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ARTICLE

HCV and HGV Infection in Hodgkin's Disease

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Numerous observations imply that the pathogenesis of malignant lymphomas is multifactorial and that viruses probably play an important etiologic role. Besides Epstein-Barr virus, there might be other viruses among the causes of Hodgkin's disease. A total of 111 randomly selected patients with Hodgkin's disease were included in this study, and hepatitis C and G viruses were tested with polymerase chain reaction. The results were compared to hepatitis C and G virus infection ratios assessed by polymerase chain reaction in the Hungarian blood bank. Hepatitis C virus was diagnosed in 10 (9%) patients, and hepatitis G virus in 9 (8,1%), which is a 12-fold and a 1,5-fold infection rate as compared to that of the Hungarian blood bank, respectively. There was no significant difference between hepatitis positive and negative patients concerning mean age at the time of diagnosis, sex, disease stage, histology type, treatment applied, risk factors in the history of the infection and liver enzymes. Hepatitis C virus positivity in patients with Hodgkin's disease differs significantly from that in blood donors. Based on these results and data in the literature, no definite statement can be made on the etiological role of viruses, but further studies are needed. (Pathology Oncology Research Vol 9, No 4, 222–225)

Keywords: Hodgkin's disease, hepatitis C virus, hepatitis G virus

Introduction

The infectious origin of a growing number of malignant diseases – such as helicobacter pylori and MALT lymphoma, human T cell leukemia-lymphoma virus and adult T cell leukemia, hepatitis C virus and B cell non-Hodgkin's lymphoma (NHL), cervical dysplasia or carcinoma and human papilloma viruses 16 and 18 - has been confirmed in the past few decades. Though the etiology of malignant lymphomas seems to be of multifactorial origin at present, certain human viruses are supposed to play a role in their development. In some of the cases of Burkitt's lymphoma, B cell NHL and Hodgkin's disease (HD), the presence of Epstein-Barr virus has been confirmed but in negative cases – besides the hit and run mechanism of EBV – the etiologic role of other viruses is assumed.[6] Besides herpes viruses, attention has been focused on the role of hepatitis viruses since among the latter, hepatitis C (HCV) and hepatitis G (HCG) viruses may be of lymphotropic type. HCV and HGV-RNA as well as their protein products can be detected in lymphocytes, which, similarly to EBV mechanism, are able to activate cellular genes-oncogenes (c-myc, bcl-2) and induce cell transformation. Another possible mechanism may be that HCV and HGV, as chronic antigenic stimuli, cause lymphoid hyperplasia which, in the late phase of the process, leads to the clonal expansion of lymphocytes and to the development of malignant lymphomas.[12] In this study, our aim was to analyse the occurrence of HCV and HGV infections in our patients with HD.

Materials and Methods

From all the patients treated for Hodgkin's disease at our clinic, 111 (59 females and 52 males) were randomly selected for the study. No HIV infected patients were found among the selected patients and they had no clinical symptoms suggesting chronic liver disease. Histologic subtypes were determined according to Lukes' and Butler's criteria. HD staging was based on clinical examinations, Ann Arbor's principles and their Cotswolds modification. HCV and HGV were detected by nested poly-

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merase chain reaction (PCR) according to the methodology described in the literature.[3,8] In addition to this, the occurrence of hepatitis B virus (HBV) was assessed by enzyme linked immunosorbent assay (ELISA) (HBsAg was identified). Our results were compared to the ratio of infections in Hungarian blood donors detected by nested PCR and by ELISA in HBV infections. Serum aspartate aminotransferase (GOT), alanine aminotransferase (GPT), gamma-glutamil-transferase (GGT) levels were measured by methods used in routine diagnosis and cryoglobulin by standard serological methods. By statistical analysis (κ^2 – test) $p<0,05$ probability level was considered significant.

Table 1. **Clinical characteristics and treatment results of HCV and HGV positive and negative HD patients (111 patients)**

	Without HCV and HGV infection	*With HCV or HGV infection*	*p*
Number of patients	94	19	
Gender			0.142
Female	47	13	
Male	47	6	
Histologic subtypes			0.899
MC	53	10	
NS	31	7	
LP	2		
LD	8	2	
Stage			0.334
I-II	43	11	
III-IV	51	8	
General symptoms			0.032
A	60	17	
B	34	2	
Mean age at diagnosis of HD (years)	32 (12-68)	31 (15-57)	
Mean duration of HD at PCR diagnosis of HCV and HGV (years)	10 (1-33)	8 (1-22)	
Treatment			0.760
Radiotherapy	16	4	
Chemotherapy	38	6	
Combined treatment	40	9	
Course of disease			0.910
From first treatment CR	67	14	

Results

From the 111 HD patients, HCV was confirmed in 10 cases (9%), HGV in 9 patients (8,1%) and from the latter HCV and HGV coinfection was confirmed in 2 cases (1,8%) by PCR. The clinical signs of HD patients with hepatitis virus positivity and negativity are summarised in *Table 1*. No significant differences were found in gender distribution, histologic subtypes, disease stage, mean age at the diagnosis of HD, treatment employed or course of the disease. The ratio of "B" symptoms was found to be significantly lower in patients with HCV or HGV infections. *Table 2* shows liver function enzyme levels of HD patients with HCV and HGV positivity and negativity. The laboratory values of patients with hepatitis virus positivity were also within the normal range. The factors of HCV and HGV infections inducing increased risks are well known: medical history data are compared in *Table 3*. No differences were found between the patient groups with hepatitis virus positivity and negativity. Of the 111 HD patients, 1 patient was found to be infected with HBV (0,9%) by ELISA. Data on the occurrence of HBV, HGV and HCV in HD patients are compared to the infection ratio of Hungarian blood donors in *Table 4*. Cryoglobulin was assessed in the 10 HCV positive patients and 1 was found positive.

Table 2. **Enzyme levels in HD patients with and without HCV or HGV infection**

	Without HCV and HGV	*With HCV*	*With HGV*	*With HCV and HGV*
GOT (U/l)	24 (13-62)	25 (20-45)	18 (15-32)	21 (15-32)
GPT (U/l)	26 (7-124)	22 (13-64)	22 (8-61)	35 (26-44)
GGT (U/l)	39 (8-253)	39 (12-158)	39 (8-86)	22 (20-24)

Normal level: GOT, GPT<40; GGT 7-50 U/l

Discussion

HGV-positivity in Hungarian blood donors was found to be 5,5% by nested PCR,[13] the mean ratio of infections in Europe is 1-4%.[5] In our HD patients, HGV was assessed in 8,1%, which is about 1,5 times greater than that of the infection rate among Hungarian blood donors. Persico et al. found an infection ratio of 15% in 71 HD patients, which compared to the 1,4% infection rate of healthy controls showed a significant difference.[11] Keenan et al. did not experience any increase in the occurrence of HGV infections in lymphoproliferative diseases or in HD as compared to the normal population.[7] Data in the literature

Table 3. **Comparison of medical history data suggestive of HCV-, or HGV infection in HD patients with hepatitis virus-positivity and negativity**

	Without HCV and HGV infection (94 patients)	*With HCV or HGV infection (19 patients)*	*p*
Blood and blood preparation before 1992[1]	2	1	
Blood and blood preparation after 1992	1		
Acupuncture, tattoo, ear piercing, body piercing, i.v. substance abuse, operation	52	12	0.372
Homosexuality, promiscuity	2		
Health professional	3		
Bad social background and hygiene	4	1	

[1]Blood and blood products are screened for HCV since 1992

are contradictory, and our results do not prove a direct relationship between HGV positivity and HD. HCV infection was assessed in Hungarian blood donors 0,73%.[1] The 9% HCV positivity of HD is approximately twelve times higher, respectively than that of Hungarian blood donors. Italian authors detected HCV infection in 2 cases out of 47 HD patients, which does not differ from values in the normal population.[11] In contrast with these data, our results show that the ratio of HCV infection is significant in HD, though it is not as high as the 23,8% HCV infection rate of NHL patients in Hungary[4]. The presence of cryoglobulinemia or autoimmune diseases is known in HCV infections. No clinical signs of these were found in our HD patients with HCV positivity, and only 1 patient was positive for cryoglobulin. HCV infection may trigger an autoimmune response, activate lymphocytes, increase cytokine production, cause pathologic MHC expression, and through liver necrosis, modify the expression of host epitopes. The absence of clinical signs of manifest autoimmune diseases may be explained by the small number of cases (10 HCV positive patients) as well as by the non-appearance of liver necrosis. By ELISA, HBV infection was 0,5%[10] in Hungarian blood donors and 0,9% in HD patients - no significant difference was found. With the exception of "B" symptoms, no significant differences were found in the clinical signs, ratio of treatments or disease course between hepatitis virus positive and negative groups. Similarly, no differences were found in their medical history data that would predispose to hepatitis infection. The analysis of liver function test results revealed that the laboratory results of both HCV and HGV patients were within the normal range, which, however, does not mean that these patients do not develop chronic liver diseases. It is known that liver cirrhosis may produce normal liver function test results.[2] HD as the basic disease and its treatment may result in a state of decreased immune reactivity, which may lead to the reactivation of the former hepatitis infection. In our study, HCV, HBV and HGV were assessed in patients who had been previously treated for HD (mean duration of HD was 9,1 /1-33/ years). In HD and NHL patients, 83% of HBV infection activation were attributed to the chemotherapy and corticosteroid treatments employed.[9] No HCV reactivation was found in malignant hematologic diseases, such as NHL or HD.[9,14] Based on the above date we believe that reactivation of HCV infection during HD treatment is not to be expected, thus our retrospective study – as related to HCV infection of HD patients - reflects the infection ratio of these patients. Our findings suggest the following: Though the epidemiology of HCV, HGV, HBV shows strong similarities, it is only the occurrence of HCV infection that shows a significant difference as compared to the control population. Although literary data refer primarily to NHL patients, HBV reactivation is also considered to be highly probable in HD during treatment, and HCV reactivation is less probable.[9,14] Thus the etiologic role of HCV is not clear but may be possible. The etiologic role of HCV is more or less accepted in the development of B cell NHL. In spite of this, significant differences can be found in the infection rate of NHL patients according to countries, regions, and ethnic groups. Similar differences are supposed to exist in relation to HD and HCV or HGV. For the clarification of the etiologic role of HCV and HGV infections, further studies should be performed on a great number of patients.

Table 4. **HCV, HGV** (by nested PCR)**, HBV-infection** (by ELISA) **in HD patients and in Hungarian blood donors**

	HD patients (number of patients 111)	*Occurrence in Hungarian blood donors*
HBV	0.9% (1)	0.5%
HGV	8.1% (9)	5.5%
HCV+HGV	1.8% (2)	
HCV	9% (10)	0.73%

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