

# Cutaneous Vasculitis and Asthenia in a Patient with HCV-Related Chronic Liver Disease without Detectable Serum Cryoglobulinemia

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## Abstract

This paper reports a case of 47-year-old lady with Hepatitis C virus-related chronic liver disease who presented with asthenia and purpuric skin eruption involving her lower limbs. Punched skin biopsy from one of those lesions was consistent with small vessels vasculitis. Although Hepatitis C virus-related vasculitis is usually associated with cryoglobulinemia, in the present case the serum Cryoglobulins were not detected on three different occasions. Moreover, testing for indirect biomarkers for mixed cryoglobulinemia (rheumatoid factor and low complement-4) were negative. The patient treated with PEG-interferon alfa-2a plus ribavirin for 24 weeks and showed partial virological response. However, after two months from the start of treatment the cutaneous lesion disappeared completely with marked improvement of asthenia and remained asymptomatic during a follow-up period of 12 months after the antiviral treatment stopped. This case highlights that patients with Hepatitis C virus may have cutaneous vasculitis without detectable serum Cryoglobulins. Combination therapy with PEG-interferon alfa-2a and ribavirin is an effective treatment approach for such patients.

## Keywords

Hepatitis C virus, Asthenia, Purpuric skin eruption, Small vessels vasculitis, Mixed cryoglobulinemia, Cutaneous vasculitis.

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## Introduction

About 3% of the world's populations are chronically infected with hepatitis C virus (HCV), and it's a leading cause of chronic liver disease, cirrhosis and hepatocellular carcinoma<sup>[1]</sup>.

In addition to the liver inflammation, chronic HCV may be associated with a series of extrahepatic manifestations ranging from neuropathies to different skin diseases. A variety of skin manifestations can be seen in association with HCV infection, cutaneous

vasculitis is the commonest one, and it is usually related to mixed cryoglobulinemia (MC)<sup>[2-4]</sup>.

However, in this report, a lady with HCV-related chronic liver disease presented with asthenia and cutaneous vasculitis in the absence of serum MC.

## Case Report

A 47-year-old woman was referred to the hepatology clinic because of abnormal liver enzymes. She also

gave a history of the marked asthenia and purpuric skin eruption involving her lower limbs of 5 week's duration. She denied a history of joints pain or swelling. About twenty years ago, she was diagnosed to have HCV infection in another hospital but she didn't have a follow-up for that. No treatment for HCV had been offered for her at that time. There was no risk factor for acquiring the virus. The patient is known to have *diabetes mellitus* type 2 for eight years on Glibenclamide, and she was not on any other type of medication including herbal medicine. She denied smoking and alcohol abuse.

Physical examination revealed palpable purpuric rash over the lower limbs, distributed symmetrically, more over the legs with different sizes ranging from 3-5 mm. No other skin lesions over the rest of the body. General examination was unremarkable. No stigmata of chronic liver disease. The chest, cardiovascular, abdominal, rheumatological and neurological examinations were unremarkable.

Laboratory findings revealed; Leukocytes count 6,000/mm<sup>3</sup> (4.5-11.5), Hemoglobin 15.2 g/dL (12-15), Platelets 160,000/mm<sup>3</sup> (150-450), Alanine transaminase (ALT) 131 U/L (12-78), Aspartate aminotransferase (AST) 186 U/L (15-37), Alkaline phosphatase (ALP) 176 U/L (36-50), Gamma-glutamyltransferase (GGT) 168 U/L (5-85), Total bilirubin 16  $\mu$ mol/L (0-17), Direct bilirubin 8  $\mu$ mol/L, Albumin 35 g/L (40-47). Kidney function test and coagulation profile were normal. Urine analysis was negative for proteinuria and casts. Hepatitis C virus-RNA level was 3,525,827 IU/mL, genotype 1a. Hepatitis B surface antigen, hepatitis B core antibodies (total), Human immunodeficiency virus antibodies 1 & 2 and Antineutrophil cytoplasmic antibodies (ANCA) were negative. Rheumatoid factor (RF), complements (C-3 & C-4), Immunoglobulins (IgG) and Double Stranded DNA Antibodies were within normal ranges. Serum Cryoglobulins on three different occasions was negative. Anti-nuclear antibodies (ANA) was weakly positive. The skin biopsy of one of the purpuric lesions was consistent with small vessels vasculitis. Abdominal Ultrasound showed coarse echo pattern of the liver, normal portal vein, and there was no splenomegaly. Esophagogastroduodenoscopy (EGD) showed no varices. FibroScan score was (32 KPa), indicating advanced liver fibrosis (metavir fibrosis score stage-4).

The patient was treated with PEG-interferon alfa-2a (180  $\mu$ g/week) plus ribavirin 1000 mg/day (that was before the availability of the new antiviral therapy (direct acting antiviral agents) in the country). She did not achieve rapid virological response (RVR) (defined as undetectable HCV RNA at week 4 of treatment). At week 12 of treatment the HCV-RNA level dropped to 34,088 IU/mL. This level drop indicates that the patient achieved early virological response (EVR) (defined as  $\geq 2$  log<sub>10</sub> IU/mL (100 times) reduction in HCV RNA at week 12 of treatment). At week 24, HCV RNA remained positive

(1,294,550 IU/mL), so the decision was made to stop the treatment because HCV RNA would not continue to decline with continued treatment. However, after two months from the start of treatment, the skin rash resolved completely with marked improvement of asthenia and remained asymptomatic during a follow-up period of 12 months after discontinuation of treatment.

## Discussion

Several extrahepatic manifestations have been reported in association with HCV infection. Extensive liver fibrosis, long-standing infection, advanced age, and female sex are important risk factors for developing extrahepatic manifestations<sup>[2]</sup>. During the natural course of HCV infection about 40-74% of patients might develop at least one extrahepatic clinical manifestation, the most common of which is mixed cryoglobulinemia (MC)<sup>[2-4]</sup>. Cryoglobulins can be detected in up to 50% of HCV-infected individuals, but only a minority of patients (less than 15%) will have symptoms related to cryoglobulinemia<sup>[4,5]</sup>.

MC is a systemic vasculitis affecting small and medium-sized blood vessels of the skin, kidneys, and nerves. Cutaneous vasculitis, ranging from palpable purpura and petechiae to large necrotic ulcerations, is the most common manifestation seen in patients with HCV-associated MC<sup>[4]</sup>. MC is characterized by the deposition of circulating immunocomplexes containing rheumatoid factor (RF), IgG, HCV RNA, and complements on endothelial surfaces<sup>[5-7]</sup>. Besides the detection of MC in the serum of the patient with HCV-related vasculitis, other laboratory finding such as RF and low C4 may provide indirect evidence for the presence of MC.

In this case report the patient presented with asthenia and cutaneous vasculitis in association with HCV infection without detectable serum MC. It's possible that the patient with HCV-related vasculitis may have positive cryoglobulinemia from time to time<sup>[9]</sup>. However, the serum Cryoglobulin was not detected on three different occasions. Furthermore, testing for indirect biomarkers for MC, such as RF or low C4, were negative. On the other hand, the other possible causes of vasculitis like ANCA, HBV or HIV coinfection, or other autoimmune disorders were not present.

In the literature, there are only a few reports described patients with HCV-related vasculitis in the absence of detectable serum MC<sup>[8-10]</sup>. Terrier *et al.*<sup>[10]</sup> found that patients with HCV-related vasculitis without MC have quite similar epidemiological, clinical, biological, virologic, and histological features of MC vasculitis, except for low rate of arthralgias and purpura and the absence of indirect biomarkers of MC.

HCV-related vasculitis without detectable MC probably results from immune complex mediated

mechanism<sup>[5,9,10]</sup>. However, the exact pathogenic mechanism is not fully known.

Eradication of HCV with Interferon-based therapy is an effective treatment approach for cutaneous manifestations related to HCV MC<sup>[11-13]</sup>. The duration of therapy for patients with HCV MC vasculitis is similar to that in patients with HCV infection who do not have MC<sup>[11-13]</sup>. Cutaneous vasculitis related to HCV MC has a higher response rate to interferon-based therapy than neural or renal manifestations related to HCV MC vasculitis<sup>[12,13]</sup>. Although the clinical response is correlated with the improvement in HCV viremia, a small number of patients with HCV-MC vasculitis may remain in clinical remission despite the persistence of viremia<sup>[11-13]</sup>.

Saadoun *et al.*<sup>[12]</sup> treated 72 patients with HCV MC vasculitis with Interferon alfa-2b (IFN alfa-2b) plus ribavirin (n = 32 patients) or PEG-IFN alfa-2b plus ribavirin (n = 40 patients). These treatments were continued for at least 6 months (mean duration 18 months with IFN alfa-2b and 13 months with PEG-IFN alfa-2b), and the patients were followed for a mean of 40 months after discontinuation of treatment. 6 months after completion of antiviral therapy, patients who received PEG-IFN alfa-2b plus ribavirin had somewhat higher rate of clinical response (68 versus 56%), sustained virologic response (62 versus 53%). According to the manifestations of vasculitis, complete improvement of purpura occurred in 86.3% of patients, neuropathy in 68.2%, and renal involvement in 40.9%. About 27% of the complete clinical responders were not sustained virologic responders. In a study published recently<sup>[14]</sup>, the same authors treated 23 patients with HCV MC vasculitis with triple therapy (PEG-IFN alfa/ribavirin/protease inhibitor). Complete clinical response occurred in 13 patients (56.5%) at week 24, and 69.6% had virological response (*i.e.*, undetectable HCV-RNA) at week 24. Although such triple therapy was highly effective in this study, adverse effects were reported in 44% of cases and the majority of patients required erythropoietin and red cell transfusions. Such therapeutic regimen should be administered cautiously considering the high rate of side effects. Long-term follow-up is warranted to assess the sustained clinical and virological responses.

Approximately 15% of patients with HCV genotype 1 achieve rapid virologic response (RVR), patients who achieve RVR have the highest rate (up to 88%) of sustained virologic response (SVR) (defined as HCV RNA is not detected 6 months after treatment end)<sup>[15]</sup>. Unfortunately, the patient in this case report did not achieve RVR, so the prediction of achieving SVR was low. At week 24 of therapy the patient achieved partial virological response (defined as a decline in serum HCV RNA  $\geq 2 \log_{10}$  IU/mL (100 times) from baseline at week 12 but does not develop undetectable HCV RNA at 24 weeks of treatment). This pattern of non-response occurs in approximately 15-20% of patients with HCV

genotype1<sup>[15]</sup>. Serum HCV RNA level in patients with partial virological response does not continue to decline with further therapy, and the treatment should be discontinued after 24 weeks if the virus remains detectable<sup>[15]</sup>. HCV genotype 1, high score fibrosis and high baseline viral load  $> 8 \times 10^5$  IU/mL were important factors associated with nonvirological response in the present case. However, after two months from the start of treatment the skin lesions disappeared completely with marked improvement of asthenia, and the patient remained asymptomatic during a follow-up period of 12 months following discontinuation of antiviral treatment. Besides its antiviral activity, IFN alfa also has antiproliferative and immunomodulatory properties<sup>[12]</sup>, which may explain the clinical response despite the persistence of viremia in this patient. However, re-treatment of this patient with the new effective antiviral agents would result in clearance of the virus.

In summary, this case highlights that patients with HCV may have cutaneous vasculitis without detectable serum Cryoglobulins. Combination therapy with PEG-interferon alfa-2a and ribavirin is an effective treatment approach in such patients.

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## التهاب الأوعية الجلدية والوهن لمريضة تعاني من مرض الكبد المزمن المرتبط بالتهاب الكبد الوبائي ج دون وجود للجلوبيولينات الباردة في المصل

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**المستخلص.** هذا التقرير عن حالة سيدة تبلغ من العمر ٤٧ عاما تعاني من مرض الكبد المزمن المرتبط بالتهاب الكبد الوبائي ج، حيث كانت تشتكي من الوهن وطفح جلدي فريري في الأطراف السفلية. فحص خزعة الجلد بين وجود التهاب الأوعية الدموية الصغيرة. على الرغم من أن التهاب الأوعية الدموية المتصل بالتهاب الكبد الوبائي ج يترافق عادة مع الكريوجلوبولينيميا، إلا أنه في هذه الحالة عند فحص الجلوبيولينات الباردة في المصل لثلاث مرات متفاوتة كانت النتائج سلبية. علاوة على ذلك، كانت مؤشرات فحوصات الدم غير المباشرة للكريوجلوبولينيميا المختلطة مثل (عامل الروماتويد وانخفاض كومبلمنت-٤ سلبية). عولجت المريضة ببيج-انترفيرون ألفا ٢-أ بالإضافة إلى ريبافيرين لمدة ٢٤ أسبوعا وأظهرت استجابة جزئية للفيروس. ومع ذلك، وبعد شهرين من بدء العلاج اختفت الآفة الجلدية تماما مع تحسن ملحوظ من الوهن، وظلت الأعراض مختفية خلال فترة المتابعة لمدة اثني عشر شهرا بعد توقف العلاج المضاد للفيروس. هذه الحالة تسلط الضوء على أن المرضى الذين يعانون من التهاب الكبد الوبائي ج قد يصابون بالتهاب الأوعية الجلدية دون وجود للجلوبيولينات الباردة في المصل وأن العلاج المضاد لفيروس ج هو العلاج الفعال لمثل هؤلاء المرضى.