Case Report

Hepatitis Associated Autoimmune Haemolytic Anaemia

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There are numerous associations between diseases traditionally considered non-infectious with infectious agents. These include peptic ulcer, coronary heart disease, neuropsychiatric disorders, haematological disorders and malignancies. Out of infectious diseases, viral hepatitis is also associated with many extra hepatic complications, with articular, renal, neurologic, cutaneous and haemopoietic system involvement. Several autoimmune phenomena can be observed in the course of viral hepatitis, including cryoglobulinemia, glomerulonephritis, systemic lupus erythematoses and arthritis. Beside these well-documented problems a rare haematological complication of viral hepatitis is Autoimmune Haemolytic Anaemia (AIHA).\(^1\)\(^2\)

Clinical significance of extrahepatic autoimmune haemolytic manifestations of hepatitis is highly variable ranging from sub clinical features or laboratory abnormalities to overt clinical manifestations that may be severe in some patients. Diagnosis and treatment of HCV-related autoimmune features has become a clinical challenge in patients with HCV infection, in whom the combination of a chronic liver disease and severe autoimmune features may contribute to an unfavourable prognosis.\(^3\)

In the present series four cases of viral hepatitis with AIHA will be described

Case No 1

A seven years old male child presented with complaints of nausea, vomiting, dark coloured urine, yellowish discolouration of sclera. On examination he was having jaundice along with pallor and mild hepatosplenomegaly. On laboratory investigations he was found anaemic with a haemoglobin level of 5.1 g/dl. Red Blood cells morphology was microcytic hypochromic, with spherocytosis and a reticulocyte count of 5.0%. His liver function tests showed a bilirubin level of 5.0 mg/dl with a predominant conjugated component, ALT of 2500 U/l, Alkaline Phosphatase level of 295 U/l and Albumin level of 4.5 g/dl. A blood transfusion was suggested. In blood bank the patient’s blood failed to show compatibility with blood group compatible donors. His Coombs’ test (Direct and Indirect) was performed and that was found to be positive. Serum LDH showed raised levels (1200 IU/l). Hepatitis Viral studies showed negative results for Antibodies to Hepatitis C Virus and Hepatitis B Surface Antigen, but Anti Hepatitis A virus IgM was positive. Subsequently the patient was put on steroids and he showed response to treatment with an improvement in Haemoglobin level (10.0 g/dl). At present his liver function tests are within normal limits, but Coombs’ test is positive.

Case No 2

A 60 years old lady, who was a known case of hepatitis C infection. At presentation her ALT was moderately increased, while her blood counts were within normal limits. She was on conservative management and was not receiving interferon and ribavarin. She remained stable for some time then subsequently she developed anaemia. The anaemia worsened with the course of time and did not responded to blood transfusions or haematemics administration. Due to progressive anaemia she was admitted to hospital. Her peripheral blood films revealed spherocytosis with reticulocytosis. Her Coombs’s test(direct) was performed and that was turned out as positive.
Case No 3

A thirty-five years old lady was diagnosed as a case of Hepatitis C viral infection, with Anti HCV positivity and detection of Hepatitis C virus on PCR studies. At presentation her blood counts were within normal limits. She was put on Interferon along with Ribavarin. During third month of therapy she developed severe anaemia. Her blood counts showed a haemoglobin level of 5.0 g/dl along with mild thrombocytopenia and leucopenia. The examination of red blood cells morphology showed microcytosis, anisocytosis, poikilocytosis, fragmented cells and spherocytes, along with a reticulocyte count of 9.0%. Serum LDH was found raised (910 IU/l). Her direct Coombs’ test was performed and it was positive.

Case No 4

A thirty years old girl, diagnosed as a case of von Willebrands’ disease 9 years ago, became hepatitis C seropositive. She manifested mucosal bleeds (epistaxis, bleeding gums, etc) and ecchymoses frequently. She was admitted 4 or 5 times, and was given FFPs as a part of her management. This time, she came with bleeding from her gums, epistaxis and menorrhagia along with progressive pallor. Her lab investigations showed: Hb 7.5 G/dl, white cell count 10.5x10^9/l, platelets 75x10^9/l, bleeding time 9 minutes; prothrombin time 15 seconds (control 12 sec); APTT 65 seconds (control 29 seconds); Red cell morphology showed spherocytosis and macrocytosis. Her direct comb’s test was positive. Bone marrow biopsy showed marked increase and left shift of megakaryocytes. Her APTT was corrected by adding absorbed plasma (33 seconds) and not corrected by adding aged serum (69 seconds). On the basis of her investigations, she was diagnosed as having hepatitis C associated AIHA along with immune-mediated thrombocytopenia. The patient responded promptly, to corticosteroids treatment.

Discussion

Extrahepatic immune problems have a well defined association with hepatitis, and autoimmune haemolytic anaemia is a rare accompaniment out of these. Hepatitis C viral infection is the main reported, but cases of hepatitis B and A viral infection with AIHA are also recorded. Most of the reported cases revealed a sudden and rapid drop in the haemoglobin level during the course of their disease and this fall in haemoglobin can not be explained on the basis of hypersplenism or any bleeding episode. The blood film examination showed findings of red blood cells haemolysis, i.e., anisopikilocytosis, red cells fragmentation, polychromasia and variable degree of spherocytosis with reticulocytosis and positive Coombs’ test (direct and/or indirect). These cases were diagnosed as autoimmune haemolytic after excluding all the other causes of anaemia, haemolysis and autoimmunity. Most of these patients responded to corticosteroids. The cases of present study revealed the manifestations similar to those reported by other workers. All had a rapid drop in their haemoglobin levels. Two cases received corticosteroids and showed improvement in blood counts.

Ramos – Casals M et al (2003) identified the following cytopenias in Hepatitis - C infection patients: AIHA (17 cases), severe thrombocytopenia (16 cases), aplastic anaemia (2 cases), severe neutropenia (1 case), refractory sideroblastic anaemia (1 case) and pure red cell aplasia (1 case). Patients with HCV related AIHA showed a higher prevalence of associated autoimmune diseases (71%), cryoglobulinemia (57%) and Cirrhosis (59%).

The pathogenic mechanisms behind hepatic and extrahepatic manifestations of viral hepatitis are poorly understood. In particular, the importance of viral genomic changes and host immune factors remain unclear. Nevertheless, the interaction between host immune system and virus antigens might play a significant role in triggering immunopathologic phenomena. It has been shown that immune complexes containing HCV antigen – antibodies and complement can be localized in the liver, kidney, red blood cells and/or skin of some subjects following the onset of an immunologic response to HCV chronic infection. Presumably, the production of antibodies reacting with self antigens in these conditions is due to abnormalities of regulation that are induced in the immune cells by the infection. According to Fellermann K two mechanisms are responsible for hepatocyte damage in hepatitis. First a direct cytopathogenic effect and second a T-cell mediated, MHC I and II restricted immune response. Shared epitopes of viral and human antigens presented by antigen – presenting cells might be capable of causing an autoimmune trigger.

Interferons are clinically used as antiviral and antineoplastic agents as well as potentiator of cellular differentiation. Their mechanism of action is not well defined, but it is dependent on their recognition by specific receptors located in some cell membranes,
and their subsequent internalization. Thereafter, activation/ inhibition processes on different enzymatic system take place, and these are the basis of the modification of DNA and of protein synthesis caused by α-IFN. The known biological effects of α-IFN are mainly the participation in the inhibition of cellular proliferation, the induction of cellular differentiation, suppression of viral replication, regulation of haemopoiesis and a modulatory effect on the immune system. Several reports have documented the modification of some parameters of the immune response by α-IFN. A decrease in CD8 lymphocytes, an increase in natural killer cells, low complement levels, enhanced activity of HLA class I and II molecules, activation of antibody producing cells and stimulation of cytotoxic T-lymphocyte have been described. Hizawana N et al (1994) demonstrated a positive lymphocyte stimulation test for IFN-α in a case of HCV-infection. All these altered parameters are partly considered responsible for the development of autoimmune disorder in patients taking IFN. Apart from the above mentioned immunological alterations it has been pointed out recently that α-IFN treatment can modify some cellular membranes. Consequently these modified proteins could behave as autoantigens for an already activated immune system.

Immunosuppressants such as steroids or azathioprine indicated to control AIHA are unfavourable for chronic hepatitis C. In addition, interferon was contraindicated due to AIHA. So, the therapeutic dilemma is unresolved. By considering the rapid fall in haemoglobin most of the cases received corticosteroids. The steroids administration showed a favourable response with pronounced increase in hemoglobin levels without any deterioration of the HCV liver disease. It is possible that different immune alterations as well as the occurrence of AIHA are more frequent then reported up to now. The patients could have been under diagnosed because their anaemia could have been attributed to other causes. In a case of hepatitis with rapidly deteriorating haemoglobin level consideration can be given to AIHA, if all the other causes are excluded. The relationship of AIHA with overall course and prognosis of the disease must also be evaluated.

References