Regression of Hodgkin Lymphoma in Response to Antiviral Therapy for Hepatitis C Virus Infection

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Abstract

Links between hepatitis C virus (HCV) infection and several non-Hodgkin lymphomas have been suggested by epidemiological studies. We herein report the first documented case of a patient with HCV-associated Hodgkin lymphoma who showed a marked regression following interferon-based antiviral therapy. This unique case extends the spectrum of HCV-associated malignant lymphomas, confirms the efficacy of antiviral therapy for this rare extrahepatic manifestation and provides valuable clues for achieving a better understanding of lymphomagenesis in HCV.

Key words: hepatitis C virus, Hodgkin lymphoma, interferon

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Introduction

The hepatitis C virus (HCV) is well recognized as being the main causative agent of chronic hepatitis, cirrhosis and hepatocellular carcinoma (1). Recent epidemiological studies have indicated links between HCV infection and several types of malignant lymphomas (2). Importantly, all of these cases have been categorized as B cell non-Hodgkin lymphomas (NHL). The development of Hodgkin lymphomas has not been previously reported. We herein report a case of HCV-associated Hodgkin lymphoma classified as nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) in which a marked response to interferon (IFN)-based therapy was achieved.

Case Report

A 64-year-old man was referred to our hospital for treatment of chronic hepatitis C (CHC). He was infected with the HCV genotype 1b and had a viral titer of 5.2 Log copies/mL. A physical examination showed no specific findings. Liver function test results and tumor markers, including alpha fetoprotein (AFP), protein induced by vitamin K absence or antagonist II (PIVKAII) and soluble IL-2 receptor (sIL2-R), were within normal ranges. An initial contrast-enhanced computed tomographic (CE-CT) scan revealed enlargement of multiple lymph nodes with a maximum size of

Figure 1. CE-CT scans performed before (A) and 24 weeks after (B) IFN-based therapy revealed a marked reduction in the amount of para-aortic lymph node swelling (arrows).
4 cm in the para-aortic and external iliac regions (Fig. 1A). Hepatocellular carcinoma was not detected. The tentative diagnosis was malignant lymphoma. Laparoscopic resection of the left external iliac lymph node was performed in order to make a definitive diagnosis. A histopathological analysis demonstrated the presence of a vaguely nodular lymphoid proliferation with mottled areas (Fig. 2A). A higher power view revealed the presence of Reed Stenberg cell (RSC)-like large atypical cells (Fig. 2B) that showed positivity for cluster of differentiation (CD) 20 (Fig. 2C), B-cell lymphoma (BCL) 6 (Fig. 2D) and epithelial membrane antigen (EMA) (Fig. 2E) and negativity for CD30 and CD15 (not shown) surrounded by small CD3-positive T cells (not shown). Based on these findings, a diagnosis of NLPHL was thus made.

Considering the indolent nature of NLPHL and the growing consensus that NLPHL may not require aggressive treatment, unlike classical Hodgkin lymphoma (CHL) (3, 4), we gave higher priority to the treatment of CHC and thus started Peg-IFNα2a and Ribavirin combination therapy in the standard regimen for 48 weeks. Serum HCV RNA was undetectable after two weeks and a sustained virological response was achieved. A series of follow-up CE-CT studies demonstrated a striking regression of lymphadenopathy after 24 weeks (Fig. 1B) and durable remission throughout the course of therapy.

**Discussion**

Previous clinical observations have indicated links between HCV infection and several types of lymphoma, including marginal zone lymphoma, lymphoplasmacytic lymphoma and diffuse large B cell lymphoma (2). Importantly, all of these are categorized as B cell NHL. This is the first documented case of HCV-associated Hodgkin lymphoma classified as NLPHL. The response to antiviral therapy observed in this case, which was analogous to that reported in B cell NHL (5-7), strongly supports the existence of an etio-
logic link between NLPHL and HCV infection.

In contrast to CHL, NLPHL is characterized by the presence of large atypical variants of RSCs, termed lymphocytic and histiocytic cells or popcorn cells, with a germinal center B cell-like phenotype (i.e., CD20+/BCL6+) (3, 4, 8). This phenotype indicates a close relationship between NLPHL and B cell NHL. Indeed, NLPHL reportedly overlaps with or progresses to T cell/histiocyte rich B cell lymphoma, a subtype of diffuse large B cell lymphoma (3). Although the mechanisms whereby HCV infection causes B cell malignant lymphoma remain to be clarified, working hypotheses propose that either persistent HCV antigen stimulation results in clonal expansion of B cells that finally leads to the development of lymphoma or that HCV infection itself is directly oncogenic in B cells (2, 5). Therefore, considering the resemblance of NLPHL to B cell NHL, it is tempting to speculate that these mechanisms could also be applied to the development of NLPHL. Accordingly, the anti-lymphoma effects of IFN observed in the present case might be attributable to the eradication of HCV by IFN. In addition, the direct anti-tumor effects of IFN through such mechanisms as the upregulation of major histocompatibility complex antigens or activation of natural killer and cytotoxic T cell activity might also operate and synergistically contribute to the regression of NLPHL (9).

In summary, we herein report a case of HCV-associated NLPHL in which a marked regression was achieved with IFN-based antiviral therapy. The current case not only extends the spectrum of HCV-associated malignant lymphoma, but also provides clues for better understanding lymphoma-ogenesis in HCV. Primary treatment of HCV infection with IFN should be considered for this rare type of HCV-associated lymphoma.

The authors state that they have no Conflict of Interest (COI).

References