.3×3.2 cm at the largest axial diameters (blue arrow), located at the back of the liver left lobe.

Figure 3 Lobulated tumoral mass, whitish, extrapolar the organ limits and reaching the hilum.

Several mechanisms have been proposed and involvement of HCV in the pathophysiology of lymphoproliferative syndromes, especially B cell NHL, can be explained by viral lymphotropism, which can be detected in mononuclear peripheral blood cells in chronically infected cases. This fact translates into the expansion of monoclonal or polyclonal lymphocytes at which point

establishing in some cases EMC. The presence of HCV in peripheral blood mononuclear cells causes intense stimulation of the B lymphocytes resulting in an increase in the production of immunoglobulins. In theory, the presence of HCV proteins in infected lymphocytes could initiate an increasing deregulation and predispose lymphocytes towards the additional development of genetic

Figure 4 Diffused non-Hodgkin's lymphoma with large cells showed by arrows.

Figure 5 Immunohistochemical study showing positiveness for CD 20 (see arrows).

mutations, first leading to polyclonal rather than monoclonal expansion and, subsequently, to the development of B cell NHL.⁹

Another possibility would be that the infected B lymphocytes are able to self-regulate the expression of a particular oncogene (eg, c-myc) or overproduce cytokines responsible for B cell proliferation and differentiation. The first target of a humoral solution to HCV infection would be the E2 protein in the viral envelope. Anti-E2 antibodies are immunoglobulins detected in 88% of the chronic hepatitis C carriers. These antibodies are thought to be

related to high genetic mutation frequencies leading to the expansion process.⁹ Based on these observations, it has been assumed that chronic HCV infection, combined or not with other factors (genetic and environmental), could lead to the development of B cell NHL.⁹

A majority of authors agree that there is not a specific HCV genotype involved with the lymphoproliferative syndromes. The genotype present in such disorders is directly associated with its prevalence in the geographical area.

Patients with PSL usually present with splenomegaly and a variety of symptoms, such as abdominal discomfort

in the upper quadrants, weight loss, tiredness, anorexia, fever and nocturnal sweating.⁷ Splenomegaly may occur as a consequence of splenic involvement and sequestration of normal cells or through a combination of these two factors.⁹ In most cases, the diagnosis is made through splenomegaly; however, resection is not necessary except when haematological alterations are clinically present.⁷⁻⁹ For this reason, PSL is often diagnosed too late when it has already disseminated to other organs.⁷

In this case, the disease remained limited to the spleen and followed the criterion proposed by Das Gupta *et al*,⁶ configuring to the criteria for a NHL with high-level malignancy, as opposed to most of the reported PSL cases. Non-invasive imaging techniques such as ultrasound and CT are useful for documenting splenomegaly and for properly visualising possible focal lesions in the spleen smaller than 1 cm in diameter. Detection of such lesions might suggest lymphoma development, confirming the diagnosis by ultrasound-guided fine needle biopsy, as reported by Cavanna *et al*.⁷

Splenectomy is both diagnostic and therapeutic, which is considered to be effective in PSL. Because NHL is a systemic condition, adjuvant treatment may be very useful. In this reported case, there was an associated hypersplenism reinforcing the indication for surgery. The procedure of choice in these cases is diagnosis by ultrasound-guided needle biopsy, and the first option of treatment is with chemotherapy and/or radiotherapy avoiding surgery if there is a full remission.^{6-8 10}

Competing interests None.

Learning points

- The importance of this report is based on the fact that PSL is an unusual condition.
- Additionally, it points to the relevance in considering the coexistence of PSL in cases of chronic infection by HCV.

Patient consent Obtained.

REFERENCES

1. **Hermine O**, Lefrère F, Bronowicki JP, *et al*. Regression of splenic lymphoma with villous lymphocytes after treatment of hepatitis C virus infection. *N Engl J Med* 2002;**347**:89–94.
2. **Turner NC**, Dusheiko G, Jones A. Hepatitis C and B-cell lymphoma. *Ann Oncol* 2003;**14**:1341–5.
3. **Davis GL**. Clinical manifestation on Hepatitis C. *Clin Liv Dis* 1997;**1**:574–5.
4. **Ferri C**, La Civita L, Caracciolo F, *et al*. Non-Hodgkin's lymphoma: possible role of hepatitis C virus. *JAMA* 1994;**272**:355–6.
5. **Matone J**, Lopes Filho GD, Scalabrin M, *et al*. Primary splenic lymphoma in patient with hepatitis C virus infection: case report and review of the literature. *Int Surg* 2000;**85**:248–51.
6. **Dasgupta T**, Coombes B, Brasfield RD. Primary malignant neoplasms of the spleen. *Surg Gynecol Obstet* 1965;**120**:947–60.
7. **Cavanna L**, Artioli F, Vallisa D, *et al*. Primary lymphoma of the spleen. Report of a case with diagnosis by fine-needle guided biopsy. *Haematologica* 1995;**80**:241–3.
8. **Ahmann DL**, Kiely JM, Harrison EG Jr, *et al*. Malignant lymphoma of the spleen. A review of 49 cases in which the diagnosis was made at splenectomy. *Cancer* 1966;**19**:461–9.
9. **Nocente R**, Ceccanti M, Bertazzoni G, *et al*. HCV infection and extrahepatic manifestations. *Hepatogastroenterology* 2003;**50**:1149–54.
10. **Skarin AT**, Davey FR, Moloney WC. Lymphosarcoma of the spleen. Results of diagnostic splenectomy in 11 patients. *Arch Intern Med* 1971;**127**:259–65.

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Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Cotta-Pereira R, Acar R, Mello CEB, Iglesias AC, Basilio-de-Oliveira CA. Primary spleen lymphoma associated with hepatitis C virus infection. *BMJ Case Reports* 2011;10.1136/bcr.11.2010.3474, date of publication

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