

Life-Threatening Cryoglobulinemic Patients With Hepatitis C

Clinical Description and Outcome of 279 Patients

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Abstract: Cryoglobulinemia is characterized by a wide range of causes, symptoms, and outcomes. Hepatitis C virus (HCV) infection is detected in 30%–100% of patients with cryoglobulins. Although more than half the patients with cryoglobulinemic vasculitis present a relatively benign clinical course, some may present with potentially life-threatening situations. We conducted the current study to analyze the clinical characteristics and outcomes of HCV patients presenting with life-threatening cryoglobulinemic vasculitis. We evaluated 181 admissions from 89 HCV patients diagnosed with cryoglobulinemic vasculitis consecutively admitted to our department between 1995 and 2010. In addition, we performed a systematic analysis of cases reported to date through a MEDLINE search.

The following organ involvements were considered to be potentially life-threatening in HCV patients with cryoglobulinemic vasculitis: cryoglobulinemic, biopsy-proven glomerulonephritis presenting with renal failure; gastrointestinal vasculitis; pulmonary hemorrhage; central nervous system (CNS) involvement; and myocardial involvement. A total of 279 patients (30 from our department and 249 from the literature search) fulfilled the inclusion criteria: 205 presented with renal failure, 45 with gastrointestinal vasculitis, 38 with CNS involvement, 18 with pulmonary hemorrhage, and 3 with myocardial involvement; 30 patients presented with more than 1 life-threatening cryoglobulinemic manifestation. There were 146 (52%) women and 133 (48%) men, with a mean age at diagnosis of cryoglobulinemia of 54 years (range, 25–87 yr) and a mean age at life-threatening involvement of 55 years (range, 25–87 yr). In 232 (83%) patients, life-threatening involvement was the first clinical manifestation of cryoglobulinemia. Severe involvement appeared a mean of 1.2 years (range, 1–11 yr) after the diagnosis of cryoglobulinemic vasculitis. Patients were followed for a mean of 14 months (range, 3–120 mo) after the diagnosis of life-threatening cryoglobulinemia. Sixty-three patients (22%) died. The main cause of death was sepsis (42%) in patients with glomerulonephritis, and cryoglobulinemic vasculitis itself in patients with gastrointestinal, pulmonary, and CNS involvement (60%, 57%, and 62%, respectively). In conclusion, HCV-related

cryoglobulinemia may result in progressive (renal involvement) or acute (pulmonary hemorrhage, gastrointestinal ischemia, CNS involvement) life-threatening organ damage. The mortality rate of these manifestations ranges between 20% and 80%. Unfortunately, this may be the first cryoglobulinemic involvement in almost two-thirds of cases, highlighting the complex management and very elevated mortality of these cases.

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Abbreviations: BVAS = Birmingham Vasculitis Activity Score, CI = confidence interval, CNS = central nervous system, FFS = Five-Factor Score, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = human immunodeficiency virus, HR = hazard ratio, IFN- α = interferon, GFR = glomerular filtration rate, MDRD = Modification of Diet in Renal Disease, MRI = magnetic resonance imaging.

INTRODUCTION

Cryoglobulins are immunoglobulins that precipitate in vitro at temperatures less than 37°C and redissolve after re-warming.⁷⁸ Cryoglobulinemia refers to the presence of cryoglobulins in serum, while the terms *cryoglobulinemic disease* or *cryoglobulinemic vasculitis* are used to describe patients with symptoms related to the presence of cryoglobulins, since many patients with cryoglobulinemia remain asymptomatic.⁷⁸ Cryoglobulinemic vasculitis mainly affects the small and, less frequently, medium-size arteries and veins,²⁹ which are thought to be damaged by the deposition of immune complexes on their walls, with the subsequent activation of the complement cascade.⁹⁰ The distinctive etiopathogenic feature of cryoglobulinemia is an underlying B-cell clonal expansion that mainly involves rheumatoid factor-secreting cells.^{79,87} Cryoglobulins have been observed in a wide variety of diseases, principally infections, neoplasia, and systemic autoimmune diseases.^{1,30} A viral origin of cryoglobulinemia was long suspected, but it was not until the early 1990s that evidence emerged of a close relationship with the hepatitis C virus (HCV),^{1,30,76} which is responsible for more than 80% of cases. In 1966, Meltzer et al⁵⁸ described the typical clinical symptoms associated with cryoglobulinemia (purpura, arthralgia, and weakness). Subsequent studies have described a broad spectrum of clinical features involving the skin, joints, kidneys, and nervous system.^{45,46,70,78,94,97}

Although more than 50% of patients with cryoglobulinemia have a relatively benign clinical course with a good prognosis and survival,³¹ some may present with potentially life-threatening situations involving the internal organs and resulting in progressive (renal involvement) or acute (pulmonary hemorrhage, gastrointestinal ischemia, central nervous system

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[CNS] involvement) organ damage as occurs in other systemic vasculitides.³⁷ Ferri et al³¹ found that 35% of patients with cryoglobulinemic vasculitis had a moderate-to-severe clinical course, with the prognosis being severely affected not only by cryoglobulinemic involvement, but also by associated processes such as HCV-related chronic liver disease. In a previous study,⁷⁷ we found life-threatening cryoglobulinemia in 14% of patients with cryoglobulinemic syndrome, irrespective of the underlying etiologies, with a differentiated prognosis according to the organ involved. It remains unclear why some patients present with this severe form of vasculitis, and there is very limited information on the clinical presentation and prognosis of these patients. We conducted the current study to analyze the clinical characteristics and outcomes of HCV patients presenting with life-threatening cryoglobulinemic vasculitis.

METHODS

Definition of Life-Threatening Cryoglobulinemia

The following organ involvements were considered to be potentially life-threatening in HCV patients with cryoglobulinemic vasculitis according to previous reports:^{77,97}

- Renal failure*: cryoglobulinemic glomerulonephritis presenting with raised serum creatinine > 1.5 mg/dL; glomerular disease was diagnosed by renal biopsy and classified as membranoproliferative glomerulonephritis, mesangial proliferative glomerulonephritis, or focal proliferative glomerulonephritis.
- Gastrointestinal involvement* of the esophagus, stomach, small and large intestine, or any intraabdominal viscera, presenting as gastrointestinal hemorrhage, intestinal ischemia, acute pancreatitis, or acute cholecystitis.
- Pulmonary hemorrhage* leading to respiratory failure, in the absence of pulmonary edema, adult respiratory distress syndrome, infectious pneumonia, lung cancer, or granulomatous disease.
- CNS involvement*: cerebral ischemia (in the absence of hypercoagulability or previously diagnosed cerebrovascular disease), cerebral hemorrhage, spinal cord or cranial nerve involvement.
- Cardiac involvement*: coronary involvement leading to myocardial infarction, in the absence of cardiovascular disease.

The 1996 Five-Factor Score (FFS) and the Birmingham Vasculitis Activity Score (BVAS), which are used to score the severity of systemic necrotizing vasculitides,^{40,53} were retrospectively measured at diagnosis of life-threatening involvement.

Selection of Cases

Patients

We evaluated 89 patients diagnosed with cryoglobulinemic vasculitis consecutively admitted to our department between 1995 and 2010. All patients fulfilled the 2010 classification criteria for cryoglobulinemic vasculitis.²³ We reviewed clinical charts of the 181 admissions of these patients searching for life-threatening presentations of cryoglobulinemia according to the above-mentioned definitions. We identified 37 patients with 43 admissions due to life-threatening cryoglobulinemia, of whom 30 had HCV-related cryoglobulinemia (the remaining 7 had essential cryoglobulinemia).

Literature Review

In addition to the cases identified in our department, we systematically analyzed cases reported to date through a

MEDLINE (National Library of Medicine, Bethesda, MD) and EMBASE (Elsevier) search.

- Search strategy*: We searched MEDLINE using the MeSH term *cryoglobulinemia* combined with the following MeSH terms: *kidney failure*, *lung diseases*, *gastrointestinal diseases*, *central nervous system*, and *heart failure* with these PubMed restrictions: date (January 1, 1990, to June 15, 2010), species (humans), and age (all adult).
- Eligibility criteria*: Studies were eligible when 1) the study population included adults with cryoglobulinemic vasculitis that fulfilled the definitions included in the clinical and laboratory items of the 2010 classification criteria;²³ 2) the patient/patients fulfilled the definition for at least 1 of the above-mentioned life-threatening presentations; 3) studies contained sufficient, clear information about the clinical characteristics and outcomes; and 4) patients had chronic HCV infection.
- Study selection*: Three authors (SR, CD-L, XB) read the titles and abstracts (if available) identified by the search and selected studies that might comply with the eligibility criteria. Five authors (SR, CD-L, XB, AB, PB-Z) fully reviewed the selected studies to determine criteria fulfillment, and disagreements were discussed among all authors until consensus was reached. We also searched the reference lists of relevant articles retrieved. Figure 1 shows a flow diagram of the MEDLINE literature search.

Statistical Methods

Categorical data were compared using the chi-square test. The Fisher exact test was used to confirm statistical differences where sample sizes were small. Continuous variables were analyzed using the Student t-test in large samples of similar variance, with results indicated as mean ± standard error of the mean (SEM), and the nonparametric Mann-Whitney U test for small samples, with results indicated as median and interquartiles. A 2-tailed value of $p < 0.05$ was taken to indicate statistical significance. When several independent variables appeared to have statistical significance in the univariate analysis, a multivariate Cox regression analysis was performed using a backward conditional stepwise method allowing adjustment for age, sex, and the variables that were statistically significant in the univariate analysis. The hazard ratios (HRs) and their 95% confidence intervals (CIs) obtained in the adjusted regression analysis were calculated. Kaplan–Meier survival curves were compared using the log-rank and Breslow tests. The statistical analysis was performed with the SPSS program (SPSS 18.0, Chicago, IL).

RESULTS

Clinical Description

A total of 279 patients (30 from our department and 249 from the literature search)^{2–9,11,12,15–19,24,25,27,32,33,35,36,38,39,42–52,54,55,59–75,81,82,84–86,89,91–95,98–100} fulfilled the inclusion criteria (Table 1). There were 146 (52%) female patients and 133 (48%) male, with a mean age at diagnosis of cryoglobulinemia of 54 years (range, 25–87 yr) and a mean age at life-threatening involvement of 55 years (range, 25–87 yr). In 232 (83%) patients, life-threatening involvement was the first clinical manifestation of cryoglobulinemia. In the remaining cases, severe involvement appeared a mean of 1.2 years (range, 1–11 yr) after the diagnosis of cryoglobulinemic vasculitis. In 207 (74%) patients, the clinical presentation required emergency room admission. Only 109 (39%) patients had

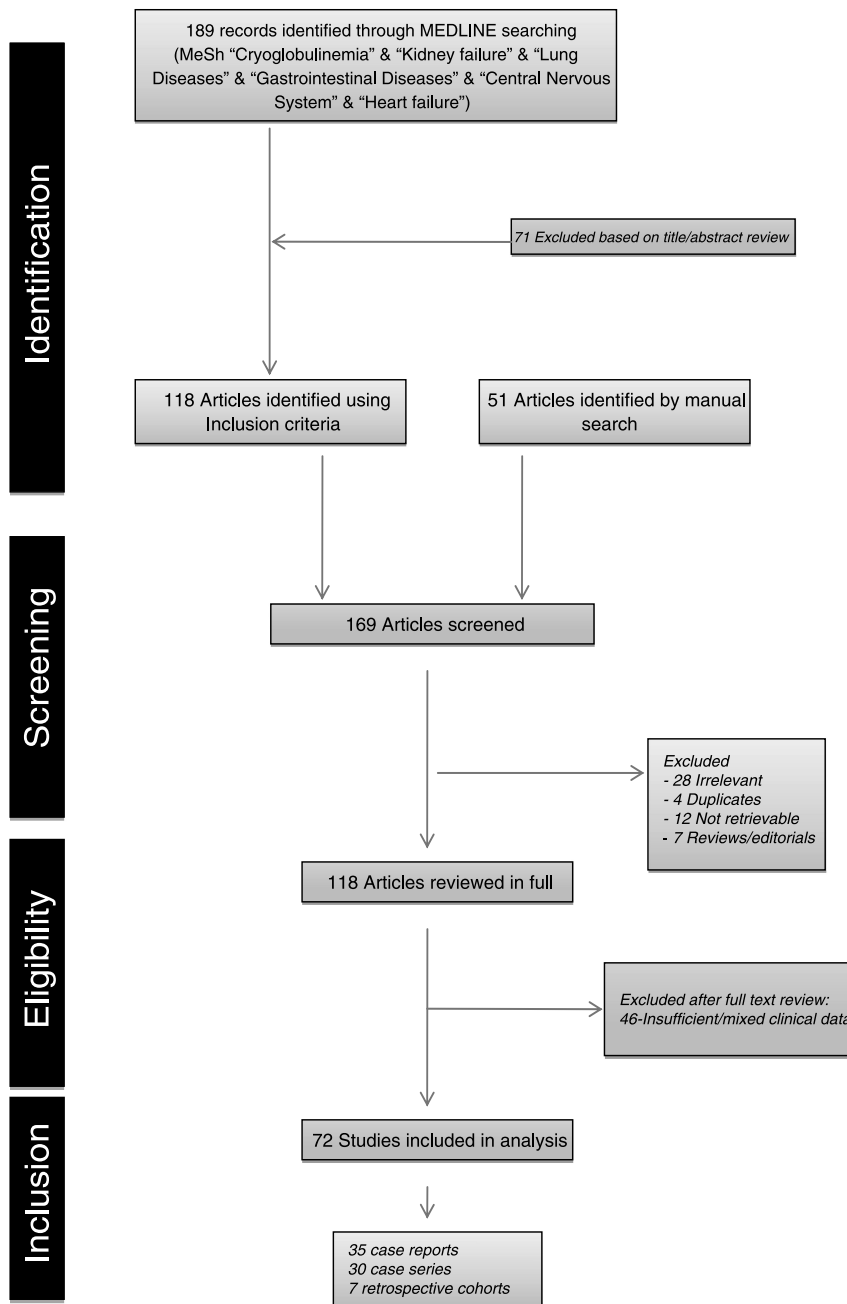


FIGURE 1. Flow chart of the MEDLINE literature search.

positive cryoglobulins before the life-threatening presentation. In 92 (33%) patients, HCV infection was discovered due to the life-threatening presentation of cryoglobulinemic vasculitis.

Fifty-five (20%) patients had other diseases associated with cryoglobulinemia in addition to chronic HCV infection, including human immunodeficiency virus (HIV) infection (n = 25), chronic hepatitis B virus (HBV) infection (n = 7), systemic autoimmune diseases (n = 15), and neoplasia (n = 8). Treatment of life-threatening cryoglobulinemia included corticosteroids in 167 cases, plasma exchanges in 148, immunosuppressive agents in 83, rituximab in 24, and infliximab in 2 cases. Antiviral

therapy was administered in 157 patients (interferon [IFN- α] monotherapy in 83, and combined IFN- α and ribavirin in 74).

Renal Failure Due to Glomerulonephritis

Of the 205 patients with biopsy-proven cryoglobulinemic glomerulonephritis^{3-8,12,16,18,19,24,25,36,39,42-47,50-52,54,55,60-67,69-71,74,75,77,81,82,84-86,91-95,98,99} (Table 2), 106 were male and 99 were female, with a mean age of 50 years at diagnosis of cryoglobulinemic vasculitis and 52 years at diagnosis of glomerulonephritis. The clinical presentation was nephrotic

TABLE 1. Epidemiologic Features, Associated Processes, Mean Cryocrit, and Causes of Death in 279 HCV Patients With Life-Threatening Cryoglobulinemia

Feature	HCV Patients With Life-Threatening Cryoglobulinemia (n=279) No. (%)
Sex (female)	146 (52)
Mean age at diagnosis of cryoglobulinemia (range), yr	54 (25–87)
Mean age at life-threatening involvement (range), yr	55 (25–87)
First clinical manifestation of cryoglobulinemia	232 (83)
Associated conditions	
Chronic viral infection	
HIV coinfection	25 (8.9)
HBV coinfection	7 (2.5)
Autoimmune diseases	15 (5.3)
Sjögren syndrome	6 (40)
SLE	4 (26.6)
Polyarteritis nodosa	2 (13.3)
Mixed connective tissue disease	1 (6.6)
Rheumatoid arthritis	1 (6.6)
Vasculitis ANCA (+)	1 (6.6)
Neoplasia	8 (2.8)
Immunologic features	
Mean cryocrit, % (n=66)	6.8 (0.5–80)
Mean cryocrit, mg/dL (n=50)	102.1 (0.36–1113)
Low C3 levels (<0.82 g/L)	112/156 (71.8)
Low C4 levels (<0.11 g/L)	96/125 (76.8)
Clinical presentations	
Renal failure due to glomerulonephritis	205 (73.4)
Gastrointestinal	45 (16.1)
CNS involvement	38 (13.6)
Pulmonary involvement	18 (6.4)
Cardiac involvement	3 (1)
Other cryoglobulinemic manifestations at diagnosis	
Cutaneous purpura	185 (66.3)
Articular involvement	151 (54.1)
Peripheral neuropathy	125 (44.8)
Fever	56 (20)
Treatment	
Corticosteroids	167 (59.8)
Plasma exchanges	148 (53)
Interferon- α	83 (29.7)
Immunosuppressive agents	83 (29.7)
Interferon- α + ribavirin	74 (26.5)
Rituximab	24 (8.6)
Infliximab	2 (0.71)
Mean follow-up of life-threatening cryoglobulinemia, mo	14 (3–120)

TABLE 1. (Continued)

Feature	HCV Patients With Life-Threatening Cryoglobulinemia (n=279) No. (%)
Outcomes	
Chronic renal failure	38 (13.6)
Relapse	33 (11.8)
Neoplasia	10 (3.5)
Death	63 (22.5)
Causes of death	
Infectious process	26 (41.2)
Cryoglobulinemia vasculitis	24 (38)
Neoplasia	6 (9.5)
Liver-related process	4 (6.3)
Cardiovascular events	2 (3.1)
Other causes	1 (1.5)

Abbreviations: ANCA = antineutrophil cytoplasmic antibodies, SLE = systemic lupus erythematosus.

syndrome in 96 (47%) patients and nephritic syndrome (proteinuria, hypertension, general edema) in 19 (9%), while the remaining 90 (44%) patients had an indolent presentation with asymptomatic raised creatinine levels. Renal biopsy disclosed membranoproliferative glomerulonephritis in 175 (85%) cases, mesangial proliferative glomerulonephritis in 15 (7%), focal proliferative glomerulonephritis in 10 (5%), and other histopathologic lesions in 5 (2%) patients.

Specific treatment for cryoglobulinemia consisted of combined therapy including antiviral agents in 121 cases (59%), plasma exchange in 110 (54%), corticosteroids in 95 (47%), immunosuppressive agents in 50 (24%), hemodialysis in 26 (13%), and biological agents in 13 cases (6%) (rituximab in 12 and infliximab in 1). After a mean follow-up of 13.2 months (range, 3–120 mo) from the diagnosis of glomerulonephritis, 39 (19%) patients developed chronic renal failure and 10 (5%) evolved to end-stage renal disease. Baseline renal function was associated with survival. In comparison with survivors, patients who died had higher baseline levels of serum creatinine (2.03 ± 0.76 mg/dL vs. 2.40 ± 0.20 mg/dL; $p = 0.044$) and glomerular filtration rate (GFR) estimated by the Modification of Diet in Renal Disease (MDRD) formula (38.37 ± 1.01 vs. 30.67 ± 1.48 ; $p < 0.001$). We also analyzed the influence of each therapy on the main outcomes (chronic renal failure defined as serum creatinine > 2 mg/dL at the end of follow-up, and death). With respect to renal outcome, patients with chronic renal failure were treated less frequently with antiviral therapies ($p = 0.008$). Patients who died had more frequently received corticosteroids ($p = 0.001$), immunosuppressants ($p = 0.024$), plasma exchanges ($p = 0.043$) and hemodialysis ($p = 0.043$), results that may have been related to a more severe clinical presentation. In contrast, patients who died had less frequently received antiviral therapies ($p < 0.001$).

Gastrointestinal Vasculitis

Gastrointestinal involvement was the second most frequently reported life-threatening cryoglobulinemic presentation

TABLE 2. Epidemiologic Features, Associated Processes, Mean Cryocrit, and Causes of Death in 205 HCV Patients With Renal Failure Caused by Biopsy-Proven Cryoglobulinemic Glomerulonephritis

Feature	HCV Patients With Renal Failure (n=205) No. (%)
Sex (female)	99 (48.2)
Mean age at diagnosis of cryoglobulinemia (range), yr	50 (25–81)
Mean age at life-threatening involvement (range), yr	52 (25–81)
Mean time between cryoglobulinemia and life-threatening involvement (range), mo	18.6 (0–168)
Associated conditions	
Chronic viral infection	
HIV coinfection	21 (10.2)
HBV coinfection	4 (1.9)
Autoimmune diseases	6 (2.9)
Sjögren syndrome	2 (33.3)
SLE	1(16.6)
Polyarteritis nodosa	1(16.6)
Rheumatoid arthritis	1(16.6)
Vasculitis ANCA (+)	1(16.6)
Neoplasia	7 (3.4)
Immunologic features	
Mean cryocrit, % (n=43)	7 (0.5–80)
Mean cryocrit, mg/dL (n=10)	16.7 (0.36–50)
Low C3 levels (<0.82 g/L)	97/132 (73.5)
Low C4 levels (<0.11 g/L)	90/102 (88.2)
Renal presentations	
Renal failure	205 (100)
Nephrotic syndrome	96 (46.8)
Nephritic syndrome	19 (9.2)
Renal involvement	
Membranoproliferative glomerulonephritis	175 (85.3)
Mesangial proliferative glomerulonephritis	15 (7.3)
Focal proliferative glomerulonephritis	10 (4.8)
Other	5 (2.4)
Other cryoglobulinemic manifestations at diagnosis	
Cutaneous purpura	136 (66.3)
Articular involvement	116 (56.5)
Peripheral neuropathy	78 (38)
Fever	6 (2.9)
Treatment	
Plasma exchanges	110 (53.6)
Corticosteroids	95 (47.5)
Interferon-α + ribavirin	65 (31.7)
Interferon-α	56 (27.3)
Immunosuppressive agents	50 (24.3)
Hemodialysis	26 (12.6)
Rituximab	12 (5.8)
Infliximab	1 (0.5)

TABLE 2. (Continued)

Feature	HCV Patients With Renal Failure (n=205) No. (%)
Mean follow-up of life-threatening cryoglobulinemia, mo	13.2 (3–120)
Outcomes	
Chronic renal failure	39 (19)
Relapse	12 (5.8)
Hemodialysis	10 (4.8)
Neoplasia	7 (3.4)
Death	43 (20.9)
Causes of death	
Infectious processes	18 (41.8)
Cryoglobulinemia vasculitis	10 (23.2)
Multiorgan failure	6 (13.9)
Liver-related processes	3 (6.9)
Neoplasia	3 (6.9)
Cardiovascular events	2 (4.6)
Iatrogenic	1 (2.3)

Abbreviations: See previous table.

(45 cases)^{11,19,24,33,42,43,48,49,51,59,69,73,77,81,83,89,93,98} (Table 3). There were 25 female patients and 20 male, with a mean age of 54 years at diagnosis of cryoglobulinemic vasculitis and 57 years at diagnosis of gastrointestinal vasculitis. The mean time between diagnosis of cryoglobulinemia and life-threatening involvement was 35 months. The clinical presentation included intestinal ischemia in 38 (84%) patients, abdominal pain in the upper right quadrant suggestive of cholecystitis in 3 (7%), cryoglobulinemic pancreatitis in 3 (7%), and cryoglobulinemic vasculitis of the adnexa and greater omentum in 1 (2%) patient. Clinical symptoms included severe abdominal pain and general malaise in 39 patients, bloody stool in 9, intestinal perforation in 3, hematemesis in 2, and hypermenorrhagia in 1 patient. Intestinal vasculitis was confirmed histopathologically in 23 patients; in 6 patients, gastrointestinal involvement was confirmed by endoscopy, in 2 by endoscopic retrograde cholangiopancreatography, and in the remaining 14 patients the diagnosis was based on the clinical and laboratory features. Treatment included corticosteroids (n = 36), immunosuppressive agents (n = 17), antiviral agents (n = 20), surgery (n = 12), plasma exchanges (n = 10), and rituximab (n = 9).

CNS Involvement

Thirty-eight patients had cryoglobulinemic CNS involvement^{2,3,6,8,9,15,17,27,32,35,39,42,47,51,59,68,70,72,77,81,95,100} (Table 4). There were 21 female patients and 17 male, with a mean age of 52 years at diagnosis of cryoglobulinemic vasculitis and 54 years at diagnosis of CNS cryoglobulinemic involvement. The clinical presentation consisted of hemiplegia in 18 (47%) patients, coma in 8 (21%), visual impairment in 6 (16%), encephalopathy in 5 (13%), seizures in 4 (10%), paraplegia in 3 (8%), disturbances of the bladder in 3 (8%), and generalized pyramidal syndrome in 3 patients (8%). CNS involvement consisted of cerebral ischemia in 18 (47%) cases, CNS vasculitis in 15 (40%) (demonstrated by magnetic resonance imaging

TABLE 3. Epidemiologic Features, Associated Processes, Mean Cryocrit, and Causes of Death in 45 HCV Patients With Cryoglobulinemic Gastrointestinal Involvement

Feature	HCV Patients With Gastrointestinal Involvement (n=45) No. (%)
Sex (female)	25 (55.5)
Mean age at diagnosis of cryoglobulinemia (range), yr	54.4 (28–81)
Mean age at life-threatening involvement (range), yr	57 (28–81)
Mean time between cryoglobulinemia and life-threatening involvement (range), mo	35 (0–132)
Associated conditions	
Chronic viral infection	
HBV coinfection	1 (2.2)
HIV coinfection	1 (2.2)
Autoimmune diseases	4 (8.8)
Sjögren syndrome	2 (50)
Polyarteritis nodosa	2 (50)
Immunologic features	
Mean cryocrit, % (n=2)	7 (1–25)
Mean cryocrit, mg/dL (n=7)	396 (0.18–1113)
Low C3 levels (<0.82 g/L)	11/17 (64.7)
Low C4 levels (<0.11 g/L)	12/17 (70.1)
Clinical presentation	
Abdominal pain	39 (86.6)
Bloody stool	9 (20)
Intestinal perforation	3 (6.6)
Hematemesis	2 (4.4)
Hypermenorrhagia	1 (2.2)
Gastrointestinal involvement	
Intestinal ischemia	38 (84.4)
Cholecystitis	3 (6.6)
Pancreatitis	3 (6.6)
Adnexa and greater omentum	1 (2.2)
Other cryoglobulinemic manifestations at diagnosis	
Cutaneous purpura	29 (64.4)
Articular involvement	16 (35.5)
Peripheral neuropathy	12 (28.5)
Fever	5 (11.1)
Raynaud phenomenon	4 (8.8)
Treatment	
Corticosteroids	36 (80)
Immunosuppressive agents	17 (37.7)
Interferon- α	15 (33.3)
Surgery	12 (28.5)
Plasma exchanges	10 (22.2)
Rituximab	9 (20)
Interferon- α + ribavirin	5 (11.1)
Mean follow-up of life-threatening cryoglobulinemia, mo	11.2 (6–24)
Outcomes	
Relapse	2 (4.4)
Neoplasia	2 (4.4)
Death	15 (33.3)

TABLE 3. (Continued)

Feature	HCV Patients With Gastrointestinal Involvement (n=45) No. (%)
Causes of death	
Cryoglobulinemia vasculitis (ischemia intestinal)	9 (60)
Infectious processes	5 (33.3)
Liver disease	1 (6.6)

[MRI] in all patients and postmortem studies in 4), transverse myelitis in 4 (10%), and cerebral hemorrhage in 2 (5%) patients. Treatment included corticosteroids (n = 33), immunosuppressive agents (n = 20), plasma exchange (n = 17), antiviral agents (n = 13), and biological therapies (n = 2). After a mean follow-up of 16 months (range, 6–84 mo) from the diagnosis of CNS involvement, 5 patients had established neurologic impairment (pyramidal syndrome and paraplegia in 2; pyramidal syndrome in 1; dysbasia, dysarthria, and spasticity in 1; and sensory alteration in 1).

Pulmonary Hemorrhage

Eighteen patients presented with pulmonary hemorrhage^{3,38,43,47,69,71,77,84,85,92,93} (Table 5). There were 11 female patients and 7 male, with a mean age of 56 years at diagnosis of cryoglobulinemic vasculitis and 58 years at diagnosis of pulmonary hemorrhage. The clinical features included respiratory failure in 11 (61.1%) patients, hemoptysis in 9 (50%), and dyspnea in 6 (33.3%) patients. All patients showed pulmonary infiltrates in the chest X-ray and required admission to the intensive care unit. Thirteen (72%) patients concomitantly had glomerulonephritis. Treatment included intravenous methylprednisolone (n = 18), immunosuppressive agents (n = 9), plasma exchanges (n = 8), antiviral agents (n = 6), and biological therapies (n = 2).

Cardiac Involvement

Three cases of cryoglobulinemic cardiac involvement have been reported.⁸¹ All 3 were male, with a mean age of 60 years at diagnosis of cryoglobulinemic vasculitis and 63 years at diagnosis of myocardial involvement. All 3 patients presented with ischemic heart attack demonstrated by arteriography. No patient had associated cardiovascular risk factors. Other cryoglobulinemic manifestations included purpura, peripheral neuropathy, joint involvement, and Raynaud phenomenon in all patients. Treatment consisted of high-dose corticosteroids (1–1.5 mg/kg per d) and plasma exchange in all patients.

Activity, Survival Analysis, and Risk Factors

At diagnosis, the mean FFS score was 1.58 ± 0.31 and the mean BVAS score was 15.00 ± 0.30 . Patients were followed for a mean of 14 months (range, 3–120 mo) after the diagnosis of life-threatening cryoglobulinemia. Sixty-three patients (22%) died. The stated cause of death was sepsis in 26 (41%) cases, cryoglobulinemic vasculitis (multisystem vasculitis in 8, chronic renal failure in 5, ischemic colitis in 4, pulmonary hemorrhage

TABLE 4. Epidemiologic Features, Associated Processes, Mean Cryocrit, and Causes of Death in 38 HCV Patients With Cryoglobulinemic CNS Involvement

Feature	HCV Patients With CNS Involvement (n=38) No. (%)
Sex (female)	21 (55.2)
Mean age at diagnosis of cryoglobulinemia (range), yr	52.4 (33–74)
Mean age at life-threatening involvement (range), yr	53.7 (34–76)
Mean time between cryoglobulinemia to life-threatening involvement (range), mo	12 (0–60)
Associated conditions	
HBV coinfection	2 (5.2)
HIV coinfection	1 (2.6)
Autoimmune diseases	5 (13.1)
SLE	2 (40)
Sjögren syndrome	1 (20)
Rheumatoid arthritis	1 (20)
Vasculitis ANCA (+)	1 (20)
Neoplasia	1 (2.6)
Immunologic features	
Mean cryocrit, % (n=14)	3.2 (1–13)
Mean cryocrit, mg/dL (n=7)	6.5 (0.3–13)
Low C3 levels (<0.82 g/L)	11/15 (73.3)
Low C4 levels (<0.11 g/L)	13/18 (72.2)
Neurologic presentations	
Hemiplegic	18 (47.3)
Coma	8 (21)
Visual impairment	6 (15.7)
Encephalopathy	5 (13.1)
Seizures	4 (10.5)
Paraplegia	3 (7.8)
Disturbances of the bladder	3 (7.8)
Generalized pyramidal syndrome	3 (7.8)
CNS involvement	
Cerebral ischemia	18 (47.3)
CNS vasculitis	15 (39.4)
Transverse myelitis	4 (10.5)
Cerebral hemorrhage	2 (5.2)
Other cryoglobulinemic manifestations at diagnosis	
Cutaneous purpura	22 (57.8)
Peripheral neuropathy	18 (47.3)
Articular involvement	11 (28.9)
Treatment	
Corticosteroids	33 (86.8)
Immunosuppressive agents	20 (52.6)
Plasma exchange	17 (44.7)
Interferon- α	11 (28.9)
Interferon- α + ribavirin	2 (5.2)
Infliximab (anti-TNF)	1 (2.6)
Rituximab	1 (2.6)

TABLE 4. (Continued)

Feature	HCV Patients With CNS Involvement (n=38) No. (%)
Mean follow-up of life-threatening cryoglobulinemia, mo	16 (6–84)
Outcomes	
Relapse	9 (23.6)
Neurologic damage	5 (13.1)
Neoplasia	1 (2.6)
Death	13 (34.2)
Causes of death	
Cryoglobulinemia vasculitis	8 (61.5)
Infectious processes	1 (7.6)
Neoplasia	2 (15.3)
Other	2 (15.3)

Abbreviations: TNF = tumor necrosis factor.

in 4, CNS vasculitis in 2, and cerebral hemorrhage in 1 patient) in 24 (38%), neoplasia in 6 (10%), chronic liver disease in 4 (6%), cardiovascular disease in 2 (3%), and post-renal biopsy bleeding complication in 1 (1%) patient. The main cause of death was sepsis (42%) in patients with glomerulonephritis, and cryoglobulinemic vasculitis itself in patients with gastrointestinal, pulmonary, and CNS involvement (60%, 57%, and 62%, respectively). No patient with myocardial involvement died. Survivors had a lower baseline FFS score (1.57 ± 0.03 vs. 1.62 ± 0.07 ; $p = 0.548$) and a lower BVAS score (14.63 ± 0.30 vs. 16.27 ± 0.84 ; $p = 0.025$) in comparison with patients who died.

Figure 2 shows the survival rate of the entire cohort (77%). Kaplan–Meier survival plots of patients classified according to the organ involved (renal, gastrointestinal, pulmonary, cardiac, CNS, and multiple organ life-threatening involvement) are shown in Figure 3. The poorest survival rates were observed in patients presenting with multiple involvement and those with pulmonary involvement (log rank and Breslow tests <0.001). Antiviral therapy was used in 157 patients (83 received monotherapy with IFN- α and 74 received combined therapy with IFN- α and ribavirin); life-threatening involvement occurred after or during the administration of antiviral therapy in 25 patients. Adjusted multivariate Cox regression analysis identified age (HR, 1.036; 95% CI, 1.007–1.067; $p = 0.016$) and use of antiviral therapy (HR, 0.296; 95% CI, 0.162–0.540; $p < 0.001$) as the baseline risk factors at diagnosis associated with survival. Figure 4 shows the Kaplan–Meier survival plots of patients classified according to the use of antiviral therapy.

DISCUSSION

The prevalence of HCV infection in cryoglobulinemic patients ranges between 30% and 100%, with the highest prevalence found in Mediterranean countries.⁷⁸ Conversely, between 12% and 56% of HCV-infected patients have circulating cryoglobulins, with the frequency also being highest in Mediterranean patients.⁷⁸ However, only 5%–10% of HCV patients with cryoglobulinemia are estimated to have symptomatic disease.⁸⁷ The severity of the cryoglobulinemic disease varies widely, with nearly half the cases having chronic disease with no vital organ

TABLE 5. Epidemiologic Features, Associated Processes, Mean Cryocrit, and Causes of Death in 18 HCV Patients With Cryoglobulinemic Pulmonary Hemorrhage

Feature	HCV Patients With Pulmonary Involvement (n=18) No. (%)
Sex (female)	11 (61.1)
Mean age at diagnosis of cryoglobulinemia (range), yr	56 (36–75)
Mean age at life-threatening involvement (range), yr	58 (36–75)
Mean time between cryoglobulinemia and life-threatening involvement (range), mo	21.3 (0–108)
Associated conditions	
Chronic viral infection	
HBV coinfection	2 (11.1)
CMV coinfection	1 (5.5)
Autoimmune diseases	2 (11.1)
Sjögren syndrome	1 (50)
Mixed connective tissue disease	1 (50)
Immunologic features	
Mean cryocrit, % (n=10)	11.7 (1–60)
Low C3 levels (<0.82 g/L)	8/9 (88.8)
Low C4 levels (<0.11 g/L)	8/9 (88.8)
Pulmonary presentations	
Respiratory failure	11 (61.1)
Hemoptysis	9 (50)
Dyspnea	6 (33.3)
Pulmonary involvement	
Pulmonary hemorrhage	18 (100)
Other cryoglobulinemic manifestations at diagnosis	
Cutaneous purpura	10 (55.5)
Fever	5 (27.7)
Articular involvement	3 (16.6)
Peripheral neuropathy	2 (11.1)
Treatment	
Corticosteroids	18 (100)
Immunosuppressive agents	9 (50)
Plasma exchange	8 (44.4)
Interferon- α	4 (22.2)
Interferon- α + ribavirin	2 (11.1)
Rituximab	2 (11.1)
Mean follow-up of life-threatening cryoglobulinemia, mo	
	9.5 (4–12)
Outcomes	
Relapse	6 (33.3)
Death	14 (77.7)
Causes of death	
Cryoglobulinemia vasculitis	8 (57.1)
Infectious processes	6 (42.8)

Abbreviations: CMV = cytomegalovirus.

involvement, one-third having moderate-to-severe disease, and less than 15% presenting with sudden, life-threatening disease.⁷⁸

The most frequent type of life-threatening presentation identified in the current study was renal failure caused by

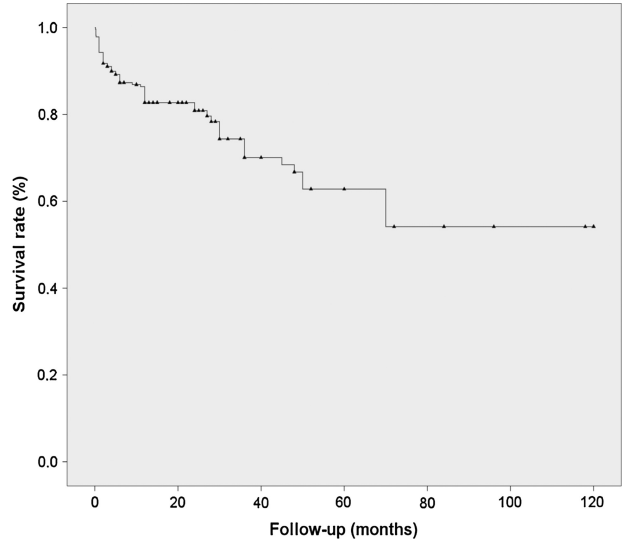
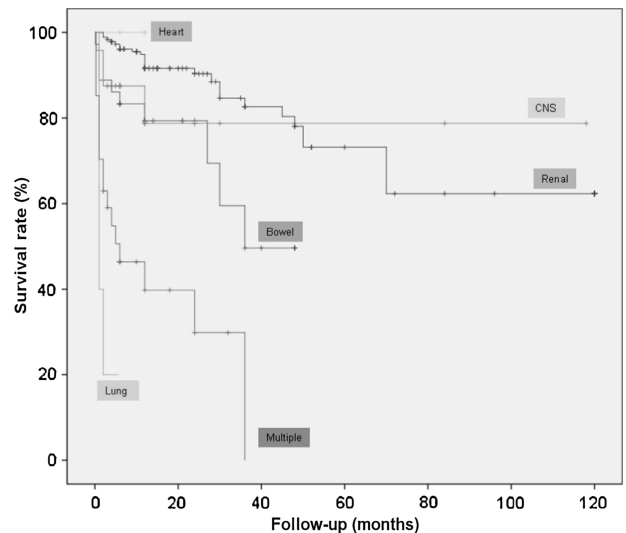


FIGURE 2. Kaplan-Meier survival curve in 279 patients with HCV-related life-threatening cryoglobulinemia.

cryoglobulinemic glomerulonephritis, with 20% of patients developing chronic renal failure and 5% progressing to end-stage renal disease. Studies have suggested that cryoglobulinemic glomerulonephritis significantly affects the prognosis and survival and is a major cause of death, either directly or secondary to infection or cardiovascular disease, with series from the 1990s showing 10-year survival rates ranging between 33% and 49%.^{31,94} However, authors of a 2007 multicenter Italian study⁸³ including 146 patients with cryoglobulinemic



	Heart	CNS	Renal	Bowel	Lung	Multiple
Cumulative proportion surviving (Kaplan-Meier)	100%	78.8%	62.3%	49.6%	20%	0%

FIGURE 3. Kaplan-Meier survival curves in patients with HCV-related life-threatening cryoglobulinemia by organ involvement in clinical presentation (renal, gastrointestinal, pulmonary, cardiac, CNS, and multiple organ life-threatening involvement).

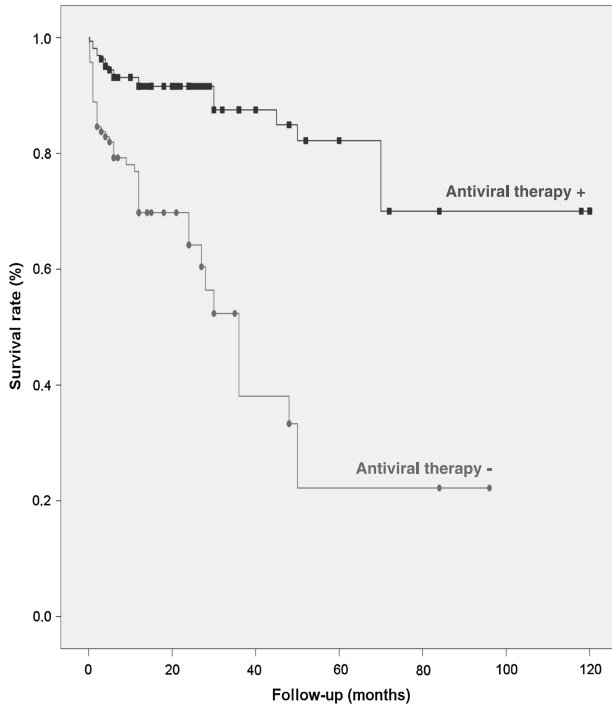


FIGURE 4. Kaplan-Meier survival curves in patients with HCV-related life-threatening cryoglobulinemia treated (“Antiviral therapy +”) and not treated (“Antiviral therapy -”) with antiviral therapy.

glomerulonephritis reported a better survival rate of nearly 80%, probably due to improved therapeutic management. We found a survival rate of 70% in HCV patients presenting with renal failure, with cryoglobulinemic involvement contributing directly to death in less than 10% of cases, and with cardiovascular disease and infection being the most frequent causes of death, as found by the largest reported series of patients with cryoglobulinemic glomerulonephritis.^{83,94} In 2002 Beddhu et al⁶ reported that all their cryoglobulinemic patients whose serum creatinine doubled or who progressed to end-stage renal disease were HCV positive, suggesting that HCV-related cryoglobulinemic glomerulonephritis seems to have a poor prognosis compared with non-HCV cryoglobulinemia. However, more recently, Matignon et al⁵⁶ found that 10% of non-HCV patients with cryoglobulinemic glomerulonephritis entered end-stage renal failure, a percentage double that found in our study in HCV patients presenting with renal failure, suggesting that the prognosis may have improved in HCV patients, possibly related to the progressive standardization of the use of antiviral therapies.

Gastrointestinal vasculitis was the second most-frequently reported life-threatening situation, with more than 80% of patients presenting with intestinal vasculitis and with a mortality rate of 40%. A 2010 single-center study found a mortality rate of nearly 20% in 12 HCV patients presenting with gastrointestinal involvement.⁹⁶ This range of 20%–40% is markedly better than the 87% we found in 2006 in patients with cryoglobulinemia of all etiologies,⁷⁷ which may have been due to various reasons: the majority of deaths were reported before the standardization of antiviral therapies; some cases were probably nonviral cryoglobulinemia, in which severe vasculitic involvement seems to be more frequent;³⁴ and possible delays in the diagnosis may have influenced the poor prognosis, as reported in systemic lupus erythematosus patients with intestinal vasculitis.⁵⁷

We found nearly 40 cases of CNS involvement in HCV patients, a similar number to that reported for gastrointestinal involvement and twice that reported for pulmonary hemorrhage, suggesting that CNS vasculitic cryoglobulinemia may be more frequent than previously supposed. The main clinical presentations include stroke (overwhelmingly cerebral ischemia, with only 2 cases of cerebral hemorrhage) and CNS vasculitis, with a mortality rate of 34%. Casato et al¹³ described a higher frequency of impaired cognitive function and MRI abnormalities in patients with HCV-related cryoglobulinemia compared with healthy controls or HCV patients without cryoglobulinemia, suggesting a potential role for cryoglobulins in CNS vasculitic damage. CNS cryoglobulinemic vasculitis should be included in the differential diagnosis of HCV patients presenting with focal neurologic deficits.⁸⁰

Although we found only 18 cases of pulmonary hemorrhage in HCV-related cryoglobulinemia, this vasculitic presentation had the highest mortality rate (80%). Some cryoglobulinemic patients survived the first episode of pulmonary hemorrhage but died after a second episode. These results confirm that cryoglobulinemic pulmonary hemorrhage, which has a very poor prognosis, as do other types of systemic vasculitis, is one of the main challenges in dealing with HCV patients.¹⁴

The uncontrolled design of the current study is a limitation when generalizing the results to all HCV patients. We included only the most severe presentation of HCV-related cryoglobulinemia, thus creating a patient selection bias, and the clinical and therapeutic data were retrospectively collected. This makes it impossible to compare our results with those of controlled studies, a bias that, in our opinion, is very difficult to avoid due to the rarity of the life-threatening presentation of cryoglobulinemia. In addition, the heterogeneous therapeutic approaches may limit the accurate evaluation of the therapeutic response in these patients. Nevertheless, in spite of these limitations, we believe that the recruitment of 279 cases with this rare, very severe presentation represents a significant, representative number that provides useful information on the management of these patients.

The current results, which demonstrated a global mortality rate of about 25% (and of >50% in some types of involvement), emphasize that the optimal therapeutic strategy for life-threatening cryoglobulinemic vasculitis remains to be defined. The clinical scenario is much more complicated when we consider that, for the majority of HCV patients, this life-threatening involvement presentation was the first clinical manifestation of cryoglobulinemia. This suggests that some cryoglobulinemic HCV patients may have a higher risk of developing a catastrophic presentation of cryoglobulinemic vasculitis: in these patients, we found a more profound autoimmune response (higher levels of serum cryoglobulins and complement consumption).⁷⁷ In addition, we found significant differences according to the different life-threatening involvements. Pulmonary hemorrhage and multiple organ involvement should be considered as devastating situations with a mortality rate of 63%–80%, with the majority of deaths caused by the vasculitic disease. In contrast, patients with renal cryoglobulinemic failure had a mortality rate of 15%, with the causes of death being unrelated to cryoglobulinemic vasculitis in most cases. Although the retrospective character of this study does not permit a differentiated analysis of the different therapeutic regimens used, the adjusted Cox regression model showed that the use of antiviral therapy was independently associated with survival, emphasizing the key role of antiviral therapy in HCV-related cryoglobulinemia.^{10,28,88} In addition, we found a positive trend for the use of rituximab in the adjusted multivariate analysis, reinforcing the usefulness of B cell-depleting agents

in cryoglobulinemia^{22,26} together with plasma exchange, as proposed for other systemic vasculitides.⁴¹ In spite of the limited data and the lack of case-control studies, the high mortality rate of HCV-related life-threatening cryoglobulinemia suggests the use of an aggressive therapeutic schedule including a combination of immunosuppressive agents and plasma exchanges or rituximab, followed by antiviral therapy,⁷⁸ together with an exhaustive follow-up, especially of the development of nonvasculitic complications including infection, liver cirrhosis, and cardiovascular disease.^{20,21,51}

REFERENCES

- Agnello V, Chung RT, Kaplan LM. A role for hepatitis C virus infection in type II cryoglobulinemia. *N Engl J Med*. 1992;327:1490–1495.
- Aktipi KM, Ravaglia S, Ceroni M, Nemni R, Debiaggi M, Bastianello S, Alfonsi E, Zardini E, Minoli L, Tavazzi E, Marchioni E. Severe recurrent myelitis in patients with hepatitis C virus infection. *Neurology*. 2007;68:468–469.
- Amital H, Rubinow A, Naparstek Y. Alveolar hemorrhage in cryoglobulinemia an indicator of poor prognosis. *Clin Exp Rheumatol*. 2005;23:616–620.
- Bartolucci P, Ramanoelina J, Cohen P, Mahr A, Godmer P, Le Hello C, Guillevin L. Efficacy of the anti-TNF- α antibody infliximab against refractory systemic vasculitides: an open pilot study on 10 patients. *Rheumatology (Oxford)*. 2002;41:1126–1132.
- Basse G, Ribes D, Kamar N, Mehrenberger M, Sallusto F, Esposito L, Guitard J, Lavayssiere L, Oksman F, Durand D, Rostaing L. Rituximab therapy for de novo mixed cryoglobulinemia in renal transplant patients. *Transplantation*. 2005;80:1560–1564.
- Beddhu S, Bastacky S, Johnson JP. The clinical and morphologic spectrum of renal cryoglobulinemia. *Medicine (Baltimore)*. 2002;81:398–409.
- Bestard O, Cruzado JM, Ercilla G, Goma M, Torras J, Seron D, Rama I, Ibernón M, Vinas O, Carrera M, Grinyo JM. Rituximab induces regression of hepatitis C virus-related membranoproliferative glomerulonephritis in a renal allograft. *Nephrol Dial Transplant*. 2006;21:2320–2324.
- Bruchfeld A, Lindahl K, Stahle L, Soderberg M, Schvarcz R. Interferon and ribavirin treatment in patients with hepatitis C-associated renal disease and renal insufficiency. *Nephrol Dial Transplant*. 2003;18:1573–1580.
- Buccoliero R, Gambelli S, Sicurelli F, Malandrini A, Palmeri S, De Santis M, Stromillo ML, De Stefano N, Sperduto A, Musumeci SA, Federico A. Leukoencephalopathy as a rare complication of hepatitis C infection. *Neurol Sci*. 2006;27:360–363.
- Cacoub P, Saadoun D, Limal N, Sene D, Lidove O, Piette JC. PEGylated interferon α -2b and ribavirin treatment in patients with hepatitis C virus-related systemic vasculitis. *Arthritis Rheum*. 2005;52:911–915.
- Cai FZ, Ahern M, Smith M. Treatment of cryoglobulinemia associated peripheral neuropathy with rituximab. *J Rheumatol*. 2006;33:1197–1198.
- Canada R, Chaudry S, Gaber L, Waters B, Martinez A, Wall B. Polyarteritis nodosa and cryoglobulinemic glomerulonephritis related to chronic hepatitis C. *Am J Med Sci*. 2006;331:329–333.
- Casato M, Saadoun D, Marchetti A, Limal N, Picq C, Pantano P, Galanaud D, Cianci R, Duhaut P, Piette JC, Fiorilli M, Cacoub P. Central nervous system involvement in hepatitis C virus cryoglobulinemia vasculitis: a multicenter case-control study using magnetic resonance imaging and neuropsychological tests. *J Rheumatol*. 2005;32:484–488.
- Casian A, Jayne D. Management of alveolar hemorrhage in lung vasculitides. *Semin Respir Crit Care Med*. 2011;32:335–345.
- Chandesris MO, Gayet S, Schleinitz N, Doudier B, Harle JR, Kaplanski G. Infliximab in the treatment of refractory vasculitis secondary to hepatitis C-associated mixed cryoglobulinaemia. *Rheumatology (Oxford)*. 2004;43:532–533.
- Cheng JT, Anderson HL Jr, Markowitz GS, Appel GB, Pogue VA, D'Agati VD. Hepatitis C virus-associated glomerular disease in patients with human immunodeficiency virus coinfection. *J Am Soc Nephrol*. 1999;10:1566–1574.
- Chepyala P, Velchala N, Brown D, Olden K. Encephalopathy, a rare initial presentation of HCV related cryoglobulinemia. *Am J Gastroenterol*. 2009;104:S289.
- D'Amico G. Renal involvement in hepatitis C infection: cryoglobulinemic glomerulonephritis. *Kidney Int*. 1998;54:650–671.
- Daoud MS, El-Azhary RA, Gibson LE, Lutz ME, Daoud S. Chronic hepatitis C, cryoglobulinemia, and cutaneous necrotizing vasculitis. Clinical, pathologic, and immunopathologic study of twelve patients. *J Am Acad Dermatol*. 1996;34:219–223.
- Della Rossa A, Marchi F, Catarsi E, Tavoni A, Bombardieri S. Mixed cryoglobulinemia and mortality: a review of the literature. *Clin Exp Rheumatol*. 2008;26(5 Suppl 51):S105–S108.
- Della Rossa A, Tavoni A, D'Ascanio A, Catarsi E, Marchi F, Bencivelli W, Salvadori S, Migliorini P, Bombardieri S. Mortality rate and outcome factors in mixed cryoglobulinaemia: the impact of hepatitis C virus. *Scand J Rheumatol*. 2010;39:167–170.
- De Vita S, Quartuccio L, Isola M, Mazzaro C, Scaini P, Lenzi M, Campanini M, Naclerio C, Tavoni A, Pietrogrande M, Ferri C, Mascia MT, Masolini P, Zabotti A, Maset M, Roccatello D, Zignego AL, Pioltelli P, Gabrielli A, Filippini D, Perrella O, Migliaresi S, Galli M, Bombardieri S, Monti G. A randomized controlled trial of rituximab for the treatment of severe cryoglobulinemic vasculitis. *Arthritis Rheum*. 2012;64:843–853.
- De Vita S, Soldano F, Isola M, Monti G, Gabrielli A, Tzioufas A, Ferri C, Ferraccioli GF, Quartuccio L, Corazza L, De Marchi G, Ramos Casals M, Voulgarelis M, Lenzi M, Saccardo F, Fraticelli P, Mascia MT, Sansonno D, Cacoub P, Tomsic M, Tavoni A, Pietrogrande M, Zignego AL, Scarpato S, Mazzaro C, Pioltelli P, Steinfeld S, Lamprecht P, Bombardieri S, Galli M. Preliminary classification criteria for the cryoglobulinaemic vasculitis. *Ann Rheum Dis*. 2011;70:1183–1190.
- Dhib M, Francois A, Godin M. Gallbladder vasculitis and mixed cryoglobulinemia. *Histopathology*. 1994;25:399–400.
- Dussol B, Moal V, Daniel L, Pain C, Berland Y. Spontaneous remission of HCV-induced cryoglobulinaemic glomerulonephritis. *Nephrol Dial Transplant*. 2001;16:156–159.
- Engel P, Gomez-Puerta JA, Ramos-Casals M, Lozano F, Bosch X. Therapeutic targeting of B cells for rheumatic autoimmune diseases. *Pharmacol Rev*. 2011;63:127–156.
- Erro Aguirre ME, Ayuso Blanco T, Tunon Alvarez T, Herrera Isasi M. Brain hemorrhage as a complication of chronic hepatitis C virus-related vasculitis. *J Neurol*. 2008;255:944–945.
- Feld JJ, Hoofnagle JH. Mechanism of action of interferon and ribavirin in treatment of hepatitis C. *Nature*. 2005;436:967–972.
- Ferri C. Mixed cryoglobulinemia. *Orphanet J Rare Dis*. 2008;3:25.
- Ferri C, Greco F, Longombardo G, Palla P, Moretti A, Marzo E, Fosella PV, Pasero G, Bombardieri S. Antibodies to hepatitis C virus in patients with mixed cryoglobulinemia. *Arthritis Rheum*. 1991;34:1606–1610.
- Ferri C, Sebastiani M, Giuggioli D, Cazzato M, Longombardo G, Antonelli A, Puccini R, Michelassi C, Zignego AL. Mixed cryoglobulinemia: demographic, clinical, and serologic features and survival in 231 patients. *Semin Arthritis Rheum*. 2004;33:355–374.
- Filippini D, Colombo F, Jann S, Cornero R, Canesi B. Central nervous system involvement in patients with HCV-related cryoglobulinemia: literature review and a case report. *Reumatismo*. 2002;54:150–155.

33. Fine GD, Trainer TD, Krawitt EL. Gastrointestinal bleeding, cryoglobulinemia, and hepatitis C. *Am J Gastroenterol*. 2004;99:964–965.
34. Foessel L, Besancenot JF, Blaison G, Magy-Bertrand N, Jaussaud R, Etienne Y, Maurier F, Audia S, Martin T. Clinical spectrum, treatment, and outcome of patients with type II mixed cryoglobulinemia without evidence of hepatitis C infection. *J Rheumatol*. 2011;38:716–722.
35. Fragoso M, Carneado J, Tuduri I, Jimenez-Ortiz C. Essential mixed cryoglobulinemia as a cause of ischemic cerebrovascular accident. *Rev Neurol*. 2000;30:444–446.
36. Garini G, Allegri L, Carnevali ML, Iannuzzella F, Buzio C. Successful treatment of severe/active cryoglobulinaemic membranoproliferative glomerulonephritis associated with hepatitis C virus infection by means of the sequential administration of immunosuppressive and antiviral agents. *Nephrol Dial Transplant*. 2006;21:3333–3334.
37. Geetha D, Seo P. Life-threatening presentations of ANCA-associated vasculitis. In: Khamashta MA, Ramos-Casals M, eds. *Autoimmune Diseases. Acute and Complex Situations*. London: Springer-Verlag; 2011:101–118.
38. Gomez-Tello V, Onoro-Canaveral JJ, de la Casa Monje RM, Gomez-Casero RB, Moreno Hurtrez JL, Garcia-Montes M, Armas LC. Diffuse recidivating alveolar hemorrhage in a patient with hepatitis C virus-related mixed cryoglobulinemia. *Intensive Care Med*. 1999;25:319–322.
39. Gournay J, Ferrell LD, Roberts JP, Ascher NL, Wright TL, Lake JR. Cryoglobulinemia presenting after liver transplantation. *Gastroenterology*. 1996;110:265–270.
40. Guillevin L, Lhote F, Gayraud M, Cohen P, Jarrousse B, Lortholary O, Thibault N, Casassus P. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients. *Medicine (Baltimore)*. 1996;75:17–28.
41. Guillevin L, Pagnoux C. Indication for plasma exchange for systemic necrotizing vasculitides. *Transfus Apher Sci*. 2007;36:179–185.
42. Heckmann JG, Kayser C, Heuss D, Manger B, Blum HE, Neundorfer B. Neurological manifestations of chronic hepatitis C. *J Neurol*. 1999;246:486–491.
43. Iusova OI, Krivosheev OG, Semenkova EN, Kogan EA. [Cryoglobulinemic vasculitis]. *Arkh Patol*. 2000;62:51–54.
44. Izzedine H, Sene D, Cacoub P, Jansen H, Camous L, Brocheriou I, Bourry E, Deray G. Kidney diseases in HIV/HCV-co-infected patients. *AIDS*. 2009;23:1219–1226.
45. Johnson R, Gretch D, Couser WG, Alpers CE, Wilson J, Chung M, Hart J, Willson R. Hepatitis C virus-associated glomerulonephritis. Effect of α -interferon therapy. *Kidney Int*. 1994;46:1700–1704.
46. Johnson RJ, Gretch DR, Yamabe H, Hart J, Bacchi CE, Hartwell P, Couser WG, Corey L, Wener MH, Alpers CE, Willson R. Membranoproliferative glomerulonephritis associated with hepatitis C virus infection. *N Engl J Med*. 1993;328:465–470.
47. Johnson SL, Bander J. Pulmonary hemorrhage in a patient with hepatitis C induced essential mixed cryoglobulinemia. *Chest*. 1998;114:422S–425S.
48. Lamprecht P, Lerin-Lozano C, Merz H, Dennin RH, Gause A, Voswinkel J, Peters SO, Gutzeit O, Arlt AC, Solbach W, Gross WL. Rituximab induces remission in refractory HCV associated cryoglobulinaemic vasculitis. *Ann Rheum Dis*. 2003;62:1230–1233.
49. Lamprecht P, Moubayed P, Donhuijsen K, Gause A, Gross WL. Vasculitis of adnexa, greater omentum and gallbladder as abdominal manifestations of cryoglobulinemic vasculitis. *Clin Exp Rheumatol*. 2001;19:112–113.
50. Lamprecht P, Schmitt WH, Gross WL. Mixed cryoglobulinaemia, glomerulonephritis, and ANCA: essential cryoglobulinaemic vasculitis or ANCA-associated vasculitis? *Nephrol Dial Transplant*. 1998;13:213–221.
51. Landau DA, Scerra S, Sene D, Resche-Rigon M, Saadoun D, Cacoub P. Causes and predictive factors of mortality in a cohort of patients with hepatitis C virus-related cryoglobulinemic vasculitis treated with antiviral therapy. *J Rheumatol*. 2010;37:615–621.
52. Lozano Maya M, Aldeguer Martinez M, Banares Canizares R, Yepes Barreto I, Ponferrada Diaz A, Rodriguez Benitez P, Niembro de Rasche E, Cos Arregui E. Mixed cryoglobulinemia associated with hepatitis C virus. Diagnosis by transjugular renal biopsy. *Rev Esp Enferm Dig*. 2009;101:658–659.
53. Luqmani RA, Bacon PA, Moots RJ, Janssen BA, Pall A, Emery P, Savage C, Adu D. Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. *Q J Med*. 1994;87:671–678.
54. Markowitz GS, Cheng JT, Colvin RB, Trebbin WM, D'Agati VD. Hepatitis C viral infection is associated with fibrillary glomerulonephritis and immunotactoid glomerulopathy. *J Am Soc Nephrol*. 1998;9:2244–2252.
55. Massari M, Catania A, Magnani G. Efficacy and risk of rituximab in type II mixed cryoglobulinemia: a significant case report. *Dig Liver Dis*. 2007;39:S134–S135.
56. Matignon M, Cacoub P, Colombat M, Saadoun D, Brocheriou I, Mougnot B, Roudot-Thoraval F, Vanhille P, Moranne O, Hachulla E, Hatron PY, Fermand JP, Fakhouri F, Ronco P, Plaisier E, Grimbert P. Clinical and morphologic spectrum of renal involvement in patients with mixed cryoglobulinemia without evidence of hepatitis C virus infection. *Medicine (Baltimore)*. 2009;88:341–348.
57. Medina F, Ayala A, Jara LJ, Becerra M, Miranda JM, Fraga A. Acute abdomen in systemic lupus erythematosus: the importance of early laparotomy. *Am J Med*. 1997;103:100–105.
58. Meltzer M, Franklin EC. Cryoglobulinemia—a study of twenty-nine patients. I. IgG and IgM cryoglobulins and factors affecting cryoprecipitability. *Am J Med*. 1966;40:828–836.
59. Mendez P, Saeian K, Reddy KR, Younossi ZM, Kerdel F, Badalamenti S, Jeffers LJ, Schiff ER. Hepatitis C, cryoglobulinemia, and cutaneous vasculitis associated with unusual and serious manifestations. *Am J Gastroenterol*. 2001;96:2489–2493.
60. Misiani R, Bellavita P, Baio P, Caldara R, Ferruzzi S, Rossi P, Tengattini F. Successful treatment of HCV-associated cryoglobulinaemic glomerulonephritis with a combination of interferon-alpha and ribavirin. *Nephrol Dial Transplant*. 1999;14:1558–1560.
61. Mohan S, Jaitly M, Cheng JT, D'Agati VD, Pogue VA. Unusual biopsy findings in a hepatitis C-infected white man with cryoglobulinemia, purpuric rash, and renal failure. *Am J Kidney Dis*. 2006;48:513–517.
62. Montagna G, Piazza V, Banfi G, Bellotti V, Segagni S, Picardi L, Mangione P, Giorgetti S, Zorzoli I, Cerino A, Salvadeo A. Hepatitis C virus-associated cryoglobulinaemic glomerulonephritis with delayed appearance of monoclonal cryoglobulinaemia. *Nephrol Dial Transplant*. 2001;16:432–434.
63. Monti G, Saccardo F. Emergency in cryoglobulinemic syndrome: what to do? *Dig Liver Dis*. 2007;39(Suppl 1):S112–S115.
64. Morales E, Alegre R, Herrero J, Morales J, Ortuno T, Praga M. Hepatitis-C-virus-associated cryoglobulinaemic membranoproliferative glomerulonephritis in patients infected by HIV. *Nephrol Dial Transplant*. 1997;12:1980–1984.
65. Morosetti M, Sciarra G, Meloni C, Palmieri G, Palombo G, Taccone Gallucci M, Casciani CU. Membranoproliferative glomerulonephritis and hepatitis C: effects of interferon- α therapy on clinical outcome and histological pattern. *Nephrol Dial Transplant*. 1996;11:532–534.
66. Moses P, Krawitt E, Aziz W, Corwin H. Renal failure associated with hepatitis C virus infection. Improvement in renal function after treatment with interferon-alpha. *Dig Dis Sci*. 1997;42:443–446.

67. Myers JP, Di Bisceglie AM, Mann ES. Cryoglobulinemia associated with Purtscher-like retinopathy. *Am J Ophthalmol.* 2001;131:802–804.
68. Origgi L, Vanoli M, Carbone A, Grasso M, Scorza R. Central nervous system involvement in patients with HCV-related cryoglobulinemia. *Am J Med Sci.* 1998;315:208–210.
69. Perello Carbonel R, Supervia Caparros A, Nolla Salas J, Vazquez Sanchez A, Torrente Segarra V, Gutierrez Cebollada J. [Alveolar haemorrhage and hepatitis virus C related mixed cryoglobulinemia. Report of three cases]. *An Med Interna.* 2005;22:529–531.
70. Petty GW, Duffy J, Houston J III. Cerebral ischemia in patients with hepatitis C virus infection and mixed cryoglobulinemia. *Mayo Clin Proc.* 1996;71:671–678.
71. Prasad M, Buller G, Mena CI, Sofair AN. Sum of the parts. *N Engl J Med.* 2006;355:2468–2473.
72. Propst T, Propst A, Nachbauer K, Graziadei I, Willeit H, Margreiter R, Vogel W. Papillitis and vasculitis of the arteria spinalis anterior as complications of hepatitis C reinfection after liver transplantation. *Transpl Int.* 1997;10:234–237.
73. Quartuccio L, Petrarca A, Mansutti E, Pieroni S, Calcabrini L, Avellini C, Zignego A, De Vita S. Efficacy of rituximab in severe and mild abdominal vasculitis in the course of mixed cryoglobulinemia. *Clin Exp Rheumatol.* 2010;28:S84–S87.
74. Quartuccio L, Soardo G, Romano G, Zaja F, Scott CA, De Marchi G, Fabris M, Ferraccioli G, De Vita S. Rituximab treatment for glomerulonephritis in HCV-associated mixed cryoglobulinaemia: efficacy and safety in the absence of steroids. *Rheumatology (Oxford).* 2006;45:842–846.
75. Quigg RJ, Brathwaite M, Gardner DF, Gretch DR, Ruddy S. Successful cyclophosphamide treatment of cryoglobulinemic membranoproliferative glomerulonephritis associated with hepatitis C virus infection. *Am J Kidney Dis.* 1995;25:798–800.
76. Ramos-Casals M, Font J. Extrahepatic manifestations in patients with chronic hepatitis C virus infection. *Curr Opin Rheumatol.* 2005;17:447–455.
77. Ramos-Casals M, Robles A, Brito-Zeron P, Nardi N, Nicolas JM, Forns X, Plaza J, Yague J, Sanchez-Tapias JM, Font J. Life-threatening cryoglobulinemia: clinical and immunological characterization of 29 cases. *Semin Arthritis Rheum.* 2006;36:189–196.
78. Ramos-Casals M, Stone JH, Cid MC, Bosch X. The cryoglobulinaemias. *Lancet.* 2012;379:348–360.
79. Ramos-Casals M, Trejo O, Garcia-Carrasco M, Cervera R, Font J. Mixed cryoglobulinemia: new concepts. *Lupus.* 2000;9:83–91.
80. Retamozo S, Diaz-Lagares C, Bosch X, De Vita S, Ramos-Casals M. Life-threatening cryoglobulinemia. In: Khamashta MA, Ramos-Casals M, eds. *Autoimmune Diseases. Acute and Complex Situations.* London: Springer-Verlag; 2011:133–162.
81. Rieu V, Cohen P, Andre MH, Mouthon L, Godmer P, Jarrousse B, Lhote F, Ferriere F, Deny P, Buchet P, Guillevin L. Characteristics and outcome of 49 patients with symptomatic cryoglobulinaemia. *Rheumatology (Oxford).* 2002;41:290–300.
82. Roccatello D, Baldovino S, Rossi D, Mansouri M, Naretto C, Gennaro M, Cavallo R, Alpa M, Costanzo P, Giachino O, Mazzucco G, Sena LM. Long-term effects of anti-CD20 monoclonal antibody treatment of cryoglobulinaemic glomerulonephritis. *Nephrol Dial Transplant.* 2004;19:3054–3061.
83. Roccatello D, Fornasieri A, Giachino O, Rossi D, Beltrame A, Banfi G, Confalonieri R, Tarantino A, Pasquali S, Amoroso A, Savoldi S, Colombo V, Manno C, Ponzetto A, Moriconi L, Pani A, Rustichelli R, Di Belgiojoso GB, Comotti C, Quarenghi MI. Multicenter study on hepatitis C virus-related cryoglobulinemic glomerulonephritis. *Am J Kidney Dis.* 2007;49:69–82.
84. Rodriguez-Vidigal FF, Roig Figueroa V, Perez-Lucena E, Ledesma Jurado V, Ramirez Gurruchaga P, Aguilar Escobar FJ, Relea Calatayud MF, Baz MJ. [Alveolar hemorrhage in mixed cryoglobulinemia associated with hepatitis C virus infection]. *An Med Interna.* 1998;15:661–663.
85. Roithinger FX, Allinger S, Kirchgatterer A, Prischl F, Balon R, Haidenthaler A, Knoflach P. A lethal course of chronic hepatitis C, glomerulonephritis, and pulmonary vasculitis unresponsive to interferon treatment. *Am J Gastroenterol.* 1995;90:1006–1008.
86. Rossi P, Bertani T, Baio P, Caldara R, Luliri P, Tengattini F, Bellavita P, Mazzucco G, Misiani R. Hepatitis C virus-related cryoglobulinemic glomerulonephritis: long-term remission after antiviral therapy. *Kidney Int.* 2003;63:2236–2241.
87. Saadoun D, Landau DA, Calabrese LH, Cacoub PP. Hepatitis C-associated mixed cryoglobulinaemia: a crossroad between autoimmunity and lymphoproliferation. *Rheumatology (Oxford).* 2007;46:1234–1242.
88. Saadoun D, Resche-Rigon M, Thibault V, Piette JC, Cacoub P. Antiviral therapy for hepatitis C virus associated mixed cryoglobulinemia vasculitis: a long-term follow-up study. *Arthritis Rheum.* 2006;54:3696–3706.
89. Salamone F, Puzzo L. Intestinal HCV-related mixed cryoglobulinemia. *Gastroenterology.* 2010;138:e9–e10.
90. Sansonno D, Dammacco F. Hepatitis C virus, cryoglobulinaemia, and vasculitis: immune complex relations. *Lancet Infect Dis.* 2005;5:227–236.
91. Shibasaki K, Iguchi Y, Kimura K, Wada K, Ueno Y, Sunada Y. Paradoxical brain embolism associated with HCV-related type II mixed cryoglobulinemia. *J Clin Neurosci.* 2007;14:780–782.
92. Suzuki R, Morita H, Komukai D, Hasegawa T, Nakao N, Ideura T, Yoshimura A. Mixed cryoglobulinemia due to chronic hepatitis C with severe pulmonary involvement. *Intern Med.* 2003;42:1210–1214.
93. Tada M, Naruse S, Arai A, Sato A, Tanaka K, Piao YS, Kakita A, Takahashi H, Nishizawa M, Tsuji S. An autopsy case of systemic vasculitis associated with hepatitis C virus-related mixed cryoglobulinemia presenting severe peripheral neuropathy. *Rinsho Shinkeigaku.* 2004;44:686–690.
94. Tarantino A, Campise M, Banfi G, Confalonieri R, Bucci A, Montoli A, Colasanti G, D'Amico I, D'Amico G, Minetti L, Ponticelli C. Long-term predictors of survival in essential mixed cryoglobulinemic glomerulonephritis. *Kidney Int.* 1995;47:618–623.
95. Tembl JJ, Ferrer JM, Sevilla MT, Lago A, Mayordomo F, Vilchez JJ. Neurologic complications associated with hepatitis C virus infection. *Neurology.* 1999;53:861–864.
96. Terrier B, Saadoun D, Sene D, Scerra S, Musset L, Cacoub P. Presentation and outcome of gastrointestinal involvement in hepatitis C virus-related systemic vasculitis: a case-control study from a single-centre cohort of 163 patients. *Gut.* 2010;59:1709–1715.
97. Trejo O, Ramos-Casals M, Garcia-Carrasco M, Yague J, Jimenez S, de la Red G, Cervera R, Font J, Ingelmo M. Cryoglobulinemia: study of etiologic factors and clinical and immunologic features in 443 patients from a single center. *Medicine (Baltimore).* 2001;80:252–262.
98. Visentini M, Granata M, Veneziano ML, Borghese F, Carlesimo M, Pimpinelli F, Fiorilli M, Casato M. Efficacy of low-dose rituximab for mixed cryoglobulinemia. *Clin Immunol.* 2007;125:30–33.
99. Zaja F, De Vita S, Russo D, Michelutti A, Fanin R, Ferraccioli G, Baccarani M. Rituximab for the treatment of type II mixed cryoglobulinemia. *Arthritis Rheum.* 2002;46:2252–2254.
100. Zandman-Goddard G, Levy Y, Weiss P, Shoenfeld Y, Langevitz P. Transverse myelitis associated with chronic hepatitis C. *Clin Exp Rheumatol.* 2003;21:111–113.