Case Report

HCV related severe cryoglobulinemic vasculitis treated with plasma exchange and rituximab: case report and literature review

Snezana Arandjelovic1,2, Branka Bonaci-Nikolic1,2, Aleksandra Peric-Popadic1,2, Vesna Tomic-Spiric1,2, Jasna Bolpacic1,2, Sanvila Raskovic1,2, Sladjana Andrejevic1,2

1 Clinic of Allergology and Immunology, Clinical Centre of Serbia, Belgrade, Serbia
2 Faculty of Medicine, University of Belgrade, Belgrade Serbia

Abstract

Mixed cryoglobulinemia is the most prevalent extrahepatic manifestation of chronic HCV infection. It is usually a benign lymphoproliferative disorder which presents as vasculitis affecting different organs. Although life-threatening cryoglobulinemic vasculitis (CryoVas) is rare, it is sometimes the first and possibly lethal complication. Its treatment depends on the severity of vasculitis and can be challenging. High dose of corticosteroids, immunosuppressive agents and plasma exchange represent the first-line treatment, which should be followed by antiviral therapy. Rituximab is an effective and safe treatment option. However, the data about its use in life-threatening conditions are scarce. We report the case of a patient with severe, relapsing and life-threatening HCV-related CryoVas resistant to standard therapy who had had an initial beneficial response to rituximab added to plasma exchange that was later compromised by the development of sepsis. We also review the literature and discuss manifestations and therapy of life-threatening Cryovas with focus on rituximab use.

Key words: hepatitis C virus; HCV; cryoglobulinemic vasculitis; life-threatening cryoglobulinemia; rituximab.


(Received 25 February 2016 – Accepted 02 March 2016)

Copyright © 2017 Arandjelovic et al. This is an open-access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Introduction

Cryoglobulinemic vasculitis (CryoVas) is the most prevalent extrahepatic manifestation of chronic hepatitis C virus infection (HCV) which affects 150-170 million people worldwide. Circulating mixed cryoglobulins are detectable in about 40% of HCV-infected individuals but overt CryoVas develops in only 5-10% of those [1]. It is an immune-complex-mediated systemic vasculitis which most frequently affects small to medium sized blood vessels in the skin, joints and kidneys; however, any organ system can be involved [2]. HCV is present in more than 80% cases of CryoVas and has predilection for Mediterranean countries. Clinical picture of CryoVas is heterogeneous ranging from very mild symptoms to severe and life-threatening ones which may be the first manifestation of HCV infection [3].

Treatment of HCV-induced CryoVas depends on the severity of vascular lesions and it is challenging in patients with severe relapsing and life-threatening disease. It is associated with problems such as the choice of medications, risk of treatment failure and possible severe side effects. High-dose corticosteroids (HDC), immunosuppressive agents (ISA) and plasma exchange (PE) still make a standard initial treatment [4] that should be followed by antiviral drugs. Rituximab (Rtx) (an anti CD-20 monoclonal antibody) has been shown to be safe and efficient in CryoVas [5-7]. However, the data of its use in the treatment of life-threatening forms of the disease are scarce. Hence, we present our clinical experience with rituximab in the treatment of a patient with severe resistant, life-threatening form of CryoVas, in whom initially beneficial response was unfortunately followed by lethal septic condition.

Case Report

A 53-year-old female patient was readmitted to Clinic of Allergology and Immunology, Clinical Centre of Serbia in September 2015 due to exacerbation of the palpable purpura on lower limbs, arthralgia, high-grade fever (38.9 °C), fatigue, acute abdominal pain with diarrhea and occasional hematochezia.

The disease started in 2005 with a relapsing purpura and arthralgia, two years before she had been diagnosed with HCV (genotype 4) infection, mixed cryoglobulinemia type II (polyclonal IgG/monoclonal IgMk) and compensated liver cirrhosis. Initial antiviral
treatment with peginterferon-2a and ribavirin failed and vasculitis flares were subsequently treated with short courses of corticosteroids. The disease gradually worsened and in addition to the purpura she developed burning paresthesia of the lower limbs due to peripheral polyneuropathy (confirmed by electroneuromyography) as well as renal disease with erythrocyturia and subnephrotic proteinuria which were consistent with a clinical diagnosis of cryoglobulinemic glomerulonephritis (Cryo-GN). In 2008 the patient experienced the first renal failure episode, which was treated with hemodialysis (three procedures) and HDC, resulting in complete recovery of renal function. In 2012 and 2015 she experienced two more similar episodes of impaired renal function, which were treated with HDC. Creatinine level (around 130μmol/L) was slightly elevated since 2012 (stable chronic renal failure). Vasculitic relapses were also provoked by repeated respiratory and urinary tract infections. The prevention of flares consisted of continuous oral prednisone (OP) therapy for the last two years (Figure 1).

Physical examination on the admission revealed prominent purpuric rash predominantly on the lower limbs (Figure 2), peripheral edema, elevated blood pressure (160/100 mmHg) and tenderness in the left side of the abdomen. Relevant laboratory findings were as follows: elevated inflammatory markers (ESR 46 mm/h, CRP 38.4 mg/L), anemia (Hgb 74.8 g/L), elevated creatinine level (292 mol/L), hypoalbuminemia (24 g/L), erythrocyturia (3+), proteinuria (3.9g/24h), hypogammaglobulinemia (IgG 4.43 g/L), low level of complement C3 (0.33 g/L) and C4 (< 0.05 g/L), positive rheumatoid factor (RF) (94 IU/mL), high concentration of cryoglobulin type II (monoclonal IgMk/polyclonal IgG) (4.29 g/L), and positive occult blood stool test. Autoantibodies other than RF were not detected. HCV RNA was positive with 1,030,076 copies/mL while transaminases were within the normal range. Colonoscopy revealed mucosal inflammation, deep ulcerations and signs of ischemic colitis. Histological findings in the biopsy specimens were consistent with vasculitis.

The diagnosis of HCV-related CryoVas flare involving the skin, kidneys, and gastrointestinal (GI) system was made.

The patient was given IVM pulses (1000mg/day for 3 days), one session of PE three times every other day, empirical antibiotics, intravenous immunoglobulins (IVIg) and symptomatic treatment. Her condition gradually improved and the oral steroids were slowly tapered over a period of 4–6 weeks. Unfortunately, improvement did not last long and she experienced a new flare of the disease. Then rituximab (375mg/m²/week for 4 weeks) was introduced into the treatment, combined with a new course of PE.

There was a prompt initial improvement with the resolution of skin changes, disappearance of GI disturbances and improved renal function. Laboratory
tests revealed disappearance of cryoglobulin and paraprotein (for the first time since they were discovered), increase in levels of C3 (0.46 g/L) and C4 (0.05 g/L) and decreased RF (45 IU/mL) concentration. Three weeks after the last rituximab dose was given, the patient got high fever and her general condition started to gradually deteriorate. Laboratory tests showed raised ESR (96 mm/h) and CRP (379 mg/L) along with a low WBC (1.6×10^9/L) and platelet (14×10^9/L) count and low hemoglobin (78 g/L) and IgG concentration (1.9 g/L). Serum procalcitonin was elevated to 3.54 μg/L and blood culture revealed the presence of Pseudomonas aeruginosa. Despite intensive treatment with broad spectrum and antipseudomonal antibiotics, IVlg and other supportive therapy, the patient developed severe respiratory and renal failure that resulted in death from multiple organ dysfunction and septic shock.

**Discussion**

CryoVas is associated with a wide spectrum of manifestations, ranging from various mild and relapsing symptoms and signs such as weakness, purpura and arthralgia, to moderate or severe (35%) and potentially life-threatening conditions (less than 15%) [8] (Table 1). Ramos-Casals et al. gave a description of 29 patients with life-threatening CryoVas out of 209 patients affected by the disease [9]. Retamozo et al. reviewed a total of 279 cases with life-threatening CryoVas (30 from their department) and found that in 232 patients (83%) it was the first manifestation of cryoglobulinemia [10]. They suggested awareness of life-threatening CryoVas as a differential diagnosis in ICU [11].

In our patient the disease gradually evolved from a moderate, well controlled disease on low-dose steroids to a severe, widespread type of vasculitis with multiple organ involvement and life-threatening conditions.

Renal involvement is the most common severe visceral manifestation of CryoVas. Cryo-GN appears in more than 20% of cases and it usually presents itself with mild proteinuria, microscopic hematuria and hypertension. In 70%-80% of those cases renal biopsy reveals type 1 membranoproliferative GN [11]. Our patient was uncooperative for kidney biopsy and therefore Cryo-GN was diagnosed in accordance with the previously defined clinical criteria [12,13]. More than 50% of patients with CryoVas have mild renal failure, which in 1/3 of them becomes chronic within the next six years [14]. The reported survival rate for patients with chronic GN is 33% [8] and 39% after a mean follow-up of ten years [9]. It seems that Cryo-GN has the worst prognosis in patients with HCV-related cryoglobulinemia due to hesitation in giving o cyclophosphamide [15].

Less than 5% of patients with CryoVas have GI disease, which may be associated with GI bleeding, ischemic bowel disease, perforation and acute lesions involving any organ in the abdomen [16]. In a case-controlled study that included 163 patients with HCV-related CryoVas and polyarteritis nodosa-like vasculitis GI lesions were detected in only four of them [16]. One study showed that GI vasculitis has a very poor prognosis with mortality of 100% [9]. However, in our case CryoVas GI initially responded well to HDC.

CryoVas involves lungs in less than 5% of patients. Nevertheless, in those affected the prognosis is poor, particularly if it is associated with pulmonary hemorrhage [9] and/or Cryo-GN (renal-pulmonary syndrome) [15]. When CryoVas presents itself as primary cardiac disease it usually causes heart dysfunction with pulmonary edema, but this is rare [11]. CryoVas-related coronary heart disease involves small blood vessels and angiography shows that major arteries are spared [17]. Life-threatening CNS manifestations, including thrombosis, hemorrhage and

---

**Table 1. Definition of life-threatening cryoglobulinemic vasculitis [9,11].**

| **The diagnosis can be established if there are any of the following:** |
|-----------------|-----------------|
| **1 Renal involvement** | cryoglobulinemic GN with raised serum creatinine (> 2 mg/dL); Glomerular injury is diagnosed by renal biopsy and classified as membranoproliferative GN, or focal proliferative GN |
| **2 Gastrointestinal involvement** | vasculitic involvement of the esophagus, stomach, small intestine, colon, or any intraabdominal viscera presenting as gastrointestinal hemorrhage, intestinal ischemia, acute pancreatitis, or acute cholecystitis |
| **3 Lung involvement** | pulmonary hemorrhage leading to respiratory failure, in the absence of pulmonary edema, adult respiratory distress syndrome, infectious pneumonia, lung cancer, or granulomatous disease |
| **4 CNS involvement** | cerebral ischemia (in absence of hypercoagulability or cardiovascular disease), encephalopathy with impaired cognitive function, brain hemorrhage, spinal cord, or cranial nerve involvement |
| **5 Heart involvement** | acute heart failure or acute coronary syndrome in absence previous cardiovascular disease |
| **6 Widespread vasculitis** | multiple organ involvement, including the skin and at least two other organs (kidneys, gastrointestinal organs, lungs, CNS) |
| **7 Other** | hyperviscosity syndrome, liver failure in HCV-related mixed cryoglobulinemia (acute-on-chronic hepatitis and cirrhosis) |
encephalopathy with cognitive dysfunction are extremely rare presentations of CryoVas [18].

In critically ill CryoVas patients, the first-line treatment ought to be tailored to quickly alleviate the symptoms and signs of the disease. Early therapy consists of high-dose IVM pulses of 500–1000mg/day for three days, followed by OP 1mg/kg/day and ISA (e.g. cyclophosphamide 2mg/kg/day orally, or one pulse of 600mg/m²/month i.v.) are useful in reversing pathogenic mechanisms of the disease, reducing production of cryoglobulins and limiting inflammation of blood vessel walls [3]. PE should quickly reduce a level of circulating cryoimmune complexes [19] and it is usually followed by HDC pulses, ISA [9] or rituximab [5]. It should be emphasized that replacement fluid needs to be pre-wormed during the PE in order to avoid paradoxical precipitation of cryoglobulins [20].

PE initially performed and followed by HDC had short-term benefits for our patient. The ISA were never given due to a fear of HCV disease progression and infection, which eventually caused her death.

Eradication of HCV infection is important in curing HCV-related CryoVas [21] and antivirals are part of the standard treatment for more than a decade. However, combination of pegylated interferon and ribavirin works in a relatively small number of patients (41–55%) [22]. Data about efficacy and safety of the first generation viral protease inhibitors (boceprevir, telaprevir) [23] and the new interferon-free protocols [12] in the treatment of HCV-related CryoVas are still limited. Antiviral therapy in our patient was not well tolerated and proved to be ineffective.

Since uncontrolled proliferation of B cells plays a key role in the pathogenesis of cryoglobulinemia, it seems logical to use therapy that can selectively prevent it. Rituximab is a mouse/human chimeric monoclonal antibody that binds itself to a CD20 transmembrane protein and its use in humans results in quick and lasting depletion of peripheral blood B lymphocytes [6]. It is licensed for the treatment of various malignancies as well as for refractory rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis. During the last decade several authors have shown that rituximab could be efficient in the treatment of HCV-related CryoVas [5–7]. In an open-labeled randomized controlled trial Sneller et al.

### Table 2. - Literature review: Rituximab in therapy of HCV related life-threatening cryoglobulinemic vasculitis.

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of patients on Rtx therapy</th>
<th>Etiology CryoVas</th>
<th>Manifestations</th>
<th>Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamprecht, et al</td>
<td>1</td>
<td>HCV/NHL</td>
<td>Purpura, polyneuropathy progressive and resistant to standard therapy, ischemic colitis</td>
<td>PE, gcs, CYF, Rtx6×500mg/every three weeks</td>
<td>Remission</td>
</tr>
<tr>
<td>Ramos Casals, et al 2006</td>
<td>1</td>
<td>HCV</td>
<td>Pulmonary hemorrhage</td>
<td>PE, gcs, CYF, Rtx</td>
<td>Death</td>
</tr>
<tr>
<td>Monti G, et al 2007</td>
<td>1</td>
<td>HCV</td>
<td>Purpura, leg ulcers, acute renal failure, widespread vasculitis (&quot;catastrophic sy&quot;)</td>
<td>PE, gcs, Rtx375mg/m²/week for 4 weeks</td>
<td>Death</td>
</tr>
<tr>
<td>Visentini M, et al 2007</td>
<td>6</td>
<td>HCV</td>
<td>Necrotizing leg ulcers, renal failure, hyperviscosity or intestinal vasculitis.</td>
<td>Low doses of gcs, Rtx 250mg/m²/week for 2 weeks</td>
<td>Death2/6</td>
</tr>
<tr>
<td>Quartuccio L, et al 2010</td>
<td>5</td>
<td>HCV</td>
<td>Abdominal vasculitis</td>
<td>Gcs, Rtx 375mg/m²/week for 4 weeks</td>
<td>Death1/5</td>
</tr>
<tr>
<td>Zaidan M, et al 2012</td>
<td>1</td>
<td>HCV</td>
<td>Skin ulcers, renal laesion, GIT laesion, heart failure</td>
<td>Gcs1mg/kg/day, PE, Rtx 375mg/m²/week for 4 weeks</td>
<td>Remission</td>
</tr>
<tr>
<td>Meillier A, et al 2014</td>
<td>1</td>
<td>HCV/NHL</td>
<td>Leg ulcers, ARF</td>
<td>Gcs, Rtx 700mg/week for 4 weeks</td>
<td>Remission</td>
</tr>
<tr>
<td>Bitar ZI, et al 2014</td>
<td>1</td>
<td>HCV</td>
<td>Alveolar hemorrhage, ARF, fulminant hepatitis</td>
<td>Gcs, PE, Rtx 375mg/m²/week for 2 weeks</td>
<td>Death</td>
</tr>
<tr>
<td>Mahieu R, et al 2015</td>
<td>1</td>
<td>HCV</td>
<td>Heart failure, renal involvement</td>
<td>Rtx375mg/m²/week for 4 weeks, simprevir, sofosbuvir</td>
<td>Remission</td>
</tr>
<tr>
<td>ArandjelovicS, et al (present case) 2016</td>
<td>1</td>
<td>HCV</td>
<td>Renal failure, GIT laesion</td>
<td>Gcs, PE, Rtx 375mg/m²/week for 4 weeks</td>
<td>Death</td>
</tr>
</tbody>
</table>

Abbreviations: HCV-hepatitis C virus; CryoVas-cryoglobulinemic vasculitis; NHL-non Hodgkin lymphoma; ARF-acute renal failure; GIT-gastrointestinal tract; PE-plasma exchange; gcs-glucocorticosteroids; Rtx-rituximab; CYF-cyclofosamide; IVIG-intravenous immunoglobulins.
compared rituximab and standard immunosuppressive therapy in 24 patients with HCV-related CryoVas resistant to antiviral drugs and found significantly higher six-month remission in the rituximab group (83% vs. 8%) [7].

Literature review indicates that rituximab was mostly used for HCV-related CryoVas patients who did not respond or were intolerant to standard treatment or already had an associated lymphoma [24], which makes it a kind of a “rescue” therapy. It seems that ineffective monotherapy with rituximab can be improved by previous PE [25].

A combination of rituximab and antiviral drugs may target both cryoglobulin-producing B cells and a viral intruder [24]. Uraro et al. presented a case of successful treatment of HCV-related CryoVas with a combination of Peg-IFN/ribavirin/boceprevir and rituximab [23]. Terrier et al. showed that rituximab plus HDC treatment was more efficient compared to standard HDC and ISA. However, Rtx plus corticosteroids was associated with severe infections [26].

To the best of our knowledge, up to now there are 18 published cases in which rituximab was used for life-threatening HVC-related CryoVas (Table 2). In our patient the drug was used after previous PE in order to avoid possible systemic reactions due to high concentration of cryoglobulin and low C4 levels [24,27].

Serious life-threatening infections may occur in HCV-related CryoVas patients treated with HDC, ISA or PE [5,14,16,18]. Chronic renal failure often enhances already existing immunosuppression and the risk of infection. Ramos-Casals et al. found that four out of five patients who died of infection also had chronic renal failure due to Cryo-GN [9]. In addition, HCV infection per se, leading to immune dysregulation, contributes to immunosuppression of the host who has already been severely immunocompromised by the previous treatment [28]. In our patient treatment with varying doses of corticosteroids, which were tailored to control disease activity, was relatively effective for several years. However, during that time her HCV-related CryoVas had a progressive course. She became exhausted with her disease and immunocompromised due to long lasting use of HDC. Our patient’s poor tolerance to Rtx administration remains unclear. Hypogammaglobulinemia and severe infection have been documented in patients treated with Rtx but causal association is questionable due to confounding effects associated with immunosuppressive therapy and immune dysregulation caused by underlying disease [29].

Conclusions

Long-lasting evolution of chronic HCV infection is burdened with unpredictability and it can go in many different directions, CryoVas being one of the possible ones. Natural course of CryoVas is usually slow, but sometimes may be characterized with acute and life-threatening manifestations. Careful evaluation of every single patient is crucial as well as the introduction of appropriate therapy on time, while the overall condition is still good. The application of Rtx in early phase of disease is a reasonable treatment option and it should lead to the expected therapeutic benefit and diminish possible side effects of its use.

It seems that a low baseline immunoglobulin level is a risk factor for development of significant hypogammaglobulinemia after the Rtx administration. Serious non-opportunistic infections may occur in this setting and can be prevented by administration of IVIg to maintain an IgG level above 4 g/L.

Available literature concerning the efficacy Rtx in treatment of life-threatening CryoVas is restricted to case reports and case series. These data and our own experience are in some manner encouraging and emphasize the need for long-lasting careful monitoring in order to avoid the occurrence of infections. The risk of infections in some HCV patients with Rtx-therapy is not yet well understood and it requires further research.

References


Corresponding author
Snezana Arandjelovic, MD, MSc
Clinic of Allergy and Immunology
Clinical Center of Serbia
Koste Todorovića 2
11000 Belgrade
Serbia
Phone: +381 11 366 3700
Fax: +381 11 3615807
E-mail: snezana.arandjelovic@kcs.ac.rs

Conflict of interests: No conflict of interests is declared.