

# The Association of Hepatitis B and C Virus Co-infections with B-Cell Non-Hodgkin Lymphoma

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**Abstract:** *Non-Hodgkin lymphoma (NHL) is the hematologic malignancy with the highest prevalence worldwide. Hepatitis B virus (HBV) and hepatitis C virus (HCV) are hepatotropic viruses that can also replicate in lymphoid cells. This has led to evaluation of potential associations between HCV and HBV infection with B-cell non-Hodgkin's lymphoma (BNHL) as well as other hematologic malignancies. HCV has been the most frequently studied association between a hepatitis virus and NHL. Recent literature has associated hepatitis C virus with the development of non-Hodgkin lymphoma. The association of NHL with HBV has been studied much less intensively than with HCV. The aim of this paper was to report the case of a 43-year-old male patient, who was diagnosed and treated for chronic hepatitis B and hepatitis C in our service. The patient developed Non-Hodgkin B cell malign lymphoma while being on treatment with Pegylated Interferon for HCV and HBV infection.*

**Keywords:** Non-Hodgkin lymphoma (NHL), hematologic malignancies, Hepatitis B virus, Hepatitis C virus

## 1. Introduction

Non-Hodgkin lymphoma (NHL) is the hematologic malignancy with the highest prevalence worldwide. Incidence rates have grown fast up to the beginning of the new millennium, with an annual percentage increase of nearly 3%, which is faster than for most cancers (1). Hepatitis B virus (HBV) and hepatitis C virus (HCV) are hepatotropic viruses that can also replicate in lymphoid cells (2, 3). This has led to evaluation of potential associations between HCV and HBV infection with B-cell non-Hodgkin's lymphoma (BNHL) as well as other hematologic malignancies.

The most frequently studied association between a hepatitis virus and NHL has been with HCV. Hepatitis C virus (HCV) has been recognized as a potential cause of B-cell lymphoma. The management of these lymphomas is also complicated by the presence of the underlying chronic HCV infection (4, 5). The potential association of HCV and non-Hodgkin's lymphomas (NHL) was first recognized while studying patients with essential mixed cryoglobulinaemia (EMC), a chronic autoimmune disease with an underlying bone marrow B-cell clonal proliferation (6). Chronic hepatitis C infection was recognized as the principle cause of EMC, with antibodies to the virus found in 84–98% (7, 8) of patients with EMC. EMC predisposed to development of malignant lymphoma (9), prompting further studies on the association between hepatitis C and lymphomas.

The association of NHL with HBV has been studied much less intensively than with HCV. Epidemiological studies performed over the last decade have demonstrated a positive association between persistent, hepatitis B surface antigen (HBsAg)-positive hepatitis B virus (HBV) infection and B-cell non-Hodgkin lymphoma (NHL), with HBV-infected

patients having a 2-3-fold higher risk to develop NHL than non-infected patients. Moreover, there is evidence that also occult HBV infection (HBsAg-negative, HBV DNA-positive) associates with NHL (10). The majority of lymphomas presenting concurrently with HCV carriage should be managed in a similar manner to their HCV-negative counterparts. For certain low-grade lymphomas there is increasing evidence that treatment of the HCV with antiviral therapy can lead to remission of the lymphoma. The underlying B-cell monoclonal proliferation associated with EMC can be cleared when the HCV is treated with interferon- $\alpha$  (IFN- $\alpha$ ) (11) and there are case reports of long-lasting complete remission of frank lymphoplasmacytoid lymphoma concurrent with eradication of the virus with IFN- $\alpha$  (12).

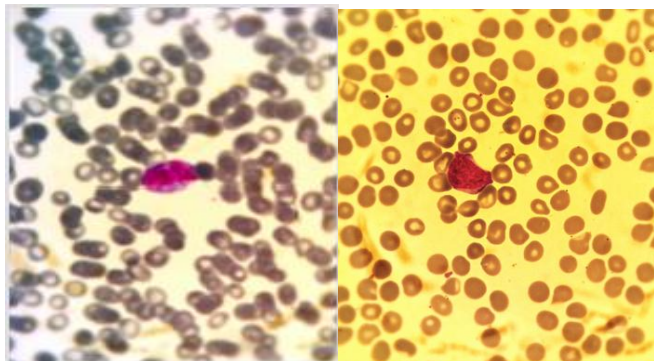
We represent who developed non-Hodgkin lymphoma while being on treatment with Pegylated INF for the HBV and HCV chronic infection.

## 2. Case Presentation

A 43 years old male presented to the Department of Gastroenterology and Hepatology, Mother Teresa Hospital, Albania, as an HCV and HBV positive patient from 3 months in order to be further diagnosed and treated. Pegylated Interferon and Ribavirine treatment was started to the patient. During the treatment the patient HCV RNA got negative, while the HBV DNA was constantly positive. He had a 10 year history for venous ulcer of the leg. Beside this the medical history was unremarkable.

At the 52 week of the treatment the patient complaint of abdominal pain of the right upper quadrant, fatigue, high grade fever, throat ache, head ache, weight loss and difficulty in breathing.

On examination patient was conscious, oriented and febrile, the liver and spleen were enlarged, peripheral lymph nodules were palpable and there were mild bilateral lower extremity edema. Blood profile showed decreased hemoglobin level and severe thrombocytopenia (Table Nr.1). Leucocyte formula in microscope showed mononuclear elements with single big nucleus and basophilic cytoplasm. This image was suggestive of a typical view of a lymphoma cell (Figure nr. 1).



**Figure 1:** Periferic blood smear. Limfoma cell

Biochemistry blood test showed low value of protein, albumin and cholesterol (Table Nr. 1). Beside this the liver and renal biochemical profiles were between the ranges of normal. Serum protein electrophoresis was normal. Prothrombin time level was also normal.

**Table 1**

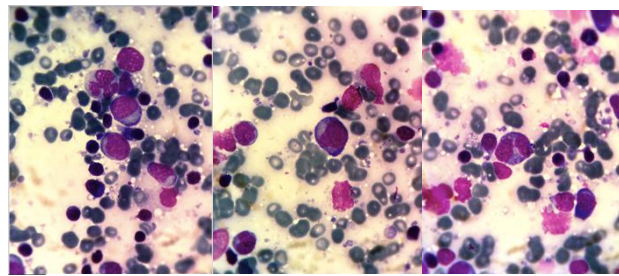
Parameters	Value	Normal level
RBC	$3.74 \times 10^6$	$4.4 - 10.0 \times 10^6$
Hemoglobin	9.8 g/dl	12.0 – 16.5
PLT	$14 \times 10^3$	$150 - 400 \times 10^3$
Total protein	5.8 g/dl	6.0 – 8.3
Albumin	2.9 g/dl	3.5 – 5.2
Cholesterol	19 mg/dl	140 – 220

The patient was tested positive for HbsAg and anti.HCV, while anti HDV was negative. HCV RNA was negative during the treatment while HBV DNA remained positive. HCV genotype was 3.

The patient was further recommended for abdominal ultrasound. Enlarged liver and also periportal lymphadenopathy were seen. Also there were sign of portal hypertension with portal vein diameter 18 mm and much enlarged spleen. Liver elastography value was 14.8 kPa which correlate with F4 liver stiffness. On upper endoscopy there were esophageal varices.

The immunophenotype for lymphoma was positive for CD45, CD19 and CD20 suggesting for malignant non-Hodgkin's B cell lymphoma.

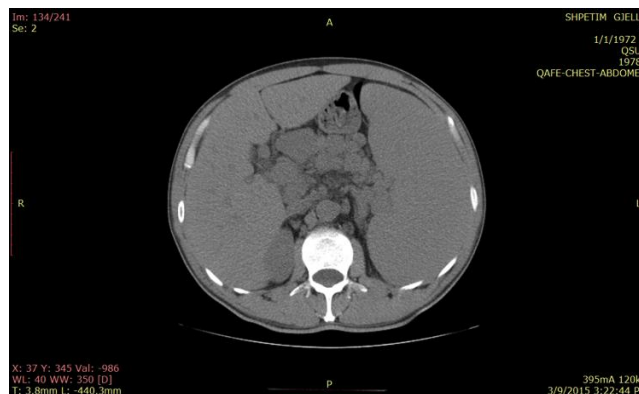
FNAC (fine needle aspiration cytology) of the peripheral axillar lymph nodes showed high grade malignant non-Hodgkin's B cell lymphoma (Figure Nr. 2).



**Figure 2:** Fine needle aspiration of axillar limfonodul.

Lymphoma cell

Computed Tomography (CT) of the abdomen showed mediastinal, bilateral axillar, inguinal and retroperitoneal lymphadenopathy (Figure nr 3),hepatosplenomegaly and no peritoneal ascites. The chest X-ray was normal. In our service the patient was treated with Dexamethasone infusion 16 mg daily and tramadol infusion according the patient pain level. After diagnose confirmation the patient was presented to the oncologic department for further diagnose and treatment.



**Figure 3:** Aksial non-enhanced CT Images of the upper abdomen

### 3. Conclusion

Non Hodgkin B cell lymphoma is a life threatening disease which should be diagnosed and treated adequately. The clinic presentation, laboratory analyses and radiologic images information are needed to put the right diagnose. On the other hand HBV and HCV chronic infection are known to be associated with higher risk of non-Hodgkin B cell lymphoma. The treatment of choice for HBV and HCV confection is Pegylated INF and Ribavirine treatment. This treatment is known to be associated with multiple adverse effects including head ache, fatigue, abdominal pain, throat ache, head ache, anemia and thrombocytopenia. Most of the mentioned side effects are also present in patient with non-Hodgkin lymphoma. That is why we recommend checking for non-Hodgkin B cell lymphoma in HBV and HCV patients with continuously severe thrombocytopenia and rapid progression of the clinic presentation while on treatment with Pegylated INF.

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