



## Autoimmune Hemolytic Anemia with Leukemoid Reaction as a Rare Extrahepatic Manifestation in Treatment Naïve Chronic Hepatitis C

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### Abstract

*Primary autoimmune hemolytic anemia (AIHA) with leukemoid reaction is a rare extrahepatic manifestation of chronic hepatitis C virus (HCV) infection. However this can be successfully treated with prednisone therapy and does not form a contraindication to antiviral treatment. Hence, we report a case of direct Coombs'-positive AIHA with leukemoid reaction in treatment-naïve 35-year-old Indian female with past medical history of chronic hepatitis C, genotype 1 who was successfully treated with prednisone therapy followed by pegylated interferon [PEG-IFN alfa-2a (180 µg/week)] plus ribavirin [RBV (1000 mg/day)] for 48 weeks. On follow up visit she had neither HCV infection nor AIHA.*

**Keywords:** autoimmune hemolytic anemia (AIHA ), chronic hepatitis C.

### Introduction

Infection with hepatitis C virus (HCV) is often associated with extrahepatic manifestations, including autoimmune disorders. Autoimmune hemolytic anemia (AIHA) has been reported in association with HCV in the setting of interferon (IFN) treatment<sup>[1,2]</sup> and rarely as an isolated extrahepatic manifestation. Viruses, including HCV, can trigger an autoimmune response via antigenic mimicry and result in the loss of tolerance.<sup>[3,4]</sup> Our case is diagnosed to have leukemoid reaction due

to AIHA in treatment naïve chronic hepatitis C infection who was treated with pegylated interferon (PEG-IFN) alfa-2a plus ribavirin (RBV) and later on successfully achieved a sustained virological response. In conclusion AIHA due to chronic HCV infection can successfully be treated with prednisone therapy and does not form a contraindication to antiviral treatment. AIHA should be kept in mind as a possible cause of leukemoid reaction and need not be corrected separately.

### Case history

A 35-year-old Indian female with past medical history of chronic hepatitis C with HCV RNA of 12 million IU/ml, genotype 1, presented with complaints of generalized weakness, fatigability, exertional breathlessness for 10 days and jaundice for 4 days. On admission she denied chest pain, cough, fever, night sweats. There is no history of melena, hemorrhoid or weight loss. Family and personal history were non contributory. She is neither diabetic nor hypertensive nor was taking treatment for hepatitis C. She denied any history of smoking, alcohol consumption, illicit drug use, or family history of hematological or liver disease. Her physical examination revealed moderate icterus along with severe pallor with normal vital signs and higher mental functions. Per abdomen revealed splenomegaly of 3 cm and absence of ascitis. Review of other systemic examinations were unremarkable. No rash, joint tenderness, oral ulcers, or peripheral lymphadenopathy were seen. On admission, laboratory evaluation revealed haemoglobin 2.9 g/dl with, MCV 145 fl, total bilirubin of 11.8mg/dl, indirect bilirubin of 9.3 mg/dl with a raised lactate dehydrogenase (LDH) at 2883 IU/L (normal value 230-460 IU/L) and marked leucocytosis (57,000 cell/cumm.). Total platelet count and renal function test were within normal limit. Albumin globulin ratio, serum transaminases and alkaline phosphatase were normal. Serum iron and TIBC was 140mg and 211 respectively. Peripheral blood smear showed anisopoikilocytosis, microspherocytosis, macrocytosis, normoblast. The reticulocyte count was 42% (corrected reticulocyte count – 13.44%). Leucocyte alkaline phosphatase (LAP) score was increased. There were no bite cells or Heinz bodies or malarial parasite. Stool for occult blood was negative. Urine microscopy and Chest X ray was normal. Ultrasound abdomen showed moderate splenomegaly with no evidence of cirrhosis, ascitis and abdominal lymphadenopathy. The clinical and biochemical picture was suggestive of hemolytic anemia with leukemoid reaction. Direct antiglobulin test was positive for warm antibodies (IgG type).

Cryoglobulins were absent. On screening for secondary causes for autoimmune hemolysis, collagen profile, anti nuclear antibody (ANA) and autoimmune liver profile were negative. Serology for HIV and hepatitis B was negative. Bone marrow biopsy demonstrated erythroid hyperplasia with normal megakaryocytes, lymphocytes, eosinophils and mature plasma cells. No tumor, granuloma, or lymphoma were noted. CT scan of abdomen and thorax were inconclusive. She had never received ribavirin, interferon, cephalosporins or any other medications associated with drug induced hemolytic anemia. She was diagnosed AIHA presenting with leukemoid reaction as an extrahepatic manifestation of chronic hepatitis C. On day 3 of hospitalization high-dose oral prednisone (75 mg PO daily) and folic acid was administered and was continued at this dose until the patient's hemoglobin reached the target of 10 g/dL. The dose of Prednisone was gradually tapered over a period of four months. Within one month anemia and leucocytosis improved respectively (Hb 10.8 g/dl and 5600 cells/cumm) with decrease in LDH (460 U/l) and reticulocytosis (corrected Rc = 2%) [Table 1]. Directly after prednisone therapy, she started HCV treatment with PEG-IFN alfa-2a (180 µg/week) plus RBV (1000 mg/day) for 48 weeks. During this period the patient's lowest haemoglobin level was 7.6 mg/dl and dose reduction was not required. The patient successfully achieved a sustained virological response. When last seen, the patient was well and had neither signs of HCV infection, nor of AIHA.

**Table 1** showing the changes in blood parameters during the course of hospitalization stay

Blood parameters	Course during hospitalization stay (Day of Prednisone [75mg po daily])				
	Day 0	Day 3	Day 7	Day 15	Day 30
Hb (g/dl)	2.9	3.5	4.5	6.2	10.8
TLC (cells/cumm)	57,000	27,000	21,000	16,000	5600
LDH (IU/ml)	2880	1800	1200	600	460
Corrected RC(%)	16	10	9	5	2

## Discussion

Chronic HCV infection can lead to cirrhosis, hepatocellular carcinoma and ultimately liver failure. We report a unique case of 35-year-old female patient with leukemoid reaction due to AIHA in treatment naïve chronic Hepatitis C genotype 1 (HCV RNA = 12 million IU/ml). She responded to prednisone therapy and folic acid. In 1973, Panush and colleague described a patient suffered from chronic active hepatitis with AIHA and positive-Coombs' test, and responded to treatment with steroids.<sup>[5]</sup> This disease may occur during the natural course of the infection and either during or after interferon(IFN) therapy.<sup>[6,7]</sup> Ribavirin (RBV) is the main drug responsible for anemia. In a very recent study, 17 cases of HCV-related AIHA were described as well as 16 cases of HCV-related thrombocytopenia.<sup>[8]</sup> In hemolytic anemia, leukemoid reaction can be seen as non-specific increases in leukocyte production and release occur in association with increased red blood cell production; marrow growth factors are likely contributors.<sup>[9]</sup>

The current best treatment of choice for chronic HCV infection is PEG-IFN plus RBV. However, RBV causes a dose-dependent reversible haemolytic anaemia. PEG-IFN may contribute to anaemia by suppressing haematopoiesis.<sup>[10]</sup> In addition, PEG-IFN can exacerbate pre-existing autoimmune disorders. As a consequence cytopenias and autoimmune diseases are relative contraindications to HCV therapy. Thus, the concomitant presence of AIHA and chronic hepatitis C was posing treatment delima. However our patient was started HCV treatment with PEG-IFN alfa-2a (180 µg/week) plus RBV (1000 mg/day) for 48 weeks following stabilization of hemoglobin. She successfully achieved a sustained virological response and showed neither signs of HCV infection, nor of AIHA on follow up visit. In conclusion AIHA due to chronic HCV infection can successfully be treated with prednisone therapy and does not form a contraindication to antiviral treatment. Autoimmune hemolytic anemia should be kept in mind as a

possible cause of leukemoid reaction and need not be corrected separately.

## References

1. Takase K, Nakano T, Hamada M, Shiraki K, Oohashi Y, Kihira T et al. Hemolytic anemia provoked by recombinant alpha-interferon. *J Gastroenterol* 1995;30: 795–797.
2. de-la-Serna-Higuera C, Barcena-Marugan R, sanz-de- Villalobos E. Hemolytic anemia secondary to alpha-interferon treatment in a patient with chronic C hepatitis. *J Clin Gastroenterol* 1999; 28: 358–359.
3. Greer JP. *Wintrobe's Clinical Hematology*. Philadelphia:Lippincott 1998: Vol II:959–961.
4. Ji Q, Perchellet A, Goverman JM. Viral infection triggers central nervous system autoimmunity via activation of CD8(?) T cells expressing dual TCRs. *Nat Immunol* 2010; 11:628–34.
5. Panush RS, Wilkinson LS, Fagin RR. Chronic active hepatitis associated with eosinophilia and Coombs'-positive hemolytic anemia. *Gastroenterology* 1973; 64(5):1015-9.
6. Gastroenterol, Srinivasan R. Autoimmune hemolytic anemia in treatment-naïve chronic hepatitis C infection. *J Clin* 2001;32(3):245-7.
7. Cauli C, Serra G, Chessa L, Balestrieri C, Scioscia R, Lai ME, et al. Severe autoimmune hemolytic anemia in a patient with chronic hepatitis C during treatment with peginterferon alfa-2a and ribavirin. *Haematologica* 2006; Suppl:ECR26, 91(6).
8. Ramos-Casals M, Garcia-Carrasco M, Lopez-Medrano F, Trejo O, Forns X, Lopez-Guillermo A et al. Severe autoimmune cytopenias in treatment-naïve hepatitis C virus infection. Clinical description of 35 cases. *Medicine* 2003 ;82: 87–96.
9. Abramson N, Melton B. Leukocytosis: Basics of Clinical Assessment: Am Fa Physician 2000;62(9):2053-2060.

10. McHutchison JG, Manns MP, Longo DL.  
Definition and management of anemia in  
patients infected with hepatitis C virus.  
Liver Int 2006;26:389-98.