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Analysis of 69 Hepatocellular Carcinoma Cases from the National Center for Pathology in Mongolia : A Comprehensive Study of Samples Collected Nationwide

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Abstract : The high rate of chronic hepatitis, including hepatitis B, C and D, in Mongolia creates a large health burden of advanced liver disease. This includes liver failure and the highest incidence rate of hepatocellular carcinoma (HCC) worldwide. In the present study, we histopathologically examined 69 recent cases of HCC from the Mongolian National Center for Pathology, which collects specimens from across the country. The background liver histology of HCC exhibited a bimodal distribution, with one peak corresponding to advanced liver fibrosis and another to mild liver fibrosis. The fibrosis severity negatively correlated with age. Additionally, the frequency of poorly differentiated tumors was significantly higher in the HCC with early stage of fibrosis. A comparison of the pathological characteristics of HCC in urban and rural areas showed that poorly differentiated tumors were highly prevalent in urban areas. The characteristics of HCC in Mongolia are different from those in other countries, suggesting that the causes of liver disease are not only related to viruses but also other factors that depend on the region. This study will provide insight into what research is needed next for liver cancer control in Mongolia. J. Med. Invest. 72 : 47-53, February, 2025

Keywords **:** *hepatocellular carcinoma, chronic hepatitis, surgical dissection, urban, rural*

INTRODUCTION

Liver disease poses a critical public health challenge in Mongolia, with liver cancer and cirrhosis rates among the highest in the world (1, 2). In 2022, the age-standardized rate (ASR) of liver cancer in Mongolia was reported at 37.7 per 100,000 population, which is significantly higher than the global average of 8.6 per 100,000 (3). Viral hepatitis including hepatitis B virus (HBV) and hepatitis C virus (HCV) have been known to elevate the risk of cirrhosis and hepatocellular carcinoma (HCC) (4), and are considered a major risk factor for the liver cancer in Mongolia. In Mongolia, the prevalence of hepatitis B virus (HBV) remained high, with a hepatitis B surface antigen (HBsAg) positivity rate of 10.6% among the general population aged 10-64 years (5). The prevalence of hepatitis C virus (HCV) infection is also significant, with the reported rate being as high as 9.9% in the same age group (5). Moreover, hepatitis D virus (HDV) is highly endemic in Mongolia, with coinfection rates of 60% among HBsAg-positive cases (6). The HBV vaccine has successfully reduced infection rates worldwide, particularly in high-risk regions like Asia and Africa, whereas challenges persist in ensuring the widespread vaccination coverage in rural parts of Mongolia remains a big challenge (7). Moreover, extraordinarily high HDV co-infection rate complicates efforts of controlling liver disease in Mongolia, as HDV accelerates the progression of liver damage in HBV-infected individuals (8, 9).

In addition to viral hepatitis, the rapid urbanization of Mongolia has led to lifestyle changes that are driving an increase in metabolic syndrome-related liver diseases, such as metabolic dysfunction associated steatotic liver disease (MASLD) and metabolic dysfunction associated steatohepatitis (MASH)(10). A diet rich in animal fats but low in fruits and vegetables and excessive alcohol consumption are considered as causes of MASLD/MASH particularly in rural areas (10). These trends, along with the prevalence of viral hepatitis, are contributing to a growing liver disease burden in both urban and rural areas. Efforts by the Mongolian government, including national initiatives such as the “Healthy Liver” campaign, have focused on improving public awareness, expanding vaccination programs and increasing access to antiviral treatments (11). However, significant disparities exist between urban and rural regions, particularly in terms of healthcare infrastructure, public awareness, and access to medical services (12). These gaps hinder comprehensive liver disease control and prevention efforts.

The aim of this study is to clarify the current pathological situation of HCC in Mongolia, and to compare the pathological differences between urban and rural areas for addressing

Received for publication October 10, 2024 ; accepted October 15, 2024.

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regional disparities of medicine. Given the high prevalence of HDV infection in Mongolia, the present study, which focuses on HCC in Mongolia, is also able to elucidate the impact of HDV on HCC pathology and the behavior of HDV in HCC tissue.

MATERIALS AND METHODS

Selection of Cases

All the cases were surgical resections for the treatment of liver cancer at several institutions in Mongolia from January 1, 2019 to December 1, 2023. All of the samples were sent to the National Center for Pathology and prepared as formalin-fixed paraffin-embedded (FFPE) specimens. As a first step, 76 specimens were selected from over 100 specimens by the Mongolian pathologists based on the storage conditions of the FFPE specimens and the quality of the tissue sections, which were not damaged and were suitable for histological observation. Seven cases were excluded due to insufficient tissue volume or severe artifacts after re-evaluation by Japanese liver pathologist (K.T.). A total of 69 cases of HCC were analyzed (age : 63 [IQR 57, 69] ; sex : male 39, female 30). Only 3 cases were examined for viral infection, all of which had a co-infection of HBV/HDV, while clinical data including viral infection status, liver function and blood biochemistry were missing for most cases. This study was approved by ethics committees of the Mongolian National University of Medical Sciences (Mongolia), the Mongolia–Japan Hospital of MNUMS (Mongolia), and the National Center for Pathology (Mongolia, Permission number : 24/066). All research was conducted in accordance with the declaration of Helsinki.

Histopathological Analysis

Histopathological evaluation was performed on hematoxylin and eosin (HE)-stained slides, selected from both cancerous and non-cancerous liver tissue (background liver). A consensus evaluation of liver pathology was performed by 3 expert liver pathologists (J.O., S.W., and K.T.). For the assessment of background liver histology, activity of inflammation was graded on a 4-point scale (A0 : no activity, A1 : mild activity, A2 : moderate activity and A3 : severe activity), and fibrosis stage was assessed on a 5-point scale (F0 : no fibrosis, F1 : portal fibrosis without septa, F2 : portal fibrosis with few septa, F3 : numerous septa without cirrhosis and F4 : cirrhosis) based on METAVIR score (13). The tumor differentiation was classified into 3 grades (poorly-, moderately-, and well-differentiated). Histological characteristics of HCC were also evaluated by focusing on the clear cells, fat deposition, significant fibrosis, and vascular invasion in the tumor. Each of these features was scored on a binary scale (presence or absence). The degree of lymphocytic infiltration within and around the tumor (intratumoral and peritumoral) was classified as either prominent or not.

Investigating Regional Disparities in Mongolia

The National Center for Pathology receives specimens from core hospitals, including the First Central Hospital, as well as from regional core, countryside and private hospitals. The First Central Hospital, located in Ulaanbaatar, recognized as one of the country's top medical facilities, serves as a tertiary medical center and frequently admits patients from rural and remote areas who require specialized treatment not available at local or regional clinics. It is estimated that approximately most of HCC patients reside in rural areas in Mongolia. Conversely, other core hospitals and private facilities are located in Ulaanbaatar. In order to investigate the features of HCC related to regional disparities, The First Central Hospital and several regional hospitals in provincial centers were categorized as rural, as these serve the broader rural population of Mongolia. The Second and Third Central Hospitals, also located in Ulaanbaatar, as well as private medical facilities, were classified as urban.

Statistical Analysis

All data are expressed as median (interquartile range), or frequency (percentages) as applicable. The statistical significance of differences in continuous variables between two groups was determined using Mann-Whitney U test. For categorical variables, the statistical significance of differences was determined using chi-square test and Fisher's exact tests. Correlation was determined using Spearman's correlation coefficient. A p-value of less than 0.05 was considered statistically significant. All tests were conducted using IBM SPSS 29.0 (IBM, Armonk, NY).

RESULTS

General background liver pathology of the HCC cases

The clinical and pathological characteristics of the analyzed HCC cases are summarized in Table 1. Serological data on viral infection status were incomplete, although serological evidence confirmed HBV/HDV co-infection in 3 cases. Steatosis was seen in 14 out of the 69 cases (Table 1), but none of the cases showed signs of steatohepatitis, such as ballooning degeneration or marked perivenular-pericellular fibrosis. There were no cases indicative of primary biliary cholangitis, which included biliary damage. The observation that plasma cells and eosinophils were not prominent in any of the liver specimens could have ruled out to diagnose autoimmune hepatitis or drug-induced liver damage, although the lack of clinical data cannot be neglected. Based on the pathological findings and previous epidemiological reports, it was supposed that the most HCC cases were primarily associated with viral hepatitis at the National Center for Pathology in Mongolia.

Pathological characteristics of background liver tissue of HCC

Most cases exhibited active hepatitis at the time of HCC surgery, with 36 out of 69 cases showing interface hepatitis graded A2 or higher (Table 1). Fourteen out of 69 cases showed liver cirrhosis at the time of surgical resection of HCC. In contrast, 26 out of 69 cases showed HCC with mild fibrosis (F1 or less), suggesting that carcinogenesis is not entirely dependent on the severity of fibrosis (Table 1 and Fig. 1A). The fibrosis stage was negatively correlated with the age of patients ($r=-0.250$, $P=0.041$, Fig. 1B). Since it is well known that aging is a major aggravating factor for the progression of liver fibrosis in chronic liver disease, the absence of a positive correlation between the severity of fibrosis and age suggests that Mongolia may have different causes and treatment interventions for liver disease compared to Japan.

Histological images of the three HDV-positive cases are shown in Figure 2. These cases exhibited severe fibrosis with marked lymphocytic infiltration in the portal area and fibrous septa, accompanied by interface hepatitis. No significant bile duct involvement was observed. Necroinflammatory changes in the liver parenchyma ranged from mild to moderate, and two cases showed marked cholestasis with cellular atypia. Morphologically, no cytoplasmic inclusions with the characteristic ground-glass appearance of HBV infection were observed on HE staining. It is likely that HDV acts suppressively on the HBV replication process, reducing the amount of hepatocellular HBsAg, which appears as a typical ground-glass change.

Pathological Features of HCC in Mongolia

Most HCC cases were of the simple nodular type with fibrous

Table 1. Individual Histopathological features of HCC patients in Mongolia

Resident area	№	Age	Sex	Background			Tumor						
				Activity	Fibrosis	Remarks	Differentiation	Clear cells	Fat	Intratumor fibrosis	Vascular invasion	Intratumor lymhocytes	Peritumor lymphocytes
Rural	1	55	F	1	2	-	mod	-	-	-	-	-	-
	2	63	M	1	1	-	mod	-	-	+	+	+	+
	3	73	M	1	1	-	por	-	-	-	+	-	-
	4	76	M	2	2	steatosis	mod	-	-	-	-	-	-
	5	64	F	1	4	-	mod	-	-	+	+	+	+
	6	71	M	2	1	-	mod	-	-	-	+	-	-
	7	53	F	2	2	-	mod	-	-	+	+	+	+
	8	57	F	1	1	-	mod	+	-	-	+	-	-
	9	59	M	2	2	-	mod	+	-	-	+	-	-
	10	53	M	3	4	-	mod	-	+	-	+	-	-
	11	62	F	2	4	-	mod	-	-	-	-	+	+
	12	60	M	2	1	-	well	-	+	+	-	-	-
	13	56	F	1	1	-	mod	-	-	-	-	-	-
	14	54	F	2	4		Well	-	-	+	-	-	-
	15	74	F	1	1	-	mod	-	+	+	-	-	-
	16	50	M	2	4	steatosis	mod	-	+	-	-	-	-
	17	72	M	1	1	-	mod	-	-	-	+	-	-
	18	62	F	2	4	steatosis	mod	-	-	-	-	-	-
	19	54	F	1	1	steatosis	mod	-	-	-	-	-	-
	20	70	M	2	2	steatosis	ND	ND	ND	ND	ND	ND	ND
	21	62	M	1	2	-	mod	-	-	-	-	+	+
	22	52	F	2	2	-	mod	-	-	-	+	-	-
	23	62	M	2	4	-	mod	-	-	-	+	-	-
	24	71	F	0	2	-	mod	-	-	-	+	+	-
	25	53	M	2	4		mod	-	+	-	-	-	-
	26	63	M	2	2	-	mod	-	+	-	+	-	-
	27	62	M	1	1	steatosis	mod	-	-	-	-	-	-
	28	63	M	2	2	-	mod	+	-	-	-	-	-
	29	61	M	1	1	-	mod	-	+	-	+	-	-
	30	65	M	2	1	-	mod	+	-	-	+	+	+
	31	53	F	2	2	-	ND	ND	ND	ND	ND	ND	ND
	32	77	F	1	2	-	mod	-	-	-	+	+	+
	33	71	F	1	1	-	mod	-	-	+	+	+	-
	34	42	M	2	2	-	-	-	-	+	+	-	-
	35	65	M	2	4	-	mod	-	-	-	+	+	+
	36	68	M	2	2	-	mod	-	-	-	+	-	-
	37	65	M	0	2	-	poor	-	-	-	+	+	-
	38	57	M	1	2	-	mod	-	-	-	+	-	-
	39	59	F	1	1	-	mod	-	-	-	-	-	-
	40	57	M	2	4	-	mod	+	-	-	-	+	+
	41	61	F	2	2	-	mod	-	+	-	+	+	
	42	78	F	3	4	-	mod	-	-	-	+	-	-
	43	66	M	1	1	steatosis	mod	-	+	-	+	-	-
	44	67	F	2	2	steatosis	mod	-	-	-	-	-	-
	45	71	F	1	1	-	mod	+	+	-	+	-	-
	46	58	M	1	2	-	well	-	-	-	+	-	-
	47	66	M	2	3	-	-	-	-	-	-	-	-
	48	71	M	2	1	-	poor	-	-	-	-	-	-

Resident area	№	Age	Sex	Background			Tumor						
				Activity	Fibrosis	Remarks	Differentiation	Clear cells	Fat	Intratumor fibrosis	Vascular invasion	Intratumor lymhocytes	Peritumor lymphocytes
Rural	49	60	F	0	0	steatosis	mod	-	-	-	-	-	-
	50	67	F	2	2	steatosis	mod	-	-	-	-	-	-
	51	75	F	2	2	-	mod	-	-	-	-	-	-
	52	69	F	1	1	steatosis	mod	+	+	-	+	-	-
	53	44	M	2	2	-	mod	+	-	-	-	-	-
	54	58	M	1	1	-	mod	-	-	-	+	-	-
	55	54	M	1	2	-	mod	-	-	-	+	-	-
	56	63	F	2	4	steatosis	mod	-	-	-	+	-	-
Urban	57	76	F	1	1	-	poor	-	-	-	+	-	-
	58	78	M	1	1	-	poor	-	-	-	+	-	-
	59	65	F	3	2	-	poor	-	-	+	+	-	-
	60	70	M	1	2	-	mod	-	-	-	-	-	-
	61	62	M	1	1	-	poor	-	-	-	+	-	-
	62	54	M	2	4	-	mod	-	-	-	-	-	-
	63	66	F	2	4	-	mod	+	-	-	-	-	-
	64	63	F	1	0	mild steatosis	mod	-	-	-	+	-	-
	65	71	M	1	1	-	mod	-	-	+	-	-	-
	66	50	F	2	2	-	poor	+	+	-	+	-	-
	67	49	M	2	3	steatosis	well	-	-	-	+	-	-
	68	61	M	2	1	-	mod	+	-	-	+	+	+
	69	67	M	1	2	-	mod	-	-	-	-	-	-

The differentiation of liver tumors was classfied into 3 grade : well-differentiated (well), moderately-differentiated (mod), and poorly-differentiated (por). No cancer in specimens in case No.20 and 31. ND : Not Done.

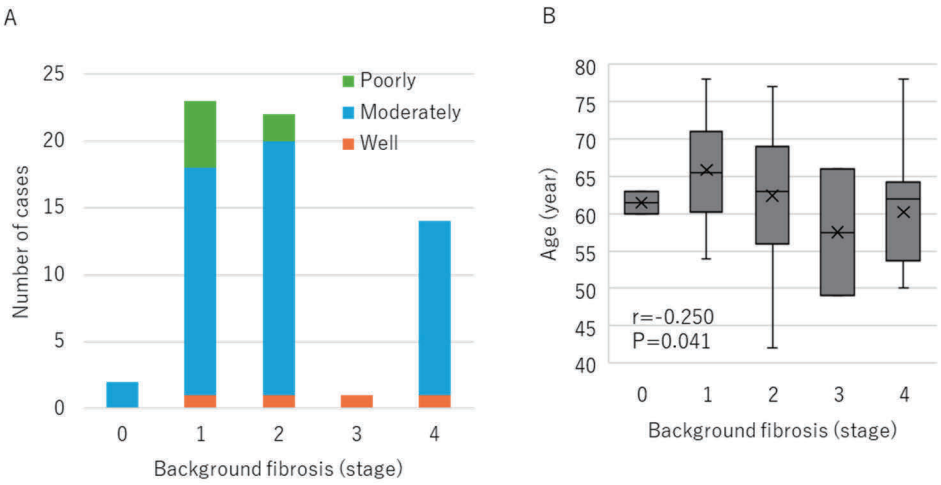

Figure 1. Histopathological Features of Background Liver tissue of HCC cases
Panel A illustrates the distribution of HCC cases based on liver fibrosis stages. In the background tissue of the liver tumors, the fibrosis severity showed a bimodal distribution, with one peak corresponding to advanced (F4) liver fibrosis and the other to mild (F1-2) liver fibrosis. The frequency of differentiation grade of tumors was significantly differences among the fibrosis stage in the background liver ($P<0.001$). Panel B shows an association between fibrosis severity and age. There is a weak negative correlation between them ($r=-0.250$, $P=0.041$).

capsules. The tumors typically consisted of a mixture of well- and moderately-differentiated components, while poorly differentiated tumor was observed in 8 cases (Fig. 3, Table 1). Interestingly, the frequency of poorly differentiated tumors was significantly higher in the HCC with mild fibrosis stage (F1-2) in the background liver (Fig. 1, $P<0.001$). Common tumor features included clear cell changes, fat deposition, intratumoral fibrosis, lymphocytic infiltration, and varying degrees of vascular invasion in several cases (Table 1).

Pathological Differences of HCC in Urban and Rural Areas

There are concerns about the widening regional disparities in healthcare policy in Mongolia. Since accessibility to hospitals is linked to the early diagnosis and treatment of diseases, it is

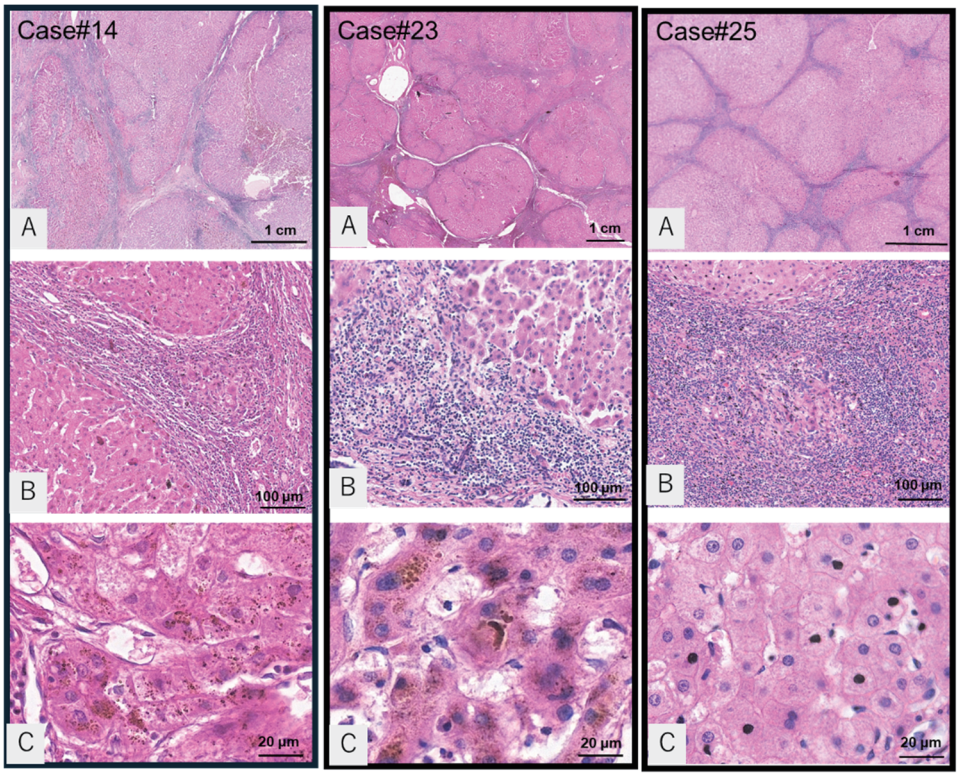

Figure 2. Histopathological Features of HBV/HDV Co-infection Cases
HE-stained liver images from 3 cases (Case Nos. 14, 23, and 25) are shown. Panel A displays an overall image at low magnification, Panel B focuses on the inflammatory changes in the portal area extending to the fibrous septa at medium magnification, and Panel C provides a high-magnification view. All three cases exhibited F4 stage cirrhosis, with active inflammation and interface hepatitis seen in the portal area and fibrous septa. Additionally, bilirubin accumulation was noted in Cases 14 and 23. None of the specimens showed a ground-glass appearance of hepatocytes, which would suggest HBs antigen accumulation.

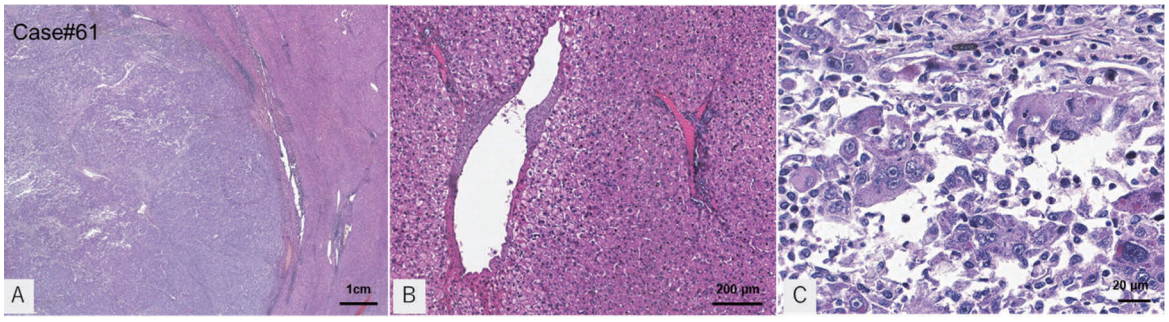

Figure 3. Poorly Differentiated Tumor in HCC
Pathological images of Case No. 39 are presented. Panel A shows a low-magnification view of a single nodular liver tumor against a background of mild fibrosis (F1). Panel B, at medium magnification, highlights the background liver with mild inflammatory cell infiltration in the portal area, mild fibrous septa extension, and no evidence of bridging formation. Panel C, at high magnification, reveals poorly differentiated HCC components with pronounced nuclear and structural atypia.

important to determine the regional dependency of disease prevalence and status in order to develop better healthcare policies. We hypothesized that patients in rural areas with limited access to hospitals would have HCC with more severe inflammation and fibrosis. In the HCC cases in the present study, there were no significant differences in age, sex, and background liver pathology between urban and rural Mongolia. However, the frequency of poorly differentiated tumors was significantly higher in urban areas compared to rural areas (Fig. 4, P=0.006).

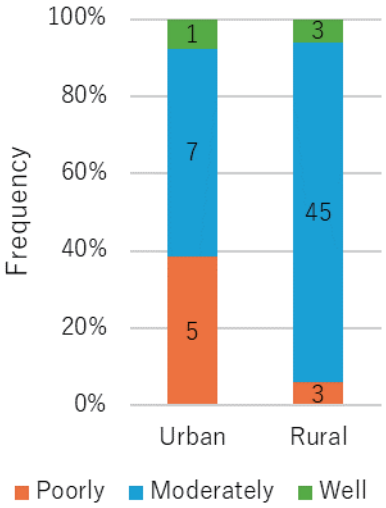

Figure 4. Frequency of Differentiation Grade of Tumor in Urban and Rural Areas in Mongolia
The numbers in the bar graph indicate the number of cases. The frequency of tumor differentiation grade was significantly different between urban and rural areas (P=0.006).

DISCUSSION

This study suggests that viral hepatitis could be the main cause of HCC in Mongolia, while steatotic liver disease play little role. In Mongolia, the high infection rates of HBV and HCV is a major concern, with reports indicating that 60% of HBV patients are co-infected with HDV (6). Although testing for HBV and HCV through blood samples is common in Mongolia, testing for HDV is less frequent, as it places a significant burden on the patient. In this study, there was a lack of serological data, making it impossible to confirm the exact number of HDV-positive patients. However, the extremely high rate of HDV infection compared to other countries may be a distinctive feature of liver pathology in Mongolia.

One of the notable findings of the present study is the high incidence of HCC at low fibrosis stages in Mongolia. It is generally known that the risk of liver cancer increases as inflammation persists and fibrosis progresses. Indeed, liver cancer cases with viral hepatitis typically show stages F3 or F4 in Japan and in Western countries (14-16). In Mongolia, there are both cancer cases that develops at severe and mild fibrosis stages. This suggests the existence of a carcinogenesis mechanism distinct from the one associated with advanced fibrosis, where various factors, such as alterations in liver tissue structure due to fibrosis, contribute to cancer development. A limitation of this study is the lack of detailed viral background information for the patients, preventing definitive conclusions. Nevertheless, the unusually high rate of HDV infection in Mongolia, along with the fact that HDV infection is associated with persistent high-activity inflammation, should be considered as a potential cause of liver carcinogenesis in the early stages of fibrosis. Recently, Johnson *et al*. reported that among HCC patients, 28% exhibited no signs of cirrhosis prior to their HCC diagnosis, and only 31% of HBV-related HCC cases progressed to cirrhosis (17-18). It is a crucial question for future research whether our results reflect the high rate of HBV infection or the unique co-infection with HDV in Mongolia. Nonetheless, the finding that cirrhosis is not an essential factor in the development of HCC is believed to provide significant insights for HCC control efforts in the future. We are currently planning a virological study using fresh samples in collaboration with medical institutions in Mongolia to investigate the direct carcinogenic effects of the virus in the future. In addition, the study using Mongolian specimens will elucidate the impact and pathological role of HDV on the development of HCC.

Another interesting finding is that HCC in cases with mild fibrosis showed a significantly high rate of poorly differentiated components. It is known that HCC tends to develop poorly differentiated or undifferentiated components as treatment is repeated (19). However, in the Mongolian cases, there was little prior treatment before surgery, suggesting that this characteristic may be intrinsic to the tumor itself. As previously mentioned, viruses may play a direct role in carcinogenesis in cases with low fibrosis stages. While it is generally believed that viruses do not replicate within tumors, the behavior of the HDV virus in human HCC tissue is still poorly understood (20). It is possible that HDV acts on cancer cells in a sustained manner within HCC, altering their degree of differentiation. Therefore, it is imperative to conduct studies using fresh human material to explore this possibility.

In the present study, we compared HCC characters between the tissue samples from urban and rural areas in order to identify the medical challenges facing Mongolia. The high frequency of HCC with poorly differentiated components in urban areas implies to us an unexplained etiology of HCC in Mongolia. In Ulaanbaatar, heavy metals such as lead, cadmium, and mercury, along with various chemical substances, enter the water supply when industrial and mining wastewater contaminates waterways, affecting drinking and agricultural water and posing health risks to residents (21). Air pollution including fine particulate matter (PM2.5) is a significant issue in Ulaanbaatar. The primary source of air pollution in Ulaanbaatar is the burning of raw coal for heating in traditional gers (felt dwellings), particularly during the winter. The levels of PM2.5 can be up to 14 times higher than those considered safe by the World Health Organization (WHO) in Ulaanbaatar during winter. It has been well known that PM2.5 affects respiratory and cardiovascular health, but recent studies also reported that it can be a risk factor for HCC in the US, Asia and Europe (22-24). Meanwhile, influence of chemical substances on the differentiation grade of tumors is still unknown. In order to clarify the link between the differentiation of tumors and regional characteristics, it will be necessary to analyze them from a complex perspective such as genetic background, viral infections, and other environmental factors. Therefore, more accurate analyses using cases from the National Center for Pathology, which collects data across the country, are necessary for a better understanding of the current situation of liver disease in Mongolia. We expect that this histopathological investigation of HCC will also clarify the disease structure in Mongolia and become the cornerstone of appropriate prevention and treatment strategies.

COMPETING INTERESTS

All authors declare no conflict of interest for this article.

ACKNOWLEDGEMENTS

We are grateful to Japan International Cooperation Agency (Japan) for the support via Project for Strengthening of Hospital Management and Education for Medical Staff at the Mongolia-Japan Hospital. This work was supported by funding from the Research Clusters program of Tokushima University (T.K.), the Takeda Science Foundation (T.K.) and the Heiwa Nakajima Foundation (T.K.).

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