Letter to the Editor

Severe acute autoimmune hemolytic anemia in a patient during therapy for chronic hepatitis C

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TO THE EDITOR

Hepatitis C virus (HCV) has been rarely reported to induce extrahepatic autoimmune phenomena including thyroid autoimmune disorders, cryoglobulinemia, thrombocytopenia and autoimmune hemolytic anemia (AIHA).[1,2] Hepatitis C virus (HCV) treatment includes the combined administration of interferon-alpha (IFNa) and ribavirin. However, IFN has been reported to trigger autoimmune phenomena in up to 3% of cases with AIHA being the most prevalent and the most important in clinical practice.[3] Interferon induced AIHA in HCV patients is usually a direct Coombs positive anemia in which red blood cell surface antigens represent the autoimmune attack targets.[4] This type of anemia simulates the methyldopa-induced anemia[5] and has been reported during or after IFN therapy representing, thus, the early and the late onset pattern of AIHA. Pegylated interferon-alpha (PEF-IFNa) has been recently approved for chronic hepatitis C treatment. It is administered once weekly and has been reported to produce equal or even better results compared with 'classic' (non-pegylated) interferons. Side effects during PEG-IFNa administration have been reported to be similar to those of 'classic' interferons.

Herein we report a patient with hepatitis C virus who

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was diagnosed with severe autoimmune hemolytic anemia (AIHA), antiplatelet and antinuclear antibodies (ANA) during PEG-IFNa treatment.

A 68-year-old woman diagnosed with chronic hepatitis C and receiving combination treatment with pegylated interferon-alpha 2a (PEG-IFNa-2a) and ribavirin was admitted because of severe anemia (hemoglobin at 5.5g/dl). The patient was diagnosed four years ago with chronic hepatitis C virus infection (genotype 1b) and liver biopsy showed grade 3 and stage 2 histological changes. At that period of follow up, alanine aminotransferase (ALT) levels were 2-fold increased while hepatitis C virus ribonucleic acid (HCV-RNA) was 1.6×10^6 units/ml (branch method, Bayer). The patient was then started on therapy with IFNa-2a subcutaneous administration (3MU three times/week) and 1000 mg ribavirin P.O for one year. During follow up there was no evidence of interferon or ribavirin induced side effects while the patient tolerated well the whole therapy and achieved biochemical and virological response at the end of treatment. However, two years later HCV infection relapsed with ALT and HCV-RNA turning to the pre-treatment levels. Pegylated interferon-alpha 2a was started at a dose of 100 μg/week subcutaneously combined with 1000 mg of ribavirin. During initiation of treatment peripheral blood tests, thyroid function, immunology and all biochemistry except for abnormal ALT levels were within normal limits. Abdominal ultrasound was within normal limits including signs of splenomegaly. Serology for hepatitis A, B and E was negative and IgM antibodies against cytomegalovirus, herpes virus and Ebstein-Barr virus

were absent. Six-month treatment was well tolerated and the patient was symptom free achieving a sustained biochemical and virological response.

At the end of treatment the patient complained of acute unexplained fatigue. Peripheral blood tests showed hemoglobin 5.8g/dl, white blood cell count 1970/mm³, platelet count 67,000/mm³, reticulocytes 173,000/mm³, lactate dehydrogenase 970UI/ml (normal up to 450 UI/ml), alkaline aminotransferase 47 UI/ml (normal up to 40 UI/ml), γ-GT=56UI/ml (normal up to 44 UI/ml) and unconjugated bilirubin levels at 1.9 mg/dl. Direct and indirect Coombs tests were strongly positive (4+/4+) and antiplatelet antibodies were also detectable (SPRCA test, Norcross U.S.A and indirect immunofluorescence method). At that time HCV-RNA was below the cut off value (cut off 521 units/ml, branch method, Bayer) and no cryoglobulins were detected in the serum. Bone marrow smear was compatible with peripheral type hemolytic anemia and abdominal radiology including computed tomography showed nothing remarkable. Pegylated interferon and ribavirin were discontinued and the patient was started on prednisone at a daily dose of 75 mg. A week later peripheral blood was dramatically improved and fifteen days later hemoglobin levels were normalized while Coombs tests and antiplatelet antibodies were negative. Surprisingly, antinuclear antibodies (ANA) reached a titer of 1/1280 (double tested) while complement components and serum immunoglobulins were within normal limits. On a close 3-month follow up, the titer of ANA was substantially decreased (at 1/160) and all other laboratory tests were normalized.

The patient had no evidence of hepatic or extra-hepatic autoimmune disorders before, thus, autoimmune hemolytic anemia and probably antiplatelet and antinuclear antibody presence could be attributed to pegylated interferon or ribavirin administration.[5] In fact, it has been shown that ribavirin decreases in vitro erythrocyte adenosine triphosphate content and increases hexosemonophosphate shunt suggesting the presence of red cell susceptibility to oxidative damage and, probably, subsequent hemolysis.[6]

In addition, interferons can regulate immune effects or functions. This latter feature led them to be reconsidered as signals linking innate and adaptive immunity, and potentially orchestrating autoimmunity associated with viral infection and IFN-alpha therapy.[7] However, only one HCV patient under IFN treatment who developed severe autoimmune phenomena including interstitial pneumonia, AIHA and cholestatic liver disease has so far been reported.[8]

Chronic HCV infection in the absence of treatment is associated with diverse autoimmune manifestations, including haematological, articular, renal, neurologic or cutaneous involvement. Except for autoimmune haemolytic anemia, other severe HDV-related cytopenias have been reported including autoimmune neutropenia, aplastic anemia, pure red cell aplasia and refractory sideroblastic anemia as well as thrombocytopenia.[9,10]

Thus, decrease of both blood cell count and platelet count in addition to hemolytic anemia, could indicate that this patient may belong to the group of "autoimmune cytopenias" during HCV infection.

It is noteworthy that in this patient hepatitis C virus RNA (HCV-RNA) and cryoglobulins were not detected at the period of acute hemolysis and bone marrow smear as well as the increased reticulocyte production excluded the possibility of aplastic anemia occurrence.

Although HCV-related cytopenias are not uncommon, they are usually considered mild laboratory abnormalities with no clinical significance, especially in HCV patients with hypersplenism. However the development of mild anemia is not infrequent in patients receiving antiviral therapies and when the anemia is more severe, hemolysis should be considered. In a recent study[10] it has been shown that some clinical and immunologic differences exist between HCV patients with autoimmune haemolytic anemia and those with HCV-related severe thombocytopenia: higher prevalence of cirrhosis and of other associated autoimmune diseases in the autoimmune haemolytic anemia group compared to the thrombocytopenia group.

It is of interest that the pattern of hemolysis in our patient was that of late onset, occurring six months after continuous and uneventful PEG-IFNa administration. In fact, the patient had no evidence of other interferon-induced side effects.

The presence of antiplatelet antibodies during PEG-IFNa administration seems to represent a new issue of PEG-IFNa induced autoimmunity. However, antiplatelet antibodies were not tested when the patient started on 'standard' IFN treatment. In addition, polythyenoglucol molecule has never been so far reported to induce autoimmune phenomena.

The question of whether PEG-IFNa triggers autoimmune phenomena more easily than 'standard' IFNa seems to require further discussion and hypothesis. Other parameters of interest that could be further investigated are, the time of onset, the predictors of severity, and the

risk factors of all autoimmune phenomena occuring during –pegylated or not- IFN therapy.

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