Mixed cryoglobulinemia and mortality: a review of the literature

A. Della Rossa[1], F. Marchi[2], E. Catarsi[2], A. Tavoni[2], S. Bombardieri[1]

[1]*Rheumatic Disease Unit and*
[2]*Clinical Immunology Unit, University of Pisa, Pisa, Italy.*

Alessandra Della Rossa, MD
Francesco Marchi, MD
Eleonora Catarsi, MD
Antonio Tavoni, MD
Stefano Bombardieri, MD

Please address correspondence to: Prof. Stefano Bombardieri, Rheumatic Disease Unit, Department of Internal Medicine, University of Pisa, via Roma 67, 56126 Pisa, Italy. E-mail: s.bombardieri@int.med.unipi.it.

Received and accepted on September 9, 2008.

Clin Exp Rheumatol 2008; 26 (Suppl. 51): S105-S108.

Key words: Mixed cryloglobulinemia, HCV infection, mortality, risk factors.

Competing interests: none declared.

ABSTRACT

Mixed cryoglobulinemia is a highly heterogeneous clinical syndrome in terms of clinical presentation, extent and severity of organ involvement, immunological abnormalities and clinical course. Modern management began with the discovery of the close association between this syndrome and hepatitis C virus (HCV) infection. In this review we examined previously published studies on mortality in different series of patients with mixed cryoglobulinemia (MC). Patients with mixed cryoglobulinemia have higher mortality rates, predicted by age, renal involvement, intestinal vasculitis, widespread vasculitis and type of cryoglobulins.

Introduction

Mixed cryoglobulinemia is a clinical syndrome characterized by the classic triad of purpura, weakness and Raynaud's phenomenon, first described by Meltzer and Franklin in a small series of patients in 1966 (1). Brouet *et al*. classified three main types of cryoglobulins: type I - a monoclonal immunoglobulin; type II, or mixed cryoglobulins, - a polyclonal IgG which combines with a monoclonal IgM rheumatoid factor; type III - polyclonal immunoglobulins (2, 3). Since 1989, with the discovery of the etiologic agent of non-A, non-B hepatitis, a growing number of reports have confirmed chronic hepatitis C virus (HCV) infection in the primary aetiology of mixed cryoglobulinemia (4-9).

Mixed cryoglobulinemia is complex in its pathogenesis and clinical presentation. The primary pathogenetic aspects involve chronic HCV infection, the deposition of immune-complexes in the target organs and a smouldering lymphoproliferative process which can evolve into a malignant lymphoma in a minority of patients (10).

The clinical picture may vary from a relatively benign course with minor clinical manifestations to dramatic presentation with multi-system involvement and life threatening complications (11). Patients with mixed cryoglobulinemia have increased mortality rates relative to the general population. Several early anecdotal observations suggested that renal involvement, infection and widespread vasculitis were the primary cause of death (12-14).

Saccardo *et al* (13), found that the ratio of type II/III cryoglobulins was associated with increased mortality.

After the discovery of the association with HCV infection a number of longitudinal studies focused on Mixed cryoglobulinemia patients, usually in series with a variable proportion of HCV-infected individuals (15-19). Some studies reported clinical features and survival rates similar in HCV positive and HCV-negative cryoglobulinemia patients (16, 18, 20). However HCV-negative patients might show a lower percentage of the typical clinical triad, especially purpura. Patients with mixed cryoglobulinemia and Sjögren's syndrome or other connective tissue disease are often characterized as having clinical-prognostic features comparable to classical cryoglobulinemic vasculitis (21), although increased frequencies of renal involvement and B-cell non-Hodgkin's lymphoma, lower gammaglobulins and higher mortality rates in MC are claimed (22).

Studies of mortality in mixed cryoglobulinemia

Four patient series concerning mortality in mixed cryoglobulinemia are illustrated in Table I.

Cumulative survival after 10 years from diagnosis was 56% in the study of Ferri *et al*. (16) and 58% in the study of Bryce *et al*. (19). Rieu and coworker (18) found a survival of 77% of HCV-positive versus 84% of HCV-negative

Table I. Clinical and epidemiological data as well mortality rates in 4 recent series in the literature.

Study (year)	*Rieu 2002 (18)	**Ferri 2004 (16)	***Ramos Casals 2006 (17)	*Bryce 2006 (19)
No. patients	49	231	29	66
Mortality	8/49	97/231	19/29	14/66
Follow-up	38.7±36.7 months	6.7±6 years	3.6 years	3.2±2.84 years
F/M	-	3.7	-	0.8
Hepatitis C virus (HCV)+ (%)	67.3	92	72	61
Raynaud's phenomenon	17 (34.7%)	91/190 (48%)	-	8 (12%)
Weakness	-	210/210 (100)	-	-
Purpura	33 (67.3%)	187/231 (81%)	14 (48%)	36 (55%)
Skin ulcers	20 (40.8%)	25/231 (11%)	-	
Joint involvement	-	196/200 (98%)	8 (28%)	17 (26%)
Peripheral neuropathy	27 (55.1%)	134/231 (58%)	9 (31%)	12 (18%)
Sicca syndrome	17 (34.7%)	65/225 (29%)	-	-
Liver involvement	-	134/231 (58%)	-	-
Renal involvement	12 (24.5%)	46/231 (20%)	-	17 (26%)
Gastrointestinal vasculitis	-	-	-	-
B-cell lymphoma	-	21/2331 (10)	-	2 (3%)

* Cumulative data
** Data at disease onset
*** Cumulative data only in patients with "life-threatening" cryoglobulinemia.

Table II. Acute causes of death in 4 patient series.

Study	Rieu 2002 (18)	Ferri 2004 (16)	Ramos Casals 2006 (17)	Bryce 2006 (19)
No. patients	49	231	29	66
Mortality	8/49	97/231	19/29	14/66
Stroke	2 (25%)		1 (5%)**	-
Hepato-cellular carcinoma (HCC)	1 (12.5%)	7 (10%)**	-	-
Liver involvement	-	19§ (13%)**	3 (18%)**	-
Lymphoma	-	9 (13%)**	-	3 (21%)
Pulmonary	-	7 (10%)**	4 (21%)**	-
Renal	-	23 (33%)**	4 (21%)**	-
Gastrointestinal	1 (12.5%)	-	-	-
Infection	2 (25%)	-	5 (26%)**	-
Vasculitis	-	9 (13%)**	6 (31%)**/***	-
More than one*	2 (25%)	-	-	5 (36%)
Miscellaneous	-	17 (25%)**	-	-
Unknown	-	18 (18%)	-	6 (43%)

* More than one cause mixed cryoglobulinemia-related
** In some patients, multiple organ involvement was responsible for death
*** Gastrointestinal vasculitis
§ as reported in the original paper (16)

patients after 5 years of follow-up. On the other hand, Ramos Casals *et al*. (17) found a strikingly higher mortality rate in his small cohort of patients with what they defined "life threatening involvement" (66% died after a mean period of follow-up of 3.6 years).

Rieu *et al*. (18) described mortality outcomes in 49 patients with symptomatic HCV-positive and HCV-negative cryoglobulinemia. Eight patients (16%) died during the follow-up, 38.7±36.7 months after diagnosis. The only variable associated with a higher risk of mortality was the use of plasma exchange, possibly reflecting more severe clinical status in patients undergoing this procedure.

Ferri *et al*. (16) reported that 97 of 231 MC mixed cryoglobulinemia patients seen between 1972 and 2001 died over a mean of 6.7 years. The attributed causes of death included renal failure in 33%, chronic hepatitis with cirrhosis in 13%, widespread vasculitis in 13% and B-cell non-Hodgkin's lymphoma in 13% (Table II). The risk for mortality was significantly greater in men and in patients with renal involvement. By contrast, the presence of sicca syndrome seemed to predict a better outcome. Moreover, the 10-year survival was reduced in type II as compared to type III cryoglobulins.

Cox multivariate analysis of 10-year survival revealed that age, male sex and renal involvement were significant independent risk factors for mortality. A benign course occurs in up to half of the patients, while a more severe course was seen in 35% of the cases.

Ramos Casals *et al*. (17) analyzed the

clinical and immunological features of 29 MC patients with what was termed "life-threatening cryoglobulinemia" defined as having glomerulonephritis with renal failure, catastrophic GI vasculitis, lung involvement with respiratory failure, or severe central nervous system, spinal cord or cranial nerve involvement attributable to mixed cryoglobulinemia. In a series of 209 mixed cryoglobulinemia patients consecutively followed since 1991, the 29 (14%) patients with "life threatening cryoglobulinemia" were matched with a control group of 58 patients without life threatening manifestations. The rate of HCV in these patients was 72% and 78%, respectively.

Nineteen (66%) of the 29 patients with life threatening manifestations died after a mean follow-up of 3.6 years (range 1-11). Mortality was 100% for patients with pulmonary haemorrage and intestinal ischemia, seen primarily in older patients. By contrast, patients with renal failure were younger and had a mortality rate of 60%.

Bryce *et al*. (19) found that 14 (21%) of 66 patients died during a median follow-up of 3.2±2.8 years. The attributed causes of death included 3 with a lymphoproliferative disorder, 2 with complications of hepatitis C and lymphoproliferative disorder, and 9 whose cause of death was unknown. The only significant predictor of mortality was age.

Following the breakthrough of the discovery of HCV infection, on the basis of the analysis of the present data, it is not known whether the outcome of MC has changed. HCV is apparently not linked to mortality, however, the discovery that MC is mostly a viral triggered disease, has changed a great deal the management of this disease, as profound immune-suppression have been discouraged in favour of antiviral therapy (23-24). Ferri *et al*. (16) analysed a series of patients whose disease onset started before and after the discovery of HCV, but it is not known whether mortality has changed according to the onset of the disease. HCV status did not seem to affect survival, although this result was blunted by the small number of HCV negative subjects. Ramos Casals *et al*. (17) started to collect patients beginning in 1991. The outcome of his small series, however, was worse due to a selection bias of more severe cases. Finally, according to Rieu *et al*. (18), although survival rate was slightly better in HCV-negative patients, no statistical significant difference in mortality emerged according to HCV status.

In order to overcome this problem, we selected seventy HCV-positive subjects whose disease onset occurred after 1990, from our series of 250 MC patients, with the purpose of evaluating the mortality rate in this population (manuscript in preparation). Cumulative survival after 10 years from diagnosis was 71.5 % *vs*. 56% of the series of Ferri *et al*. (16).

The most frequent causes of death were confirmed to be renal involvement (28%), GI vasculitis (21%), liver involvement (21%) and infection (14%), most frequently occurring during immune suppressive treatment. Other causes of death were stroke and myocardial infarction.

Causes of death in mixed cryoglobulinemia

Table II shows the acute causes of death throughout the different series. The most frequent causes of death were renal involvement and widespread vasculitis (most often involving the gastrointestinal tract). Other frequent causes of death were liver involvement and infections. In a significant number of cases, the causes of death remained unknown. No comparison with standardized data is available except for the study of Ferri *et al*. (16)

In this study survival curves were significantly lower when compared to the general Italian population.

Table III shows the hazard ratio of clinical and epidemiological variables in the study of Ferri *et al*. (16).

In conclusion, data on mortality in mixed cryoglobulinemia patients give heterogeneous results that could depend on the different features of the patients recruited, different time of enrolment and different periods of follow-up. However, a number of prognostic factors have been almost invariably associated with a higher mortality, in particular, age, renal involvement, intestinal vasculitis, widespread vasculitis, type of cryoglobulins.

Table III. The hazard ratio of clinical and epidemiological data correlated to mortality in the study of Ferri *et al*. (16).

Study	Ferri *et al*. (16)
Age	1,086
Male sex	1,978
Renal involvement	2,967

References

1. MELTZER M, FRANKLIN EC, ELIAS K, McCLUSKEY RT, COOPER N: Cryoglobulinemia. A clinical and laboratory study. Cryoglobulins with rheumatoid factor activity. *Am J Med* 1966; 40: 837-56.
2. BROUET JC, CLOUVEL JP, DANON F, KLEIN M, SELIGMAN M: Biologic and clinical significance of cryoglobulins. *Am J Med* 1974; 57: 775-88.
3. ROZIN AP, LEWIN M, BRAUN-MOSCOVICI Y, ITZHAK OB, BERGMAN R, BALBIR_GURMAN A: Essential mixed cryoglobulinemia type II. *Clin Exp Rheumatol* 2006; 24: 329-32.
4. CHOO QL, KUO G, WEINER AJ *et al*.: Isolation of a c-DNA clone derived from a blood borne non-A, non-B viral hepatitis genome. *Science* 1989; 244: 359-62.
5. VASSILOPOULOS D, YOUNOSSI ZM, HADZIYANNIS E *et al*.: Study of host and virological factors of patients with chronic HCV infection and associated laboratory or clinical autoimmune manifestations. *Clin Exp Rheumatol* 2003; 21 (Suppl. 32): S101-S111.
6. FERRI C, GIUGGIOLI D, CAZZATO M, SEBASTIANI M, MASCIA MT, ZIGNEGO AL: HCV-related cryoglobulinemic vasculitis: an update on its etiopathogenesis and therapeutic strategies. *Clin Exp Rheumatol* 2003; 21 (Suppl. 32): S78-84.
7. PAGNOUX C, COHEN P, GUILLEVIN L: Vasculitides secondary to infections. *Clin Exp Rheumatol* 2006; 24 (Suppl. 41): S71-81.
8. ANTONELLI A, FERRI C, GALEAZZI M *et al*.: HCV infection: pathogenesis, clinical manifestations and therapy. *Clin Exp Rheumatol* 2008; 26 (Suppl. 48): S39-47.
9. GATTA A, GIANNINI C, LAMPERTICO P *et al*.: Hepatotropic viruses: new insights in pathogenesis and treatment. *Clin Exp Rheumatol* 2008; 26 (Suppl. 48): S33-8.
10. FERRI C, ZIGNEGO AL, PILERI SA: Cryoglobulins (review). *J Clin Pathol* 2002; 55: 4-13.
11. DELLA ROSSA A, TAVONI A, BOMBARDIERI S: Cryoglobulinemia in: Rheumatology, Hochberg, 2004.
12. GOREVIC PD, KASSAB HJ, LEVO Y *et al*.: Mixed cryoglobulinemia: clinical aspects and long term follow up of 40 patients. *Am J Med* 1980; 69: 287-308.
13. SACCARDO F, MASSARO P, MONTI G, ANGELOPULOS N, GALLI M: Causes of death in essential mixed cryoglobulinemia. *Ric Clin Lab* 1986; 16: 389-91.
14. TARANTINO A, DE VECCHI A, MONTAGNINO G *et al*.: Renal disease in essential mixed cryoglobulinaemia. Long-term follow-up of 44 patients. *Q J Med* 1981; 50: 1-30.

15. MONTI G, SACCARDO F, PIOLTELLI P, RINALDI G: The natural history of cryoglobulinemia: symptoms at onset and during follow-up. A report by the Italian Group for the Study of Cryoglobulinemias (GISC). *Clin Exp Rheumatol* 1995; 13 (Suppl. 13): S129-33.
16. FERRI C, SEBASTIANI M, GIUGGIOLI D *et al.*: Mixed Cryoglobulinemia: demographic, clinical and serologic features and survival in 231 patients. *Semin Arthritis Rheum* 2004; 33: 355-74.
17. RAMOS-CASALS M, ROBLES A, BRITO-ZERON P *et al.*: Life threatening cryoglobulinemia: Clinical and immunological characterization of 29 cases. *Semin Arthritis Rheum* 2006; 36: 189-96.
18. RIEU V, COHEN P, ANDRÈ MH *et al.*: Characteristics and outcome of 49 patients with symptomatic cryoglobulinemia. *Rheumatology* 2002; 41: 290-300.
19. BRYCE AH, KYLE RA, DISPENZIERI A, GERTZ MA: Natural history and therapy of 66 patients with mixed cryoglobulinemia. *Am J Hematol* 2006; 81: 511-8.
20. TREJO O, RAMOS-CASALS M, GARCIA-CARRASCO M *et al.*: Cryoglobulinemia: study of etiologic factors and clinical and immunologic features in 443 patients from a single center. *Medicine* (Baltimore) 2001; 80: 252 62.
21. MASCIA MT, FERRARI D, CAMPIOLI D, SANDRI G, MUSSINI C, FERRI C: Non HCV related mixed cryoglobulinemia. *Dig and Liver Dis* 2007; 39 (Suppl.1): S61-S64.
22. SAADOUN D, SELLA J, GHILLANI-DALBIN P, CRECEL R, JEAN-CHARLES PIETTE JC, CACOUB P: Increased risks of lymphoma and death among patients with non–hepatitis C virus-related mixed cryoglobulinemia *Arch Intern Med* 2006;166: 2101-8.
23. ABEL G, ZHANG Q, AGNELLO V: Hepatitis C virus infection in type II mixed cryoglobulinemia. *Arthritis Rheum* 1993; 36: 1341-49.
24. BOMBARDIERI S, DELLA ROSSA A: How HCV infection has changed the clinical approach to mixed cryoglobulinemia. *Ann Rheum Dis* 2007; 2007; Suppl. II: 45.