for AHC in HIV-1 co-infected patients [18–20]. However, data of AHC among HIV-1 infected patients is still limited, especially from Asian countries.

The response to treatment with PEG-IFN plus RBV is closely associated with the interleukin-28B (IL-28B) genotype, which encodes interferon-λ3 (IFN-λ3), in chronic HCV hepatitis, even in HIV-1 co-infected cases [21–23]. Furthermore, HCV mono-infected individuals with favorable IL-28B genotype (CC at rs12979860, TT at rs8099917) seem to achieve spontaneous clearance of HCV compared to those with non-favorable genotypes [21,22,24,25]. To our knowledge, there are no studies on the effect of IL-28B genotype on the natural course and response to treatment of AHC in HIV-1 infected individuals in Asian population [24,26,27].

In the last 12 years, 35 patients with HIV-1 infection were diagnosed with AHC in our hospital. In the present retrospective study, we report the results of analysis of data of 32 of these cases, and discuss the factors associated with spontaneous HCV clearance and response to treatment with PEG-IFN plus RBV (Fig. 1).

Methods

Study Design

This single-center retrospective cohort study was conducted in accordance with the ethical principles of the Declaration of Helsinki and of Good Clinical Practice. The ethics committee of National Center for Global Health and Medicine approved the study. All patients provided written informed consent.

Study Participants

The medical records of HIV-1 infected patients in our institution, the largest HIV clinic in Japan, admitted and treated between January 2001 and December 2012, were retrospectively reviewed. AHC was defined according to the following criteria; elevation of alanine transferase (ALT) >100 IU/L accompanied by seroconversion of anti-HCV antibody, and exclusion of other causes (e.g., acute hepatitis B and drug-induced hepatitis). Patients who were lost to follow-up within 1 year from the diagnosis of AHC were excluded from the analysis since they could not be assessed for clinical presentation including spontaneous clearance. Spontaneous clearance was defined as a decrease in HCV RNA to undetectable level without treatment within one year from the diagnosis and remaining as such thereafter. For patients receiving PEG-IFN plus RBV treatment, we assessed the SVR rate. SVR was defined as continued undetectable HCV RNA at 24 weeks

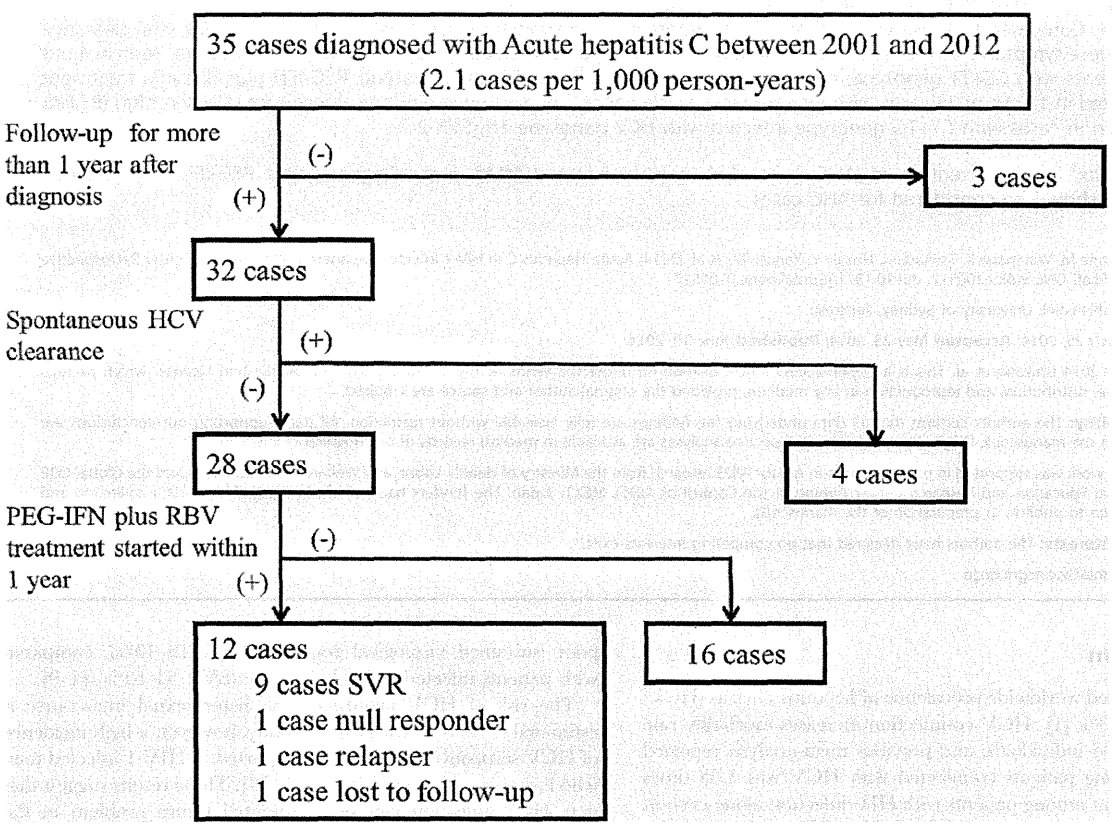

Figure 1. Patient enrollment process. Acute hepatitis C (AHC) was defined as elevation of alanine transaminase (ALT) >100 IU/L accompanied by seroconversion of anti-hepatitis C virus (HCV) antibody. Three patients could not be followed up for 1 year after diagnosis and were excluded from further analysis. HCV cleared spontaneously in 4 cases. PEG-IFN plus RBV treatment was initiated within 1 year of diagnosis of AHC in 12 out of 28 patients who did not show spontaneous clearance. One patient with missing treatment data following transfer to another clinic about two weeks after initiation of IFN plus RBV, was excluded from analysis related to the effect of PEG-IFN plus RBV. PEG-IFN: pegylated interferon, RBV: ribavirin.
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Table 1. Characteristics of AHC patients (n = 32).

	All patients (n = 32)	Spontaneous clearance (n = 4)	Non-spontaneous clearance (n = 28)	P-value
Age (years)	40 [30–58]	44 [37–56]	40 [30–58]	0.361
Male sex	32 (100)	4 (100)	28 (100)	-
Men who have sex with men	31(96.9)	4 (100)	27 (96.4)	1.000
IL-28B genotypes (rs12979860+rs8099917)				
CC+TT genotype	26 (81.2)	4 (100)	22 (78.6)	0.416
CT+TG genotype	6 (18.8)	none	6 (21.4)	-
TT+GG genotype	none	none	none	-
Injecting drug users	4 (12.5)	none	4 (14.3)	1.000
Received ART at diagnosis	29 (90.6)	4 (100)	25 (89.3)	1.000
CD4 count at diagnosis (cells/μL)	420 [167–824]	317 [184–616]	424 [167–824]	0.424
HIV-RNA at diagnosis (copies/mL)	UD [UD–9.4×10^4]	50 [UD-50]	42.5 [UD-9.4×10^4]	0.737

Data are number (%) of patients or median [range].
ART, antiretroviral therapy; UD, undetectable.
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after completion of therapy. Baseline characteristics, status of HIV-1 infection, history of injecting drug usage (IDU), symptoms related to AHC (fatigue and jaundice), laboratory data abnormalities from AHC (ALT, T-bil), treatment of HCV infection and histological findings of liver biopsy, where available, and were collected from the medical records. We compared these variables between patients with and without spontaneous clearance of HCV and between responders and non-responders to treatment with PEG-IFN plus RBV.

HCV Analysis

For each patient, titers of anti-HCV antibody were measured by a third-generation Latex aggregation assay (Ortho HCV Ab LPIA test III, Ortho Clinical Diagnostics, NJ) at first visit to our hospital and at diagnosis of AHC. Serum HCV RNA at each time point was extracted automatically (Cobas Ampliprep, Roche InVitro Diagnostics, Switzerland). Thereafter, cDNA was prepared and its titer was measured by quantitative polymerase chain reaction (Cobas TaqMan 48, Roche In Vitro Diagnostics). Direct sequencing was performed using DNA probe assay by ABI PRISM 3100 (Applied Biosystems, Foster City, CA). Finally, the

Table 2. Clinical presentation of AHC patients (n = 32).

	All patients (n = 32)	Spontaneous clearance (n = 4)	Non-spontaneous clearance (n = 28)	P-value
No symptoms	24 (75)	1 (25)	23 (82.1)	-
Symptoms	8 (25)	3 (75)	5 (17.9)	0.039
Fatigue	8 (25)	3 (75)	5 (17.9)	-
Jaundice	2 (6.25)	1 (25)	1(3.6)	-
Peak Alanine transaminase level (IU/L)	661 [117–2194]	707 [1237–2126]	614 [117–2194]	0.072
Peak total bilirubin level (mg/dL)	1.9 [0.7–17.0]	9.8 [4.2–17.0]	1.6 [0.7–6.8]	0.002
HCV genotype				
1a	1/27 (3.7)	None	1/2 (4.3)	-
1b	19/27 (70.4)	3/4 (75)	16/23 (69.6)	-
2a	4/27 (14.8)	1/4 (25)	3/23 (13)	-
2b	3/27 (11.1)	None	3/23 (13)	-
Not available	5	None	5	
HCV-RNA at diagnosis (Log IU/mL)	6.6 [1.9–7.8]¶	6.6 [4.9–6.8]†	6.6 [1.9–7.8]‡	0.594
Latency to HCV clearance (wks)*	-	11 [7–31]	-	-

Data are number (%) of patients or median [range] values.
*Time between AHC diagnosis and HCV clearance (weeks).
¶Data of 6 patients not available for analysis.
†Data of 5 patients not available for analysis.
‡Data of 1 patient not available for analysis.
doi:10.1371/journal.pone.0100517.t002

Table 3. Comparison of patients of the SVR and non-SVR groups.

	All patients (n = 11)	SVR (n = 9)	Non-SVR (n = 2)
Age (years)	38 [30–58]	38 [30–48]	52 [47–58]
Male sex	11 (100)	9 (100)	2 (100)
Men who have sex with men	11 (100)	9 (100)	2 (100)
IL-28B genotype			
CC+TT genotype	9 (81.8)	7 (77.8)	2 (100)
CT+TG genotype	2 (18.2)	2 (22.2)	None
Injecting drug users	1 (9.1)	None	1 (50)
Received ART before treatment	10 (90.9)	8 (88.9)	2 (100)
CD4 count before treatment (cells/μL)	382 [230–655]	440 [272–655]	238 [254–278]
HIV-RNA before treatment (copies/mL)	UD [UD-3.3×10^4]	UD [UD-3.3×10^4]	UD [305–610]
HCV genotype			
1b	10 (90.9)	8 (88.9)	2 (100)
2a	1 (9.1)	1 (11.1)	None
HCV-RNA before treatment (Log IU/mL)	6.3 [3.3–7.8]	6.3 [5–7.8]	5.7 [3.6–8.0]
Latency to AHC diagnosis (months)*	3.2 [0.9–6.9]	3.2 [0.9–6.9]	4.4 [3.7–5.1]
Duration of PEG-IFN+RBV therapy (wks)	43 [11–72]	43 [11–72]	36 [11–60]
Latency to HCV clearance (wks)¶	-	8 [3–16]	-
RVR	3 (27.2)	3 (33.3)	None
EVR	7 (63.6)	6 (66.7)	1 (50)
Histopathology positive for liver fibrosis			
F0	3/6	3	0
F1	2/6	1	1
F2	1/6	0	1
F3	0	0	0

Data are number (%) of patients or median [range] values.
*Time between AHC diagnosis and initiation of therapy (months).
¶Time between initiation of therapy and HCV clearance (weeks).
ART, antiretroviral therapy; UD, undetectable; PEG-IFN+RBV, pegylated interferon plus ribavirin; SVR, sustained viral response; EVR, early viral response; RVR, rapid viral response.
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genotype was determined from the amino acid sequences of 5 – untranslated region [28].

Genotyping of IL-28b Alleles

Genomic DNA was isolated from peripheral blood mononuclear cells, using QIAamp DNA Mini Kit (Qiagen, Hilden, Germany). SNPs, rs12979860, and rs 8099917 were genotyped, using the TaqMan Drug Metabolism Assays by ABI PRISM 7900 HT sequence detection system (Applied Biosystems) according to the instructions provided by the manufacturer. The researchers responsible for genotyping were blinded to clinical data of the patients.

Statistical Analysis

The patients' characteristics and results of differences in viral clearance and virological response were compared using chi-square test (for qualitative variables) or Mann-Whitney U-test (for quantitative variables). Statistical significance was defined at two-sided p value of <0.05. All statistical analyses were performed with The Statistical Package for Social Sciences Version 21 (SPSS Inc, Chicago, IL).

Results

Patient Enrollment

A total of 35 patients were diagnosed with AHC during the study period. The incidence of AHC was 2.1 cases per 1,000 person-years. Three patients who were lost to follow-up within 1 year after diagnosis of AHC were excluded from the analysis. No deaths or fulminant hepatitis were recorded during the study period. Spontaneous HCV clearance was achieved by 4 patients, including 2 patients in whom HCV clearance was achieved within 3 months of diagnosis of AHC. The median time between diagnosis of AHC and HCV clearance was 11 weeks (range, 7–31 weeks). Among the 28 patients who did not show spontaneous HCV clearance, treatment with PEG-IFN plus RBV was initiated within 6 months of diagnosis in 9 patients and between 6 and 12 months of diagnosis of AHC in 3 patients (6.1, 6.4 and 6.9 months, respectively), whereas treatment was not initiated in the remaining 16 patients due to cost (n = 7) or other comorbidity (depression, history of epilepsy) (**Fig. 1**).

Patients' Characteristics and Clinical Presentations of AHC

The characteristics and clinical presentation of AHC patients are listed in **Tables 1** and **2**, respectively. All patients were

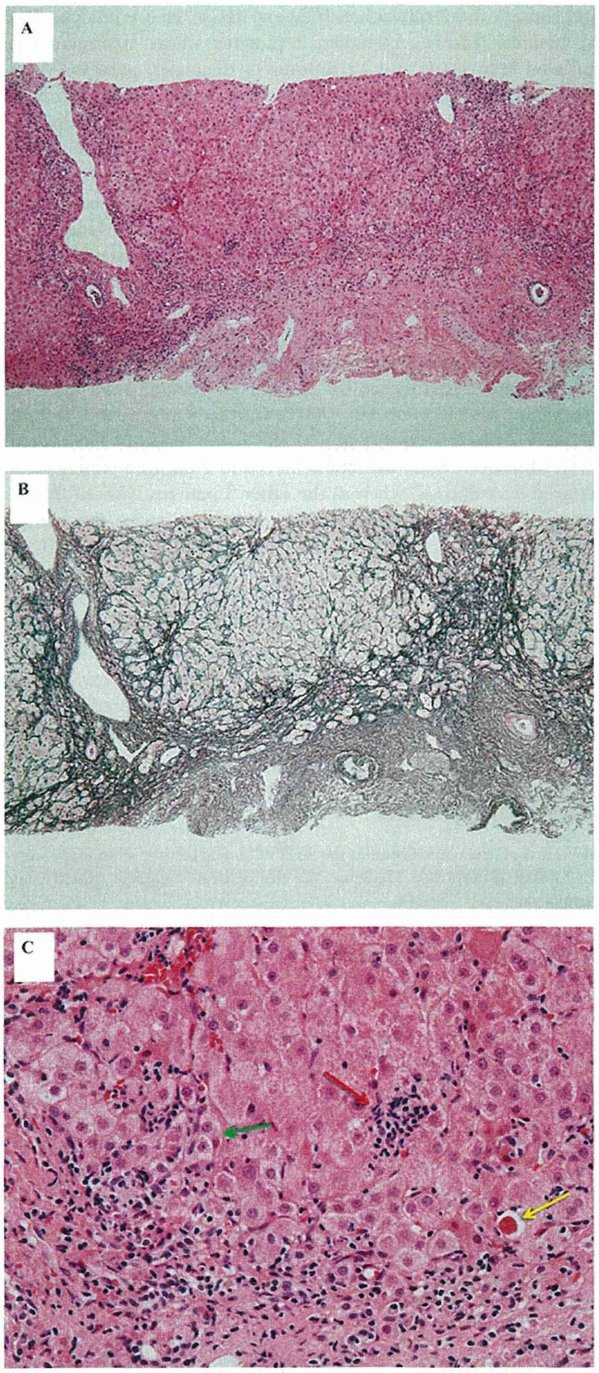

Figure 2. Histological findings in needle liver biopsy specimen from the patient who showed null-response (Table 3). The pre-treatment biopsy specimen obtained at 13 weeks after AHC diagnosis showed stage 2 fibrosis (F2) according to the classification of chronic hepatitis C (New Inuyama Classification). (A and B) Formation of bridging fibrosis by fibrous and cellular expansion in the portal tract. (C) Magnified view showing centrilobular piece-meal necrosis (green arrow), acid folic body (yellow arrow) and spotty necrosis (red arrow). (A) Hematoxylin-eosin stain, x100, (B) Silver impregnation stain, x100, (C) Hematoxylin-eosin stain, x400. PEG-IFN: pegylated interferon, RBV: ribavirin, AHC: acute C hepatitis.
doi:10.1371/journal.pone.0100517.g002

Japanese men, including 31 (96.9%) MSM. Twenty nine patients (90.6%) received antiretroviral therapy (ART) and HIV-RNA was well suppressed in these patients. Four patients (12.5%) had a history of IDU, whereas none had a history of occupational exposure to HCV or blood transfusion. Although there was no significant difference between patients with and without spontaneous HCV clearance, the IL-28B CC+TT genotype was rs12979860 and rs8099917 in all 4 patients who showed spontaneous clearance and none of the patients with IL-28B CT+TG genotype showed spontaneous clearance (**Table 1**).

The majority of patients with AHC (24/32, 75%) were asymptomatic at the onset of AHC. High ALT was identified incidentally at routine visit for HIV-1 infection, with subsequent tests confirming the diagnosis of AHC. Compared to patients who did not show spontaneous clearance, patients with spontaneous clearance showed more severe clinical presentation of hepatitis (symptomatic, with higher serum total bilirubin and ALT value at diagnosis). The most frequent HCV genotype was 1b (70.4%). At diagnosis, HCV RNA was higher than 5.0 LC/mL in 24 out of 26 patients (**Table 2**).

Response to Treatment with PEG-IFN Plus RBV

Treatment with PEG-IFN plus RBV was initiated in 12 patients within 1 year of diagnosis of AHC (median interval from AHC diagnosis, 3.2 months). We assessed the response to treatment in only 11 patients; the other patient was lost to follow-up within two weeks of treatment initiation (**Fig. 1**, **Table 3**). SVR was achieved in 9 of 11 patients (81.8%) despite the high incidence of HCV genotype 1b and high viral load.

Two patients did not achieve SVR. Both patients were infected by genotype 1b with high viral load, and treatment was initiated within 6 months of diagnosis. One achieved viral clearance within 12 weeks (early virological response: EVR) but showed viral rebound at 15 weeks after completion of the treatment (relapser), whereas viral clearance was not achieved during treatment in the other patient (null-responder). Both patients were relatively older and their CD4 counts were lower, compared to those with SVR, although statistical analysis was not performed due to the small number of cases. In patients with SVR, the median time between initiation of therapy and clearance of HCV was 8 weeks (range, 3–16 weeks). Surprisingly, both patients with IL-28B CT+TG alleles achieved SVR despite genotype 1b and high viral load, although we could not compare the SVR rate among different genotypes since only one patient was infected with genotype 2a in this study.

Histological Findings of AHC in HIV-1 Co-infected Patients

HBs antigen was negative and ALT was within the normal range in the year preceding AHC in all 6 patients, whereas HBs Ab and/or HBc Ab was positive in 5 patients. No pre-existing factors of liver fibrosis other than HIV infection were evident before AHC. Liver biopsy was performed in 6 patients before treatment with PEG-IFN plus RBV. The median interval between diagnosis of AHC and biopsy was 4.3 months (range, 3.3–6.1 months). Fibrotic changes were confirmed in 3 cases by hematoxylin-eosin staining and silver impregnation staining (**Fig. 2**, **Table 3**). These lesions were paler-staining by Victoria Blue stain, indicating that the fibrotic areas did not reflect chronic changes.

Discussion

In the present study, we identified 35 cases of AHC during the study period and nearly all such patients (34/35) were MSM, and

the most frequent HCV genotype was 1b (19/27). These findings are consistent with previous reports from other countries [11–13]. In this regard, a high incidence of HCV seroconversion in HIV-1 infected MSM was reported recently by two separate groups [11–13]. The same studies also reported that genotype 1b was the major genotype among their patients [11–13], and that HCV infection was frequently not detected during the acute phase and diagnosed only at the chronic stage mainly due to the lack of symptoms.

Similar to the previous reports on AHC, 75% of our cases were asymptomatic, and only 6.3% of the study population showed mild elevation of serum ALT (100 IU/L < ALT <150 IU/L). In this regard, ALT elevation during acute HCV infection is often relatively transient, and therefore could be easily missed during routine clinical care. The need of regular screening for anti-HCV antibody in HIV-1 infected MSM is controversial, and the recommendations are different in guidelines from different developed countries [29,30]. Our results emphasize the importance of regular ALT monitoring and HCV re-screening at the time of mild ALT elevation during follow-up, especially in high-risk populations such as sexually active MSM.

There are few reports on the relationship between IL-28B CC+TT genotype and spontaneous clearance of HCV [21,31]. In the present study, spontaneous HCV clearance was seen in 4 out of 26 patients with IL-28B CC+TT genotype, whereas no spontaneous HCV clearance was seen in all 6 patients with IL-28B CT+TG genotype. Although this difference could not be confirmed to be statistically significant due to the small number of patients (4 patients), this is, to our knowledge, the first report on the relation between IL-28B and spontaneous HCV clearance during AHC in HIV-1 co-infected patients in Asian population. Our study also showed that the severity of clinical symptoms was an important factor related to spontaneous HCV clearance. Further investigation is needed for a better understanding of the pathogenesis of AHC, especially factors involved in spontaneous clearance.

The use of PEG-IFN plus RBV treatment for AHC within 6 months of diagnosis is now recommended for HIV-1 co-infected cases [17–19] although data on the response of HIV-1 infected individuals with AHC to the PEG-IFN plus RBV remain limited. One study reported spontaneous clearance of HCV between 6 and 12 months of diagnosis [32]. In this regard, it is sometimes difficult in the clinical setting to start PEG-IFN plus RBV treatment within 6 months of diagnosis because some patients have comorbidities and complications other than HIV and HCV. In our analysis, 9 of 11 patients (81.8%), including 2 patients whose treatment was initiated between 6 and 12 months of diagnosis, achieved SVR despite high rate of genotype 1b infection (SVR 90.0% among those with genotype 1b virus). Furthermore, HCV genotype 1b-infected patients carrying the IL-28B CT+TG genotype (n = 2), which is a predictor of poor response to the treatment of chronic HCV infection, achieved SVR. These results emphasize the advantage of the PEG-IFN plus RBV treatment for AHC.

Little is known about the progression of AHC to liver fibrosis in patients with HIV/HCV co-infection [33], although rapid progression of liver fibrosis during the chronic phase is well recognized [3]. Fierer et al. [34] reported that the development of fibrosis occurs even in the acute phase of HCV infection in HIV-Infected men. In the present study with limited cross-sectional analysis of liver biopsies after AHC, fibrosis was detected in 3 out of 6 cases, which is consistent with the above report of Fierer et al. [34]. Moreover, SVR was not achieved in 2 out of 3 patients who showed liver fibrosis, whereas the other 3 patients without fibrosis achieved SVR (**Table 3**). These results emphasize the clinical importance of early diagnosis and early treatment for AHC in HIV-1 infected individuals.

In conclusion, the potential of AHC should always be considered in HIV-1 infected MSM, even in asymptomatic case, who present with mild ALT elevation. Favorable response can be expected if anti-HCV treatment is initiated during the early phase. Further investigation is needed to determine the predictor(s) of spontaneous HCV clearance, appropriate timing of treatment initiation, and duration of treatment.

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Author Contributions

Conceived and designed the experiments: MI KW TK YK SO HG. Performed the experiments: MI KW TK YN MY TI NM. Analyzed the data: MI KW TK HG. Contributed reagents/materials/analysis tools: MI KW TK YN MY TI NM YK SO HG. Contributed to the writing of the manuscript: MI KW KT HG.

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特集II 高齢者肝胆膵疾患の現状と対策

高齢者肝癌症例の特徴と予後についての検討*

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市川辰樹**
中尾一彦**

Key Words：hepatocellular carcinoma, elderly patients

はじめに

日本において肝癌症例の70～80％がB型肝炎ウイルス(HBV)やC型肝炎ウイルス(HCV)のウイルス性肝炎を背景に有する．HCVは全体の60～70％を占めていたが，インターフェロン治療による介入やC型慢性肝疾患症例の高齢化に伴いHCVを背景にした肝癌症例の比率が減少している[1]．それに対し，近年，HBVやHCVを背景としない非ウイルス性の肝癌(非B非C肝癌)症例が増加傾向を示している．九州地区においても非B非C肝癌は，1996年に7.1％であったのに対し，2008年は20.7％と約3倍へと増加している[2]．

非B非C肝癌症例の特徴の一つに，高齢者に多いとの報告がされている[3]．非B非C肝癌は，肥満や糖尿病との関連が報告されており，欧米において糖尿病を有する症例では，有しない症例と比較し，約3倍以上肝癌を発症する危険が高いと報告されている[4]．厚生労働省の報告では，「糖尿病が強く疑われる人」および「糖尿病の可能性を否定できない人」の割合は，60～69歳で35.5％，70歳以上で37.6％と高齢者3分の1以上を占めている．今後も糖尿病を有する高齢な非B非C肝癌症例が増加することが予測される．

ウイルス性肝炎の治療，非B非C肝癌症例の増加，高齢者の高い糖尿病有病率と肝癌の背景が大きく変化するに伴い，高齢者肝癌の様相・治療にも変化が散見されるも，高齢者肝癌の背景についての検討は少ない．本稿では，肝癌症例における高齢者肝癌の特徴について，2002年から2010年までの期間，新規肝癌と診断され長崎肝疾患研究会に登録された症例を対象に検討した結果を述べる．

高齢者肝癌の頻度と推移

はじめに高齢者の定義を日本老年医学会の定義を基に，64歳以下を「現役世代」，65歳から74歳までを「前期高齢者」，75歳から84歳までを「後期高齢者」，85歳以上を「超高齢者」と区分した．全体では，現役世代が30％，前期高齢者が37％，後期高齢者が30％，超高齢者が3％と肝癌の症例において70％が高齢者であった(図1)．

年次推移については，2002年から2003年の期間，現役世代が38％，前期高齢者が44％，後期高齢者が17％，超高齢者が1％であったのに対し，2010年から2011年の期間では，現役世代が25％，前期高齢者が30％，後期高齢者が40％，超高齢者が5％と肝癌症例の急速な高齢化がみられた(図2)．

高齢者肝癌の特徴

長崎肝疾患研究会で集積した，2,370例の初発肝癌症例で，65歳以上の特徴について，ロジス

* Clinical characteristics of hepatocellular carcinoma in elderly patients : a retrospective, multicenter study.

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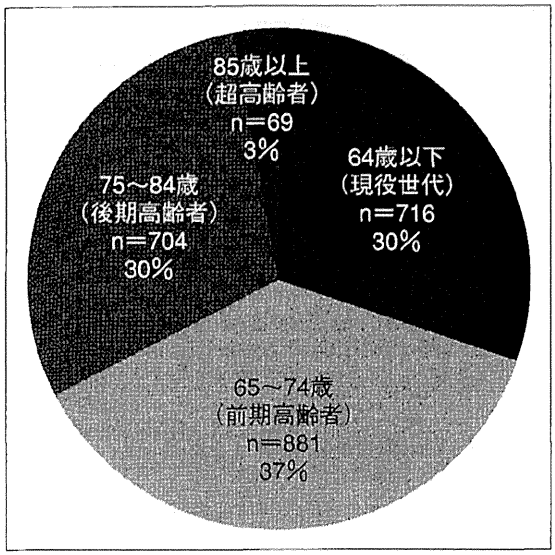

図1　肝癌症例における高齢者の頻度

ティック回帰分析によって検討した．単変量において有意であった因子を用い多変量解析を行った結果，女性($P<0.001$ HR=2.20)，BMI≧25($P=0.035$ HR=0.35)，飲酒歴(常習飲酒：$P=0.002$ HR=0.64，多量飲酒：$P<0.001$ HR=0.36)，Child-Pugh grade(B：$P=0.016$ HR=0.68，C：$P<0.001$ HR=0.32)，成因(HCV：$P<0.001$ HR=9.12，HBV+HCV：$P=0.005$ HR=4.32，NBNC：$P<0.001$ HR=11.28)，ALT(>46 IU/l：$P<0.001$ HR=0.53)が，高齢者肝癌症例の特徴として有意な因子であった(表1)．

ロジスティック回帰分析で有意であった因子を各世代間で検討した．性別は，現役世代の80%を男性が占めていたのに対し，前期高齢者，後期高齢者，超高齢者では，それぞれ64%，61%，58%と高齢になると女性の比率が増加し，BMIは，現役世代と前期高齢者が23 kg/m²であったのに対し，後期高齢者では22 kg/m²，超高齢者では21 kg/m²と，高齢化に伴い低下，飲酒歴がない症例が現役世代では60%であったのに対し，前期高齢者，後期高齢者，超高齢者では，それぞれ69%，79%，74%と高齢者に多くみられた．また，成因については，B型関連肝癌症例やC型関連肝癌などのウイルス性慢性肝疾患を背景に持たない非B非C肝癌症例が現役世代で17%であったのに対し，前期高齢者，後期高齢者，超高齢者では，それぞれ25%，30%，43%と高齢者に多くみられ，ALT値は，現役世代50 IU/l，前期高齢者43 IU/l，後期高齢者39 IU/l，超高齢者28 IU/lと高齢者ではALTの上昇がみられず，Child-pugh grade Aは，現役世代60%，前期高齢者75%，後期高齢者74%，超高齢者80%と肝予備能が良好な症例は高齢者に多くみられた(表2)．

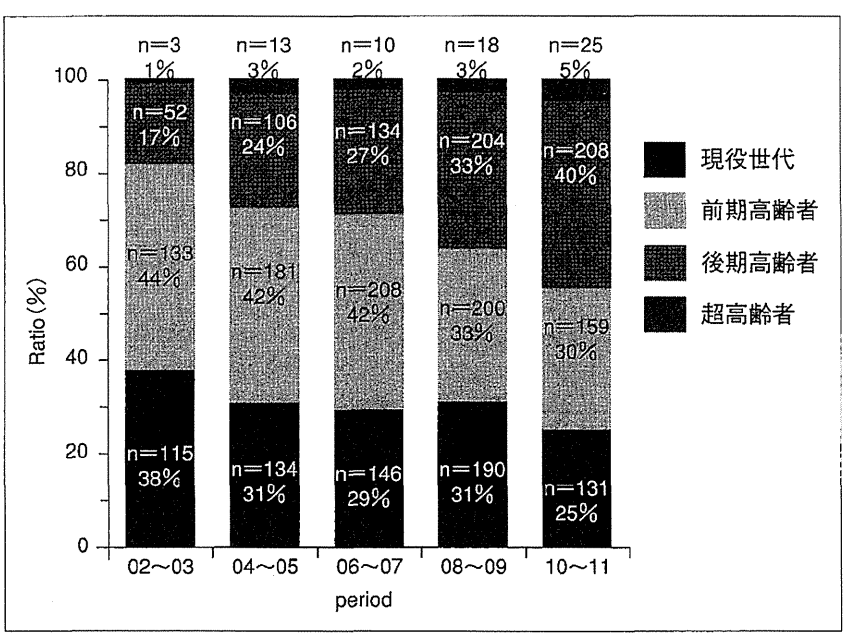

図2　肝癌症例における年齢層の推移

表1　多変量解析による65歳以上の発癌についての検討

Variable		*P*	HR(95%CI)
性別	女性	<0.001	2.20(1.65～2.93)
BMI	≧25	0.035	0.35(0.59～0.98)
飲酒歴	常習未満	—	—
	常習	0.002	0.64(0.48～0.85)
	多量飲酒	<0.001	0.36(0.23～0.55)
背景肝	肝硬変	0.173	1.23(0.91～1.65)
Child-Pugh score	A	—	—
	B	0.016	0.68(0.50～0.93)
	C	<0.001	0.32(0.18～0.55)
成因	HBV	—	—
	HCV	<0.001	9.12(6.69～12.39)
	HBV+HCV	0.005	4.32(1.55～12.06)
	NBNC	<0.001	11.28(7.73～16.47)
Plt(10^4/ml)	<12.0	0.100	0.79(0.60～1.05)
PT(%)	<83	0.401	0.89(0.67～1.17)
T-Bill(mg/dl)	>0.9	0.945	1.01(0.78～1.30)
ALT(IU/l)	>46	<0.001	0.53(0.42～0.68)
AFP(ng/ml)	<20	—	—
	20～199	0.103	0.79(0.60～1.05)
	≧200	<0.001	0.53(0.39～0.74)
PIVKA-II(mAU/ml)	<40	—	—
	40～199	0.943	1.01(0.74～1.38)
	≧200	0.070	1.34(0.98～1.83)
TNM stage	I	—	—
	II	0.001	1.65(1.21～2.24)
	III	0.087	1.37(0.96～1.95)
	IVa	0.153	0.91(0.91～2.57)
	IVb	0.351	0.73(0.38～1.41)

CI：confidence interval,　HR：hazard ratio

表2　各世代間の特徴

		現役世代	前期高齢者	後期高齢者	超高齢者	Total
Number		716	881	704	69	2,370
性別	男性	572	565	428	40	1,605
	女性	144	316	276	29	765
	男女比	4.0	1.8	1.6	1.4	2.1
BMI median		23.0	23.0	22.0	21.6	22.7
		(13.0～76.3)	(15.4～43.3)	(13.9～46.4)	(14.6～36.9)	(13.0～96.0)
飲酒量(%)	なし	431(60)	607(69)	559(79)	51(74)	1,648(70)
	常習	202(28)	191(22)	112(16)	17(25)	522(22)
	多量飲酒	83(12)	83(9)	33(5)	1(1)	200(8)
Child Pugh grade(%)	A	430(60)	611(75)	522(74)	55(80)	1,618(68)
	B	192(27)	201(23)	136(19)	13(19)	542(23)
	C	75(10)	36(4)	17(2)	1(1)	129(5)
	Unknown	19	33	29	0	81
成因(%)	HBV	298(42)	89(10)	35(5)	4(6)	426(18)
	HCV	287(40)	563(64)	452(64)	35(51)	1,337(56)
	HBV+HCV	10(1)	6(1)	7(1)	0(0)	23(1)
	NBNC	121(17)	223(25)	210(30)	30(43)	584(25)
ALT(IU/l)	median	50	43	39	28	43
	(range)	(8～781)	(6～1,802)	(4～19,679)	(9～295)	(4～19,679)

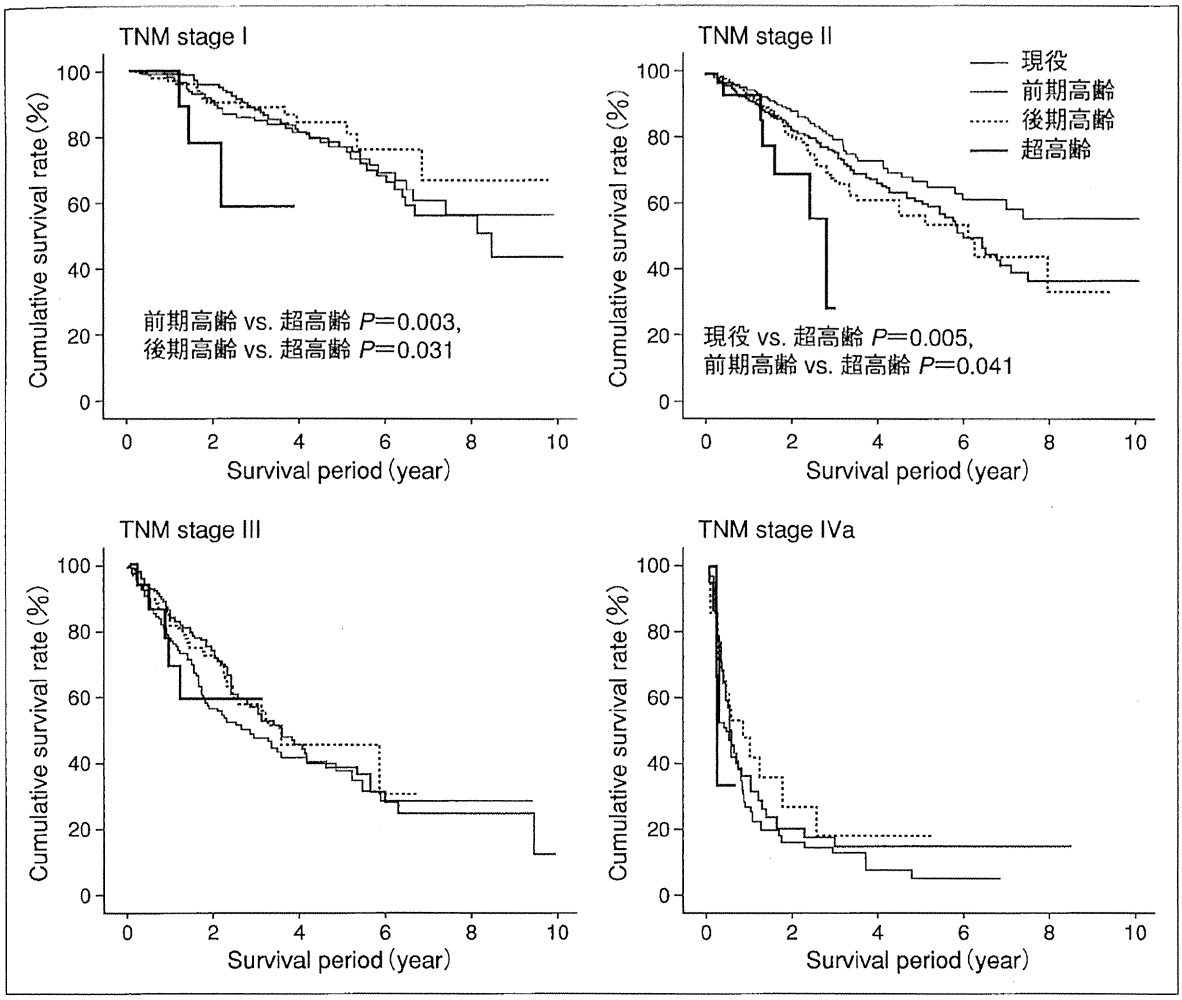

図3　世代別，TNM stage別，予後

これらを要約すると，高齢者肝癌症例の特徴は，女性に多く，飲酒量が少ない，BMIは比較的低値，肝炎ウイルスを基礎疾患に持たず，ALTの異常を示す症例が少なく，肝予備能は良好な症例である．

高齢者肝癌症例の治療と予後

各世代間の予後についてTNM stage別に検討を行ったところ，stage III, IVaでは，世代間に差異はみられなかったのに対し，stage Iでは，前期高齢者と後期高齢者，stage IIでは，現役世代と前期高齢者と比較し有意に超高齢者の予後が不良であった(図3)．さらに，stage別の肝癌初回治療についてみるとTNM stage I もしくはIIの症例において，超高齢者ではほかの世代と比較し有意に肝切除やラジオ波焼灼療法(RFA)を行う症例が少なかった(図4)．また，肝切除もしくは，RFAを行った症例のみで，世代間の予後について検討したところ，世代間に予後の差は認めなかった(図5)．

すなわち，現役世代から後期高齢者において肝癌診断後予後に差異はみられないが，超高齢者では，初回治療で肝切除やRFAを選択する症例が少なく予後が不良であった．

おわりに

高齢者肝癌症例は，今後増加していくことが予測される．高齢者は，糖尿病など他疾患を合併している頻度が多く，高度侵襲的治療が困難である症例をしばしば経験する．しかし，腹腔鏡治療の進歩，ラジオ波治療，定位放射線治療など低侵襲で根治性が高い治療が開発，実践さ

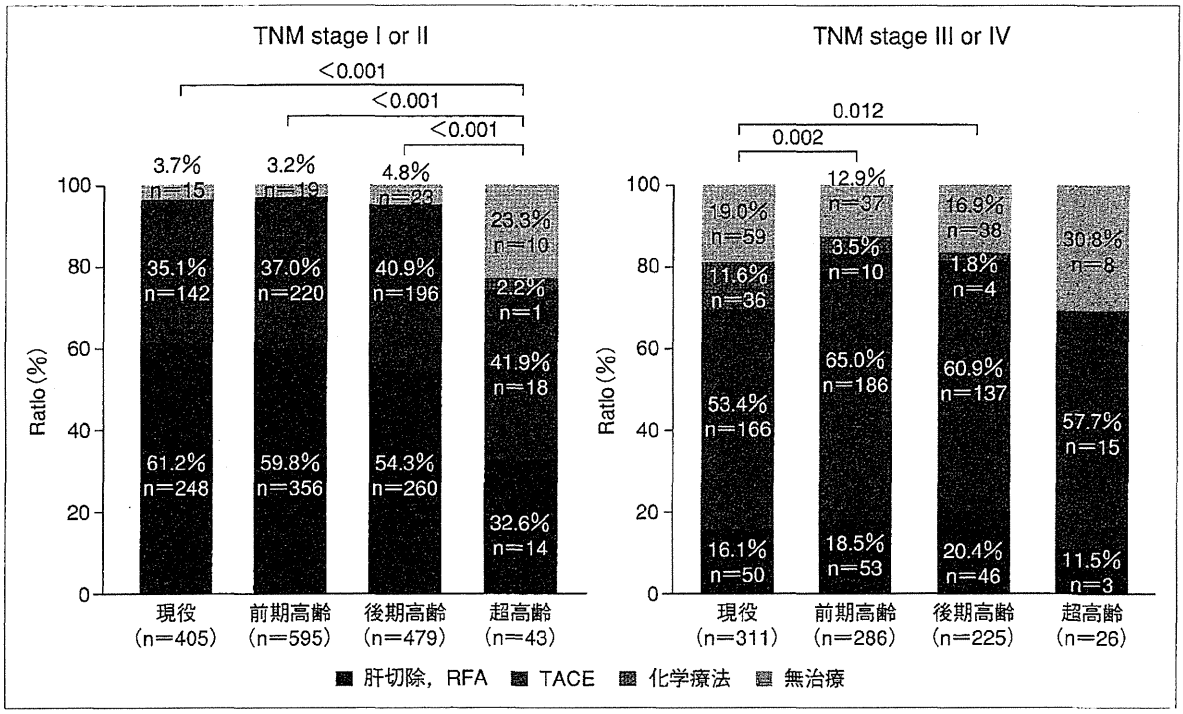

図4　世代別，TNM stage別，初回治療

れており，高齢者の症例に対しても根治度が高い治療を受ける機会が増えることにより，さらなる予後の改善を期待する．

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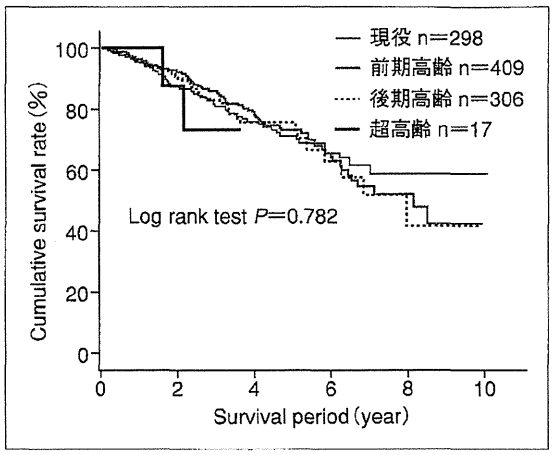

図5　肝切除・RFA症例における予後の検討

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特集II　B型肝炎の概念の変遷とその臨床的意義

住民検診によるT地区におけるHBs抗原消失についての検討*

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Key Words : HBsAg, hepatitis B

はじめに

HBs抗原は，B型肝炎ウイルス(HBV)に感染を示す最も有用な指標である．さらに，HBs抗原は，血中HBVの存在を示すだけでなく，肝細胞内のcccDNA量を反映していると考えられている．

エンテカビルなどの核酸アナログ製剤の登場により，耐性ウイルスの問題が残るものの，血中のHBV DNA量のコントロールが核酸アナログ製剤登場以前と比べると容易となった．しかし，核酸アナログ製剤の中止は，HBVの再燃を誘発するため原則継続的に内服する必要がある．そのため，厚生労働省の研究班では，HBs抗原量とHBcrAgを指標とし，核酸アナログ製剤の中止基準を定めることが検討されるも，核酸アナログ製剤では，HBs抗原量の低下は緩やかである[1]．また，HBs抗原量は，ペグインターフェロン治療における治療効果予測因子として有用であると報告されている[2)3)]．また，B型慢性肝疾患における肝発癌についてHBV DNA量とともにHBs抗原量が発癌予測因子として報告されている[4]．このように，HBs抗原は，HBV感染を示す指標だけなく，HBVに対する治療，肝発癌の予測因子として広く使われている．

近年，HBV genotype Aに伴う急性肝炎，それに伴う慢性化が問題となっている[5]．そのため，ユニバーサルワクチンによるB型急性肝炎対策が，日本において導入が検討されているが，一般人口におけるHBs抗体陽性率についての報告は少ない．

本研究では，T地区における住民検診により知りえたHBs抗原およびHBs抗体陽性率，自然経過におけるHBs抗原の陰性化率，陰性化がもたらす影響について検討した結果を述べる．

対象・方法

対象は，1972年から2004年の32年間，T地区の住民検診の際にRPHA法によってHBs抗原，HBs抗体の測定が可能であった4,482例を対象とした．対象者の性別は，男性1,863例(42%)，女性2,619例(58%)，年齢の中央値は52歳(3～96)，HBs抗原陽性例は227例(5%)，HBs抗体陽性例は1,322例(30%)であった(表1)．これらの症例をHBs抗原陽性症例はHBs抗原群，HBs抗体陽性症例はHBs抗体群，両者陰性症例は陰性群と3群に分け検討を行った．

* Spontaneous loss of hepatitis B surface antigen in chronic carriers, based on a long-term follow-up study in Japan.

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表1　対象症例の背景

症例数	4,482	
年齢(rage)	52	(3～96)
性別(%)		
男性	1,863	(42)
女性	2,619	(58)
HBsAg(%)		
positive	227	(5)
negative	4,255	(95)
HBsAb(%)		
postive	1,322	(30)
negative	3,160	(70)

年代別HBs抗原，HBs抗体陽性率

生年別に，HBs抗原およびHBs抗体の陽性率を検討したところ，1902～1961年生まれは，HBs抗原陽性率が5～6%であったの対し，1962年以降，抗原陽性率は低下し，1982年以降は，0%であった．また，HBs抗体陽性率は，1892～1901年生まれの陽性率が51%をピークに，その後徐々に低下し，1962～1971年は13%，1972～1981年では5%，1982年以降は0%であった(図1)．

HBs抗原，HBs抗体陽性率における死因の検討

HBs抗原群，HBs抗体群，陰性群における死因について検討を行った．HBs抗原群，HBs抗体群，陰性群において死亡が確認できた症例は，それぞれ57例，408例，620例であった．これらの症例で死因が明らかであったのは，HBs抗原群31例，HBs抗体群234例，陰性群316例であり各群半数以上で死因が特定可能であった．HBs抗原群では，肝疾患による死亡が32%を占めたのに対し，HBs抗体群では5%，陰性群では4%と有意にHBs抗原において肝疾患による死亡率が高く，HBs抗原群と陰性群に差異はみられなかった(表2)．

HBs抗原陰性化率と陰性症例における予後の検討

HBs抗原群227例のうち，2年以上HBs抗原陽性を確認できた170例を対象とし，2年連続HBs抗原陰性を確認できた症例を陰性例と定義し，HBs抗原陰性化率について検討した．HBs抗原の累積陰性化率は10年で18%，20年で43%であった(図2)．

また，HBs抗原陽性症例のうち，HBs抗原陽性が持続した症例を持続陽性群，HBs抗原が陰性化した症例を陰性化群に分け累積生存率を検討したところ，持続陽性群の20年累積生存率が65%であったのに対し陰性化群では85%と有意に陰性化群の予後が良好であった(図3)．

さらに，持続陽性群と陰性化群の死因について検討したところ，持続陽性群における肝疾患による死亡率が35%(肝癌22%，肝不全13%)であったのに対し陰性化群では，17%と陰性化群

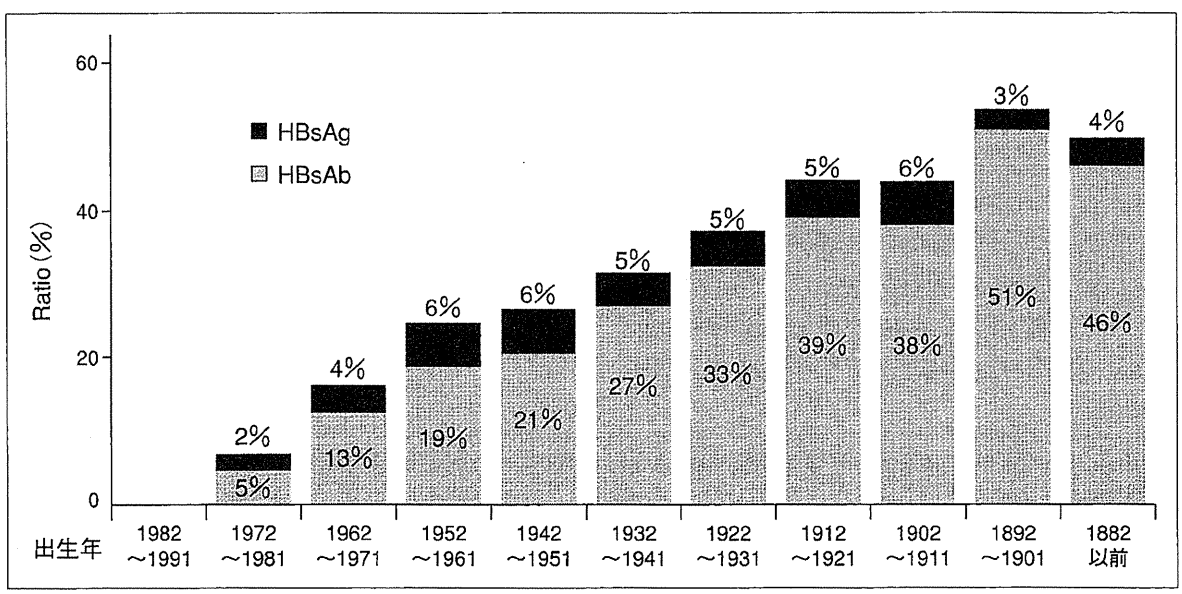

図1　出生年別HBs抗原，HBs抗体陽性率

表２　各群間の死因についての検討(n=581)

死因	HBsAg(%)	HBs Ab(%)	negative(%)
肝疾患	10(32)	11(5)	14(4)
消化管	5(16)	33(14)	32(10)
胆膵	0	13(6)	15(5)
血液	0	9(4)	21(7)
呼吸器	4(13)	36(15)	58(18)
循環器	2(7)	42(18)	66(21)
泌尿器	1(3)	11(5)	11(4)
脳神経	1(3)	33(14)	37(12)
原発不明悪性疾患	0	5(2)	11(4)
事故・自殺	5(16)	17(7)	24(8)
老衰	3(10)	16(7)	17(5)
その他	0	8(3)	10(3)
合計	31(100)	234(100)	316(100)

HBsAg vs. HBs Ab ＜0.05；HBsAg vs. negative ＜0.05

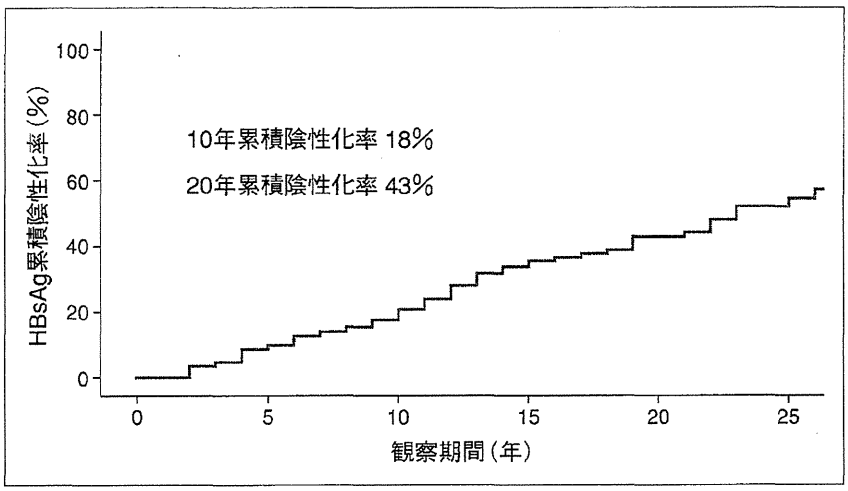

図２　HBs抗原累積陰性化率

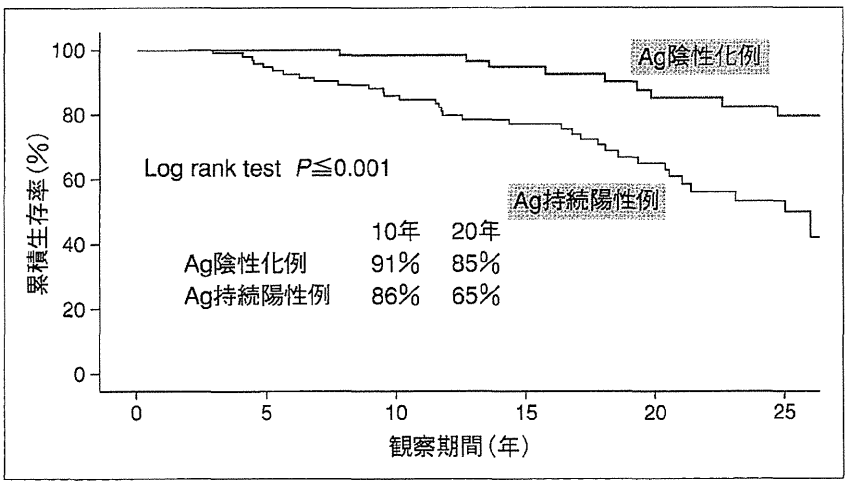

図３　HBs抗原陰性化例と持続陽性例における予後の検討

表3　各群間の死亡原因についての検討

死因	陰性化群(%)	持続陽性群(%)
肝疾患		
肝癌	1(17)	5(22)
肝不全	0	3(13)
他疾患	5(83)	15(65)
合計	6(100)	23(100)

死亡確認52例中，死因が判明した29例.

において肝疾患の死亡率が低かった(表3).

おわりに

HBs抗原は，年率1.8～2.0%の頻度で陰性化していた．さらに，HBs抗原が陰性化した症例は，陰性化しなかった症例に比べ予後が良好であり，自然経過においてB型慢性肝疾患のHBs抗原陰性化は予後を予測する因子の一つである可能性が示唆された.

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Review Article

Endoscopic management of esophagogastric varices in Japan

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Abstract: Esophagogastric varices are the most common complication in patients with portal hypertension, and endoscopy plays an important role in their diagnosis and in the prevention of acute bleeding from these structures. Recently, new modalities such as endoscopic ultrasonography (EUS) and narrow-band imaging have been introduced for the diagnosis of esophagogastric varices. In Japan, endoscopic therapy has become the first choice for the treatment of acutely bleeding esophageal or gastric varices. The two principal methods used to treat esophageal varices are endoscopic injection sclerotherapy (EIS) and endoscopic variceal ligation (EVL). Recently, combinations of EIS plus EVL and EVL plus argon plasma coagulation were reported to be more effective than EVL or EIS alone. Additionally, endoscopic cyanoacrylate injection is superior to EIS and EVL for the treatment of acutely bleeding gastric varices.

Keywords: Endoscopic management; esophagogastric varices; endoscopic injection sclerotherapy (EIS); endoscopic variceal ligation (EVL)

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Introduction

Portal hypertension is the primary complication of liver cirrhosis and is defined as a pathological increase in the portal venous pressure or an increase in the hepatic venous pressure gradient (HVPVG) above the normal range (1-5 mmHg).

Portal hypertension induces the development of port-systemic collateral vessels. Of these, esophagogastric varices are the most relevant because their rupture results in variceal hemorrhage, which is among the most common lethal complications of cirrhosis. In patients diagnosed with cirrhosis, esophagogastric variceal development occurs at an annual rate of 5-7% (1). Initial esophagogastric variceal bleeding occurs in approximately 12% of patients within 1 year (5% and 15% of small and large varices, respectively) (2,3). Moreover, patients with advanced liver disease and varices that feature red wale marks have a high risk of variceal hemorrhage (4). These complications are a major cause of death, with a 6-week mortality rate of 15-20%, and are the main indication for liver transplantation in patients with liver cirrhosis (5,6).

Variceal hemorrhage is managed as follows: primary prophylaxis to prevent an initial episode of variceal hemorrhage, treatment of acute bleeding episodes, and secondary prophylaxis to prevent recurrent hemorrhage.

Previously, surgery was the only treatment for esophagogastric varices. Interventional radiology (IVR) was introduced in the 1970s; endoscopic treatment was subsequently developed in the 1980s and led to improved survival rates. Currently, endoscopy plays an important role in the diagnosis and prevention of esophagogastric varices and the treatment of acute variceal bleeding.

In this review, we evaluate the current status of the endoscopic management of esophageal varices.

General rules for recording the endoscopic findings of esophagogastric varices in Japan (*Table 1*)

A precise system for the systemic evaluation and recording of esophagogastric varices is essential to the management of portal hypertension. In Japan, a general system is used to record the endoscopic findings of esophageal varices.

Table 1 General rules for recording the endoscopic findings of esophagogastric varices in Japan

Location (L)
Ls: locus superior
Lm: locus medialis
Li: locus inferior
Lg-c: adjacent to the cardiac orifice
Lg-cf: extension from the cardiac orifice to the fornix
Lg-f: isolated in the fornix
Lg-b: located in the gastric body
Lg-a: located in the gastric antrum
Form (F)
F0: no varicose appearance
F1: straight, small-caliber varices
F2: moderately enlarged, beady varices
F3: markedly enlarged, nodular or tumor-shaped varices
Color (C)
Cw: white varices
Cb: blue varices
Cw-Th: thrombosed white varices
Cb-Th: thrombosed blue varices
Red color signs (RC)
RWM: red wale markings
CRS: cherry red spots
HCS: hematocystic spots
Esophageal varices: RC0, RC1, RC2, RC3

This system was initially proposed by the Japanese Research Society for Portal Hypertension in 1980 and was revised in 1991 (7). In this system, esophageal and gastric varices are classified according to the color (white and blue), form (small and straight, F1; nodular, F2; and large or coiled, F3), and red color signs (RC 0-3). Gastric varices are divided into those that involve the cardia (Lg-c), the fundus (Lg-f), or both the cardia and fundus (Lg-cf). Bleeding is classified as gushing, spurting, or oozing. As a result of recent progress in this field, these rules were revised to include the newly recognized findings of portal hypertensive gastropathy (PHG) and a new classification for endoscopic ultrasonographic findings (8).

Utility of endoscopic ultrasonography (EUS) for esophagogastric varices

In principal, endoscopic diagnoses are based on endoscopic findings that have been assessed with the naked eye. However, it is impossible to assess deep collateral vessels in this manner. EUS was introduced to visualize the collateral channels that surround the distal esophagus and upper stomach. On EUS images, esophageal varices appear as an echo-free or hyperechoic lumen in the esophageal submucosa. The technique of EUS is noninvasive and can show high resolution images of the collaterals in close proximity to the gut lumen. Various institutions have reported the utility of EUS for evaluating esophagogastric varix hemodynamics and predicting variceal bleeding (9-11). Irisawa *et al.* demonstrated that EUS-detected, severe-type peri-esophageal collateral vessels could be significant predictors of esophageal varix recurrence (9). EUS can visualize and evaluate collateral veins around the esophagus with portal hypertension. EUS allows visualization of the left gastric vein. The diameter of the left gastric vein is associated with variceal size (12). Moreover, Iwase *et al.* showed that color Doppler EUS could also detect left gastric vein and rapid hepatofugal velocity, which might indicate the risk of esophageal varix recurrence (13).

Endoscopic therapy is difficult to perform on acutely bleeding gastric varices; however, an EUS-guided cyanoacrylate adhesive treatment for gastric variceal bleeding was recently reported (14,15).

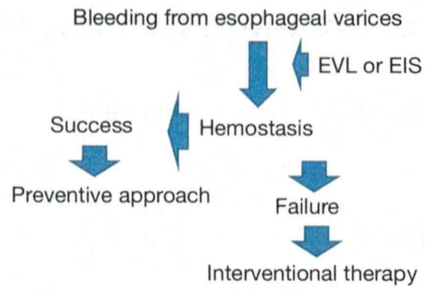

Figure 1 Endoscopic treatment of acute esophageal varices. EVL, endoscopic variceal ligation; EIS, endoscopic injection sclerotherapy.

Endoscopic management of esophageal varices (*Figure 1*)

Endoscopic techniques are considered optimal treatments for acutely bleeding varices and are also well suited for long-term management to prevent recurrences. Therefore, endoscopic therapy is considered a first-line treatment for bleeding esophageal varices and is also used to prevent initial variceal hemorrhage and to provide secondary

prophylaxis.

In Japan, F2 (nodular, moderately enlarged) and F3 (markedly enlarged) esophageal varices with RC sighs is high risk sign of bleeding. Therefore, this high risk group is performed prophylactic endoscopic treatment.

Endoscopic injection sclerotherapy (EIS) and endoscopic variceal ligation (EVL) are the two primary endoscopic methods used to prevent the initial episodes of variceal hemorrhage or to treat acutely bleeding esophageal varices.

Endoscopic injection sclerotherapy (EIS)

For many years, EIS has been used to treat esophageal varices. Flexible endoscopic sclerotherapy was introduced in the 1980s, and has been widely used since then, resulting in an improved survival rate for these patients.

This technique was introduced in Japan in 1980s and was reported to be an efficacious therapy.

Some sclerosants such as sodium nitrate, podicocanol, ethanolamine, alcohol, and sodium tetradecyl sulfate have been widely used for EIS (16,17). In Japan, ethanolamine oleate (EO) is the most commonly used sclerosant. Injection of EO causes an acute, dose-related inflammatory reaction of the intimal endothelium of the vein. This leads to scarring and possible occlusion of the vein. However, EO is hemolytic, and the resultant free hemoglobin can cause renal failure, Therefore, haptogloblin are used as preventive (18). In other countries, its complications and lack of experience with EO has made its use infrequent.

EIS comprises an injection into the variceal lumen or area adjacent to the varix to induce vessel thrombosis. With repeated sessions, the vascular wall inflammation promotes fibrosis and subsequent variceal obliteration. There are some technical variations associated with EIS, including the device used and the type and concentration of the sclerosant (19). Some endoscopists perform this technique in a free-hand manner, whereas others incorporate a balloon placed on the end of the endoscope to compress the varices following the injections.

The sclerosant can be injected either intravariceally or paravariceally. Paravariceal injections, when administered immediately adjacent and slightly distal to the bleeding site, form a protective fibrotic layer around the varices. In contrast, intravariceal injections directly induce variceal thrombosis.

EIS is inexpensive, easily performed, and effective. However, there are several complications associated with this technique. Minor complications such as a low-grade fever, chest pain, and dysphagia can occur within the first 24-48-hrs after the procedure and do not require treatment (20,21).

Local complications such as esophageal ulcers, ulcer-related bleeding, and esophageal strictures are also associated with EIS. Most of these complications are induced by incorrect injections or high sclerosant concentrations (20) and usually heal with omeprazole treatment. Esophageal stenosis occurs in 2-10% of cases.

Sclerotherapy-related mortalities have been reported in 2% of treated patients; these often result from major complications such as recurrent bleeding, perforation, sepsis, and respiratory disease (22).

Endoscopic variceal ligation (EVL)

In 1989, Stiegmannand and Golf reported the use of EVL for the treatment of esophageal varices (23). EIS chemically occludes the variceal walls, whereas EVL obliterates varices via mechanical strictures induced by rubber bands.

First, the endoscope is introduced along with a flexible sheath for EVL. Next, the endoscope is removed to allow the attachment of an EVL device. As each varix is drawn into the cap of the endoscope tip, air is injected into the tube to stricture the varix. During the first EVL session, the varices are ligated on the oral side of the gastroesophageal junction. Varix eradication usually requires 2 or 3 sessions.

For actively bleeding esophageal varices, the rubber band should be introduced at the bleeding point. If the bleeding point cannot be identified, varices should be ligated at the oral side of the gastroesophageal junction.

Varix eradication is achieved in approximately 90% of patients, although recurrence is not rare (24). However, recurrence after EVL does not carry a high risk of recurrent bleeding.

Recurrent varices can usually be treated with repeated ligation. Yoshida *et al.* reported a lower recurrence rate when EVL was performed once every 2 months versus every 2 weeks (25).

Both EIS and EVL are reportedly effective for acute variceal bleeding; however, EVL is the first-choice therapy because of its safety and ease of use. The complications associated with EVL include esophageal laceration or perforation, transient dysphagia, chest pain, esophageal stricture, and ulcer-related bleeding (26). The reported incidence of bacteremia and infection was higher after EIS than after EVL. Some meta-analyses have shown that EVL was well suited for the treatment of acute bleeding and was

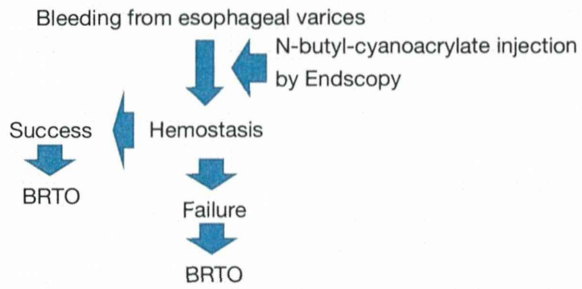

Figure 2 Endoscopic treatment of acute gastric varices.

associated with fewer adverse events and improved mortality when compared with EIS (27).

Currently, EVL is considered the gold standard for variceal eradication. However, EVL is plagued by a high recurrence rate after variceal eradication because it does not obliterate the deeper varices and perforating veins (28,29), whereas the chemical effect of EIS reaches deeper varices and perforating veins. Therefore, the combinations of EIS plus EVL are reportedly more effective than EVL alone (30). Likewise, EVL plus argon plasma laser induce fibrosis of the esophageal mucosa; result in suppression of variceal recurrence (31). A meta-analysis revealed that, compared with drug therapy alone, a combination of endoscopy and drug therapy further reduced the incidence of overall and variceal bleeding (32). Therefore, combined therapy is required to reduce the recurrence rate.

Endoscopic management of acutely bleeding gastric varices (*Figure 2*)

Unlike esophageal varices, EIS and EVL do not efficiently treat gastric varices. Regarding EIS, the higher volume of blood flow in gastric varices leads to the rapid flushing of the sclerosant from the blood stream. EIS for gastric varices requires larger volumes of sclerosants than those required for esophageal varices and consequently induces more side effects (33).

High recurrent bleeding rates (up to 90%) have been reported with EIS for gastric varices (33,34). Although EVL is generally safe, its ability to control gastric variceal bleeding is limited (35-37). Some case series initially demonstrated the safety and efficacy of EVL for the treatment of acute gastric variceal bleeding. The reported 3-year re-bleeding rate associated with EVL for gastric variceal bleeding was 72% (37).

Obstruction resulting from the injection of a tissue adhesive such as N-butyl-cyanoacrylate (Histoacryl®) was found to be more effective than sclerotherapy for the treatment of acute gastric variceal bleeding (38,39). The re-bleeding rate associated with gastric variceal obstruction ranges from 22-37% (38,40-43). Prospective and randomized controlled studies designed to evaluate the optimal management of bleeding from gastric varices (44) demonstrated that gastric variceal obstruction resulted in improved clinical benefit compared to EIS and EVL.

Kumar *et al.* reported that undiluted Histoacryl was effective in achieving initial hemostasis in case of actively bleeding gastric varices and not associated with embolic complications (45). However, in many Japanese institutions, Histoacryl is diluted with lipiodol, a radiopaque contrast agent to (1) prevention of polymerization of Histoacryl so that it may be injected easily into varices and (2) to enable radiographic visualization of obliterated varices (46).

Some of the common complications associated with gastric variceal obstruction include pyrexia and abdominal pain/discomfort; severe complications include systemic thromboembolic phenomena such as cerebral, pulmonary, portal vein, and splenic infarction (47-49).

Taken together, gastric variceal obstruction is recommended as the treatment of choice for acute gastric variceal bleeding because of its high efficacy as a treatment for acute bleeding and its association with a lower re-bleeding rate relative to EIS and EVL.

Acknowledgements

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