Successful retreatment of recurrent HCV infection in a sustained responder after chemotherapy for non - Hodgkin's lymphoma

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Abstract

It is known that sustained virological response in patients with chronic hepatitis C is associated with sustained elimination of hepatitis C virus and that late relapse after SVR in HCV patients is doubtful.
 47- year old man with chronic hepatitis C genotype 3, achieved sustained virological response after combination treatment with pegylated interferon and ribavirine for six months. Sixteen months later non Hodgkin's lymphoma was diagnosed. After successful completion of chemotherapy for non Hodgkin's lymphoma he presented with HCV infection recurrence of the same genotype. Retreatment with the same schedule resulted in normalization of aminotransferases and disappearance of HCVRNA from the serum.
This case suggests that recurrence of CV infection in a sustained responder may be probable after immunosuppressive therapy. Prevention is currently impossible but retreatment may be successful.

INTRODUCTION

Hepatitis C virus infection is characterized by a high rate of persistence. It is a major cause of chronic liver disease and the most frequent indication for liver transplantation. Apart from liver disease and hepatocellular carcinoma HCV infection is also associated with a wide range of extra hepatic diseases, including mixed cryoglobulinemia and non Hodgkin lymphoma ([1]). A recent meta-analysis confirmed a strong positive association between anti-HCV seropositivity and risk of NHL occurrence. ([2]).

In recent years, major advances have been made in the treatment of HCV infection. Sustained virological response (SVR) in patients with chronic hepatitis C (HCVRNA remaining negative, by polymerase chain reaction, 6 months after the end of treatment) can be achieved in 42-52% of patients with genotype 1 and in 80% of patients with genotype 2 or 3 ([3],[4],[5]).

Long term follow up studies have shown that sustained virological response in patients with chronic hepatitis C is associated with sustained elimination of HCV ([6],[7],[8],[9]). Even among HIV/HCV co-infected patients none of those with SVR presented with recurrence after a mean follow - up of 48 months in a previous study ([10]).

We describe the case of a 47 year-old man with successfully treated chronic hepatitis C in whom recurrence of HCV infection happened after chemotherapy for non Hodgkin's lymphoma.

CASE REPORT

A 47- year old man was found to be anti HCV positive in 2001 with mildly elevated aminotransferases for at least six months. He reported intravenous drug use and moderate alcohol consumption until six months ago. The patient suffered from type 2 diabetes mellitus and was treated with insulin from two years. The liver was palpable 2cm below the costal margin, spleen was not palpable and there was no lymphadenopathy and no signs of ascites or peripheral edema.

HCVRNA was positive by polymerase chain reaction and before treatment viral load was 3.400.000 IU/ml. HCV genotype was 3. Antinuclear antibodies were positive with a titre of 1: 160 but anti-smooth muscle antibodies were

negative. The patient was negative for HbsAg and HIV. Liver biopsy showed fatty infiltration and chronic hepatitis C with advanced fibrosis (grade 8 and stage 5 according to Ishak modified hepatic activity index (MHAI) scoring system). Serum examination for cryoglobulins was negative.

He received six months treatment with combination of pegylated interferon a-2a 180mg (Pegassys; Roche) subcutaneously once a week and ribavirin 800mg (Rebetol; Shering-Pugh) orally daily. His compliance to treatment was very good and HCVRNA was negative by polymerase chain reaction both at three months and at the end of treatment.

Six months and 1 year after treatment HCVRNA was negative by polymerase chain reaction, aminotransferases were normal and the patient's general condition was very good.

Sixteen months after the end of treatment, in January 2005, he was admitted to the Internal Medicine Department with fever, productive cough and dyspnoea. During the last weeks he had also noticed enlargement of neck lymph nodes and an abdominal pain. After receiving antibiotics for a week, the symptoms from the respiratory system were ameliorated but fever with night sweats persistented. A whole body CT scan was done which revealed massive lymphadenopathy in the mediastinum and both axillary regions, with pleural infusions, mostly right. Splenomegaly and retroperitoneal and inguinigal lymphadenopathy was also found in the abdomen CT scan. A Gallium 67 scan was also done which confirmed all sites of active disease. The tuberculin skin test was negative.

A neck lymph node biopsy was performed which showed diffuse large B cell lymphoma [CD45 ++, CD20 +++, CD10 (-), BCL-6 (30% +), CD43 +++ and bcl-2 +++, Ki-67 80%]. A bone marrow trephine biopsy was also done and showed infiltration of the marrow by the same type of lymphoma.

The hematological and biochemical profile was: Hb 13gr/dl, WBC 1850/μl (PMN 59%), PLT 90000/μl, ESR 11mm, LDH 655, BUN 44IU/ml, Cr 0.8 IU/ml, SGOT 40 IU/ml, SGPT 33 IU/ml, Bil 0.8mg/dl, Ca 8.7mg/dl. Immunological and viral profile was: ANA(+)1:160, anti-DNA (-), anti-La(-), anti-Sm(-), anti-RNP(-), anti-Cenp(-), anti-Hist(-), anti-Scl70(-), cryoglobulins (-), p-ANCA(-), c-ANCA(-), RF 215, C3 53, C4 14, IgG 2520, IgA 197, IgM 94, CMV IgM(-), IgG(+), EBV IgM(-) IgG(+), Toxo IgM (-) IgG (+), HIV(-), HAV IgM(-) IgG(-), HbsAg(-), anti HbsAb (+), anti Hbc IgG(+), b2-microglobulin 7500 μg/L. The patient was anti HCV positive but HCVRNA negative by polymerase chain reaction at that time. The disease stage of the patient was IVB with high International Prognostic Index (IPI).

He started therapy with Rituximab (375 mg/m2 d1) + CHOP-Caelyx (Caelyx 30 mg/m2 d1, Cyclophosphamide 750mg/m2 d1, vincristine 2mg d1, prednizone 100mg d1-5) every 21 days.

After the second cycle of chemotherapy he was admitted in the cardiology intensive care unit with acute myocardial infraction. Coronary arteriography showed complete obstruction of a peripheral artery without influence to the cardiac function. He started therapy with proper medications according to the cardiologist's instruction. He had a normal heart injection fraction and he continued the chemotherapy schedule. He didn't receive any blood transfusions during the period of therapy.

Three months later (after four cycles of therapy) he was restaged with whole body CT scan and all the lymphadenopathy had disappeared. He completed eight cycles of therapy in August 2005.

Six months after initiation of treatment he remained in complete remission. The bone marrow biopsy was also negative for infiltration from the lymphoma.

In September 2005, eight months after initiation of chemotherapy, the patient presented with ten fold increase in aminotransferases and a positive HCV RNA by polymerase chain reaction. Viral load was 7.600.000 IU/ml and HCV genotype was again 3. He presented no symptoms, he had no sign of hepatic decompensation but the level of aminotransferases remained elevated. There was no serological evidence for other viral infection.

He received a second course of 6month therapy with combination of pegylated interferon 180mg per week and ribavirin 800mg per day. Aminotransferases returned to normal and HCVRNA was negative by polymerase chain reaction again at three and six months (end of treatment) and remained negative six months after the completion of treatment.

DISCUSSION

An increased risk of non Hodgkin's lymphoma and multiple myeloma in patients with long lasting chronic HCV hepatitis has been reported in previous studies ([11,12]). Chronic stimulation of B cells by HCV antigens is considered the

cause of transformation of lymphoid tissue. Moreover regression of lymphoma has been described in those HCV – infected patients with splenic marginal zone lymphoma who achieved HCVRNA clearance with interferon with or without ribavirin ([13]). Two types of B cell NHL associated with HCV have been identified : NHL usually of low grade and involving the bone marrow, complicating the course of mixed cryoglobulinemia and NHL not related to mixed cryoglobulinemia which frequently follow a more aggressive course. In our patient lymphoma presented 16 months after successful treatment of HCV infection and the patient's serum examination was negative for cryoglobulins.

The prognosis of NHL in HCV patients is still debated. Some studies show that the prognosis of HCV-positive aggressive NHL is similar to HCV-negative aggressive NHL ([14]). On the other hand a recent large study from the French group (GELA LNH 93 and LNH 98 programm) showed that diffuse large B cell lymphomas (DLBL) in anti-HCV positive patients have a worse outcome in terms of overall survival and disease-free survival compared to HCV - negative patients ([15]). Our patient achieved a rapid complete remission which persists 18 months after diagnosis.

In previous studies SVR in patients with chronic HCV infection has been associated with persistently normal ALT levels, improvement in liver histology, prevention of hepatocellular carcinoma and a sustained elimination of the virus from the serum ([16],[17],[18],[19]). In a recently published study no recurrence of HCV infection was seen in any patient from a total of 187 HCV patients with SVR after a median follow up time of 29 months (range 12-172). Three out of 187 patients in this study had transiently borderline positive HCVRNA once within the follow up period but it was negative in subsequent examinations and no patient developed hepatitis ([8]). Swain et al reported that in only seven out of 845 patients who had been successfully treated with interferon monotherapy or combination therapy HCVRNA was detected after 391- 1076 days off treatment ([20]). None of these were in patients taking combination therapy for 48 weeks. These data indicate that the late relapse after SVR in HCV patients is very rare. In our patient recurrence of HCV infection happened after chemotherapy for non Hodgkin lymphoma, 24 months after the end of successful treatment.

Despite scarcity of recurrences after SVR, doubt exists whether the current treatment results in complete elimination of the virus or whether small quantities of the virus persist. Reactivation of infection in our patient took place after immunosuppressive therapy which suggests that reactivation of HCV virus may be possible like in patients with HBV infection. Hepatitis B virus and many other viruses including cytomegalovirus, herpes zoster, measles can persist for the lifetime of the host even after successful treatment. Reactivation of hepatitis B virus infection in patients undergoing cytotoxic therapy for non Hodgkin's lymphoma is a well known complication and antiviral prophylaxis with lamivudine should be initiated before any treatment in these patients. Low quantities of hepatitis C virus in serum and peripheral blood mononuclear cells were detected in asymptomatic patients who spontaneously cleared HCV infection and were negative for HCVRNA in serum by commercial assays ([20]). Also HCVRNA has been detected in hepatocytes, macrophages, lymphocytes and monocytes of patients with SVR in a previous study but the significance of this finding is unknown ([21]). Although there is no convincing evidence of viral replication in these cells negative strand HCVRNA suggestive of ongoing viral replication was detected from a minority of patients in this study ([22]).

The immunocompromised state during intense chemotherapy may allow enhanced replication of pre-existing low quantities of HCV virus. An increase in HCV viral load was reported recently in a patient with diffuse large B-NHL and HCV-cirrhosis who was treated with three courses of Rituximab ([23]). In recent years Rituximab, a chimeric humanized anti-CD20 antibody, is widely used in B-NHL and it has improved the prognosis of those patients. The use of agents like Rituximab with long lasting effects on malignant and normal B lymphocytes requires extended vigilance for accelerated replication of hepatitis B and C viruses.

This case suggests that recurrence of HCV infection in a sustained responder may be probable after immunosuppressive therapy. Prevention of HCV reactivation is currently impossible but re-treatment may lead to successful elimination of the HCV virus.

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