

Hepatitis-C Infection Incidence Among the non-Hodgkin's B-cell Lymphoma Patients in the Northeast of Iran

Seyed Amir Aledavood¹, Mohammad Reza Ghavam-Nasiri¹, Kamran Ghaffarzadegan¹, Hamid Reza Raziiee¹, Golnaz Saboori¹, Kazem Anvari¹, Samira Mohtashami¹, Mitra Ahadi¹, Bahram Memar¹

Abstract

Background: Various infectious agents like Epstein Barr Virus (EBV), HTLV-1 and Helicobacter pylori have known as etiologic factors in different sub-types of lymphoma. Although Hepatitis C virus (HCV) has not only been important for its hepatotropism and hepatitis development, but also in recent years its association with some forms of non-Hodgkin's lymphoma (NHL), especially B cell NHL, has reported.

In some countries, the rate of B cell NHL development in HCV infected patients was four times more than general population, and then association between HCV infection and B-NHL has proposed in many studies.

Methods: To assess this relationship in our geographic region, in a descriptive study; we have evaluated patients with B-NHL in an oncology center in northeast of Iran for HCV infection.

Results: Out of 128 B-NHL patients, HCV Antibody test (with third generation ELISA method) was positive in only one patient, which confirmed with Nested PCR technique. Then the frequency of HCV infection in our patients was 0.7%.

Conclusion: Respecting to the incidence of HCV infection in general population in Iran, which is between 0.5-1%, we couldn't show higher prevalence of HCV infection in NHL patients than general population, and hence couldn't confirm relation between HCV infection and B-NHL in our region.

Keywords: Hepatitis C; non-Hodgkin's lymphoma; B-cell, Epidemiology

Please cite this article as: Aledavood SA, Ghavam-Nasiri MR, Ghaffarzadegan K, Raziiee HR, Saboori G, Anvari K, et al. Hepatitis-C Infection Incidence Among the non-Hodgkin's B-cell Lymphoma Patients in the Northeast of Iran. *Iran J Cancer Prev.* 2014; 7(3):147-51.

Introduction

Non-Hodgkin's Lymphoma (NHL) has known as a heterogeneous group of the lymphoid system malignancies which have consisted of more than 40 types of different malignant entities. The most common types of lymphoma have originated from B cells.

According to Iran cancer registry (verso. 2008); out of 76159 total cancer patients, they have diagnosed 2055 new cases of Lymphoma (2.6% of total cancers).

Mozaheb. Et al study, in Mashhad University cancer research center and an outpatient hematologic clinic, from 2000 to 2009, has evaluated 391 patients

with lymphoid malignancy. Out of 92 % were Non-Hodgkin's Lymphoma. The most common histologic subtype was Diffuse Large B-cell Lymphoma (DLBL) [1].

The statistics have shown an increase in the NHL incidence, during the recent decades. Although the etiology of most cases has still remained unknown, but the role of various genetic and environmental factors have reportedly mentioned for generating this disease. Among the environmental agents; nutritional, occupational, chemical and also infectious factors have considered as responsible risk factors. The association of various infectious agents with subtypes of NHL has previously proven. The associations of the Epsteinbarr virus (EBV) with

1. Dept. of Radiation oncology, Cancer Research Center, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Corresponding Author:

Bahram Memar, MD;
Associate professor of Pathology
Tel: (+98) 511 8461518
Email: Memarb@mums.ac.ir
Received: 16 Apr. 2014
Accepted: 22 June 2014
Iran J Cancer Prev. 2014; 3:147-51

Burkit's lymphoma, HTLV-1 with ATLL, HHV-8 with primary effusion lymphoma and also Helicobacter Pylori with MALT lymphoma all have confirmed. HCV is a RNA-virus which although was globally famous, due to its hepatotropism and hepatitis development, but it would be also a lymphotropic virus which could replicate in B cells, and then it has shown that chronic antigenic stimulation of B cells by HCV could result in malignant transformation of this cell lineage.

The role of this virus in causing the other B-cell disorders, specially mixed cryoglobulinemia has previously confirmed [1]. In the recent years the relation of HCV with B-cell type NHL has proposed, and several studies have shown a higher prevalence rate of HCV in B-NHL cases in comparison to controls [2]. HCV sequences have identified in the samples that taken from involved lymph nodes in B-NHL patients. High prevalence of HCV infection in B-NHL has reported in various studies conducted in Eastern Europe, Italy, Brazil, Egypt and Japan. The rate of B-NHL development in HCV patients was 2 to 4 times higher, in comparison to the general population [3-5]. Still, other studies have not consented to this relation. Studies from England, Canada, some western European countries and Turkey have not shown a significant difference in the seroprevalence of HCV in NHL patients, compared to the control group. In a meta-analysis conducted by Matuso et al.; consisting of 23 case-control studies, a strong relation between positive serum anti-HCV tests and NHL, especially the B-NHL type, has reported [6].

Gisbert et al. in a meta-analysis on 48 studies, has reported the mean prevalence of HCV in B-NHL cases to be 13% which has shown a much higher rate in comparison to healthy individuals. Yet, a variety to evaluate the prevalence of results has reported from different countries. In order to study the role of this virus in B-NHL patients in an oncology center in northeast of Iran, this descriptive study has planned.

Materials and Methods

In two-year duration from June 2007 to Sept. 2009, 156 patients with the diagnosis of lymphoma whom have referred to the cancer research center of Omid hospital, Mashhad University of Medical Sciences, Mashhad, Iran, have enrolled in this study. At the admission their pathologic samples have reviewed by the pathologists of the center, and

complementary studies specially an Immunohistochemistry panel and NHL subtyping have performed. An informed consent has also acquired from each patient. Afterwards an intravenous blood sample has obtained, and dispensed into two experimental test tubes, one containing EDTA for DNA extraction, and the other a dry one for isolating its serum. After centrifugation of serum samples in 5 separate micro tubes, they have stored in -80°C . On the examination day each 30 blood samples have taken out of the freezer together, and after being opened in room temperature the following procedures have performed based on the mentioned protocol.

200 μl of the positive and negative controls, and also 10 μl of each patient's sample have dispensed in separate microplates and after adding 50 μl of the diluting agent, they have incubated for 45min in 37°C . The samples have then washed by a specific washer, 10 μl of an enzymatic conjugator has added to each well (except for the blank one), and incubated for 45 min in 37°C . After being washed once again, 100 μl of chromogen/substrate has added and maintained in room temperature for 15min. Subsequently, 100 μl of sulfuric acid has added to each well, and the color intensity of each one has read by a 450nm filter and blanked in 620nm. Cut-off point has measured by adding 0/350 to the mean value of the negative control samples.

The results have calculated based on the light absorption fraction of the sample to cut off (CO) as follows: In cases where this ratio was less than 0.9, it has regarded as negative; between 0.9-1.1, intermediate and more than 1.1 has considered as positive.

Results

Out of 156 patients with lymphoma, 128 patients were NHL-B cell, 13 patients were T-cell lymphoma and 15 patients were Hodgkin's Lymphoma. Among B-cell lymphomas; the most common histologic subtype was Diffuse Large B-cell Lymphoma (75.8%). 128 non-Hodgkin B-cells have studied. The mean age was 53.2years (range: 14 to 86 yrs). 81 (63.3%) cases were male and 47 (36.7%) female. In 54% of patients the initial site of involvement was nodal and in the other 46% it was extra nodal.

In between the nodal regions, the most commonly involved site was the cervical lymphatic

Table 1. Non-hodgkin's B-cell Lymphoma subgroups of patients

Non-hodgkin's B-cell Lymphoma subgroups*	percent	frequency
Small lymphocytic Lymphoma	5.0%	6
Diffuse Large B-Cell Lymphoma	75.8%	91
Follicular Lymphoma	4.2%	5
Burkit's Lymphoma	0.8%	1
Mantle Cell Lymphoma	6.7%	8
Marginal Zone Lymphoma	7.5%	9
Total	100.0%	120

*unknown in 8 cases

and after that the gastrointestinal system stood in the second place.

After pathological review and studying the IHC, the most common subtype of the disease has revealed to be DLBCL (Diffuse Large B-cell Lymphoma) (75.8%) and MALT (Mocusa-associated Lymphoid tissue) (7.5%) (Table 1).

When studying HCV-Ab with the third generation ELISA method, from the 128 cases only one has shown a strongly positive test result while the rest were all negative.

In order to confirm the only positive case of infection, HCV-RNA has investigated in the patient's serum plasma by the Nested PCR technique which has proved its positivity.

This only positive HCV case was a 71-year-old man with the diagnosis of tonsillar DLBCL.

Discussion

In the current study, and among the 128 B-NHL cases, HCV infection has confirmed in only one patient showing 0.7% prevalence in general.

The prevalence of HCV infection in the general population varies in different countries with a worldwide prevalence of about 1 to 5%, has been 1% in European countries; and more than 5% in Africa.

In Egypt the serologic evidence of HCV infection has estimated to be 12-15% in the general population. In Iran and based on several studies conducted in different provinces, among the blood donors of blood transfusion centers, the prevalence of this type of infection was between 0.12 to 1.8% [7-12].

In a recent population based study in Iran, that have evaluated 5684 cases from 3 different regions of the country (north, center and south) for HCV infection, its prevalence has proved to be 0.5% [13]. In the current study on NHL cases, this value has achieved as 0.7% which has not shown a significant difference from the normal population and therefore HCV could not be confirmed as a major risk factor in Iran.

In Cocco et al. case-control study in Italy, the rate of HCV infection in NHL cases, was significantly higher than the controls [14]. Goldman and his colleagues have conducted a study in Egypt, one of the countries with a very high prevalence for HCV. They revealed the rate of this type of infection to be 26-48% among different NHL subgroups; whereas Marginal zone lymphoma and DLBCL have shown the highest prevalence for this infection (with an Odds Ratio of 4.6 and 3.2, respectively) [15]. In a study, prevalence of HCV infection in primary hepatic lymphoma, and primary splenic lymphoma were 66%, and 68% respectively [16]. The only positive HCV case in our study was a patient with DLBCL diagnosis. In a conducted meta-analysis by Gisbert et al. the mean prevalence of HCV infection in B-NHL cases has reported 13% [17].

As it could be seen, our findings have not displayed much similarity with the results of such studies, but regarding a study by Shariff et al., conducted in Canada, have shown no significant difference in the prevalence of HCV infection in B-NHL cases in comparison to controls [18]. In Schollkopf et al. study from Denmark-Sweden, the rate of anti HCV also has not shown a statistically

significant difference in NHL cases, in comparison to controls. This difference was solely statistically significant in lymphoblastic lymphoma, but not in subgroups such as CLL, FL and DLBCL [19].

In Vahap Okan study in Turkey, anti HCV seropositivity has shown no difference between the NHL cases and controls; yet, the DLBCL subgroup has shown a significant difference [20]. In general it has seemed that the relation of HCV and NHL and specially B-NHL, has demonstrated inconsistent results in various studies, and mainly in countries where HCV infection had a relatively lower prevalence, this relationship has less supported.

According to the studies conducted so far, Iran was also one of the countries with a low prevalence for HCV and our study has proved no significant difference in the rate of this infection in B-NHL cases in comparison to the general population. Still, in order to further establish such findings, a multi-center case-control study including samples from different regions of the country was highly recommendable.

Acknowledgment

We would like to thank the members of the Radiation oncology Department of Mashhad University of Medical Sciences and staff of clinical laboratory of Omid hospital.

Conflict of Interest

The authors had no conflict of interest in this study.

Authors' Contribution

Seyed Amir Aledavood, Mohammad Reza Ghavam-Nasiri and Bahram Memar, have designed and written this article, Golnaz saboori, Kazem Anvari, Samira Mohtashami, Mitra Ahadi, Kamran Ghaffarzadegan and Hamid Reza raziee, have collected and analyzed the data. All authors have read and approved the final manuscript.

References

1. Mozaheb Z, Aledavood SA, Farzad F. Distributions of major sub-types of lymphoid malignancies among adults in Mashhad, Iran. *The International Journal of Cancer Epidemiology, Detection, and Prevention*. 2011; 35(1):26-9.

2. Viswanatha DS, Dogan A. Hepatitis C virus and lymphoma. *J Clin Pathol*. 2007; 60(12):1378-83.

3. de Sanjose S, Benavente Y, Vajdic CM, Engels EA, Morton LM, Bracci PM, et al. Hepatitis C and Non-Hodgkin Lymphoma Among 4784 Cases and 6269 Controls From the International Lymphoma Epidemiology Consortium. *Clin Gastroenterol Hepatol*. 2008; 6(4):451-8.

4. Zuckerman E, Zuckerman T, Levine AM, Douer D, Gutekunst K, Mizokami M, et al. Hepatitis C Virus Infection in Patients with B-Cell Non-Hodgkin Lymphoma. *Ann Intern Med*. 1997; 127(6):423-8.

5. Costa Jr J, Almeida lopes E, Silva N. Hepatitis C virus antibody in patients with B cell non Hodgkin lymphoma and with non-hematological solid tumors in Recife, Brazil. *Journal of Chinese clinical medicine*. 2006; 1(5):241-7.

6. Takeshita M, Sakai H, Okamura S, Higaki K, Oshiro Y, Uike N, et al. Prevalence of hepatitis C virus infection in cases of B-cell lymphoma in Japan. *Histopathology*. 2006; 48(2):189-98.

7. Matsuo K, Kusano A, Sugumar A, Nakamura S, Tajima K, Mueller N. Effect of hepatitis C virus infection on the risk of non-Hodgkin's lymphoma: A meta-analysis of epidemiological studies. *Cancer Sci*. 2004 September; 95 (9):745-52

8. Esmaeili H, Hajeyanei G, Esmaeili M. Seroprevalence of hepatitis B, C, HIV and syphilis markers among blood donors in Boushehr-Iran. *Iranian journal of infection diseases and tropical medicine*. 2007; 12(36):85-8.

9. Farshadpour F, Makvandi M, Samarbazfzadeh AR, Jalalifar MA. Determination of hepatitis C virus genotypes among blood donors in Ahvaz, Iran. *Indian Journal of Medical Microbiology*. 2010; 28(1): 54-6

10. Reza-Zade M, Mani Kashani KH, Mohammadi A, Zandevakili H, Lotfi A, Bahrami H, et al. Prevalence of human immunodeficiency, hepatitis B and hepatitis c viruses in the first time, repeat and regular donors in blood transfusion center, Hamadan, 2004-2005. *Iranian Journal of infection diseases and tropical Medicine*. 2006; 11(33):55-60.

11. Alavian SM, Gholami B, Masserat S. Hepatitis C risk factors in Iranian volunteer blood donors, a case control study. *J Gastroentrol hepatol*. 2002; 17(10):1092-7

12. Roshandel Gh, Semnani Sh, Keshtkar A, Joshaghani H, Moradi A, Kalavi Kh, et al. Seroprevalence of hepatitis B virus and its co-infection with hepatitis D virus and hepatitis C virus in Iranian adult population. *Indian J Med Sci*. 2007; 61(5):263-8

13. Merat S, Rezvan H, Nouraie M, Jafari E, Abolghasemi H, Radmard AR, et al. Seroprevalence of hepatitis C virus: the first population-based study from Iran. *Int J Infect Dis*. 2010 Sep; 14(Suppl 3): e113-6.

14. Cocco P, Piras G, Monne M, Uras A, Gabbas A, Maria G, et al. Risk of malignant lymphoma following viral hepatitis infection. *Int J Hematol*. 2008; 87(5):474-83.

15. Goldman L, Ezzat S, Mokhtar N, Abdel-Hamid A, Fowler N, Gouda I, et al. Viral and non-viral risk factors for non-Hodgkin's lymphoma in Egypt: heterogeneity by histological and immunological subtypes. *Cancer Causes Control*. 2009; 20(6): 981–7.

16. DeRenzo A, Perna F, Persico M, Notaro R, Mainolfi C, DeSio L, et al. Excellent prognosis and prevalence of HCV infection of primary hepatic and splenic non-Hodgkin's lymphoma. *European Journal of Haematology*. 2008; 81(1):51–7.

17. Gisbert JP, García-Buey L, Pajares JM, Moreno-Otero R. Prevalence of Hepatitis C Virus Infection in B-Cell Non-Hodgkin's Lymphoma:

Systematic review and meta-analysis. *Gastroenterology*. 2003; 125(6):1723–32

18. Shariff S, Yoshida E, Gascoyne RD. Hepatitis C infection and B-cell non-Hodgkin's lymphoma in British Columbia: A cross-sectional analysis. *Annals of Oncology*. 1999; 10(8): 961–4

19. Schollkopf C, EkstRom K, Hjalgrim H, Rostgaard K, Panum I. Hepatitis C infection and risk of malignant lymphoma. *Int J Cancer*. 2008; 122(8):1885–90.

20. Okan V, Yilmaz M, Bayram A, Kis C, Cifci S, Buyukhatipoglu H, et al. Prevalence of hepatitis B and C viruses in patients with lymphoproliferative disorders. *Int J Hematol*. 2008; 88(4):403–8.

Archive of SID