Observations on Cryoglobulin Testing: II. The Association of Oligoclonal Mixed Cryoglobulinemia with Cirrhosis in Patients Infected with Hepatitis C Virus

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ABSTRACT. ***Objective.*** To determine whether a mixed cryoglobulin type correlated with cirrhosis in patients infected with hepatitis C virus (HCV).

Methods. We investigated the results of mixed cryoglobulin tests performed in the clinical laboratory on patients with and without HCV infection.

Results. A higher prevalence of oligoclonal cryoglobulins designated Type IIa was present in HCV-infected patients with cirrhosis than in those without cirrhosis.

Conclusion. An association of Type IIa cryoglobulins with cirrhosis in HCV-infected patients has not previously been reported. (First Release June 15 2009; J Rheumatol 2009;36:1956–7; doi:10.3899/jrheum.090189)

Key Indexing Terms:
CRYOGLOBULINS OLIGOCLONAL HEPATITIS C VIRUS CIRRHOSIS

Cryoglobulin types were noted to be associated with different diseases in the initial study of Brouet and colleagues[1]. They defined 3 types of cryoglobulinemia. Type I consisted of a single monoclonal immunoglobulin and was associated mainly with lymphoproliferative diseases. Type II and Type III were mixed cryoglobulins. Type II consisted of polyclonal IgG and monoclonal IgM and was associated mainly with vascular, renal, and neurologic diseases. Type III consisted of polyclonal IgG and polyclonal IgM and was associated mainly with autoimmune diseases. More sensitive methodologies developed since the Brouet classification have detected multiple monoclonal immunoglobulins in cryoglobulins, i.e., oligoclonal immunoglobulins[2,3]. Oligoclonal cryoglobulins were not included in the Brouet classification. In this study a new terminology for oligoclonal cryoglobulins is proposed: Type IIa.

In early studies, cryoglobulinemic vasculitis was reported to occur predominantly in association with Type II cryoglobulinemia[4-7], and chronic hepatitis without extrahepatic disease was associated mainly with Type III[6,8]. In our recent study, Type II cryoglobulins containing rheumatoid factor (RF) were mainly associated with cryoglobulinemic vasculitis[9]. In a large metaanalysis of patients with chronic hepatitis, mixed cryoglobulinemia (with no description of any specific type) was reported to be associated with, and a prognostic indicator of, cirrhosis[10]. That report[10] conflicts with a large multi-clinic Italian study that reported the prevalence of cirrhosis was decreased in patients with Type II cryoglobulinemia and cryoglobulinemic vasculitis[6]. To determine whether a mixed cryoglobulin type did correlate with cirrhosis in HCV-infected patients, we investigated the results of mixed cryoglobulin tests performed in the clinical laboratory on patients with and without HCV infection.

MATERIALS AND METHODS

We studied cryoglobulin tests on 89 HCV-infected patients with and without cirrhosis performed between March 2001 and August 2002 in the Clinical Immunology Laboratory, Lahey Clinic. Blood specimens were collected and cryoglobulins were isolated and quantitated as described[9]. A high-resolution, semiautomated immunofixation electrophoresis system was employed for typing the cryoglobulins (Sebia Hydrasys LC system; Sebia, Issy-les-Moulineaux, France). Antibodies to HCV were detected as described[9]. HCV infection was confirmed by qualitative or quantitative tests for HCV-RNA using the COBAS Amplicor® assay (Roche Molecular Diagnostics, Branchburg, NJ, USA). Type I cryoglobulins were excluded from the study. Mixed cryoglobulins Type II, Type IIa (oligoclonal), or Type III were studied. Data collected on each patient included age, sex, cryoglobulin characterization, serum HCV-RNA concentration, anti-HCV antibodies, and serum alanine transaminase. Cirrhosis was diagnosed with histologic documentation or clinically by liver imaging consistent with cirrhosis or by evidence of decompensated liver function.

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Statistical analysis. Univariate analyses were used to compare demographics and clinical and laboratory data. Differences in proportions were examined with the chi-square test or Fisher's exact test. An unpaired t test was used for continuous variables. All calculated p values are 2-tailed and those < 0.05 are noted.

RESULTS

Among all the mixed cryoglobulins (Table 1) there was a predominance of Type II (44%) compared to Type III (20%). The prevalence of Type IIa was 36%. There was a marked predominance of males among the patients with cirrhosis compared to those without cirrhosis ($p = 0.003$). There was a significant difference in the distribution of cryoglobulin types among HCV-infected patients with and without cirrhosis ($p = 0.0045$). Type IIa was the only cryoglobulin that had a higher prevalence among patients with cirrhosis than among patients without cirrhosis.

DISCUSSION

There has been a reversal of the 2:3 ratio of Type II to Type III cryoglobulins with the use of more sensitive methods for detecting monoclonal immunoglobulin components in cryoglobulins. Type III was the predominant type in all early studies[1,6,11]. The prevalence of Type IIa, 36% in our study, was similar to the 34% prevalence previously reported[12]. The male predominance among patients with cirrhosis compared to those without cirrhosis in this study was consistent with the known male prevalence within cirrhosis. That Type IIa cryoglobulins were correlated with cirrhosis has not been reported previously. This observation requires confirmation and a determination of whether this association is unique to cirrhosis secondary to HCV infection.

The observation that a specific type of cryoglobulin may be associated with cirrhosis in HCV-infected patients differs from the study that found cirrhosis was associated with mixed cryoglobulinemia without identifying a specific cryoglobulin type[10].

A specific cryoglobulin type, Type IIa, and not mixed cryoglobulins in general, was associated with cirrhosis in patients infected with hepatitis C virus.

Table 1. Cryoglobulin types among HCV-infected patients with and without cirrhosis.

	Cirrhosis	No Cirrhosis
Total no. of patients	38	51
Male/female ratio*	6.60 (33/5)	1.22 (28/23)
Type II**, no. of patients in group (%)	11 (28.0)	28 (54.9)
Type IIa, n (%)	21 (55.3)	11 (21.6)
Type III, n (%)	6 (15.8)	12 (23.5)

* $p = 0.003$, chi-square test of difference in percentage of males with and without cirrhosis. ** $p = 0.0045$, Fisher exact test of difference in distribution of cryoglobulin types for those with and without cirrhosis.

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