Turk J Gastroenterol 1998; 1: 73-75

Hepatitis C infection in non-Hodgkin's lymphoma

Non-Hodgkin lenfomada hepatit C enfeksiyonu

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SUMMARY: *Chronic hepatitis C virus (HCV) infection was proposed as a predisposing factor in the development of non-Hodgkin's lymphoma (NHL). Although its oncogenic mechanism is far from clear, HCV is known to infect both B and T lymphocytes, and its long-term presence in the immune system may promote the infiltration of bone marrow with expanded clones of Ig-secreting lymphocytes.*

We examined the serum samples of 30 patients (17 male, 13 female, median age 52, range 16-84 ys) with NHL and 18 patients (10 male, 8 female, median age: 26, range: 17-61 ys) with Hodgkin's disease (HD) for anti-HCV antibodies by ELISA II. Anti-HCV positive sera was tested for HCV-RNA by nested-PCR as well. The serologic results from sera of 9488 healthy blood donors (age range 18-65 ys) were used as controls. Four (13.0%) patients with NHL and 74 (0.8%) blood donors were anti-HCV positive ($p<0.001$). None of the 18 patients with HD was positive for anti-HCV. There was no correlation between transfusion history and anti-HCV positivity. Serum ALT levels of 2/4 of anti-HCV positives were elevated. Liver biopsy showed chronic hepatitis in these patients. Biopsy was not performed for the other two with normal serum ALT. HCV-RNA was present in the sera of all but one of the anti-HCV positive patients.

HCV infections are more common in patients with NHL in comparison to general population. There is no correlation between the history of transfusion and anti-HCV positivity in lymphoma.

Key words: Lymphoma, hepatitis C

ÖZET: *Kronik hepatit C virus (HCV) enfeksiyonunun non-Hodgkin lenfoma (NHL) gelişiminde predispozan bir faktör olduğu iddia edilmektedir. Her ne kadar onkojenik mekanizması açık değilse de, HCV'nin B ve T lenfositlerini enfekte ettiği bilinmektedir ve bağışıklık sistemi içindeki uzun süreli varlığı, kemik iliğinin immunglobulin sekrete eden lenfosit klonlarıyla infiltrasyonuna yol açabilir.*

Bu çalışmada NHL tanısı alan 30 olgu (17 erkek, 13 kadın, ortanca yaş 52, sınırlar 16-84) ve Hodgkin hastalığı (HH) tanısı olan 18 olgu (10 erkek, 8 kadın, ortanca yaş: 26, sınırlar 17-61) hastanın serumları ELISA II yöntemiyle anti-HCV yönünden test edildi. Anti-HCV pozitif bulunan serumlar nested-PCR yöntemiyle HCV-RNA için de test edildi. Sağlıklı kan verici 9488 kişinin (yaş sınırları: 18-65) serolojik sonuçları kontrol olarak alındı. NHL tanılı 30 hastanın 4'ü (% 13.0) ve 9488 vericinin 74'ünde (% 0.8) anti-HCV antikorları saptandı ($p<0.001$). HH tanılı 18 hastanın hiçbirinde anti-HCV pozitif bulunmadı. Transfüzyon öyküsü ile anti-HCV pozitifliği arasında ilişki bulunmadı. Dört anti-HCV pozitif hastanın 2'sinde serum ALT düzeyi yüksekti ve bu hastaların karaciğer biyopsisinde kronik hepatit bulundu. Serum ALT düzeyleri normal olan diğer ikisine biyopsi yapılmadı. Bu 4 hastanın 3'ünde HCV-RNA pozitifti.

NHL tanılı hastalarda HCV enfeksiyonu genel populasyona kıyasla daha sıktır ve lenfomada transfüzyon hikayesi ile anti-HCV pozitifliği arasında ilişki bulunmamıştır

Anahtar sözcükler: Lenfoma, hepatit C

Apart from the risk of cirrhosis and hepatocellular carcinoma, chronic hepatitis C (CHC) may be associated with some extrahepatic diseases (1-8). Cryoglobulinemia, a benign lymphoproliferative disease, is a well-known example (2, 3-6). CHC was proposed as a predisposing factor in the development of non-Hodgkin's lymphoma (NHL) as well. Hepatitis C virus (HCV) is known to have a potential to infect B and T lymphocytes (2). Its long-term presence in the immune system may promote the infiltration of bone marrow with expanded clones of Ig-secreting lymphocytes (1-8).

METHODS

Thirty patients with NHL (17 male, 13 female, median age 52, range 16-84 ys) and 18 patients with HD (10 male, 8 female, median age 26, range 17-61 ys) were studied. The diagnosis was based on lymph node biopsies and grading of NHL was done according to the Working Formulation. Newly diagnosed patients as well as those under treatment were included. All patients were het-

Geliş tarihi: 23.12.1996 Kabul tarihi: 10.3.1998

Table 1. Presence of serological markers in studied groups

Group	*n*	*Anti-HCV positive*	*HCV-RNA negative*
Non-Hodgkin	30	4 (% 13)*	3 (% 9)
Hodgkin	18	0	0
Donors	9488	74 (% 0.8)*	-

*p<0.001

Table 2. Some characteristics of the anti-HCV positive patients

	Age / sex	*NHL grade*	*Tx* history*	*HCV-RNA*
1.	58/male	Low	Yes	-
2.	52/female	Intermediate	No	+
3.	55/female	Primary spleen	No	+
4.	45/male	Intermediate	Yes	+

*Transfusion

erosexual and there were no drug-addicts. A history of blood transfusion, usually in the course of chemotherapy, was present in 15/30 (50%) of patients with NHL and 5/18 (31%) of patients with HD. The control group consisted of 9488 blood donors (age range 18-65).

Antibodies against HCV was tested by second generation ELISA (Abbott, HCV EIA). HCV-RNA was tested by standard nested-PCR.

The frequency of the presence of anti-HCV antibodies in NHL, HD and blood donors were compared by chi-square test and correlation between the presence of anti-HCV antibodies and the history of blood transfusion in NHL and HD tested by Spearman's rank correlation test.

RESULTS

Four of the 30 patients with NHL (13%) were positive for anti-HCV. Anti-HCV was not present in any of the 18 with HD. Three of 4 with anti-HCV were also positive HCV-RNA as well. Anti-HCV was present in 74/9488 (0.8%) of blood donors (Table 1). The difference between the patients with NHL and blood donors was significant ($p<0.001$). There was no correlation between the transfusion history and anti-HCV positivity (2/4 of anti-HCV positives vs. 13/26 of anti-HCV negatives in NHL and 5/18 in HD). Serum ALT levels of 2/4 of anti-HCV positives were elevated. Liver biopsy showed chronic hepatitis in these patients. Biopsy was not performed in the other two with normal serum ALT. Some characteristics of the anti-HCV positive patients with NHL are shown in Table 2.

DISCUSSION

HCV is a lymphotrophic as well as hepatotrophic virus (1, 5). It is able to infect T as well as B lymphocytes (2). Mixed cryoglobulinemia, a benign lymphoproliferative disorder and a common extrahepatic manifestation of CHC, is the result of B-cell proliferation. The persistence of HCV in the immune system could greatly expand the clones of B-cells, and a mutational event could eventually lead to activation of oncogens resulting in a B-cell neoplasia (1-7). The presence of anti-HCV in 13% of NHL patients (4/30) was highly significant ($p<0.001$) in comparison to healthy blood donors (74/9488, 0.8%) in this study. There was a history of blood transfusion in 2/4 of anti-HCV positive NHLs, 13/26 anti-HCV negative NHLs and 5/18 HDs. Therefore, there was no correlation between the transfusion history and anti-HCV positivity. HCV-RNA was present in the circulation in 3/4 of anti-HCV positives. Serum ALT level was elevated in 2/4 and chronic hepatitis was present in liver biopsy. Ferri et al. found a 30-33% anti-HCV positivity in their patients with NHL, and they reported that genotype IIa/III was more common than the other genotypes (8). The predominance of genotype Ib in Turkey may explain this low prevalence in comparison to the study of Ferri.

In conclusion, we showed an increase the prevalence of CHC in the patients with NHL, but not in the patient with HD. This justifies screening for CHC in patients with NHL. The feasibility of screening for the development of NHL in CHC and the efficacy of interferon and other anti-viral agents in this respect require further studies.

REFERENCES

1. Ferri C, Caracciolo F, Zignego AL, et al. Hepatitis C virus infection in patients with non-Hodgkin's lymphoma. Br J Haematol 1994; 88; 392-4.
2. Pozzato G, Mazzaro C, Crovatto M, et al. Low-grade malignant lymphoma, hepatitis C virus infection, and mixed

cryoglobulinemia. Blood 1994; 84; 3047-53.

3. Ferri C, Civita LL, Caracciolo F, Zignego AL. Non-hodgkin's lymphoma: possible role of hepatitis C virus. JAMA 1994; 272; 355-6.
4. Mussini C, Ghini M, Mascia MT, et al. Monoclonal gammopathies and hepatitis C virus infection. Blood 1995; 85: 1144-5.
5. Ferri C, Monti M, Civita LL, et al. Infection of peripheral blood mononuclear cells by hepatitis C virus in mixed cryoglobulinemia. Blood 1993; 82; 3701-4.
6. Ferri C, Civita LL, Longombardo G, et al. Hepatitis C virus infection in mixed cryoglobulinemia and B cell lymphoma. Clin Exp Rheumatol 1994; 12; 89-90.
7. Zignego AL, Macchia D, Mont M, et al. Infection of peripheral mononuclear blood cells by hepatitis C virus. J Hepatol 1992; 15; 382-6.
8. Ferri C, La Civita L, Monti M, et al. Chronic hepatitis C and B-cell non Hodgkin's lymphoma. Quart J Med 1996; 89; 117-22.