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# Lymphoproliferative Disorders in Individuals With Chronic Hepatitis B and C in the Turkish Population

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The aims of this cohort study were to evaluate the association of malignant lymphoproliferative disorders in patients with chronic viral hepatitis and to compare the results with those in individuals with non-alcoholic fatty liver disease. A total of 3,873 patients with chronic liver disease who were seen consecutively in the Liver Disease Outpatient Clinic between January 2001 and July 2007 were assessed retrospectively. The frequency of malignant lymphoproliferative disorders including non-Hodgkin's lymphoma, Hodgkin's lymphoma, and chronic lymphocytic leukemia in these patients was investigated. Of the total, 1,999 patients had chronic hepatitis B infection (male/female: 1,226/773, mean age: $45.1 \pm 13.2$ years), 978 had chronic hepatitis C infection (male/female: 437/541, mean age: $53.8 \pm 13.7$ years), and the remaining 896 had non-alcoholic fatty liver disease (male/female: 450/446, mean age: $50.8 \pm 11.2$ years). A malignant lymphoproliferative disorder was identified in 13 patients (male/female: 9/4, mean age: $52.8 \pm 16.8$ years) with chronic viral hepatitis, while no case of malignant lymphoproliferative disorder was identified in individuals with non-alcoholic fatty liver disease ($P = 0.048$). Among the patients with malignant lymphoproliferative disorders, seven had chronic hepatitis B infection and six had chronic hepatitis C infection; 11 had non-Hodgkin's lymphoma and two had chronic lymphocytic leukemia. All non-Hodgkin's lymphoma cases were B-cell lymphoma. Based on the data obtained in this investigation, the association with malignant lymphoproliferative disorders in chronic viral hepatitis seems to be high as compared to that occurring in individuals with non-alcoholic fatty liver disease. ***J. Med. Virol. 83:974–980, 2011.*** © 2011 Wiley-Liss, Inc.

**KEY WORDS:** hepatitis B virus; hepatitis C virus; malignant lymphoproliferative disorders; non-Hodgkin's lymphoma; non-alcoholic fatty liver disease

## INTRODUCTION

Hepatitis B and C viruses are common causes of liver-related morbidity and mortality [Ganem and Prince, 2004; Shepard et al., 2005; Lok and McMahon, 2007; Craxì et al., 2008]. The World Health Organization estimates that there are more than 300 million people worldwide, who are chronic hepatitis B carriers [Ganem and Prince, 2004; Lok, 2007], whereas the prevalence of hepatitis C virus infection is estimated to be around 170 million people [Shepard et al., 2005; Craxì et al., 2008]. In Turkey, the prevalence of HBs-Ag is 5%; it is lower (3.9%) in western Turkey and higher (12.5%) in eastern Turkey [Değertekin et al., 2008]. Nearly all of the chronic hepatitis B cases in Turkey are a result of infection with genotype D [Bozdayı et al., 2004]. The prevalence of anti-hepatitis C antibodies in the Turkish population ranges from 0.5% to 1.2% [Yıldırım et al., 2005]. Essentially all of the cases of chronic hepatitis C are a result of infection with genotype 1b [Bozdayı et al., 2004]. Hepatitis B and C virus infections share the same routes of transmission, including parenteral exposure and surgical procedures [Ganem and Prince, 2004; Shepard et al., 2005; Lok, 2007; Craxì et al., 2008].

The clinical manifestations of chronic hepatitis B and C are quite variable. The histology of the liver in both

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infections ranges from nearly normal to borderline chronic hepatitis, to moderate or aggressive chronic hepatitis to cirrhosis and ultimately hepatocellular carcinoma [Ganem and Prince, 2004; Shepard et al., 2005; Lok, 2007; Craxì et al., 2008]. Both infections have been associated with extra-hepatic manifestations which include mixed cryoglobulinemia, membranoproliferative glomerulonephritis, polyarteritis nodosa, various autoimmune disorders, and malignant lymphoproliferative disorders [Gordon, 1996; Hartmann, 1997; Pyrsopoulos and Reddy, 2001; Idilman et al., 2004; Dal Maso and Franceschi, 2006; Nieters et al., 2006; Zignego et al., 2007; Chen et al., 2008]. Some of these manifestations, such as an association between hepatitis C virus and essential mixed cryoglobulinemia, have been established, whereas others are controversial.

The relationships between other infectious agents such as Epstein–Barr and human immunodeficiency viruses and malignant lymphoproliferative disorders have been recognized for years [Fisher and Fisher, 2004; Muller et al., 2005]. A causative association between hepatotropic viruses, especially hepatitis C virus, and malignant B-cell lymphoproliferative disorders has been demonstrated utilizing epidemiologic data, biologic, and molecular investigations as well as clinical observations [Gordon, 1996; Idilman et al., 2004; Dal Maso and Franceschi, 2006; Nieters et al., 2006; Zignego et al., 2007; Chen et al., 2008]. These data indicate that hepatitis C virus may be responsible for the development of some malignant lymphoproliferative disorders [Gordon, 1996; Idilman et al., 2004; Dal Maso and Franceschi, 2006; Nieters et al., 2006; Zignego et al., 2007]. Most of this data has been retrospective. Occasionally, the data reported are in conflict. The role of hepatitis B virus in the development of malignant lymphoproliferative disorders has not been recognized clearly [Chen et al., 2008].

In contrast to previous case-control studies involving individuals with malignant lymphoproliferative disorders who were identified as having either hepatitis B or C infection, in the present study, a cohort of 1,999 patients with chronic hepatitis B infection and 978 patients with chronic hepatitis C infection were evaluated for the association of a malignant lymphoproliferative disorder, and results were compare with those of 896 patients with non-alcoholic fatty liver disease. In Turkey, it was expected that about 3,000 new cases would be diagnosed with malignant lymphoproliferative disorders in 2002 [Eser, 2007].

## MATERIALS AND METHODS

### Patients

The association of malignant lymphoproliferative disorders was studied in a retrospective cross-sectional analysis of three cohorts: patients with chronic hepatitis B infection, chronic hepatitis C infection, and patients with non-alcoholic fatty liver disease. The data were collected from outpatient visit charts. A total of 3,873 patients with chronic liver disease (male/female: 2,113/1,760, age range: 16–86 years), who were seen consecutively in the Liver Disease Outpatient Clinic between January 2001 and July 2007, were included in this investigation. The patients were divided into three distinct groups based on the etiology of their chronic liver disease, as follows: Group1, Group 2, and Group 3.

The definition and diagnostic criteria used for hepatitis B infection were based on the National Institute of Health conferences on the management of hepatitis B in 2000 and 2006 [Hoofnagle et al., 2007; Lok and McMahon, 2007]. Chronic hepatitis B, both e antigen-positive and e antigen-negative, is characterized as chronic necroinflammatory disease of the liver caused by persistent infection with hepatitis B virus [Lok et al., 2007]. Inactive hepatitis B carrier state is characterized by normal serum aminotransferases levels, undetectable or low hepatitis B virus viral load (ranging between $10^3$ and $10^5$ copies/ml) and near normal or minimal histologic changes on liver biopsy [Hoofnagle et al., 2007; Lok et al., 2007; EASL, 2009]. The diagnosis of chronic hepatitis C infection was made on the basis of biochemical, serologic and histologic data consisting of anti-hepatitis C antibody positivity, normal or persistently abnormal serum aminotransferases levels, detectable of HCV-RNA level, and abnormal histologic changes on liver biopsy when available. The diagnosis of non-alcoholic fatty liver disease was based on biochemical, radiologic, and additional histologic data, when available. The criteria for inclusion in the diagnosis of non-alcoholic fatty liver disease were: (1) age greater than 16 years; (2) convincing evidence of absent or minimal alcohol consumption: $<15$ g alcohol/day for women and $<20$ g alcohol/day for men; (3) absence of confounding disease such as acute (hepatitis A, B, or C) and/or chronic viral hepatitis; (4) absence of clinically significant heart or renal disease; and (5) exclusion of other forms of liver disease such as autoimmune, drug-induced and metabolic liver disease. A single patient with a diagnosis of human immunodeficiency virus infection was also excluded.

Individuals with a known history of a malignant lymphoproliferative disorder prior to the recognition of the chronic liver disease were excluded. However, individuals diagnosed with a malignant lymphoproliferative disorder concomitant with recognition of the chronic liver disease were included into the analysis.

The development in the study population of a documented non-Hodgkin's lymphoma, Hodgkin's lymphoma, or chronic lymphocytic leukemia as a malignant lymphoproliferative disorder was determined. A malignant lymphoproliferative disorder was evaluated and diagnosed by a hemato/oncologist. The diagnosis of a malignant lymphoproliferative disorder in each case identified was established on the basis of clinical, laboratory, and histologic data [Ellis et al., 2005; Eichhorst et al., 2008; Tilly and Dreyling, 2008]. All the malignant lymphoma patients with nodal or extranodal presentation underwent tissue biopsy for confirmation of the diagnosis. The diagnosis of a malignant lymphoproliferative disorder was estab-

lished on the basis of the hematoxylin and eosin-stained sections and was also confirmed by immunohistochemical stains [Ellis et al., 2005]. Chronic lymphocytic leukemia patients were diagnosed by flow cytometry findings and bone marrow aspiration and biopsy examinations [Eichhorst et al., 2008].

### Follow-Up

All patients were seen at 3- or 6-month intervals in the outpatient clinic. At each visit, vital signs and physical examination including examination of lymph nodes, liver, and spleen were conducted and the results of biochemical, serologic, and virologic tests were reviewed.

According to the clinical policy, patients with chronic hepatitis B were treated with anti-viral drugs based on the consensus report of the management of chronic hepatitis B [Hoofnagle et al., 2007; Lok, 2007; EASL, 2009] and an inactive hepatitis B virus carrier received lamivudine for prevention of HBV reactivation during the receipt of chemo/immunosuppressive therapy. A patient with chronic hepatitis C who had detectable HCV-RNA was treated with combination treatment of standard interferon or pegylated interferon and ribavirin if there were no contraindications, such as pancytopenia or the presence of uncontrolled infection, to preclude the start of anti-viral therapy. The occurrence of malignant lymphoproliferative disorders was evaluated during the follow-up period.

### Human Research Approval

This study was approved by the local ethical committee of the Ankara University Faculty of Medicine.

### Statistical Analyses

All patients who were followed-up for at least 6 months after their first visit to the outpatient clinic were included in the analysis. Comparisons between groups were made using the Mann–Whitney *U*-test for continuous variables and the $\chi^2$ or Fisher's exact test for categorical variables. Data were summarized as mean ± SD or median (minimum–maximum) for continuous variables and as frequencies and percentiles for categorical variables.

## RESULTS

Among the 3,873 patients with chronic liver disease, Group 1 consisted of 1,999 patients (51.6%) with a chronic hepatitis B infection (male/female: 1,226/773, mean age: 45.1 ± 13.2 years). Group 2 consisted of 978 patients (25.3%) with chronic hepatitis C infection (male/female: 437/541, mean age: 53.8 ± 13.7 years). Group 3 consisted of 896 patients (23.1%) with non-alcoholic fatty liver disease (male/female: 450/446, mean age: 50.8 ± 11.2 years). The mean follow-up periods for those with Group 1, Group 2, and Group 3 were 54.0 ± 23.4 months, 56.6 ± 22.8 months, and 53.4 ± 23.6 months, respectively. In Group 1, 288 patients (14.4%) were HBe antigen positive, 1,198 (59.9%) were inactive hepatitis B carriers, 751 (37.6%) had chronic hepatitis, and 50 (2.5%) were identified as having cirrhosis. Male predominance was observed in patients with chronic hepatitis B infection (61.3% vs. 44.7% and 50.2%, respectively, $P < 0.001$). In Group 2, 877 patients (89.7%) had chronic hepatitis C and 101 (10.3%) were identified as having cirrhosis. Patients with chronic hepatitis C were older (54.0 years vs. 45.0 and 51.0, respectively, $P < 0.05$) and cirrhosis was observed more commonly (10.3% vs. 2.5% and 1%, respectively, $P < 0.0001$). In Group 3, 64.7% of the patients had abnormal serum alanine aminotransferase (ALT) levels (>37 U/L) and only nine cases (1.0%) were identified as having cirrhosis. The characteristics of the study subjects are shown in Table I.

A malignant lymphoproliferative disorder was identified in 13 patients (male/female: 9/4, average age: 52.8 ± 16.8 years [median: 57 years, range: 26–84 years]). All 13 patients had a chronic viral hepatitis (13/2,977, 0.44% vs. 0/896, 0%; $P = 0.048$). The timeframe between the diagnosis of chronic viral hepatitis and the identified malignant lymphoproliferative disorders ranged from the same time as the malignant lymphoproliferative disorder diagnosis (seven patients) to 7 years (mean: 28.3 ± 31.6 months).

Among these 13 patients, seven had chronic hepatitis B infection: three had inactive carrier status, three had an chronic hepatitis, and one had cirrhosis, and six had chronic hepatitis C infection: two had cirrhosis (Table II). A malignant lymphoproliferative disorder was identified more significantly in chronic hepatitis B and C patients as compared to those with non-alcoholic fatty liver disease (4/801 vs. 0/896, $P = 0.034$; 6/978 vs. 0/896, $P = 0.018$, respectively). No significant differences in terms of patient age and gender between chronic viral hepatitis patients with/without a malignant lymphoproliferative disorder were observed ($P > 0.05$).

TABLE I. Characteristics of All Individuals Enrolled Into the Study

| | Chronic viral hepatitis | Chronic hepatitis B (Group 1) | Chronic hepatitis C (Group 2) | NAFLD (Group 3) | *P* |
|---|---|---|---|---|---|
| Patient number | 2,977 | 1,999 | 978 | 896 | — |
| Age (years) (median) | | 45.1 ± 13.2 (45) | *53.8 ± 13.7 (54) | 50.8 ± 11.2 (51) | <0.05 |
| Gender (male/female) | 1,663/1,314 (55.9%/44.1%) | *1,226/773 (61.3%/38.7%) | 437/541 (44.7%/55.3%) | 450/446 (50.2%/49.8%) | <0.05 |
| Follow-up period (months) | | 54.0 ± 23.4 | 56.6 ± 22.8 | 53.4 ± 23.6 | >0.05 |

Mean ± SD.
*$P$-value < 0.05.

TABLE II. Clinical Characteristics of All Individuals With Viral Hepatitis and Malignant Lymphoproliferative Disorders Enrolled Into the Study

| | Patients with viral hepatitis (n = 2,977) | Patients with HBV infection (n = 1,999) | | | Patients with HCV infection (n = 978) | | Patients with NAFLD (n = 896) | |
|---|---|---|---|---|---|---|---|---|
| | | Inactive HBV carrier (n = 1,198) | Chronic hepatitis B (n = 751) | Cirrhosis (n = 50) | Chronic hepatitis C (n = 877) | Cirrhosis (n = 101) | Without cirrhosis (n = 887) | Cirrhosis (n = 9) |
| Malignant LPD (n=) | 13* (0.44%) | 3 (0.25%) | 3 (0.4%) | 1 (2%) | 4* (0.46%) | 2* (2%) | 0 (0%) | 0 (0%) |
| NHL (n=) | 11 | 3 | 2 | 1 | 3* (0.34%) | 2* (2%) | — | — |
| CLL (n=) | 2 | | 1 | | 1 | | — | — |

LPD, lymphoproliferative disorder; NHL, non-Hodgkin's lymphoma; CLL, chronic lymphocytic leukemia; NAFLD, non-alcoholic fatty liver disease.
*$P < 0.05$: 13/2,977 versus 0/896, 4/801 versus 0/896, 6/978 versus 0/896, 4/877 versus 0/896, 3/877 versus 0/896, and 2/101 versus 0/896.

However, there might be an association between the presence of cirrhosis and malignant lymphoproliferative disorders (2% (3/151) vs. 0.35% (10/2,826), $P = 0.003$) (Tables II and III). All four chronic hepatitis B patients had undetectable HBV DNA levels under oral nucleo(s)tide analogs. All patients with chronic hepatitis C had detectable HCV-RNA levels, and no case received anti-viral therapy due to primary disease and cytopenia.

Among the 13 patients with malignant lymphoproliferative disorders, all were mature B-cell neoplasms. Nine were nodal and four presented as extra-nodal disease (Table IV). The histologic subtypes were nine diffuse large B-cell lymphoma, two B-cell chronic lymphocytic leukemia, one Burkitt's lymphoma, and one splenic marginal zone lymphoma. In subgroup analysis, non-Hodgkin's lymphoma was identified more commonly in patients with chronic hepatitis C as compared to those with non-alcoholic fatty liver disease (5/978, 0.5% vs. 0/896; $P = 0.032$).

During the follow-up period, 8 of the 13 patients with a malignant lymphoproliferative disorder were alive; four hepatitis B-positive patients had normal serum ALT levels and undetectable HBV-DNA levels; three chronic hepatitis B patients were on nucleo(s)tide analogs. Four patients with chronic hepatitis C had a detectable HCV-RNA level. Five patients died. One patient with chronic hepatitis B died as a result of hepatitis B reactivation-induced acute liver failure. This individual had discontinued his lamivudine treatment. One died as a result of complications of cirrhosis, and the remaining three died due to primary malignant lymphoproliferative disorders (Table IV).

Of note, non-hepatic malignancy including multiple myeloma and thyroid cancer was detected in two chronic hepatitis B patients.

## DISCUSSION

In contrast to previous cohort studies in which data obtained in non-Hodgkin's lymphoma patients from a National Database were analyzed [Duberg et al., 2005; Ulcickas Yood et al., 2007], in the present study, the association and development of a malignant lymphoproliferative disorder were determined in patients with chronic viral hepatitis. The results indicated that malignant lymphoproliferative disorders occur more often in patients with chronic viral hepatitis as compared to occurrence in patients with non-alcoholic fatty liver disease as a non-viral chronic hepatitis ($P < 0.05$).

Although both hepatitis B and C viruses are hepatotropic and lymphotropic viruses that can replicate in hepatocytes as well as in lymphoid cells [Yoffe et al., 1986; Bronowicki et al. 1998], the role of these viruses, especially of hepatitis B virus, as an etiologic factor in the pathogenesis of non-Hodgkin's lymphoma has not been established yet. Acute infection with either agent induces a humoral and cellular immune response that can progress to a state of chronic antigenic stimulation, which can result in a variety of local and systemic disorders [Franzin et al., 1995; Racanelli et al., 2001; Weng and Levy, 2003; Viswanatha and Dogan, 2007]. An association between hepatitis C virus and malignant lymphoproliferative disorders has been demonstrated in some Italian and Turkish studies [De Rosa et al., 1997;

TABLE III. The Clinical Status of Chronic Viral Hepatitis With/Without Malignant Lymphoproliferative Disorders (LPDs)

| | Chronic viral hepatitis with malignant LPDs | Chronic viral hepatitis without malignant LPDs | *P* |
|---|---|---|---|
| Patient number | 13 | 2,964 | |
| Age (years), mean ± SD (median) | 52.8 ± 16.8 (57) | 48.0 ± 14.0 (48) | >0.05 |
| Gender (M/F) | 69.2%/30.8% | 55.8%/44.2% | >0.05 |
| Cirrhosis | 23.1% | 5.0% | =0.025 |

TABLE IV. Characteristics of the 13 Individuals With Malignant Lymphoproliferative Disorders

| Patients | Age | Gender | Histology | Type of LPD | Site | Follow-up |
|---|---|---|---|---|---|---|
| 1 | 32 | F | e-Antigen-positive CHB | NHL | LAP | Alive remission |
| 2 | 47 | M | e-Antigen-negative HBV cirrhosis | NHL | LAP | Exitus |
| 3 | 29 | F | e-Antigen-positive CHB | NHL | LAP | Alive remission |
| 4 | 60 | M | Inactive HBV carrier | NHL | LAP | Alive remission |
| 5 | 63 | M | Inactive HBV carrier | NHL | Spleen | Exitus |
| 6 | 26 | M | Inactive HBV carrier | NHL | Bone | Exitus |
| 7 | 49 | M | e-Antigen-negative CHB | CLL | Liver, LAP | Alive |
| 8 | 68 | F | CHC | NHL | LAP | Alive remission |
| 9 | 84 | M | HCV cirrhosis | NHL | LAP | Exitus |
| 10 | 46 | M | HCV cirrhosis | NHL | LAP, BM | Exitus |
| 11 | 57 | F | CHC | NHL | Liver, spleen | Alive |
| 12 | 64 | M | CHC | NHL | Liver | Alive remission |
| 13 | 62 | M | CHC | CLL | — | Alive |

CHB, chronic hepatitis B; CHC, chronic hepatitis C; F, female; M, male; NHL, non-Hodgkin's lymphoma; CLL, chronic lymphocytic leukemia; LAP, lymphadenopathy; BM, bone marrow.

Paydas et al., 2003; Yenice et al., 2003; Dal Maso and Franceschi, 2006] but has not been confirmed by other Northern European investigators [McColl et al., 1997; Hausfater et al., 2001]. The results of the present study suggest the position of an increased risk of malignant lymphoproliferative disorders, especially non-Hodgkin's lymphoma in patients with chronic hepatitis C ($P < 0.05$).

Few studies have investigated an association between hepatitis B infection and non-Hodgkin's lymphoma [Marcucci et al., 2006; Ulcickas Yood et al., 2007; Chen et al., 2008]. A previous Italian study demonstrated that HBs-Ag and other hepatitis B virus-related markers were found more significantly among B-cell non-Hodgkin's lymphoma patients than in controls [Marcucci et al., 2006]. In fact, there is some limited data regarding the prevalence of non-Hodgkin's lymphoma in patients with hepatitis B infection. Ulcickas Yood et al. [2007] investigated the incidence of non-Hodgkin's lymphoma in chronic hepatitis B patients, and compared the results with those of individuals without hepatitis B infection using United States Health Care Delivery System Data. They reported that chronic hepatitis B patients were nearly three times more likely to develop non-Hodgkin's lymphoma than their comparison group [Ulcickas Yood et al., 2007]. Ulcickas Yood's 2007 study was a cohort study; moreover, it was not possible to confirm the diagnosis of chronic hepatitis B infection in each case. In contrast, in the present study, the diagnosis of chronic hepatitis B infection in all cases was based on clinically utilized and accepted biochemical, serologic, and histologic data when available. The results of this investigation suggest that a malignant lymphoproliferative disorder was identified more significantly in chronic hepatitis B patients ($P = 0.034$).

Lymphomagenesis is a slow process. Chronic antigenic stimulation may play a role in the development of an initial polyclonal B-cell expansion, which can progress to autonomous B-cell proliferation, and eventually a B-cell malignancy [Franzin et al., 1995; Racanelli et al., 2001; Weng and Levy, 2003; Viswanatha and Dogan, 2007]. Several investigators have reported increasing risk of non-Hodgkin's lymphoma with increasing age [Idilman et al., 2004; Ulcickas Yood et al., 2007]. In the present study, the age of cases of chronic viral hepatitis with a malignant lymphoproliferative disorder was slightly higher compared to the chronic viral hepatitis patients without a malignant lymphoproliferative disorder (53 years vs. 48.0 years, respectively). Previous cohort studies attempting to show an association between hepatitis B and C viruses and malignant lymphoproliferative disorder were unable to define the timeframe between the initial diagnosis of viral infection and non-Hodgkin's lymphoma [Duberg et al., 2005; Ulcickas Yood et al., 2007]. In the present study, the timeframe between the diagnosis of viral infection and detection of malignant lymphoproliferative disorders ranged from concomitant with the malignant lymphoproliferative disorder diagnosis to a 7-year lapse between the two diagnoses. However, it should be acknowledged that the date of the initial diagnosis really has no true value in defining the exact duration of chronic viral hepatitis. The present data indicate that the interval between chronic antigenic stimulation and the development of a B-cell malignancy is possibly long.

In the present study, no differences in age or gender were observed between chronic hepatitis B and C patients with or without malignant lymphoproliferative disorder; however, some investigators have reported that there is a relationship between hepatitis C virus genotype, especially 2a and 2c, and an associated malignant lymphoproliferative disorder, despite the fact that genotype 1b is the most common hepatitis C virus genotype detected [Silvestri et al., 1997; Luppi et al., 1998]. These investigators have suggested that hepatitis C virus genotypes 2a and 2c might be uniquely involved in the pathogenesis of malignant lymphoproliferative disorders in individuals with chronic hepatitis C [Silvestri et al., 1997; Luppi et al., 1998]. Idilman et al. [2004] reported that hepatitis C virus genotype does not significantly influence the development of a lymphoproliferative disorder in patients with chronic

hepatitis C [Idilman et al., 2004]. The genotype analysis was not investigated in the present study. However, in Turkey, nearly all chronic hepatitis B patients have had hepatitis B virus genotype D infection and nearly all of the chronic hepatitis C patients have had a genotype 1b infection [Bozdayı et al., 2004]. Although there were a limited number of cirrhotics with a malignant lymphoproliferative disorder in the present study, there might be a positive association between the presence of cirrhosis and malignant lymphoproliferative disorders ($P = 0.003$). This fact is likely due to the longer disease duration in cirrhotics.

The long-term status of individuals with a malignant lymphoproliferative disorder and a chronic viral hepatitis was examined in the present investigation. During the follow-up period, eight of the 13 patients were still alive: five were in remission, and the remaining five died, two as a result of acute and chronic hepatic failure. Four hepatitis B patients had normal serum ALT levels and HBV-DNA negativity and four chronic hepatitis C patients had a detectable HCV-RNA level.

Of note, several investigators have reported that the risk of non-hepatic malignancies including multiple myeloma and thyroid cancer may be increased in chronic hepatitis C patients with extended disease duration [Montella et al., 2001; Duberg et al., 2005]. In contrast to these data, multiple myeloma and follicular thyroid cancer were detected in only two different cases of chronic hepatitis B during the follow-up period. This finding may be related to the relatively short follow-up period in the present study.

In conclusion, based on the data obtained in this investigation, it appears that there is a positive association between chronic viral hepatitis and malignant lymphoproliferative disorders, and we suggest that the risk of a malignant lymphoproliferative disorder is increased in both chronic hepatitis B as well as chronic hepatitis C patients.

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