

Haematological Malignancies in Chronic Hepatitis C Patients Referred for Bone Marrow Biopsy

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Abstract

Background: Chronic hepatitis C has a well documented association with hepatic and extra hepatic malignancies.

Objectives: To look into the spectrum of malignancies in chronic hepatitis C patients referred for bone marrow biopsy for having disturbances in haematological parameters.

Material & Methods: This descriptive cross-sectional study was conducted at Department of Pathology, Pakistan Institute of Medical Sciences (P.I.M.S), Islamabad, from July 2009 to June 2011. A total of 90 diagnosed cases of chronic hepatitis C referred with various indications for bone marrow biopsy were included in the study. A detailed account of clinical history and physical examination was taken. All the patients were subjected to peripheral blood counts and bone marrow biopsy. Data were entered on the SPSS 14 and analyzed.

Results: Amongst a total of 90 patients, 14 (15.6%) were diagnosed to have various types of haematological malignancies. Among these seven cases were diagnosed as lympho-proliferative disorders, including 3 cases of acute lymphoblastic leukemia, 3 cases of non-Hodgkin's lymphoma and 1 case of Hodgkin's disease. Chronic myeloid leukemia was observed in 2 cases. Myelofibrosis and myelofibrosis with essential thrombocythemia and multiple myeloma were observed in 1 case each and metastatic lesion was observed in 2 cases

Key words: Hepatitis, chronic liver disease, hepatitis C, malignancies

Introduction

Chronic liver diseases are very serious health issues, people are facing today and Hepatitis C is the main cause for it.¹ The progression of Hepatitis C in the body may take several years or even decades to come to chronic stage or to a stage

where severe liver damage is evident. Chronic liver disease has many systemic as well as many hematological manifestations. Chronic hepatitis C is a subtle form of liver disease which silently progresses to cirrhosis in 20% of cases over a period of 10-30 years.² HCV infection has a well-documented association with a number of extra hepatic manifestations such as mixed cryoglobulinemia and non-Hodgkin's lymphoma (B-cell type).³

Non-hepatic malignancies are increasingly seen in patients infected with HCV. Whether this phenomenon is related to the increasing prevalence of hepatitis C or to a direct causal role by HCV is unknown. Many studies were conducted to investigate the possible relationship between hepatitis infection and development of certain hematologic malignancies. The putative role of hepatitis C virus infection in the pathophysiology of lymphoproliferative diseases remains controversial. North America and southern European authors have reported high rate of HCV infection in patients with B-cell non-Hodgkin's lymphoma (B-NHL) whereas northern European authors failed to confirm this association. Italian authors suggested strong association between HCV and B-NHL with seroprevalence ranging from 21% to 37% of patients.⁴⁻¹²

Besides the so much enlightened data on lymphoma, little knowledge is however, available on possible associations between HCV infection and other lymphoid and myeloid malignancies. We conducted the present study to find the spectrum of lesions and association between HCV and other malignancies.

Material and methods

This prospective study was conducted at the Department of Pathology, Pakistan Institute of Medical Sciences (P.I.M.S), Islamabad over a period of 2 years (July 2009 to June 2011). A total of 90 diagnosed cases of Hepatitis C induced chronic liver disease, referred from different departments of PIMS with various indications for bone marrow biopsy were included in the study. All these cases were qualitative PCR-positive for HCV-RNA. Patients who had already received or were on anti-viral therapy were excluded from the study.

Table 1: Breakup of haematological Malignancies (n 14)	
Disease	No of cases
Acute lymphoblastic leukemia	3
Chronic myeloid leukemia	2
Myelofibrosis	1
Myelofibrosis with Essential Thrombocythemia	1
Multiple myeloma	1
Hodgkin's disease	1
Non-Hodgkin lymphoma	3
Metastatic lesion	2

A detailed account of clinical history and physical examination was taken especially pertaining to age, sex and clinical features [constitutional features, features of anemia, neutropenia and thrombocytopenia and history of jaundice]. History of transfusion was also recorded.

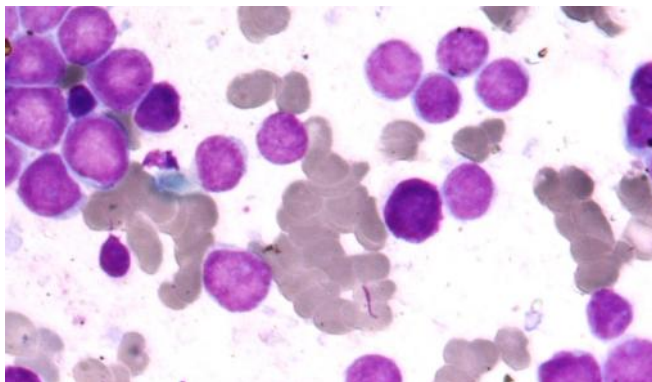


Figure 1: Acute lymphoblastic leukemia in HCV Positive patients (Wright stain x1000)

The patients were also examined for any lymphadenopathy, hepatomegaly, splenomegaly, petechial rash, ecchymosis or any skin lesions. In every patient about 2.5 ml of blood was collected in an EDTA containing tube by a clean venepuncture, using a 5 ml disposable syringe. Complete blood counts were performed on an automated haematology analyzer (sysmex KX-21). The Wright stained peripheral films were examined to verify the blood counter findings. All the patients were subjected to bone marrow aspiration using disposable lumbar puncture needle size 16 gauge. Trepchine biopsy was performed whenever was required. Data were entered on the SPSS 14 and analyzed.

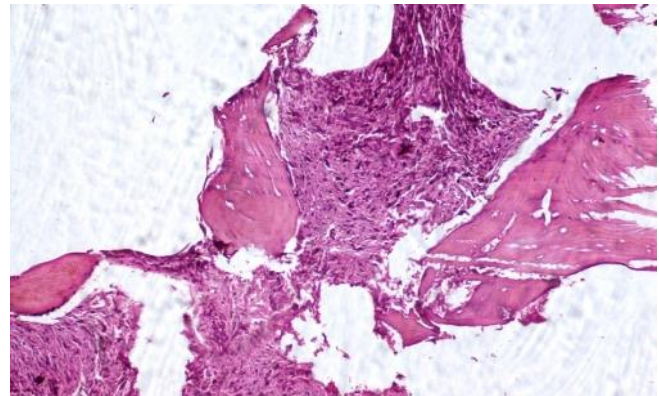


Figure 2: Myelofibrosis in (Wright stain x400)

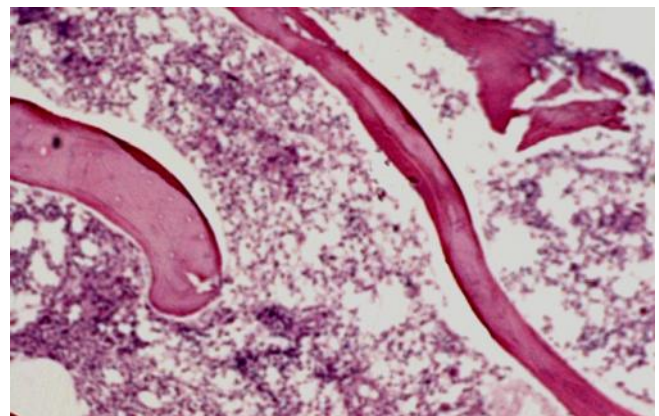


Figure 3: Bone marrow infiltration by Non Hodgkin's lymphoma (H&E x100)

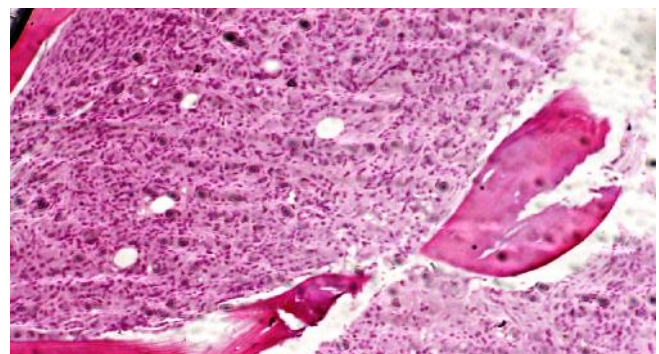


Figure 4: Metastatic lesion in the bone marrow (H&E x100)

Results

The study population consisted of 90 patients, among these 76 patients turned out to be non-malignant while 14 patients were diagnosed as malignant cases. In these 14 patients of chronic liver disease age ranged from 28-75 years with a mean age of 43 ± 16.0 SD years. Most frequent presenting complain was fever followed by bleeding. Hepatosplenomegaly and lymphadenopathy was observed in most of the patients. Lymphoproliferative disorders

including 3 cases of Acute Lymphoblastic Leukemia, 3 cases of non-Hodgkin's lymphoma and 1 case of Hodgkin's disease were found. Chronic myeloid leukemia was observed in 2 cases. Myelofibrosis and Myelofibrosis with Essential Thrombocythemia and Multiple Myeloma were observed in 1 case each. Metastatic infiltration was observed in 2 cases.

Discussion

In the current study we present a possible association between infection with HCV and lymphoid and myeloid malignancies and non hematological malignancies. Lymphoproliferative disorders were found in 5.5% of our patients. Many reports have described an association between chronic hepatitis C infection and B-cell NHL.¹³ It has been reported previously that prevalence of HCV infection in B-cell NHL was 15% greater than in the general population.¹⁴ Hausfater et reported that 2.8% of their patients have lymphoproliferative disorders, including (1.83%) B-cell non-Hodgkin's lymphoma and 1.85% cases of multiple myeloma.⁹ In another study Idilman et al reported that 4.3% cases had lympho-proliferative and plasma cell disorders, which is close to our findings.² Similarly Rabkin et al observed that 4.2% of the study group had lympho-proliferative disorder.¹⁵ Bianco et al have documented that 3.2% of their cases had Hodgkin's disease, 4.7% multiple myeloma, 9% chronic lymphocytic leukemia and T-cell non-Hodgkin's lymphoma was present in 13.8% of their HCV positive cases.¹⁶

The association of B-cell non-Hodgkin's lymphoma and B-cell lympho-proliferative disorders and HCV infection has been proven by many studies. In this regard De Rosa et al reported that 22.4% had B-cell lymphoproliferative disorders, similarly Zuckerman et al reported 22%, Montella et al found comparatively high proportion; 48% high grade, 23% intermediate and 10% low grade B-cell non-Hodgkin's lymphoma. Vallisa et al reported 37% and Mazzaro et al observed 17% cases of B-cell non-Hodgkin's lymphoma in their patients with HCV infection.^{12,17} However these findings are not universal in literature and few studies have failed to find any association between HCV-hepatitis and lymphoproliferative disorders.¹⁸

There is scientific evidence which shows that HCV can induce clonal proliferation of B-cells in patients carrying the virus chronically, with molecular alterations in the lymphocytes that may subsequently play a role in the multi-step process of malignant lymphocyte transformation. It is well recognized that HCV can infect B lymphocytes. The presence of HCV proteins in infected lymphocytes could initiate growth dys-regulation and predispose the lymphocyte to the development of further molecular changes, leading eventually to malignant lymphoma.¹⁹

In the past discrepant results on a positive association between HCV infection and lymphoproliferative disorders

have been reported depending on geographic distribution, suggesting a possible contribution of other etiological factors (e.g. environmental, genetic, infectious etc) to neoplastic transformation.¹⁶ In contrast to lymphoproliferative disorders there is little information available on possible relationship between HCV infection and other malignancies.

In the current study, 2.2% cases were diagnosed as chronic myeloid leukemia. Our results are comparable with other studies, as Hausfater et al, observed 0.5% cases of myeloproliferative disorder.⁹ Whereas another study conducted by Bianco et al, found that 12.2% cases were of Chronic Myeloid leukemia, suggesting that HCV is not only associated with B-cell non-Hodgkin's lymphoma, but also with some other lymphoid and myeloid malignancies.¹⁶

In our study Acute Lymphoblastic Leukemia was diagnosed in 3.3% patients. The study conducted by Bianco et al reported slightly higher percentage i.e. 7.6% cases.¹⁶ Myelofibrosis was found in 1.1% and Myelofibrosis with Essential Thrombocythemia was also observed in 1.1% of cases.

Bone marrow plays a prominent role as an indicator organ of occult tumor cell dissemination because it is easily accessible by aspiration, and it represents a relevant site of distant metastases. Positive association was found in patients with other malignancies also but the number of patients studied for each of these diseases was so small that no conclusion could be drawn.

In the current study the investigated patient population was so small that it is difficult to draw conclusion and association of HCV can be only a chance and there is possibility that disease was already there (undiagnosed) and hepatitis C infection has occurred later or both diseases are concomitantly present. Large patient population would be required to confirm such an association and that would be of particular interest for these malignancies in view of clarifying the pathogenic mechanisms whereby HCV might contribute to neoplastic transformation.

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