International Journal of Medical Research Professionals
P-ISSN: 2454-6356; E-ISSN: 2454-6364
DOI: 10.21276/ijmrp

IJMRP

Case Report .

Rituximab Treatment for Recurrent Skin Vasculitis Due to Cryoglobulinemia Associated with Hepatitis C Despite Viral Clearance with Sofosbuvir

Kamel El-Reshaid[1*], Shaima Al Bader[2]

[1]MB BCh, Am B Med, Am B Nephrology, FRCP (Ed),
Department of Medicine, Faculty of Medicine, Kuwait University, Kuwait.
[2]MBBCH, Asad Al-Hamad dermatology center, Ministry of health, Kuwait.

ABSTRACT

Hepatitis C (HC) is a major cause of both acute and chronic hepatitis. It is a major cause of liver cell failure and its cancer. Nearly 2/3 of patients experience extrahepatic immune-related manifestations including skin vasculitis with/without mixed cryoglobulinemia. Naturally; clearance of viral infection should lead to prevention of such complications. Unfortunately; this is not absolute true. In this case report; we describe a patient, with chronic HC infection yet without chronic liver disease, who continued to develop skin vasculitis and cryoglobulinemia despite virological clearance of RNA virus by Sofosbuvir. Her skin vasculitis improved with yearly Rituximab infusions without activation of hepatitis C infection, other autoimmune disease and hepatitis.

Key words: Hepatitis C, Skin Vasculitis, Rituximab.

***Correspondence to:**
Dr. Kamel El-Reshaid
Professor,
Dept. of Medicine,
Faculty of Medicine,
Kuwait University, Safat, Kuwait.

Article History:
Received: 21-10-2019, **Revised:** 13-11-2019, **Accepted:** 27-11-2019

Access this article online	
Website: www.ijmrp.com	Quick Response code
DOI: 10.21276/ijmrp.2019.5.6.020	

INTRODUCTION

Hepatitis C (HC) is a major cause of both acute and chronic hepatitis. Persons become infected mainly through parenteral exposure to infected material by blood transfusions or injections with non-sterile needles. Another major risk factor for HC is high-risk sexual behavior. Due to mass education, the incidence of acute HC infection has sharply decreased during the past decade. However, its prevalence remains high since chronic HC persists in approximately 75% of patients acutely infected.[1] Nearly 150–170 million people chronically infected.[2] Most patients with acute and chronic infection are asymptomatic. However, HC chronic active hepatitis is a slowly progressive diseases and result in severe morbidity in 20-30% of infected persons with cirrhosis leading to hepatic failure and hepatomata with an estimated liver-related mortality of 350,000 people/year.[3] On the other hand, in large cohort studies, 2/3 of patients experience extrahepatic immune-related manifestations. The latter include; mixed cryoglobulinemia with or without vasculitis, Sicca syndrome, B-cell non-Hodgkin's lymphoma, polyarteritis nodosa, immune-mediated thrombocytopenia, glomerulonephritis and cardiovascular disorders.[4] Naturally; clearance of viral infection should lead to prevention of such complications. Unfortunately; this is not absolute true. In this case report; we describe a patient, with chronic HC infection yet without chronic liver disease, who continued to develop skin vasculitis despite virological clearance of RNA virus by Sofosbuvir.

THE CASE

A 63-year-woman presented with progressive skin lesions lesions in both her legs for months. They were painful yet not itchy and were resistant to multiple antibiotics. The patient denied fever, shortness of breath, oedema, abdominal pain, skin rash and joint pains. She had diabetes mellitus for 28 years yet without proteinuria, peripheral neuropathy or proliferative retinopathy. Moreover, she had hypertension and hypothyroidism for years. On routine tests, 6 years ago, HC was detected. She had high viral load yet without derangement of liver function tests. At that time, she could not tolerate Interferon therapy for > 1 month. On her initial physical examination; she was conscious, oriented X3 yet was in severe pain from her leg lesions. The lesions were 10 cm violaceous patch with intact skin (Fig.1). The patient had normal vital signs and normal systemic examination. Her hemoglobin, peripheral leukocytic and platelets counts were normal. Serum sugar, urea, creatinine, electrolytes and liver functions were normal. Urine routine and microscopy did not show abnormality. Serum complements (C3 & C4), IgA level and protein electrophoresis were normal. ANA, anti-ds DNA, ANCA, anti-GBM-antibodies, RA, hepatitis B surface antigen were negative. Her anti-HC viral antibodies were positive and her HCV-RNA viral load was > 700 thousand IU/ml (Normal: < 5). She had polyclonal gammopathy with positive mixed cryoglobulins. Stool testing for ova, parasites and occult blood was normal. Chest x-ray and ECG

were normal. Abdominal and pelvic ultrasound was normal. Skin biopsy showed subepidermal leukocytoclastic vasculitis with no immune deposits (Fig. 2).

Hence diagnosis of skin vasculitis due to HC infection was established. Fortunately, she did not have clinical or laboratory evidence of significant liver or kidney disease. She was treated with 1 g of Solumedrol for 3 days and had improved dramatically. Subsequently, she received Predn isone 60 mg X1 for 1 month to be tapered down till discontinuation after 3 months. As expected, her blood sugar had increased dramatically with Corticosteroids. Hence, her dose of insulin had to be adjusted to keep it within normal range. After tapering down her Prednisone dose; she relapsed. Hence, Rituximab was added. The latter was administered as a 1 g infusion over 4 hours followed by 1 g 2 weeks later. On follow up; she relapsed 1 year after her initial treatment and had to be re-treated with the same protocol and improved. When she tends to delay or ignore her yearly treatment she tends to relapse.

Two years ago, she was treated with Sofosbuvir 1 tablet daily for 12 weeks and her viral RNA titer by PCR was negative. Unfortunately, the later treatment did not prevent her yearly relapses if she tends to ignores Rituximab nor cleared her cryoglobulinemia. Her latest skin vasculitis was few weeks ago and her HC viral titers remained undetectable.

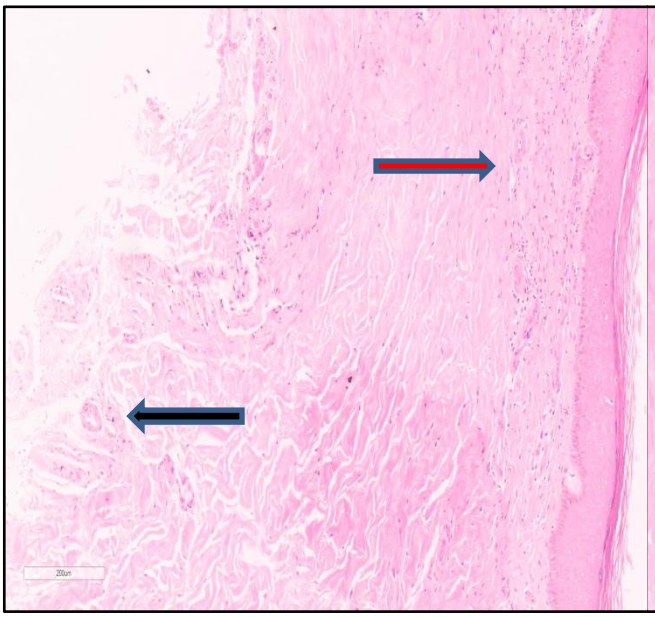

Figure 1: Photomicrograph showing subepidermal capillaries with neutrophils within the wall and around them (black arrow) with swollen of the endothelial cells (red arrow).

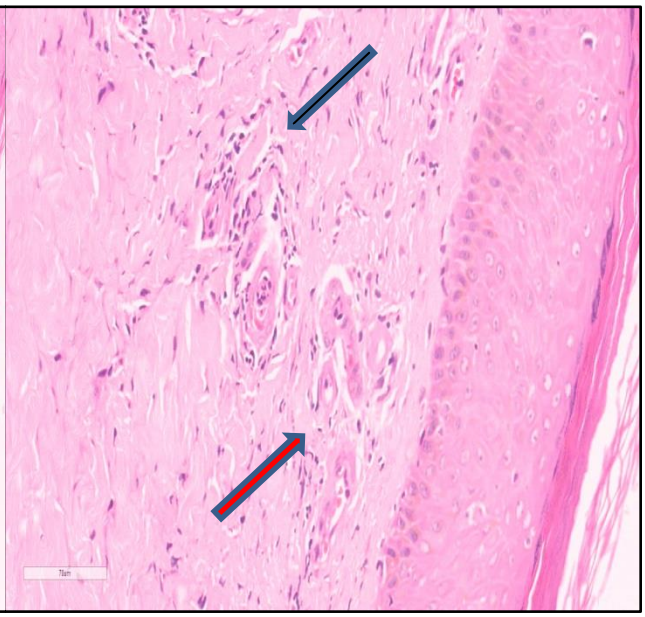

Figure 2: Photomicrograph of skin showing perivascular neutrophilic infiltrations in the subepidermal zone (red arrow) while the deeper vessels are intact (black arrow). (H&E X100)

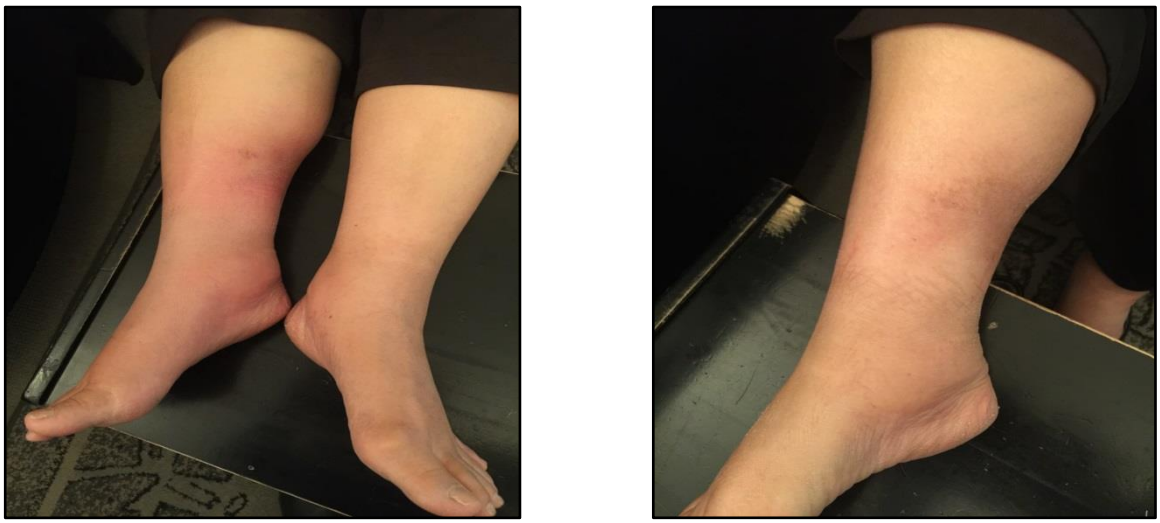

Figure 3: Skin vasculitis: (A) before and (B) 1 month after Rituximab therapy.

DISCUSSION

Mixed cryoglobulinemia vasculitis (Cryovas) is a small vessel vasculitis involving mainly the skin, the joints, the peripheral nerve system and the kidneys. HC infection is the cause of Cryovas in about 80% of cases.[5] The disease expression is variable, ranging from mild symptoms (purpura, arthralgia) to fulminant life-threatening complications (glomerulonephritis, widespread vasculitis). Skin is the most frequently involved target organ: palpable purpura, chronic cutaneous ulcers, Raynaud's phenomenon, acrocyanosis, which may evolve to digital ulcerations.[4] In HC infection, Cryovas is associated with advanced age, longer duration of infection, type II MC, a higher serum mixed cryoglobulin level and clonal B-cell expansions in both the blood and liver. The worse prognostic factors are an age greater than 60 years at diagnosis and renal involvement.[5] The overall 5-year survival rate after the diagnosis of Cryovas ranges from 90% to

50% in the case of renal involvement. Increased mortality from liver involvement, cardiovascular disease, infection and lymphoma has been reported.[4]

There are multiple factors predisposing patients with HC infection to develop Cryovas. Interaction between HC and lymphocytes directly modulates B- and T-cell function and results in polyclonal activation and expansion of B-cell-producing IgM with RF activity.[6] $CD4^+CD25^+FoxP3^+$regulatory T cells are reduced in patients with Cryovas which may account for the expansion of peripheral autoreactive B cells that drive Cryovas.[7] Human leucocyte antigen (HLA-DR11) is associated with Cryovas whereas HLA-DR7 appears to protect against Cryovas.[8]

In a recent multicenter genome-wide association study significant associations were identified on chromosome 6, a single nucleotide peptide located within an intronic region of NOTCH4 ($p = 6.2 \times 10^{-9}$) and another found in between HLA-DRB1 and HLA-DQA1 ($p = 1.2 \times 10^{-7}$).[9] Most reports indicate that; HC-Cryovas manifestations respond to clearance of HC virus during antiviral therapy with pegylated interferon (pegIFN) plus ribavirin[10] and recently with direct anti-viral agents.[11] Persistent MC with relapsing vasculitis, despite viral clearance, indicates a search for a different underlying condition, especially B-cell lymphoma.[12] Our patients had viral clearance and PET scan did not show evidence of lymphoma. Hence our next-line of treatment was aimed at decrease her hyperactive B-cells.

Rituximab is an interesting therapy in mixed cryoblobulinemia, as it targets B cells, which are responsible for cryoglobulin production and finally Cryovas lesions. Two randomized controlled trials showed that rituximab has a better efficacy than conventional treatment (i.e. glucocorticoids, azathioprine, cyclophosphamide or plasmapheresis).[13]

Two other controlled clinical trials showed that addition of rituximab to pegIFN/ribavirin led to a shorter time to clinical remission, better renal response rate and higher rates of cryoglobulin clearance.[14,15] The duration of treatment is unclear. Rituximab therapy in patients with minimal change disease has been associated with disappearance of memory cells leading to a state of tolerance after few years.[16] In conclusion; our case report indicates that Rituximab is safe and efficacious in treatment of Cryvas persisting despite Sofosbuvir therapy.

REFERENCES

1. Westbrook RH, Dusheiko G. Natural history of hepatitis C. J Hepatol 2014; 61(1 Suppl): S58-68

2. Centers for Disease Control and Prevention. Viral Hepatitis Surveillance-United States, 2017. Atlanta: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2019. Available at:
www.cdc.gov/hepatitis/statistics/2017survailence/index.htm.

3. Cacoub P, Comarmond C, Domont F, Savey L, Desbois AC, Saadoun D. Extrahepatic manifestations of chronic hepatitis C virus infection. Ther Adv Infect Dis 2016; 3: 3-14.

4. Cacoub P, Poynard T, Ghillani P, Charlotte F, Olivi M, Piette JC, Opolon P. Extrahepatic manifestations of chronic hepatitis C. MULTIVIRC Group. Multidepartment Virus C. Arthritis Rheum 1999; 42: 2204-12.

5. Terrier B., Cacoub P. Renal involvement in HCV-related vasculitis. Clin Res Hepatol Gastroenterol 2013; 37: 334–9.

6. Saadoun D, Bieche I, Maisonobe T, Asselah T, Laurendeau I, Piette J, et al. Involvement of chemokines and type 1 cytokines in the pathogenesis of hepatitis C virus-associated mixed cryoglobulinemia vasculitis neuropathy. Arthritis Rheum 2005; 52: 2917–25.

7. Boyer O, Saadoun D, Abriol J, Dodille M, Piette J, Cacoub P, et al. CD4+CD25+ regulatory T-cell deficiency in patients with hepatitis C-mixed cryoglobulinemia vasculitis. Blood 2004; 103: 3428–30.

8. Cacoub P, Renou C, Kerr G, Hüe S, Rosenthal E, Cohen P, et al. Influence of HLA-DR phenotype on the risk of hepatitis C virus-associated mixed cryoglobulinemia. Arthritis Rheum 2001; 44: 2118–24.

9. Zignego AL, Wojcik GL, Cacoub P, Visentini M, Casato M, et al. Genome-wide association study of hepatitis C virus- and cryoglobulin-related vasculitis. Genes Immunol 2014; 15: 500-5.

10. Saadoun D, Resche-Rigon M, Thibault V, Piette J, Cacoub P. Antiviral therapy for hepatitis C virus–associated mixed cryoglobulinemia vasculitis: a long-term follow up study. Arthritis Rheum 2006; 54: 3696–3706.

11. Childs-Kean LM, Hand EO. Simeprevir and sofosbuvir for treatment of chronic hepatitis C infection.ClinTher2015;37:243–67.

12. Landau D, Saadoun D, Halfon P, Martinot-Peignoux M, Marcellin P, et al. Relapse of hepatitis C virus-associated mixed cryoglobulinemia vasculitis in patients with sustained viral response. Arthritis Rheum 2008; 58: 604–11.

13. De Vita S, Quartuccio L, Isola M, Mazzaro C, Scaini P, Lenzi M, et al. A randomized controlled trial of rituximab for the treatment of severe cryoglobulinemic vasculitis.
Arthritis Rheum 2012; 64: 843-53.

14. Dammacco F, Tucci FA, Lauletta G, Gatti P, De Re V, et al. Pegylated interferon-alpha, ribavirin, and rituximab combined therapy of hepatitis C virus-related mixed cryoglobulinemia: a long-term study. Blood 2010; 116: 343-53.

15. Saadoun D, Resche Rigon M, Sene D, Terrier B, Karras A, et al. Rituximab plus Peg-interferon-alpha/ribavirin compared with Peg-interferon-alpha/ribavirin in hepatitis C-related mixed cryoglobulinemia. Blood 2010; 116: 326-34.

16. Snider RA, Book BK, Agarwal A, Bearden CM, Vieira CA, Pescovitz MD. In vivo human B-cell subset recovery after in vivo depletion with rituximab, anti-human CD20 monoclonal antibody. Hum Antibodies 2004; 55: 55-62.

Source of Support: Nil. **Conflict of Interest:** None Declared.

Cite this article as: Kamel El-Reshaid, Shaima Al Bader. Rituximab Treatment for Recurrent Skin Vasculitis Due to Cryoglobulinemia Associated with Hepatitis C Despite Viral Clearance with Sofosbuvir. Int J Med Res Prof. 2019 Nov; 5(6):86-88. DOI:10.21276/ijmrp.2019.5.6.020