Autoimmunity Reviews 15 (2016) 440–446

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

# Long term outcome of patients with low level of cryoglobulin (<0.05 g/L)

V. Eble [a], B. Legallicier [b], P. Joly [c], O. Vittecoq [d], F. Caron [e], F. Tamion [f], P. Ducrotte [g], H. Levesque [a], J.-F. Menard [h], F. Jouen [i], D. Guerrot [b], I. Marie [a,*]

[a] Department of Internal Medicine, CHU Rouen, and INSERM U 905, University of Rouen IFRMP, Institute for Biochemical Research, Rouen, France
[b] Department of Nephrology, CHU Rouen, Rouen, France
[c] Department of Dermatology and INSERM U 905, University of Rouen IFRMP, Institute for Biochemical Research, CHU Rouen, Rouen, France
[d] Department of Rheumatology and INSERM U 905, University of Rouen IFRMP, Institute for Biochemical Research, CHU Rouen, Rouen, France
[e] Department of Infectious Diseases, CHU Rouen, Rouen, France
[f] Intensive Care Unit, CHU Rouen, Rouen, France
[g] Department of Gastroenterology, CHU Rouen, Rouen, France
[h] Department of Biostatistics, CHU Rouen, Rouen, France
[i] Laboratory of Immunology and INSERM U 905, University of Rouen IFRMP, Institute for Biochemical Research, Rouen, France

ARTICLE INFO

*Article history:*
Received 5 January 2016
Accepted 20 January 2016
Available online 28 January 2016

*Keywords:*
Cryoglobulin
Connective tissue disease
Infection
Cancer
Diagnosis
Prognosis
Therapy

ABSTRACT

*Objectives:* To date, no studies have yet assessed the characteristics of non-HCV patients with low level of cryoglobulin (≤0.05 g/L). The aims of the current study were thus to: 1) determine the prevalence of cryoglobulin ≤0.05 g/L in patients with non-HCV cryoglobulin; and 2) compare clinical features and long term outcome, including organ complications and mortality rate, between non-HCV patients with cryoglobulin level ≤0.05 g/L and those exhibiting cryoglobulin level >0.05 g/L.
*Methods:* Among 6379 cryoglobulin testing, cryoglobulin was detected in 618 patients (9.69% of cases); of these 618 patients, 453 non-HCV patients were included in the study. The medical records of these patients were reviewed.
*Results:* Of the 453 non-HCV cryoglobulin-positive patients, 265 (58.6%) exhibited cryoglobulin level ≤0.05 g/L. We showed that patients with cryoglobulin level ≤0.05 g/L had: 1) less commonly: palpable purpura ($p < 0.001$), digital ulcers ($p = 0.006$), peripheral neurologic involvement ($p = 0.03$) and renal impairment ($p = 0.03$); and 2) lower median values of ESR ($p < 0.001$) and C-reactive protein ($p = 0.001$). The patients with cryoglobulin level ≤0.05 g/L less often experienced infections ($p = 0.04$) and hematological malignancies ($p = 0.01$); both groups did not differ regarding prevalence of connective tissue diseases and solid tumors. Mortality rate was as high as 13.6% in patients with cryoglobulin level ≤0.05 g/L; death was mainly due to: solid tumors (16.6%), cardiovascular complications (13.8%), hematological malignancies (11.1%), infections (8.3%), pulmonary/renal complications of cryoglobulin (8.3%) and connective tissue diseases (8.3%).
*Conclusion:* Our study shows a high prevalence of cryoglobulin level ≤0.05 g/L in clinical practice. Our findings further underscore that non-HCV cryoglobulin level ≤0.05 g/L may be responsible for severe renal and neurological complications, leading to high morbidity and mortality in these patients. Thus, our data suggest that both appropriate therapy and close follow-up may be required to improve such patients' outcome.


**Contents**



* Corresponding author at: Department of Internal Medicine, CHU de Rouen, 76031 Rouen Cedex, France. Tel.: +2 32 88 90 03; fax: +2 32 88 90 26.
*E-mail address:* isabelle.marie@chu-rouen.fr (I. Marie).

http://dx.doi.org/10.1016/j.autrev.2016.01.012
1568-9972/

## 1. Introduction

Cryoglobulins are defined by the presence of immunoglobulins that precipitate *in vitro* at temperature less than 37 °C and re-dissolve when rewarmed [1–5]; cryoglobulins are sorted according to the classification by Broult et al. [1]. Although cryoglobulinemia may be asymptomatic, it may result in small-vessel vasculitis, caused by cryoglobulin-containing immune complexes, involving mainly the skin, the kidneys and the peripheral nerves [3,6–16]. To date, patients are considered to have a significant cryoglobulin level when >0.05 g/L on two determinations [1,4,6,15]. Until now, clinical and prognostic features have thus been reported only in HCV and non-HCV patients with cryoglobulin level >0.05 g/L [3,6–16]. In these patients, higher levels of cryoglobulin were not correlated with severity of organ involvement [17–19].

However, to date, no studies have yet assessed the characteristics of non-HCV patients with low level of cryoglobulin (≤0.05 g/L). Thus, the aims of the current study were to: 1) determine the prevalence of cryoglobulin ≤0.05 g/L in non-HCV patients with cryoglobulin; and 2) compare clinical features and long term outcome, including organ complications and mortality rate, between non-HCV patients with cryoglobulin level ≤0.05 g/L and those exhibiting cryoglobulin level >0.05 g/L.

## 2. Patients and methods

### 2.1. Patients

From 2004 to 2012, circulating cryoglobulin testing was performed in overall 6379 consecutive patients at the Laboratory of Immunology at Rouen University Hospital. These patients were seen, as either in-patients or out-patients, in the Departments of Dermatology, Gastroenterology, Infectious Diseases, Internal Medicine, Intensive Care, Nephrology, Neurology, Pneumology and Rheumatology of our tertiary center.

The inclusion criteria for the study were types I, II and III cryoglobulins after detection and immunochemical typing; the exclusion criteria were the presence of anti-HCV antibodies. Among the 6379 cryoglobulin testing, cryoglobulin was detected in 618 patients (9.69% of cases); of these 618 non-HCV patients, 453 patients were included in the study.

A second search was used to isolate the subsets of non-HCV patients with cryoglobulin level ≤0.05 g/L and those exhibiting cryoglobulin level >0.05 g/L. The data from these patients were anonymously reported. This retrospective study was approved by the institutional ethics committee of CPP de Haute-Normandie with a waiver for informed consent.

First, the medical records of patients with cryoglobulin were reviewed for patients' general characteristics at diagnosis: 1) age and gender; and 2) median duration of clinical manifestations before cryoglobulin detection. All the patients had undergone the same routine clinical evaluation to investigate systemic complications, as follows:

- Constitutional symptoms: fever ≥38 °C, asthenia, and weight loss;
- Raynaud's phenomenon
- Skin involvement: palpable purpura, digital/toe ischemia/necrosis, leg ulcer, and livedo reticularis;
- Joint impairment: arthralgia and arthritis;
- Peripheral (e.g. multiple mononeuritis or polyneuritis) and central (e.g. stroke, cranial nerve impairment, epilepsy, encephalopathy related to diffuse cerebral ischemic lesions, transverse myelitis, ischemic cord dysfunction) impairment;
- Renal involvement: arterial hypertension, proteinuria >0.5 g/day, microscopic hematuria, and renal failure (determined by glomerular filtration rate <60 mL/min);
- Pulmonary dysfunction: dyspnea, dry cough, hemoptysis, interstitial lung disease (ILD), pleural effusion, and acute alveolar hemorrhage;
- Cardiac impairment: myocardial infarction related to coronary vasculitis, congestive heart failure, pericarditis, as well as mitral damage;
- Gastrointestinal manifestations: intestinal ischemia and/or perforation.

Second, the medical records of the patients were reviewed for laboratory characteristics at diagnosis of cryoglobulin: 1) erythrocyte sedimentation rate (ESR) and C-reactive protein (mg/L); 2) hemoglobin level (g/dL), leukocytosis (G/L) and platelets (/mm$^3$); 3) serum creatinine (μmol/L), serum urea (mmol/L), and glomerular filtration rate being evaluated using the modified diet in renal disease equation; 4) serum total protein (g/L) and albumin (g/L); 5) urinalysis: hematuria and proteinuria; 6) alanine aminotransferase (GPT) (IU/L) and aspartate aminotransferase (GOT) (IU/L); and 7) serum C4 fraction of complement.

Third, the patients were examined for underlying conditions associated with cryoglobulins, i.e.

- Autoimmune diseases, including primary Sjögren syndrome, systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, polymyositis/dermatomyositis, and vasculitis;
- Infections: hepatitis B virus, human immunodeficiency virus (HIV); bacterial, viral parasitic and fungal infections;
- Cancers: hematological malignancies, monoclonal gammopathy of undetermined significance, and solid cancers;
- Other causes, including alcoholic cirrhosis;
- Diagnosis of essential cryoglobulinemia was made when there was no underlying disease [15].

Furthermore, the outcome of the patients was defined as: 1) remission, characterized by complete clinical response, normalization of organ manifestations, negativation of cryoglobulin level and normalization of serum C4 fraction; 2) improvement, determined by improvement of organ signs, >50% decrease in the initial cryoglobulin level and/or >50% increase in the serum C4 fraction; and 3) deterioration, when organ manifestations worsened despite therapy. Recurrence of cryoglobulin was based on clinical relapse of clinical vasculitis [14].