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Hepatitis C Viral Infection Is Not Associated With Waldenström's Macroglobulinemia

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While a familial predisposition may exist in up to 20% of patients with Waldenström's Macroglobulinemia (WM), the precipitating cause of this B-cell malignancy remains unknown in most patients. In previous studies, an association between hepatitis C virus (HCV) infection and WM has been suggested as etiological. This relationship has been the subject of debate, however, with some studies demonstrating increased incidence of HCV infection among WM patients and other studies showing no such association exists. This discordance might be attributable to the analytical method used, HCV antibody detection, which might be ineffective in patients with immunosuppression. We therefore analyzed the prevalence of HCV in a large population of WM patients utilizing both an HCV antibody detection immunoassay as well as qualitative polymerase chain reaction assay to directly detect HCV presence in serum samples. None of 100 randomly tested WM patients in this study tested positive for HCV by either analytical method. Our results therefore demonstrate a lack of association between HCV and WM. Am. J. Hematol. 82:83–84, 2007. © 2006 Wiley-Liss, Inc.

Key words: hepatitis C virus; Waldenstrom's macroglobulinemia; B-cell disorder

INTRODUCTION

Waldenström's macroglobulinemia (WM) is a B-cell malignancy characterized by the underlying pathological diagnosis of lymphoplasmacytic lymphoma using REAL or WHO criteria and the presence of IgM monoclonal gammopathy [1]. While a familial predisposition may exist in up to 20% of patients with WM, a precipitating cause remains unknown for most patients [2]. In previous studies, an association between hepatitis C virus (HCV) infection and WM has been suggested. Using enzyme-linked immunosorbent (ELISA) and polymerase chain reaction (PCR)-based assays for HCV detection, DeRosa et al. [3] reported that 8/13 (61.5%) WM patients were positive for HCV. The prevalence of HCV among 400 patients with various B-cell malignancies was studied by Mele et al. [4] in an Italian multicenter case–control study using primarily an ELISA-based assay to determine HCV infection; this study demonstrated an overall HCV infection rate of 17.5%. However, among patients with lymphoplasmacytic lymphoma (including WM), a higher prevalence of HCV infection was observed (4/13 patients: 30.8%). In response to these studies, Veneri et al. [5] studied the prevalence of HCV infection using an ELISA-based assay among 227 patients with an IgM monoclonal gammopathy, including 60 WM patients and excluding patients with mixed cryoglobulinemia. The seroprevalence rate of HCV infection in these studies (4.4%) was similar

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between patients with an IgM monoclonal gammopathy and patients with WM, and was on par with that reported in a similar control population in northern Italy. Interestingly, Santini et al. [6] studied WM patients for HCV infection, and found 2/6 (33%) positive by ELISA and 6/6 (100%) positive by PCR-based analyses; this suggests that humoral immunoparesis, which is commonly observed in WM patients [6], might have undermined the seroprevalence rate of HCV infection in the earlier ELISA-based studies. In view of these discordant findings, we analyzed the prevalence of HCV in a large population of WM patients utilizing both an HCV antibody detection immunoassay and qualitative PCR assay to directly detect HCV presence in serum samples.

MATERIALS AND METHODS

We analyzed 100 randomly selected, previously untreated patients with the consensus panel diagnosis of WM [7] utilizing both HCV antibody detection immunoassay and qualitative PCR analysis (Quest Diagnostics, Cambridge, MA). All serum samples were collected prior to any therapy for the entire cohort, and all samples were frozen immediately after collection at -80°C. Hepatitis C viral RNA was detected by reverse transcription of genomic RNA followed by PCR amplification using the COBAS AMPLICOR (TM) Hepatitis C virus test, version 2.0 (Roche Diagnostics). The serum of a WM patient with known HCV infection was used as a positive control. The median age of patients in this study was 61 (38–83 years; Table I) and the male: female ratio was 1.44. None of the patients had a known history of cryoglobulinemia, liver disease, hepatitis B, HCV, or HIV infection. Liver function tests obtained at the time of serum collection showed normal range SGOT and SGPT levels for 97/100 patients.

TABLE I. Patient Characteristics at Blood Collection ($N = 100$ Unless Specify). All Patients Were Untreated at Time of Blood Collection

	%	Median (IQ[a])	Range[b]
Age at diagnosis (years)		61 (±14)	(38– 83)
>70	17		
Male gender	57		
Kappa light chain	75		
IgM (g/dL)		1970 (±500)	(500–8440)
>3000	34		
IgG (g/dL)		633 (±250)	(123–3900)
IgA (g/dL)		45 (±35)	(9–244)
Hemoglobin (g/dL)		12.7 (±1)	(8.8–17.3)
<10	10		
Hematocrit (%)		37 (±3)	(20–50)
<35	35		
β2 microglobulin (mg/L)		2.5 (±1)	(1.3–10)
>3.0	32		
Bone marrow involvement (%)[c]		30 (±20)	(2–90)
>50	30		
Serum viscosity relative to water		1.9 (±0.8)	(1–4.8)
>2	25		
Albumin (g/L)		39 (±3)	(26–58)
>35	18		
LDH (UI/L)		382 (±80)	(118–775)
≥250	38		
SGOT/AST (UI/L)		24 (±6)	(13–87)
SGPT/ALT (UI/L)		26 (±6)	(8–156)

[a]IQ: interquartile.
[b]Minimum/maximum range.
[c]Intertrabecular bone marrow involvement.

RESULTS AND DISCUSSION

None of the 100 WM patients in this study tested positive for HCV infection using either ELISA or PCR-based assays. In contrast, serum from a WM patient with known chronic HCV infection tested positive in both assay systems. Our findings, therefore do not demonstrate an association between HCV infection and WM, in contrast to the findings in smaller studies of WM patients by other investigators [3,4,6]. While these studies would argue against chronic HCV infection as a potential variable in the pathogenesis of WM, other sources of chronic antigen stimulation (including from other pathogens and drugs) may exist. Clearly, the effort to understand the pathogenesis of this apparently heterogenetic disease continues.

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