

FAMILIAL OCCURRENCE OF IgM κ GAMMAPATHY: NO ROLE OF HCV INFECTION

Pietro Custodi*, **Alberto Cerutti^o**, **Piero Cassani***, **Carlo Perazzi^o**, **Paolo Ravanini[#]**,
Giacomo Fortina[#]

*Divisione di Medicina Interna and ^oLaboratorio Analisi, Ospedale S. Biagio, Domodossola; and [#]Laboratorio di Microbiologia e Virologia, Ospedale Maggiore, Novara, Italy

Sir,

Waldenström's macroglobulinemia (WM) is a relatively rare lymphoproliferative disorder, but a high incidence can be observed in certain families.¹ Since the first familial case report in 1962,² many others have been described.³

Abnormal immunoglobulin levels and autoimmune features have also been described in their relatives. Although the etiologic factors for WM are unknown, possible involvement of both a genetically determined immunologic abnormality and environmental factors have been suggested.⁴ It is well known that hepatitis C virus (HCV) infection plays a role in type II cryoglobulinemia⁵ and that the monoclonal IgM of a WM may behave as a cryoglobulin.⁶ Moreover, Santini *et al.*⁷ recently investigated the presence of HCV RNA in six patients affected by WM and detected viral RNA in sera of all of them. These findings stimulated our curiosity to investigate a possible role for HCV infection in familial occurrence of IgM κ gammopathy, with observation of immunologic abnormalities in relatives.

The family studied was composed of two members: a 73-year-old brother with WM (IgM κ -type), and a 70-year-old sister with an IgM κ monoclonal gammopathy in progression. Two sons, aged 44 and 29, and a daughter, aged 25 years, of the patient with WM are healthy; the sister is without progeny. Another patient, aged 68 years with WM IgM κ -type, was also included for detection of HCV infection.

Neither the two sons nor the daughter of the patient with WM showed a serum monoclonal Ig or Bence Jones proteinuria. Urinalysis also failed to demonstrate Bence Jones proteinuria in

the sister with an IgM κ monoclonal gammopathy. Low IgA (69 mg/dL) and high IgE levels (479 UI/mL) were found in the brother's daughter and a very high level of IgE (3640 UI/mL) was observed in one son. The other son was an asymptomatic HBsAg carrier. IgG levels in the lower normal range were detected in all three of them. An antithyroglobulin antibody titer of 693 U/mL was found in the sister, despite normal thyroid function and a normal-appearing gland on physical examination. In all six cases both anti-HCV antibodies (third-generation enzyme-linked immunosorbent assay) and viral serum RNA [*nested polymerase chain reaction* with 35- and 25-fold thermal cycles, using primers 1CH, 2CH, 4CH and 1TS; any amplified sequence was detected with a DEIA method by means of a probe that links to a UTR 5' terminal sequence (3CH)] were absent and neither cryoglobulinemia nor rheumatoid factor was present.

Familial occurrences of WM or IgM κ monoclonal gammopathy are rare. In these families there is an apparent excess of quantitative and qualitative abnormalities of immunoglobulin levels, thyroid disease, and autoimmune manifestations in close relatives.⁴ Indeed all the relatives of our family showed abnormal immunoglobulin levels and the sister also demonstrated a high antithyroglobulin antibody titer. High frequencies of such anomalies seem to be a common and significant finding and suggest a possible genetic predisposition to the immune dysfunction, although environmental factors cannot be excluded. In this regard, evidence of HCV infection in the majority of patients with

type II mixed cryoglobulinemia, even without clinical or biochemical evidence of liver damage, and of the ability of HCV to infect lymphocytes, was recently shown,⁵ suggesting that HCV can be a hepatotropic as well as a lymphotropic virus.

In a recent study Santini *et al.*⁷ investigated the presence of HCV RNA in six patients affected by WM and in all cases detected viral RNA in their sera, although only two of the six showed a slight positivity for the presence of antibodies against HCV protein C22c. For this reason we investigated a possible role for HCV infection in our case of familial IgM κ gammopathy, in relatives and in another patient with WM. No evidence of HCV infection was found in any of the six cases. Therefore, while we agree with Santini *et al.*⁷ about the need to continue investigating a possible role for HCV infection in monoclonal gammopathy, our findings show that IgM gammopathy cannot be associated with HCV and suggest that genetic background rather than

environmental factors⁸ may be the prevailing cause of this disease, at least in the family we studied.

References

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