

The Incidence of Hepatitis C Virus in Patients With Lung Cancer

Kürşat Uzun, MD¹; Süleyman Alıcı, MD²; Bülent Özbay, MD¹; Mehmet Gencer, MD¹; Hasan Irmak, MD³

¹ Yüzüncü Yıl University, Medical Faculty, Department of Chest Diseases, Van, Turkey

² Yüzüncü Yıl University, Medical Faculty, Department of Medical Oncology, Van, Turkey

³ Yüzüncü Yıl University, Medical Faculty, Department of Infection Diseases, Van, Turkey

Abstract

Background: Oncogenesis is a multifactorial process affected by environmental, genetic and infectious factors. A possible role of some specific viruses has been suggested in at least 15% of human cancer cases.

Objective: The aim of the study was to evaluate the frequency of HCV infection in patients with lung cancer and thus contribute to the documentation of a possible relationship between lung cancer and HCV infection.

Methods: Anti-HCV antibodies were measured in sera from 45 patients with lung cancer and in sera from 80 patients with benign lung diseases and 135 healthy individuals. A commercial enzyme linked immunosorbent kit assay was used in the analyses.

Results: Anti-HCV antibodies were positive in 6.7% of lung cancer patients while no anti-HCV antibody was detected in

patients with benign lung diseases ($p < 0.05$). In healthy controls, anti-HCV antibodies were positive in one subject (0.7%). The histopathologic diagnosis of the 3 patients with positive anti-HCV antibodies was non-small-cell cancer (squamous cell carcinoma in one case, adenocancer in the second, and adenosquamous cell carcinoma in the third patient). Hepatitis B surface antigen was present in 4 of the 45 patients with lung cancer and in 8 of the 80 benign lung disease cases ($p > 0.05$).

Conclusions: The prevalence of anti-HCV positivity in patients with lung cancer was shown to be significantly higher than patients with benign lung disease and healthy individuals in our population. However, further studies which include a larger number of patients with HCV infection are needed to confirm this finding.

Turkish Respiratory Journal, 2000;3(3):91-93

Key words: lung cancer, HCV

Introduction

The malignant transformation of bronchial cells is best explained by the "multiple hit" theory, in which two or more cellular events, distinct in time, must occur. These events include disruption of intranuclear genetic material or other elements of the cell regulatory system by ionizing radiation, or by viral, chemical or other physical/chemical factors (1). There is substantial evidence indicating that several common viruses may act as causal factors in the etiology of specific malignancies. Oncogenesis is probably linked to an enhanced level of viral replication in the infected host, reflecting a heavy viral load or a compromised immune control (2).

Extrahepatic syndromes have been described in patients with either acute or chronic viral hepatitis (3). Hepatitis C virus (HCV), a ribonucleic acid (RNA) virus, is now recognized as the major cause of the so-called non-A, non-B transfusion-associated

Correspondence: Dr. Kürşat Uzun
Yüzüncü Yıl Üniversitesi, Araştırma
Hastanesi Tıp Fakültesi Göğüs
Hastalıkları, 65300, Van, Türkiye
Tel: 432 2156195
Fax: 432 2168352
e-mail: uzunkur@hotmail.com

| Diagnosis | N |
|--------------------------------------|----|
| <i>Patients</i> | |
| <i>Lung cancer patients</i> | 45 |
| Squamous cell ca | 17 |
| Small-cell ca | 8 |
| Adenocancer | 5 |
| Adenosquamous cell ca | 1 |
| Unknown type | 14 |
| <i>Benign lung diseases patients</i> | 80 |
| COPD | 17 |
| Tuberculosis | 25 |
| Pneumonia | 11 |
| Asthma | 12 |
| Miscellaneous | 15 |

COPD: chronic obstructive pulmonary disease

hepatitis. With improved diagnostic techniques, HCV infection is increasingly identifiable and is recognized as being associated with conditions other than hepatitis (4). The association of chronic HCV infection and hepatocellular carcinoma is well established (5).

Recently HCV has been reported to be associated with oral cancer, non-Hodgkin's lymphoma, pulmonary fibrosis, diabetes mellitus, and autoimmune diseases (3,6,7,8,9). However, the association of HCV infection and lung cancer remains to be clarified.

Material and Methods

The study included 45 (38 male, 7 female) patients with lung cancer, 80 (58 male, 22 female) patients suffering from a variety of benign respiratory diseases and 135 (84 male, 51 female) healthy controls. The mean age was 55.6±11.8 years in patients with lung cancer, 42.8±17.7 years in patients with benign respiratory diseases and 39.4±12.4 years in the healthy group. A routine evaluation including a detailed medical history, physical examination, chest radiography, thorax CT, abdominal ultrasonography, blood count and biochemistry was performed in all patients. The distribution of the etiological diagnosis of the patients with respiratory disease is shown in Table 1. Primary lung carcinoma was histologically subclassified according to the World Health Organization Guidelines (10).

Serum samples for anti-HCV antibodies were obtained on admission. Anti-HCV antibodies were detected by the 2nd generation Enzyme Linked Immunosorbent Assay (ELISA) (Abbott, USA). The Chi-square and Fisher exact test were used for the statistical analyses.

Results

Three of the 45 patients with lung cancer were positive for anti-HCV antibodies (Table 2). None of the 80 patients

| Diagnosis | n | Anti-HCV ¹ |
|----------------------|-----|-----------------------|
| Lung cancer | 45 | 3 |
| Benign lung diseases | 80 | 0 |
| Healthy | 135 | 1 |

x²; ¹p<0.05-p<0.05

with benign lung diseases had anti-HCV antibodies. In the healthy controls, anti-HCV antibody was positive in only one subject (0.7 %). There was a statistically significant difference between patients with lung cancer and patients with benign lung disease for anti-HCV antibodies (p<0.05) and also between lung cancer patients and the healthy controls (p<0.05). The histopathologic diagnosis of 3 patients who were positive for anti-HCV antibodies was non-small-cell cancer (squamous cell carcinoma in one case, adenocancer in the second, and adenosquamous cell carcinoma in the third patient). Hepatitis B surface antigen was present in 4 of the 45 patients with lung cancer and in 8 of the 80 benign lung disease cases (p>0.05).

There was no history of blood transfusion or surgical intervention in patients with anti-HCV antibodies.

Discussion

Oncogenesis is a multifactorial process in which environmental, genetic and infectious factors are variably involved. A possible role of specific viruses has been suggested in at least 15% of human cancer cases (11). HCV has been shown to be associated in the etiopathogenesis of various disorders, including hepatocellular carcinoma, non-Hodgkin's lymphoma, pulmonary fibrosis, and oral carcinoma (6,7,8). The association of lung cancer and HCV infection is not well known.

In this study, the prevalence of anti-HCV positivity (6.7%) in the lung cancer patients was significantly higher than that of the normal Turkish population, which was reported to vary between 0.0% and 0.6 % (p<0.05)(12). In our study, anti-HCV antibodies were found to be positive in 0.7% of the healthy population in our region (p<0.05).

A relationship between lung cancer and different viruses was reported by several investigators. Kasai et al. evaluated the presence of Epstein-Barr (EBV) virus in Japanese patients with lung cancer and reported the presence of EBV in two patients with adenocarcinoma and in two patients with squamous cell cancer (13). Roy et al. measured antibodies against EBV in sera of Indian patients with respiratory tract cancer using the ELISA kit. They found that antibodies against EBV were positive in 19 of 33 lung cancer patients and in three of 29 matched controls (14). Kinoshita et al. evaluated the association of human papilloma virus (HPV) with lung cancer. HPV was detected in 3 (8%) of 30 specimens (one from a squamous cell carcinoma and two from adenocancer

patients). These authors stated that HPV may play an important role in the development and progression of some lung cancer cases (15). Matsuzaki et al. suggested that in areas where human T cell leukemia virus (HTLV-1) is endemic, some small-cell lung cancers are associated with HTLV-1 (16). In our study, we found that anti-HCV antibodies were positive in 3 of 45 patients with lung cancer and that this ratio was significantly high compared to patients with benign respiratory diseases and to healthy controls. The histopathologic diagnosis in these 3 patients was adenocancer, squamous cell cancer and adenosquamous cell cancer.

In recent publications, it is suggested that human immunodeficiency virus (HIV) may be associated with lung cancer. Karp et al. reported adenocancer of the lung in 7 patients with HIV infection and suggested that patients with HIV infection may be at risk for developing adenocancer of the lung. Four of their patients were diagnosed as adenocancer, 2 as small-cell carcinoma, 1 as squamous cell cancer and 1 as mesothelioma (17). Tenholder and Jackson reported that adenocancer was the predominant cell type in lung cancer associated with HIV infection (18). Fraire and Awe reported 22 patients with HIV infection associated with lung cancer. Eleven of these patients were diagnosed as adenocancer, 6 as small-cell cancer, 3 as squamous cell cancer, and one as an adenosquamous cancer (19). In our study, among 3 HCV associated lung cancer patients, adenocancer was detected in one, adenosquamous cancer in one and squamous cell cancer in the third patient.

There are many reports about association between HCV and various organ cancers other than liver. Sikuler et al. found extrahepatic malignancies including lymphomas and breast, colon, pancreatic cancer in their patients with chronic HCV infection and suggested that an association between HCV infection and extrahepatic malignancy may exist (20). Nagao et al. reported a high prevalence of HCV infection in patients with oral cancer (6). Topeli et al. reported that anti-HCV antibodies were positive in 13.2% of their cancer patients (21).

In conclusion, the development of lung cancer is probably a multifactorial process and in patients with lung cancer, anti-HCV positivity alone may not be sufficient evidence for a causal relation between HCV infection and lung cancer.

There is a need for further prospective and more elaborate studies on large numbers of patients with HCV infection to clarify this association.

References

1. Beckett WS. Epidemiology and etiology of lung cancer. *Clin in Chest Med* 1993; 14(1): 1-17
2. Mueller N. Viral agents and cancer. *Environ-Health-Perspect.* 1995 ;103(suppl 8): 259-61
3. Willson RA. Extrahepatic manifestations of chronic viral hepatitis. *Am. J. Gastroenterol.* 1997; 92(1): 4-17
4. Egan JJ, Woodcock AA, Stewart JP. Viruses and idiopathic pulmonary fibrosis. *Eur Respir J.* 1997; 10: 1433-37
5. Maddrey WC. Viral hepatitis: A 1994 interim report. *Gastroenterol Clin of North Am.* 1994; 23(3): 429-35
6. Nagao Y, Sata M, Tanikawa K, Itoh K, Kameyama T. High prevalence of hepatitis C virus antibody and RNA in patients with oral cancer. *J Oral Pathol.* 1995; 24(8): 354-60
7. Ferri C, Caracciolo F, Zignego AL, La Civita L, Monti , Longombardo G, et al. Hepatitis C virus infection in patients with non-Hodgkin's lymphoma. *Br J Haematol.* 1994; 88: 392-4
8. Ueda T, Ohta K, Suzuki N, Yamaguchi M, Hirai K, Horiuchi T, et al. Idiopathic pulmonary fibrosis and high prevalence of serum antibodies to hepatitis C virus. *Am Rev Respir Dis.* 1992; 146: 266-8
9. Talliani G, Poliandri G, Clementi C, et al. Chronic hepatitis C and diabetes mellitus. *J Hepatol.* 1992; 16(suppl): 116
10. American Thoracic Society/European Respiratory Society. Pretreatment of non-small cell lung cancer. *Am J Respir Crit Care.* 1997; 156:320-32
11. Ferri C, La Civita L, Zignego AL, Pasero G. Viruses and cancers: possible role of hepatitis C virus. *Eur J Clin Invest.* 1997; 27(9): 711-8
12. Doganci L, Haznedaroglu T. Prevalence of hepatitis A,B and C in Turkey. *Eur J Clin Microbiol Infect Dis.* 1992; 11(7): 661-2
13. Kasai K, Sato Y, Kameya T, Inoue H, Yoshimura H, Kon S, Kikuchi K. Incidence of latent infection of Epstein-Barr virus in lung cancers-an analysis of EBV 1 expression in lung cancers by in situ hybridization. *J Pathol.* 1994; 174(4): 257-65
14. Roy A, Dey S, Chatterjee R. Prevalence of serum IgG and Ig M antibodies against Epstein-Barr virus capsid antigen in Indian patients with respiratory tract carcinomas. *Neoplasma.* 1994; 41(1): 29-33
15. Kinoshita I, Dosaka AH, Shindoh M, Fujino M, Akie K, Kato M, Fujinaga K, Kawakami Y. Human papillomavirus type 18 DNA E6-E7 mRNA are detected in squamous cell carcinoma and adenocarcinoma of the lung. *Br J Cancer.* 1995; 71(2): 344-9
16. Matsuzaki H, Asou N, Kawaguchi Y, Hata H, Yoshinaga T, Kinuwaki E, Ishii T, Yamaguchi K, Takatsuki K. Human T cell leukemia virus type 1 associated with small cell lung cancer. *Cancer* 1990 Oct 15; 66(8): 1763-8
17. Karp J, Profeta G, Marantz PR, Karpel JP. Lung cancer in patients with immunodeficiency syndrome. *Chest* 1993; 103: 410-13
18. Tenholder MF, Jackson HD. Bronchogenic carcinoma in patients seropositive for human immunodeficiency virus. *Chest* 1993; 104: 1049-53
19. Fraire AE, Awe RJ. Lung cancer in association with human immunodeficiency virus infection. *Cancer.* 1992 July 15; 70(2): 432-36
20. Sikuler E, Shnaider A, Zilberman D, Hilzenrat N, Shemer-Avni Y, Neumann L, Buskila D. Hepatitis C virus infection and extrahepatic malignancies. *J Clin Gastroenterol* 1997; 24(2): 87-9
21. Topeli A, Özyılkan Ö, Özyılkan E, Kars A, Tekuzman G, Baltalı E, Kayhan B, Telatar H, Fırat D. Prevalence of hepatitis C virus antibody in cancer patients from Turkey. *Marmara Med J* 1994; 7(1): 14-17