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CASE REPORT

Chronic hepatitis C infection in a patient with bone marrow hypoplasia

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Abstract

Chronic hepatitis C virus (HCV) infection is associated with multifarious extra-hepatic manifestations; the most described and discussed being mixed cryoglobulinemia which is strongly related to B-cell lymphoproliferative disorders (LPDs). We present a case of chronic HCV infection and mixed cryoglobulinemia, with minimal liver involvement. The case is a 53-year-old patient who was diagnosed as having bone marrow hypoplasia at the age of three. She received several blood transfusions to normalize her haemoglobin. At the age of 31, she was diagnosed with rheumatoid arthritis on account of her diffuse joint pain and inflammation, elevated rheumatoid factor (RF) and Raynaud's phenomenon. Twenty years later, monoclonal gammopathy of IgG Lambda (one year later, changed to IgM Kappa) was detected during a routine examination. A bone marrow biopsy showed hypoplasia, Kappa positive B-lymphocytes and low-grade malignant lymphoma cells. PCR of the bone marrow aspirate was not contributory. No treatment was initiated owing to her poor bone marrow function and she is under regular follow-up.

Key words: Chronic hepatitis C infection; Mixed cryoglobulinemia; Prognosis

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INTRODUCTION

Natural history of chronic hepatitis C virus (HCV) infection is still evolving. Several factors contribute to the long term consequences. Although the exact mechanism is not known, the ability of virus to modulate the immune system plays a significant role in the long term consequences. It has been observed that the extra-hepatic manifestations which appear during the chronic course do not alter HCV infection clinically. In this context we present a case of chronic HCV infection in a patient with bone marrow failure.

CASE REPORT

The patient was a 53-year-old woman. In 2004, she was found positive by a screening in a public program to track HCV infected individuals. She presented to our institution immediately and HCV genotype 1b was detected on further evaluation. The liver function test, fibrotest and ultrasound transient elastography (fibroscan) indicated liver in non-fibrosis stage (F0-F1). Retrospection into her medical history revealed a slow evolution of chronic HCV infection, paradoxically mixed cryoglobulinemia was the first diagnosis. At 3 years of age, the patient was diagnosed as having cytopenia involving leukocyte

and erythrocyte lineages secondary to Chloramphenicol toxicity. To normalize her very low hemoglobin, she received several blood transfusions at unspecified intervals. However, an early or late transfusion reaction was never reported. At age 19, she developed severe bone marrow hypoplasia and anaemia and was treated with Prednisone for 5 years until her bone marrow recovered. Twelve years later, she presented with pain, redness and swelling of inter-phalangeal joints of hand. The symptoms were characteristically bilateral and progressively involved other joints, such as wrists, shoulders, knees and hips. Simultaneously she developed Raynaud's phenomenon and blood examination showed an elevated rheumatoid factor (RF). Although the symptoms were not very typical, a diagnosis of rheumatoid arthritis was established based on her clinical spectrum. Radiography of the joints taken during the course of the disease showed neither destructive and erosive features nor obvious deformities. In 2001, a blood test showed monoclonal gammopathy of IgG Lambda isotype. In the following year, aggravating cytopenia and change in isotype of monoclonal immunoglobulin to IgM Kappa were noted. A bone marrow biopsy showed hypoplasia and infiltration with Kappa positive small B lymphocytes, with mature chromatin and a high cytoplasmic-nuclear ratio. Dispersed between the B lymphocytes were low-grade malignant lymphoma cells, however, in view of her hypoplastic bone marrow, no treatment was initiated. Persistent joint symptoms, Raynaud's phenomenon and steadily increasing values of RF (from 146 IU/mL in 1998 to 7400 IU/mL in 2004) led to the detection of mixed cryoglobulinemias (MC) in 2003. Anti- cyclic citrullinated peptide (CCP) and antikeratin antibodies were negative, suggesting the arthritis is a manifestation of cryoglobulinemia. With time she developed paraesthesia of upper and lower limbs. Nevertheless, neither sensory nor motor neuropathy was detected objectively. The common manifestation of MC, i.e. vasculitis and skin involvement was never seen in our patient. Her persisting anaemia was treated with blood transfusion and a subsequently elevated serum ferritin with Desferrioxamine.

DISCUSSION

Chronic HCV infection is associated with a variety of extra-hepatic manifestations, the prototype being MC with a prevalence rate of 19%-50%[1]. MC is associated with lymphoproliferative disorder (LPD) of small B lymphocytes in the bone marrow or the liver[2]. Two distinct mechanisms of LPD development have been suggested, the first being specific binding of HCV E2 protein with CD81 on the B-cell which promotes consistent polyclonal response to the viral antigens and favor the development of LPD, and the second being HCV induced mutations in Ig genes and oncogenes such as *Bcl-2* rearrangement (t14; 18 translocation). However, Zignego *et al* suggested a multistep process of pathogenesis involving both mechanisms. Persistent stimulation of B-cells followed by mistakes in Ig gene rearrangement and *t* (14; 18) translocation which favors the survival of abnormal B-cells[2,3]. It is estimated that 8-10% of type Ⅱ MC evolves into lymphoma (Bcell non-Hodgkins lymphoma)[2].

Based on the type of Ig, MC is classified into three types, of which, type Ⅱ MC (polyclonal IgG and Monoclonal IgM) and type Ⅲ (polyclonal IgG and IgM) are commonly seen in chronic HCV infection. The Ig participates in the formation of circulating immune complexes and exerts RF like activity, usually by IgM component which frequently displays WA cross-reactive idiotype. RF is positive in 50%-80% of the patients with MC and clinically present as polyarthritis involving large joints in contrast to rheumatoid arthritis involving smaller joints[1,3].

MC is a systemic vasculitis and circulating immune complexes are deposited in small and medium sized vessels[3]. Nevertheless, low levels of cryoglobulins can remain undetected for a long duration due to the absence of specific symptoms[2,3]. Clinical manifestations are observed in 10%-30% of the patients and the most common symptoms are weakness, arthralgias and purpura (Meltzer and Franklin triad)[2]. Apart from the triad, bilaterally symmetrical and distal neuropathy (mostly sensory) is the most frequent clinical feature of MC. Patients have variable degrees of paraesthesia and multiple mononeuritis and mononeuropathies are diagnosed infrequently[2,3]. Renal involvement is recognized in 20% of the patients with MC and is considered as one of the worst prognostic indices. Patients present with haematuria, proteinuria, edema and renal failure of variable grade. Precipitation of cryoglobulins in the capillary loops gives a histological picture similar to idiopathic membranoproliferative glomerulonephritis[2]. However, progression of renal pathology is slow and less than 15% of the affected patients develop renal failure requiring dialysis[3]. Additionally, the large spectrum of extrahepatic manifestations also include thyroid disorders, anti-thyroid antibodies, porphyria cutanea tarda, lichen planus, diabetes mellitus, sicca syndrome, cardiomyopathy, amyloidosis, alveolitis,lung fibrosis, *etc*[1-3].

There are no definite criteria for the diagnosis of MC, therefore clinical features and laboratory results such as elevated RF, reduced C4 values and presence of cryoglobulins might provide the clue[1,2]. Even in the absence of symptoms it is prudent to monitor the patients with positive HCV RNA at regular intervals for the development of MC. The mainstay treatment for HCV infection is Interferon-alpha. Several studies have proven the linear relation between clinico-immunological and virological response to anti- HCV treatment with pegylated interferon alpha (IFN-α) and Ribavirin. Virological relapse on discontinuing treatment is also associated with expansion of B-cell clones bearing *t* (14; 18) translocation. IFN-α exhibits antiproliferative and immunomodulatory effects. It effectively inhibits viral replication and B-cell clonal expansion which is considered as the pathogenetic basis of MC. Interestingly, long-term analysis of treated patients with sustained virological response have developed expansion of B-cell clone with translocation, suggesting persistent lymphatic infection[2].

The ultimate prognosis in chronic HCV infection is

determined by the development of liver cirrhosis and MC is considered as a negative prognostic indicator in this context by many authors[2-4]. In a recent publication on the natural history of chronic HCV by Vigano *et al*, 343 patients were followed up for 10 years[5]. They found that cryoglobulins did not affect the clinical course of HCV infection and had little impact on the development of extrahepatic complications. Additionally, they also cited that MC had no influence on the development of liver decompensation or hepatocellular carcinoma in chronic HCV infection. However, they could not prospectively assess any association between MC and development of cirrhosis[5]. Several factors such as male gender, older age at infection, excessive alcohol consumption and secondary hemochromatosis (due to blood transfusion) enhance the fibrotic process. Furthermore, progression to cirrhosis is more rapid in patients with compromised immunity, hepatic steatosis, obesity and diabetes. Interestingly, viral factors such as viral load and genotype determine the response to treatment; however, they do not influence the fibrosis progression[6].

The time gap between the diagnosis of rheumatoid arthritis and MC in our patient was more than twenty years. During this period, she developed progressive paraesthesia, worsening anaemia, MC and small B-cell lymphoma confined to the bone marrow. No other classical extra-hepatic manifestations were noted. Low C4 values were observed after the diagnosis of rheumatoid arthritis. It is suggested that elevated serum alanine aminotransferase (ALT) level indicates the progression of fibrosis[4] and in our patient elevated ALT values had been observed since August 2004, but the average values were always two times lower than the normal values (recent values, SGOT/AST = 41 IU/L; normal values 14-40 IU/L, and SGPT/ALT = 66 IU/L; normal values 6-40 IU/L). Patients with chronic HCV infection might demonstrate anti-LKM1 antibody as in autoimmune hepatitis type 2[4] and it was negative in our patient. The first in 2004 and recent fibroscan showed the liver in non-fibrosis stage (F0-F1). Renal manifestations and amyloidosis were excluded by a normal renal function test and normal β2 microglobulin. Her persistent anaemia was treated with regular blood transfusion after 2003 and accordingly elevated serum ferritin with Desferrioxamine. On account of her bone marrow hypoplasia anti-HCV treatment was deferred.

We believe that our patient might have acquired the virus by blood transfusion in childhood. However, acute hepatitis C is rarely recognized in childhood and children with chronic infection are typically asymptomatic[6]. Considering this fact, it was hypothesized that children under immunosuppression (induced by chemotherapeutic agents for the treatment of leukaemia) acquiring HCV through blood transfusion might not develop an immune response that could cause chronic injury[6]. Although, this postulate was questioned due to several conflicting reports, we support it in view of the normal liver function and absent fibrosis in our patient with bone marrow hypoplasia. This could also explain the absence of other organ involvement. However, we agree that the patient should be kept under surveillance for the development of other complications.

CONCLUSION

Chronic HCV infection might present with more serious extra-hepatic manifestations than hepatic disease itself. Patients' immunological status might influence the extent of liver injury and extra-hepatic manifestations.

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