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Epidemiology

No relationship between hepatitis C infection and risk of myeloid malignancy

The etiology of myeloid malignancies is related to chromosomal damage caused by irradiation, alkylating agents, viral infection and so forth;[1] however, few clinical studies have been published on the association between viral infection and the development of myeloid malignancies.

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Hepatitis C virus (HCV) is the major pathogen of post-transfusion and sporadic non-A, non-B chronic hepatitis, and one of the most important causes of chronic liver disease.[2] It involves many organs, causing extrahepatic manifestations.[2] Crovatto *et al.* demonstrated that peripheral blood neutrophils are the replication sites of HCV,[3] while it remains unknown whether the infection occurs at the level of the stem cells or subsequently during myeloid cell differentiation. A few clinical studies suggest a weak, non-significant association between acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), and antibody to HCV;[4,5] however, it remains unknown whether HCV infection might contribute to the development of myeloid malignancies. We conducted a hospital-based case-control study to evaluate this association.

We selected 94 patients with myeloid malignancies from 326 consecutively registered patients with hematologic malignancies at Toranomon Hospital between 1995 and 2001. Myeloid malignancies were classified according to the International Classification of Diseases 10th version (ICD-10). Myeloid leukemia (C92), monocytic leukemia (C-93), acute erythroleukemia (C94.0), megakaryocytic leukemia (C94.2) and myelodysplastic syndrome (D46) were included in this study. All the patients had newly diagnosed myeloid malignancies, and had never received any chemotherapy. Controls were selected randomly from hospitalized orthopedics patients (n=188) and otolaryngology patients (n=188), each group matched for age, sex and year of visit with a 1:2 case-control ratio. We excluded patients with a history of malignancy. Age was further adjusted as a continuous variable in conditional logistic regression analysis. The following data were extracted from medical records; age, sex, smoking habit, alcohol use, hepatitis B virus surface (HBs) antigen, anti-HCV antibody (anti-HCV-Ab), anti-human T-cell leukemia virus (HTLV)-1 antibody, anti-HIV antibody, and a history of malignancy. The definition of HCV infection was positive anti-HCV-Ab by enzyme immunoassay (EIA-I or EIA-II, Ortho Diagnostic Systems, Tokyo, Japan) on admission. To minimize unknown biases, we used two independent control groups in which each case was matched to four individuals for age, sex, and year of admission.

All statistical analyses were performed with STATA, version 7. (STATA Corp., College Station, TX, USA). Bivariate analyses were performed with χ^2, Fisher's exact, or Wilcoxon's signed-rank test. Attribution of HCV infection was evaluated in terms of odds ratios (OR) and 95% confidence intervals (CI). A conditional logistic regression model was applied to estimate ORs and 95% CIs. The study protocol was approved by the institutional review board.

The patients' characteristics are shown in Table 1. Five patients with myeloid malignancies had HCV infection. The prevalence of HCV infection in cases (5.3%) was comparable with that in orthopedic (6.4%), otolaryngology (6.9%) and combined controls (6.6%) (Table 1). Age-adjusted odds ratios for seropositivity of HCV are shown in Table 2. There was no significant association between seropositivity of HCV and development of myeloid malignancies.

Our study does not support an association between HCV infection and development of myeloid malignancies. These findings are comparable with those of previous reports.[4,5] While further evaluation of the association is necessary, currently available observations, including ours, suggest that HCV infection is unlikely to increase the rate of myeloid malignancies. This contrasts with the association between HCV infection and lymphoid malignancies.[1] Although the development of both myeloid and lymphoid malignancies is considered to be affected by genotoxic factors such as viral infections, irradiation, and chemotherapeutic agents, our observation suggests that the mechanisms of tumorigenesis are different between lymphoid and myeloid malignancies.

A case-control study is suitable for studying a rare disease such as myeloid malignancies; however, this study has several problems to be discussed. First, it was hospital-based, and possibly affected by an unrecognized bias in the case and the control groups. Secondly, data on

Table 1. Patients' characteristics and clinical outcomes of patients infected with hepatitis C virus.

	Case Group; Patients with Myeloid Malignancies (n=94)	*Control Group 1; Orthopedic Group (n=188)*	*Control Group 2; Otolaryngology Group (n=188)*	*Total Controls (n=376)*
Male:Female	23:71	46:142	46:142	84:284
Age range (median)	45-89 (64)	43-90 (63)	44-89 (62)	43-90 (63)
Number of patients by age groups				
40-49	12	22	26	48
50-59	25	56	55	111
60-69	37	69	77	146
70-79	14	31	24	55
80-	5	10	6	16
Clinical diagnosis of case group	ICD-10 codes			
Myeloid leukemia	C92	57		
Acute myeloid leukemia	C92.0	26		
Chronic myeloid leukemia	C92.1	13		
Acute promyelocytic leukemia	C92.4	4		
Acute myelomonocytic leukemia	C92.5	5		
Myeloid leukemia, unspecified	C92.9	9		
Monocytic leukemia	C93	5		
Acute monocytic leukemia	C93.0	2		
Chronic monocytic leukemia	C93.1	3		
Other leukemias of specified cell type	C94	3		
Acute erythroleukemia	C94.0	1		
Acute megakaryoblastic leukemia	C94.2	2		
Myelodysplastic syndrome	D46	29		
Refractory anemia without sideroblasts, so stated	D46.0	4		
Refractory anemia with sideroblasts	D46.1	1		
Refractory anemia with excess of blasts	D46.2	10		
Refractory anemia with excess of blasts with transformation	D46.3	4		
Others		10		
Anti-HCV-antibody				
Positive	5*1	12	13	25
Negative	87	174	173	347
Missing	2	2	2	4

**1: The myeloid malignancies were myelodysplastic syndrome (n=2) and acute myeloid leukemia (n=3).*

Table 2. Age-adjusted odds ratios for seropositity of HCV using a conditional logistic regression model.

	Controls		
	Combined	*Orthopedic*	*Otolaryngology*
Total*[1]	0.83 (0.31-2.24, 0.72)	0.85 (0.29-2.48, 0.82)	0.90 (0.24-3.39, 0.82)
Myeloid leukemia*[2]	1.41 (0.36-5.56, 0.63)	1.40 (0.31-6.38, 0.90)	1.80 (0.27-11.9, 0.96)
Myelodysplastic syndrome	0.86 (0.18-4.04, 0.85)	1.04 (0.19-5.73, 0.96)	0.36 (0.02-5.43, 0.46)
Chronic myeloid leukemia*[3]	0	0	0

**[1]: each column denotes the age-adjusted, 95% confidence interval and p value. *[2]: this represents C92-94 (ICD-10) excluding C92.1. *[3]: none of the 13 patients with chronic myeloid leukemia was positive for anti-HCV-Ab.*

HCV-RNA levels were not collected in this study, and it is not apparent how many of the patients were still replicating the virus. Lastly, the small number of HCV-positive patients among cases limits the interpretation of the study. The results of this study are non-confirmatory regarding an association between HCV infection and the development of myeloproliferative diseases. We are now planning a large-sized, multicenter hospital-based study. A community-based study is also warranted to investigate the association among the general population.

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Key words: acute myeloid leukemia, chronic myelogenous leukemia, myelodysplastic syndrome, hospital-based case control study

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