Casi clinici

Disseminated non-Hodgkin's lymphoma and chronic hepatitis C: a case report

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Hepatitis C virus (HCV) infection is occasionally associated to B-cell type non-Hodgkin's lymphoma. Evidence showing a possible etiological link between HCV and lymphoma has been reported from areas of high HCV prevalence. We describe the case of a 68-year-old woman with B-cell non-Hodgkin's lymphoma mainly involving the skin. Typical manifestations of disease were cutaneous nodules, red-violet in color, scattered on the entire body and adherent to the subcutaneous tissue. A 3-cm nodule excised from the leg was found at histology to consist of centroblastic-like B cells, which stained positively for CD45, CD20 and CD79a. Although the patient was treated with different chemotherapy schedules, she died 1 year later with a diagnosis of disseminated lymphoma. Our report suggests that HCV, a trigger for clonal B-cell proliferation, predisposing to immunological disorders, such as mixed cryoglobulinemia and B-cell malignancies, may also account for the "rare" extranodal high-grade non-Hodgkin's lymphoma. Further observations suggest that treating HCV infection with antiviral therapy could help to prevent the development of B-cell non-Hodgkin's lymphoma.
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Key words: **B cell; Extranodal lymphoma; Hepatitis C virus; Non-Hodgkin's lymphoma.**

Introduction

The morbidity and mortality associated with hepatitis C virus (HCV) infection are not only attributable to the long-term sequelae of liver disease, but also, though to a lesser degree, to extrahepatic manifestations. Some of these are mild and remain undiagnosed unless elicited by careful investigations, while others, such as mixed cryoglobulinemia and non-Hodgkin's lymphoma (NHL), may show a progressive course with severe symptoms and a potentially fatal outcome[1].

Accumulating epidemiological evidence supports a role for HCV in the pathogenesis of human lymphoproliferative disorders. This also has a biological plausibility, and seems to be closely linked to rearrangements in the bcl-2 region[2]. The relationship between HCV infection and B-cell lymphoma has been largely demonstrated in several geographical areas with a prevalence of HCV infection ranging from 7.4 to 37%[3]. Unfortunately, the results of published studies are discordant and the link between HCV infection and NHL is still debated[4-6], although for some subsets of NHL, such as follicular center, marginal zone and diffuse large cell lymphoma it has already been established[7]. However, in a multi-center case-control study recently performed by Mele et al.[8], the association between HCV infection and B-cell lymphoma has been confirmed. Overall, data would suggest that in Italy one out of 20 cases of B-cell lymphoma is etiologically linked to HCV infection and therefore would benefit from antiviral treatment.

Clinical observations suggest that HCV infection in patients with NHL shows some distinctive clinico-pathological features, such as older age, mild liver damage, an increased rate of autoimmune disorders and extranodal involvement[9]. In our report, we document the case of a 68-year-old woman with a history of chronic hepatitis C presenting with an extranodal high-grade lymphoma mainly involving the skin.

Case report

A 68-year-old Caucasian woman, known to have chronic hepatitis C since 1997, was admitted to the Department of Internal Medicine in September 1998 with a number of erythematous, painful nodular cutaneous lesions which manifested suddenly during the previous month.

She presented with systemic symptoms (weight loss, fatigue and fever) and mild hepatomegaly. There were no splenomegaly or pathological lymph nodes. Examination of the skin showed many nodular lesions located on the back, breasts and upper and lower limbs. The nodules measured 2 to 5 cm in diameter, were erythematous or red-violet in color, isolated, firm in consistency, adherent to the subcutaneous tissue, with undefined borders, and were painful to gentle palpation.

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Laboratory findings on admission included: hemoglobin 12.9 g/dL, white blood cells 6300/mm^3, platelets 149 000/mm^3; differential: granulocytes 78%, lymphocytes 15%, and monocytes 0.6%. Except for a mild increase in aminotransferases (3 × upper normal limit), there were no other signs of liver damage: albumin, prothrombin time, γ-glutamyltranspeptidase, alkaline phosphatase and bilirubin were within normal limits. The serum levels of lactate dehydrogenase were 1089 IU/L (normal values < 350 IU/L). Further laboratory parameters, including creatinine, electrolytes and protein electrophoresis were within the normal range. Liver specific immunology was not performed. Cryoglobulins were undetectable. Anti-HCV antibody analysis was positive at third generation enzyme immunosorbent assay, and HCV-RNA testing was positive at a reverse transcription polymerase chain reaction assay. The HCV genotype was 1b.

Abdominal ultrasound was not suggestive of portal hypertension or hepatocellular carcinoma. Two hypoechogenic lesions (5.4 and 3.2 cm) were observed within the spleen, which was of normal size. There were no pathological intra-abdominal or retroperitoneal lymph nodes. Computed tomographic scan of the neck, lungs and abdomen showed no pathological lymph nodes in the neck region, a mild pleural effusion and a nodular lesion in the left lower lobe infiltrating the diaphragm. It also confirmed the presence of two splenic lesions. Many nodular lesions ranging in size from 1 to 5 cm, were found in the subcutaneous fat of the axillae, thorax, abdomen and back.

One of the nodular masses (3 cm) was excised from the right leg. Macroscopically, it appeared as a lobulated tumor mass, with extensive infiltrates interesting the dermis and the subcutaneous fat; the epidermis was not involved. Histological analysis revealed that extensive infiltrates of a population of small cells, identified as B-lymphocytes by CD20 and CD79a, were in close apposition to the skin appendages. There were no reactive germinal centers. Cytomorphologically, small to medium size B cells, designated as centroblastic-like, with inconspicuous or irregular and prominent nucleoli predominated. Immunohistochemistry was performed on formalin-fixed, paraffin-embedded tissue sections using CD3, CD57, S-100, Vimentin, CD20, CD45, CD79a, bcl-2, CD30 and Ig κ and γ light chain monoclonal antibodies (Dako A/S, Glostrup, Denmark). The final histopathological examination showed a polymorphic centroblastic B-cell NHL positive for CD45, CD20, and CD79a; it was negative for CD30 and bcl-2. The patient refused bone marrow aspiration.

With a diagnosis of disseminated high-grade NHL, stage IV (skin, spleen), polychemotherapy was started according to the CHOP protocol[10,11] (cyclophosphamide, doxorubicin, vincristine and prednisone). Six cycles later, restaging by means of computed tomographic scan showed disappearance of the nodular cutaneous, and of the subcutaneous and splenic lesions (complete remission)[12].

Three months later, the patient returned for the reappearance of cutaneous lesions and for severe unrelated abdominal pain. An abdominal ultrasound revealed the presence of many enlarged lymph nodes. She was treated with one cycle of DHAP[13] (cisplatin, Ara-C, desamethasone) without any symptomatic improvement. Due to severe neutropenia (G3), the treatment was immediately withdrawn.

Six months later, a large mass, 6-7 cm in diameter developed in the mesogastrium. The mass was palpable at superficial examination and was associated with a new *poussée* of cutaneous nodules on the thorax. At this time laboratory findings showed increased lactate dehydrogenase serum levels reaching 1179 mg/dL and mild anemia. An ultrasound showed hepatomegaly with perihepatic and perisplenic ascites; a spleen of normal size without focal lesions and a big mass, 7 cm in diameter and including abnormal intestinal loops and enlarged lymph nodes. The patient died a few weeks later of sepsis.

Discussion

In this brief clinical presentation, we report the case of a 68-year-old patient with a one-year history of HCV infection, who developed a high-grade, stage IV (skin and spleen) B-cell NHL with a prevalent cutaneous localization. In accordance with the Ann Arbor classification[14], it could be characterized as an extranodal lymphoma. In the literature, the association between extranodal lymphoma and HCV infection is reported as uncommon, being responsible for 20% of cases[15]; this percentage is even lower when the extranodal site is the skin[16]. However, in our patient, it is possible that the cutaneous involvement was not a primary localization, but that it was a consequence of the advanced stage of the disease at the time of presentation and of the aggressive biological behavior of the tumors. In fact, usually, the NHL involving HCV-infected subjects, are characterized by extranodal locations such as the stomach and bowel, and by the presence of predisposing conditions (infectious or autoimmune diseases leading to the acquisition of MALT). Besides, they are commonly low-grade with an indolent clinical course. On the contrary, aggressive B-cell lymphomas may involve a wide variety of extranodal sites and up to 40% of these tumors are initially diagnosed in extranodal locations[17-19].

The association between HCV and lymphoma genesis exists, but the mechanism of lymphoproliferation induc-

tion seems to be largely unclear and debated[15,20]. HCV may exert its oncogenic potential either via an indirect mechanism or else directly through other pathways[3]. According to the latter hypothesis, HCV seems to infect the B cell, and *in vitro* studies have suggested that some of its proteins, the core and the nonstructural 3 protein, are capable of deregulating the cell cycle. However, neoplastic cell may be no longer permissive of viral replication and indeed, most studies, including the recent report by Hermine et al.[21], have shown that the lymphomatous tissue does not contain HCV[19]. In this case report, we were not able to demonstrate the presence of HCV-RNA or of HCV antigens within the tumor mass excised. In addition, evidence in favor of the presence of HCV in tumor cells does exist, but the specificity of these immunohistochemistry and *in situ* hybridization findings has not been independently confirmed[22].

An alternative hypothesis to establish the relationship between HCV and lymphoma genesis, envisages a chronic stimulation of immune cells by unidentified HCV antigens. According to a pathogenetic model based on a large series of clinical, immunological, histological and molecular evidences, HCV antigen-driven polyclonal B-cell lymphoproliferation could be the initial phase of a process leading, in a variable time, to a true clonal disease. Clonal expansion of B lymphocytes has been prevalently detected in the bone marrow, in the liver and in the peripheral blood of HCV-infected patients[9,15,20]. Further evidences to support this hypothesis are represented by the ability of HCV to bind to CD81, a B-cell surface protein which behaves as a receptor[23]. In fact, as recently shown, lower levels of CD81 are associated with the HCV-3 genotype and with the decline in the levels of HCV-RNA during the initial phases of antiviral therapy[24]. Thus, these data would suggest an immunomodulatory role for CD81 on the B cell either peripherally or within the liver in HCV infection, but the effect of antiviral treatment in these patients remains to be determined[25].

However, the possibility that antiviral treatment in a patient infected by HCV could be beneficial even in terms of the prevention of lymphoproliferation, as recently shown by Hermine et al.[21], constitutes an adjunctive reason to submit such patients to this treatment.

Riassunto

Una malattia cronica di fegato correlata al virus dell'epatite C (HCV) può talvolta essere complicata dallo sviluppo di un linfoma. Riportiamo la storia clinica di una donna di 68 anni, affetta da un'epatite cronica HCV-correlata, che ha sviluppato un linfoma non Hodgkin disseminato a prevalente localizzazione cutanea. Le lesioni sulla cute erano nodulari, rosso-violacee, aderenti ai piani sottocutanei, dolenti alla palpazione e disseminate in tutto il corpo. La caratterizzazione anatomo-patologica ed immunoistochimica dei noduli linfomatosi ha evidenziato la presenza di piccoli linfociti B, positivi per il CD20, CD45 e CD79a. Nonostante la paziente sia stata repentinamente trattata con diversi cicli di chemioterapia, la malattia linfoproliferativa si è mostrata molto aggressiva, per cui è deceduta dopo soltanto 1 anno dalla diagnosi.

Il caso clinico che viene brevemente presentato, conferma alcuni dati presenti in letteratura relativi all'associazione epidemiologica tra HCV ed i linfomi non Hodgkin. Inoltre ci consente di speculare sul meccanismo con cui HCV è responsabile, sia direttamente (malgrado non siano state trovate tracce di HCV-RNA nel tessuto tumorale) sia indirettamente di stimolare una proliferazione clonale predisponente a processi immunopatologici sia di tipo benigno (la crioglobulinemia), sia maligno (i linfomi).

La peculiarità di questa osservazione clinica, che rende utile la segnalazione, consiste nel fatto che nei soggetti infetti da HCV i linfomi di solito sono tipo MALT, raramente interessano la cute ed hanno un basso grado di malignità, al contrario del nostro caso in cui il linfoma era ad alto grado di malignità, disseminato con prevalente localizzazione cutanea.

Parole chiave: Cellule B; Linfoma extranodale; Linfoma non Hodgkin; Virus dell'epatite C.

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