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Achieving Sustained Viral Remission in Patients with Chronic HCV Infection and Cryoglobulinemic Vasculitis Does Not Always Correlate with Normalization of the Serologic Markers

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Abstract

Objective: We aim to describe the persistence of symptoms associated with HCV-associated cryoglobulinemic vasculitis following achievement of (SVR) with IFN- free direct acting antiviral (DAA) therapy. In particular, we describe the persistence of C4 hypocomplementemia and positive Rheumatoid Factor (RF).

Methods: We analyzed a case series of four patients enrolled from the Cleveland VA and known to have chronic HCV infection complicated by mixed cryoglobulinemia. The study included patients treated with interferon (IFN) based treatment and IFN free direct acting antiviral (DAA) therapy.

Results: Of the four patients, patients 1 and 2 experienced decline of RF without resolution following DAA therapy. Patient 1 continues to have evidence of disease following treatment. Patient 3 did not have resolution of RF during IFN-based treatment and experienced stabilization of kidney function while on treatment. Patient 4, previously a non-responder to IFN based treatment, experienced significant decline in RF titers along with resolution of cryoglobulin-associated rash with DAA therapy. C4 remained low following treatment in patients 1 and 3. Of the four patients, only patient 1 had prolonged persistence of cryoglobulinemia, measured at 3%, 17 months following achievement of SVR.

Conclusions: We highlight the complexity of the viral-mediated immunologic mechanism that causes cryoglobulinemic vasculitis. Our cases also emphasize the need to consider cryoglobulinemic vasculitis as part of the differential diagnosis even with treated HCV infection. Recognizing these findings are important in our understanding of the pathophysiology of the disease and management in the era of IFN-free DAA therapy.

Keywords: Cryoglobulinemic vasculitis; HCV infection; Tumor

Introduction

Hepatitis C virus (HCV) affects approximately 180 million people worldwide. It is associated with the development of chronic hepatitis, hepatocellular carcinoma, and liver cirrhosis. HCV can also cause extrahepatic manifestations including cryoglobulinemic vasculitis and Malignant B cell lymphoproliferative disorders [1-3].

HCV is associated with 90% of Mixed Cryoglobulinemia while less than 5% of mixed cryoglobulinemia cases are considered to be essential. In HCV infection, Cryoglobulins are circulating immune complexes of polyclonal IgG and monoclonal (Type II) or polyclonal (Type III) IgM Rheumatoid factor directed against the IgG [1-3].

HCV related cryoglobulinemic vasculitis affects small and medium-sized arteries and veins. It is characterized by the deposition of cryoglobulins on endothelial surfaces which in turn results in endotheliitis *via* complement activation. This also leads to activation of anti-endothelial antibody and platelet aggregation [4]. Clinical manifestations include palpable purpuric rash, arthritis, glomerulonephritis, and central and peripheral nerve involvement [5,6]. Serologic findings in HCV-associated cryoglobulinemia are hypocomplementemia, cryoglobulin level >0.5%, and positive rheumatoid factor.

Circulating cryoglobulins can be seen in greater than 40% of patients with chronic HCV infection, while only 1%-2% develop disease manifestations [7].

Interferon (IFN)-alpha therapy was the first approved therapy for HCV infection. Combination therapy of IFN-alpha with ribavirin was introduced later and was shown to be more effective than IFN therapy alone. Currently IFN-free direct acting antiviral (DAA) therapy is the standard for HCV treatment; however, treatment of HCV associated cryoglobulinemic vasculitis has not been well standardized yet.

It has been observed that those previously undergoing IFN based therapy for HCV, and achieving SVR, experienced improvement in clinical manifestations of their cryoglobulinemic disease. This includes patients diagnosed with glomerulonephritis [8-11].

In patients with severe disease, the addition of rituximab to antiviral therapy has resulted in better outcomes compared to antiviral therapy alone [12]. The benefits of adding rituximab to IFN alpha and ribavirin therapy results in a more rapid clinical response. A clinical improvement was observed after a mean time of 5 months with rituximab plus Peg-IFN-α/ribavirin group *vs.* 8 months with Peg-IFN-α/ribavirin therapy alone.

With IFN-free DAA therapy, the clinical response in HCV associated cryoglobulinemic vasculitis appears associated with immunologic improvement in almost all patients; however only one third of patients had complete immunologic response.

We aim to emphasize the persistence of symptoms associated with HCV-associated cryoglobulinemic vasculitis following achievement of SVR with the new IFN-free DAA therapy. In particular, we describe the persistence of C4 hypocomplementemia and positive Rheumatoid factor. Here we describe two cases of Cryoglobulin vasculitis and the varying degrees of remission after HCV IFN-free DAA therapy. We also describe two patients treated with IFN based treatment without resolution of vasculitis.

Patient 1

A 61-year-old Caucasian female known to have chronic hepatitis C, genotype 1b, infection presented to Veterans Affairs (VA) outpatient Rheumatology clinic in November 2014 with complaints of diffuse arthralgia associated with palpable purpuric rash and persistent paresthesia of her feet.

On physical exam, she was noted to have diffuse myofascial tenderness but no evidence of synovitis, nodules, joint effusions, malleolar ulcers or psoriasiform lesions. In addition, she was noted to have mild hypermobility of her fingers and elbows.

Initial labs, included ANA panel, ANCA, cryoglobulin, ESR, CRP, TSH, Urinalysis, and Renal Function Panel that were all within normal limits. Serum Creatinine was 0.7 mg/dL. RF was found to be positive at 1170 IU/mL (normal range 0-15 IU/mL). C3 was 121 mg/dL (normal range 80-180 mg/dL). C4 was low at 10 mg/dL (normal range 15-40 mg/dL). The patient was again evaluated on 12/2014 by Rheumatology and was started on 5 mg/day of Prednisone. Cryoglobulin drawn following this visit on 12/2014 was positive at 2%. Subsequent Cryoglobulin levels remained positive for Type II Cryoglobulinemia.

Dermatology performed a punch biopsy of her right buttock for continued purpuric rash. Histopathology was consistent with leukocytoclastic vasculitis, believed to be secondary to Cryoglobulinemia. There was no evidence of visceral involvement and repeated Urinalysis and Renal Function Panel that remained within normal limits.

The patient continued Prednisone at same dose for 3 months. She reported improvement in lower extremity rash, which at that time was described to be non-blanching and no longer palpable. Patient was initiated in March 2015 DAA-HCV therapy (ledipasvir/sofosbuvir) was initiated in conjunction with low dose prednisone for her cryoglobulinemia and associated rash. She subsequently achieved a sustained virologic response (SVR) to this therapy, and this was accompanied by a reduction in RF level from 1170 IU/mL to 62 IU/ml (normal range 0-15 IU/mL) following treatment. RF values continued to range from 62-249 IU/mL during the 2 years following treatment. C3 ranged from 103-138 mg/dL following treatment. C4 continued to remain below normal, ranging from 6-13 mg/dL following treatment. Prednisone was discontinued in April 2015.

Although the patient reported subjective improvement of rash following DAA-HCV therapy, she continued to note intermittent raised urticarial rash on her inner thigh 2 years following treatment. Cryoglobulin continued to remain positive during this time, despite eradication of her chronic HCV infection. She was also found to have hematuria on urinalysis 06/2016 with a reduction in GFR from 85 in 08/2015 to 56 in 06/2016. IgG 1000 mg/dL (normal range 700-1700 mg/dL), IgM 157 mg/dL (normal range 50-230 mg/dL). IgA was low at 75 mg/dL (normal range 90-450 mg/dL). Total Protein Electrophoresis was 6.8 g/dL (normal range 6.4-8.5 g/dL) with albumin fraction 3.9 g/dL (normal range 2.9-4.7 g/dL), alpha-1 globulin 0.26 g/dL (normal range 0.8 -1.35 g/dL), alpha-2 globulin 0.89 g/dL (normal range 0.44-1.66 g/dL), beta globulin 0.87 g/dL (normal range 0.65-1.45 g/dL), gamma globulin 0.92 g/dL (normal range 0.55-1.88 g/dL), and no monoclonal protein was identified. Given urinalysis revealing 1+ proteinuria, it was believed to be unlikely related to glomerular disease. Protein on subsequent Urinalyses were all negative. Patient underwent CT Abdomen and Pelvis with contrast which was unremarkable.

Patient 2

Patient is a 68-year-old male with seropositive Rheumatoid Arthritis (+CCP and +RF), treated Neuroendocrine tumor of the neck, and chronic kidney disease secondary to cryoglobulinemic vasculitis with membranoproliferative glomerulonephritis (MPGN) associated with chronic HCV genotype 2 infection that was estimated to be present since the early 1970s based upon clinical manifestations at that time, and at risk behavior.

The patient was diagnosed with MPGN on 10/2014, when he was found to have hematuria and proteinuria. Urinalysis results revealed protein >600 mg/dL, with 5 RBCs per HPF. Patient was found to have positive cryoglobulin levels at 3%. Immunofixation electrophoresis of the cryoprecipitate revealed Type III Cryoglobulinemia, with mixed polyclonal immunoglobulins. Upon retesting in 11/2014 cryoglobulin levels were at 4%. Immunofixation electrophoresis of the cryoprecipitate revealed a Type II Cryoglobulinemia.

The patient was treated with Rituximab beginning in 12/2014, at 1000 mg administered twice over 2 weeks every 6 months. Prior to rituximab, five Urinalysis collected in 2014 revealed protein ranging from 100 to >600 mg/dL and 1-5 RBC on HFP.

In 03/2015, the patient was treated with ribavirin+ledipasvir/sofosbuvir. The treatment course was complicated by progressive anemia, and ribavirin was held after 5 weeks into treatment. Following completion of 12 weeks of treatment with ledipasvir/sofosbuvir, the patient achieved a sustained virologic response. Patient also found to have HBV core antibody positivity and has remained on entecavir prophylaxis.

Continued proteinuria was noted following treatment. In 2016 and 2017, Urine protein ranged from 100-300 mg/dL on 10 separate samples with RBC on HPF </=1. Random urine total protein declined from 204.9 mg/dL in 02/2016 to 92.2 mg/dL in 03/2017.

The patient did have improvement in RF titers following treatment of HCV and maintaining virologic response, even though he has CCP+ Rheumatoid Arthritis. RF ranged from 105-788 IU/mL prior to Hepatitis C treatment. Following treatment RF ranged from 84-172 IU/mL. CCP was elevated at 133 U/mL at time of diagnosis and ranged

from 101-133 U/mL since diagnosis. There were however no significant changes in Complement levels following treatment. Prior to treatment C3 and C4 ranged from 96-144 mg/dL and 12-18 mg/dL respectively. Following treatment, C3 and C4 ranged from 104-129 mg/dL and 10-16 mg/dL.

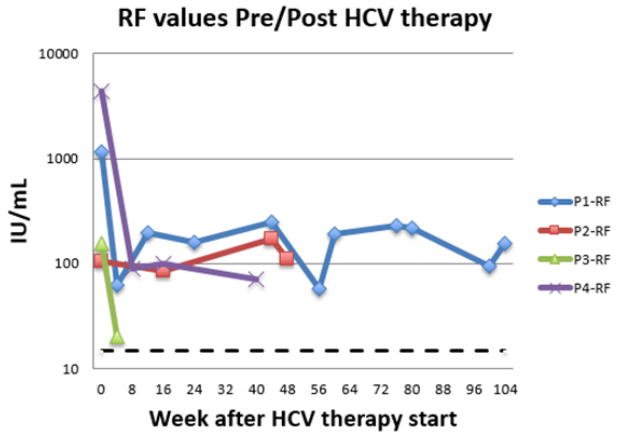

Figure 1: RF levels over the course of HCV therapy. Dotted/dashed black line indicates positive/negative cutoff for RF in all panels; RF normal range 0-15 IU/mL.

Patient 3

52-year-old Hispanic man with long standing Chronic HCV, believed to be acquired in the late 1960s, found to have nephrotic range proteinuria. Further work-up revealed 2% cryoglobulinemia in 02/2000, RF was noted to be 160 IU/mL. C3 and C4 were 63 mg/dL and <10 mg/dL respectively. He underwent kidney biopsy, which revealed findings consistent with MPGN.He was started on IFN and Ribavirin in 12/2001. Treatment was complicated by hemolytic anemia, dyspnea on exertion, fatigue. Ribavirin was discontinued and the patient was continued on IFN from 12/2001 to 06/2002, with stabilization of kidney function (creatinine ranged from 1.1-1.4 mg/dL). Cryoglobulins normalized following 1 month of IFN treatment.

Prior to treatment RF 156-160 IU/mL, and after therapy RF titers declined to <20 IU/mL. In contrast, C3 and C4 remained low at 62 mg/dL and <10 mg/dL respectively. These values were relatively unchanged from pretreatment values (see above). The patient achieved a complete response to HCV therapy while on treatment but relapsed once treatment completed. Between 2003 and 2004, when theHCV load was >2.1 million copies/ml, RF ranged 24-127 IU/mL, C3 and C4 were 88-94 mg/dL and 3 mg/dL respectively.

He was found to have worsening creatinine from 1.5-1.6 mg/dL in early 2004 to 3.3-3.5 mg/dL by late 2004. He was initiated on hemodialysis in 09/2005.

Of note, the treatment course was complicated by poor medical adherence due to co-morbid schizophrenia.

Patient	Therapy	Cryocrit	Cryoglobulin manifestations	HCV Treatment Durations	Cryoglobulin Clearnace	SVR*
1	Ledipasvir/Sofosbuvir	2%	Peripheral neuropathy, migratory arthralgia, purpura	8 weeks	Yes, Positive >17 months following treatment	Yes
2	Ledipasvir/Sofosbuvir	3%	Membranoproliferative glomerulonephritis	12 weeks	N/A**	Yes
3	Interferon + ribavirin***	2%	Membranoproliferative glomerulonephritis	6 months	Yes, 1 month following treatment	Yes
4	Ledipasvir/Sofosbuvir	3%	purpura, arthralgia, myalgia	12 weeks	Yes	Yes

Note: *SVR-Sustained Viral Response

**N/A-data not available at time of data collection

***Ribavirin discontinued early in treatment given complications: hemolytic anemia, dyspnea on exertion, fatigue.

Table 1: Clinical characteristics of the patients and HCV treatment regimen and duration of therapy.

Patient 4

59-year-old Caucasian man with Chronic Hepatitis C associated cryoglobulinemic vasculitis. He had complained of an intermittent LE rash since the 1980s in addition to occasional arthralgia and myalgia. The rash was described as intermittent and purpuric.

C-ANCA and P-ANCA were negative. RF 3350 IU/ml. C3 level was 79 mg/dL. C4 was low at 4 mg/dL. C4 levels would continue to remain low, ranging from 4-17 mg/dL from levels drawn between 2009 and 2014 prior to treatment.

He underwent biopsy of lesion located on right inner thigh in 06/2009 that revealed leukocytoclastic vasculitis.

He was treated with peg2a IFN/ribavirin for 48 weeks from 02/2010 until 01/2011. Although he was a responder to therapy, he relapsed following cessation of treatment.

During the time period of response and suppression of viral load, the RF titers continued to remain elevated at 3050 and 2750 compared to 3350 prior to HCV treatment. C3/C4 levels also remained low. In 10/2011, cryoglobulin levels were elevated with immunofixation electrophoresis of the cryoprecipitate demonstrating a Type II Cryoglobulinemia. This remained elevated on subsequent draws.

In late 2014 to 03/2015, the patient completed treatment of Hepatitis C with Ledipasvir/sofosbuvir and achieved SVR. Following treatment, patient's cryoglobulinemic associated rash resolved with a

significant decline in RF titers, without normalization. From 04/2015-06/2015 RF ranged from 89-100 IU/mL. By 09/2017, RF declined to 26 IU/ml. C3 ranged consistently from 104-130 mg/dL following treatment. C4 levels improved, ranging from 18-28 mg/dL two years following treatment. For detection of cryoglobulins, a venous blood sample was collected , promptly injected into a preheated test tube, and maintained at 37°C until the cells and serum are separated. The serum was then allowed to stand at 4°C for at least 72 hours in a hematocrit tube. Since agglutination/gelation was detected and dissolution occurred on heating, the presence of cryoglobulin was confirmed.

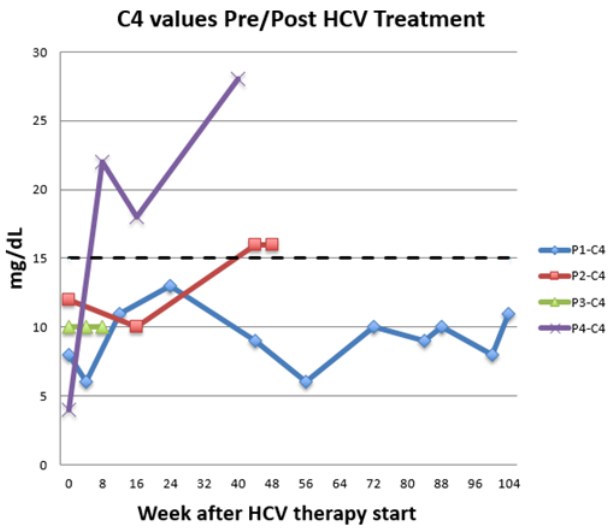

Figure 2: C4 levels over the course of HCV therapy. Dotted/dashed black line indicates positive/negative cutoff for C4 in all panels; C4 normal range 15-40 IU/mL.

Discussion

We describe two patients with HCV associated cryoglobulinemic vasculitis who remained symptomatic despite successful DAA treatment SVR. In addition, we describe one patient treated with IFN-based therapy that achieved viral suppression, but did not have resolution of HCV-associated cryoglobulin vasculitis with IFN-based therapy. We also describe one patient previously treated with IFN-based therapy that achieved viral suppression, but did not have resolution of HCV-associated cryoglobulin vasculitis with IFN-based therapy. This patient would later achieve resolution of vasculitis with DAA treatment (Figures 1 and 2).

Previous studies have demonstrated HCV-associated cryoglobulinemia vasculitis relapse following interferon-based treatments [13-15]. To our knowledge there are very few case reports describing persistent cryoglobulin vasculitis following successful treatment with DAA therapy. Of note, all data has been collected retrospectively (Table 1).

Although the elevation of RF is associated with HCV and HCV-associated Cryoglobulinemia, it is not clear if its resolution predicts resolution of cryoglobulin vasculitis. Of the 4 patients, patients 1 and 2 experienced decline of RF without resolution following treatment. Patient 1, in particular, continues to have evidence of disease. Patient 3 did not have resolution of RF during interferon-based treatment and experienced stabilization of kidney function while on treatment. Patient 4, previously a non-responder to interferon based treatment, experienced significant decline in RF titers along with resolution of cryoglobulin-associated rash with IFN-free DAA therapy.

Obata et al. also described a patient who experienced a decline in cryoglobulin and RF and remission of MPGN even while cryoglobulin levels persisted at low levels [16]. Ghosn and colleagues described a case of glomerulonephritis following treatment with DAA therapy and SVR achievement. Six months following treatment with high dose prednisone, plasma exchange and rituximab, the patient was noted to have improvement in GFR. RF titers declined significantly. C4 remained low and qualitative cryoglobulins remained positive [17].

All patients had relatively no change in C3, while C4 remained low following treatment. This phenomenon is consistent throughout the literature (Table 2) [16,17].

Of the four patients, only patient 1 had prolonged persistence of cryoglobulinemia, measured at 3%, 17 months following achievement of SVR to IFN-free DAA therapy. This phenomenon, with such a prolonged time period after SVR, has not previously been described in the literature to our knowledge. Levine and colleagues described a subset of patients with persistent cryoglobulinemic vasculitis who continued to have increasing/stable cryoglobulin titers 9-24 months following treatment, however this was with IFN-based therapy [13].

Patient	RF pre-treatment	C4 pre-treatment	RF post-treatment	C4 post-treatment
1	1170 IU/mL*	8-10 mg/dL**	62-249 IU/mL*	6-13 mg/dL**
2	105-788 IU/mL*	12-18 mg/dL**	84-172 IU/mL*	10-16 mg/dL**
3	156-160 IU/mL	<10 mg/dL	<20 IU/mL*	<10 mg/dL**
4	1350-3350 IU/mL*	4 mg/dL	70-100 IU/mL*	18-28 mg/dL**

Note: *RF Normal range 0-15 IU/mL

**C4 Normal range 15-40 mg/dL

Table 2: RF and C4 levels over the course of HCV therapy.

Solima and colleagues described 7 patients treated for HCV-associated cryoglobulinemia vasculitis. All patients were treated with

IFN-free DAA therapy and achieved SVR at 12 weeks. Only 2 of the 7 patients had response for vasculitis at 12 week follow up after treatment [18].

Sise and colleagues reported 9 patients treated with DAA therapy and had reduction in cryoglobulin levels from median of 1.5% to 0.5%. One patient, with a cryoglobulin level of 2%, experienced a relapse of HCV viremia. All other patients showed a decrease in cryoglobulin levels [19].

Previously one theory proposed persistence of cryoglobulin vasculitis was due to occult infection [13]. However, DAA drugs have shown tremendous success in treating HCV compared to IFN-based therapy with SVR exceeding 95% [20]. With successful treatment, it is presumed that viral eradication has occurred and HCV-induced clonal B cells are the cause of persistence of cryoglobulinemia. IgM-K +Memory B cell Clonal Expansion has been reported in patients with HCV infection and cryoglobulinemia [21].

Landau and colleagues proposed that B cell clones may require HCV to completely transform and proliferate, however the presence of HCV is not necessary once proliferation has begun. Our prior data indicate that RF and not viral load appears to be closely associated with B cell subset alterations in proportion and activation manifested by overrepresentation of circulating mature activated memory B cells in HCV RF+donors, this B cell subset appears to avoid deletion and persist in a state of unresponsiveness towards antigenic stimulation [15]. This would further explain the higher rate of malignant B cell lymphoproliferative disorders associated with Cryoglobulinemia [15].

In conclusion, our cases highlight the complexity of this viral mediated immunologic mechanism. Our cases also emphasize the need to consider cryoglobulinemic vasculitis as part of the differential diagnosis even with treated HCV infection. Recognizing these findings are important in our understanding of the pathophysiology of the disease and management in the era of IFN-free DAA therapy.

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