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Original Article

Expression of CD133 in human intrahepatic cholangiocarcinoma: its relation with lymph node metastasis and poor prognosis

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Abstract: Background and aim: Recent studies suggest that CD133 as a cancer stem cell marker play significant roles of promoting invasiveness and metastasis in many solid cancers such as colon cancer, breast cancer, pancreatic cancer and so on. The aim of the present study is to explore the role of CD133 in intrahepatic cholangiocarcinoma (ICC). Patients and methods: The expression of CD133 and MMP-9 was examined in seventy patients with ICC who underwent hepatic resection and lymphadenectomy by immunohistochemistry, the relationship between CD133 and clinicopathological factors and patient survival was analyzed. Results: The immunopositivity rate of CD133 was 45.7% (32/70) in all seventy patients, and the rate was 72.2% (13/18) in patients with positive lymph node metastasis. The expression of CD133 was significantly correlated with lymph node metastasis, tumor differentiation and tumor stage. A significant relationship was also found between the expression of CD133 and MMP-9 which was an important molecule involving the lymph node metastasis of malignancy. The multivariate analysis revealed that the expression of CD133 and tumor staging were independent prognostic factors. Conclusion: CD133 tended to be related to the expression of MMP-9, the incidence of lymph node metastasis and tumor stage of ICC, and it was independently related to poorprognosis.

Keywords: Intrahepatic cholangiocarcinoma, CD133, lymph node metastasis, prognosis

Introduction

Intrahepatic cholangiocarcinoma (ICC) which originates from the epithelium of intrahepatic bile ducts is the second most common primary hepatic malignancy following hepatocellular carcinoma (HCC), and it accounts for about 20% to 25% of all cholangiocarcinoma [1]. The incidence and mortality of ICC have increased all over the world in recent years [2]. ICCs are more aggressive and have a worse prognosis than hepatocellular carcinoma with unfavorable 3-year and 5-year survival rates 30% and 8%, respectively [3]. However, little is known about the better treatment strategy besides surgical resection because of the relative rarity of the ICC and nonsurgical therapies including chemotherapy and radiotherapy have not been demonstrated to improve survival and decrease recurrence independently [4]. Therefore, novel molecular markers are needed for early diagnosis and prediction of survival, and the novel markers may be served as therapeutic targets at the same time.

It has been revealed that cancer stem cells play important roles in the carcinogenesis of various kinds of cancers [5, 6], and CD133 which is a 5-transmembrane cell surface glycoprotein [7] has been accepted as a member of significant markers for cancer stem cells [8-10]. CD133 which is associated with lymph node metastasis or poor prognosis has been confirmed in many solid malignancies including pancreatic cancer [11], hepatocellular carcinoma [12], colorectal cancer [13, 14] and so on. A few studies gave different results about the role of CD133 in cholangiocarcinoma. Leelawat et al. [15] found that CD133 positive cells play an important role in the invasiveness of cholangiocarcinoma. Shimada et al. [16] demonstrated that CD133 expression tended to be related to

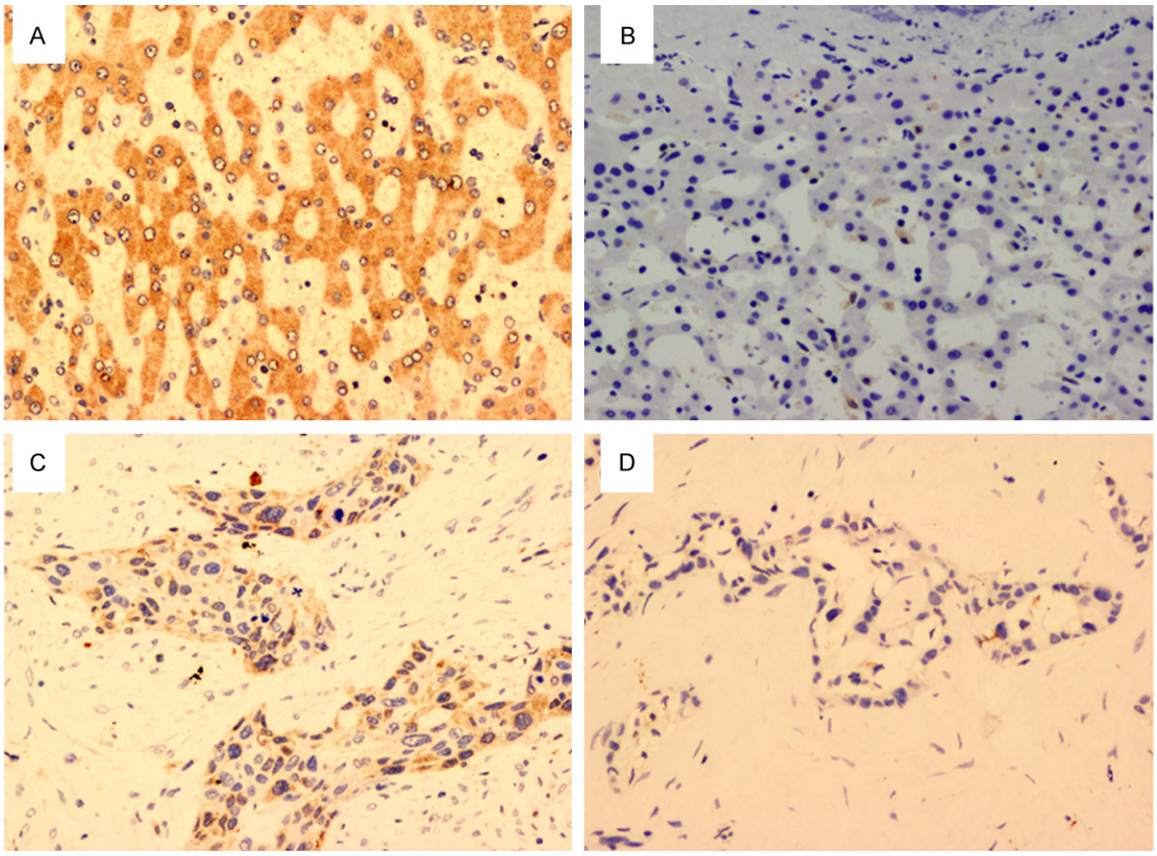

Figure 1. Immunohistochemical staining of CD133 and MMP-9 in ICC. A. ICC with positive staining of CD133. B. ICC with negative staining of CD133. C. ICC with positive staining of MMP-9. D. ICC with negative staining of MMP-9 (×200).

higher incidence of intrahepatic metastasis as well as worse prognosis in ICCs. But in another study [17], CD133 was found to be a beneficial prognostic factor and the better differentiation of the tumor, the more expression of CD133. In the present study, we will further verify its relationship with clinicopathological factors and prognosis.

Matrix metalloproteinase (MMP), a member of zinc-dependent proteinases, has been demonstrated to play important role in the dissolution of extracellular matrix (ECM) [18]. MMP-9 is a key member of MMP family, and its significance in cancer progression especially in lymph node metastasis has been confirmed in various cancers [19, 20]. In the present study, we also perform the immunohistochemistry of MMP-9 to find its relation with CD133 and confirm the relation between CD133 and lymph node metastasis indirectly.

Patients and methods

Patients

From January 2000 to December 2012, 70 patients underwent hepatectomy with lymphadenectomy at the Department of General Surgery in Xinhua Hospital affiliated to Shanghai Jiao TongUniversity School of Medicine were pathologically diagnosed as ICC. There were 41 men and 29 women with a mean age of 62.3±8.6 years (range, 36-81 years). All patients were classified as Child A and were staged according to the 7th edition staging classification for patients with ICC constructed by AJCC [21]. The tumor size was based on the measurement of the largest diameter of the specimen; if 2 or more nodules were found in the liver, we defined the satellite lesion; vascular invasion was defined by microscopic examination of the specimen or the obvious findings

Table 1. Relationship between CD133 and clinicopathological factors in human ICC

	CD133 positive	CD133 negative		
	n=32	n=38	X^2	*P*-value
Gender				
Male	17	24		
Female	15	14	0.721	0.396
Age (years)				
≤60 years	18	14		
>60 years	14	24	2.637	0.104
HBV				
Positive	25	33		
Negative	7	5	0.929	0.335
AFP				
≤7.0 ng/ml	26	34		
>7.0 ng/ml	6	4	0.959	0.495
CEA				
≤10 ng/ml	20	27		
>10 ng/ml	12	11	0.576	0.448
CA-199				
≤39 U/ml	10	14		
>39 U/ml	22	24	0.241	0.623
Satellite				
Absent	26	33		
Present	6	5	0.410	0.522
Tumor size (cm)				
≤5	13	22		
>5	19	16	2.072	0.150
Vascular invasion				
Absent	22	32		
Present	10	6	2.355	0.125
Differentiation				
Well/Moderate	20	33		
Poor/undifferentiation	12	5	5.598	0.018*
LNM				
Absent	19	33		
Present	13	5	6.861	0.009*
Staging				
I/II	12	26		
III/IV	20	12	6.693	0.010*

HBV, hepatitis B virus; CEA, carcinoembryonic antigen; AFP, alpha fetoprotein; CA-199, carbohydrate antigen 199; LNM, lymph node metastasis. *means $P<0.05$.

on the venous stage of the contrast enhancement CT scan. No patients received any preoperative therapy, such as chemotherapy or radiotherapy.

Formalin-fixed and paraffin-embedded tissues of these patients were retrieved from the Department of Pathology. All the patients were followed-up and the mean follow-up period was 40.0±13.9 months (range, 7.3 to 63.3 months). This study was previously approved by the hospital ethics committee and informed written consent was obtained from each patient.

Immunohistochemical staining

Four μm-thicksections were deparaffinized in xylene and rehydrated in a graded series of ethanol first and then were heated at 120°C in an autoclave in 10 mM sodium citrate (pH 6.0) for 10 min and cooled to room temperature. Then the sections were incubated in 3% hydrogen peroxide in methanol for 20 min to block endogenous peroxidase action. Then the slides were incubated in 5% bovine serum albumin in phosphate buffered saline (PBS) for 60 min at room temperature. And the sections were incubated overnight at 4°C with mouse monoclonal anti-CD133 antibody (Abcam, UK, diluted 1:100) and mouse monoclonal anti-MMP-9 (Santa Cruz, USA, diluted 1:100). Later on the avidin-biotin immunoperoxidase technique was used for the reactions. After washing, sections were overlaid with second antibody for 60 min at 37°C. The peroxidase reaction was developed with 3,3'-diaminobenzidine as chromogen. Finally, the sections were visualized after counterstaining with hematoxylin.The whole sections were screened and if CD133 or MMP-9 staining was detected in more than 10% of the entire tumor area the cases were defined as CD133 or MMP-9 positive [20, 22]. The evaluation was carried out by two pathologists who had nothing of clinicopathological features of the cases.

Statistical analysis

The overall survival (OS) was calculated from the date of operation to the date of death. The Pearson X^2 test or Fisher exact test was used to examine the relationship between expression

Table 2. Correlation between MMP-9 and CD-133 expression, LNM in human ICC

	MMP-9 positive	MMP-9 negative		
	n=34	n=36	X^2	*P*-value
LNM				
Absent	21	31		
Present	13	5	5.426	0.020*
CD-133 expression				
Positive	20	12		
Negative	14	24	4.578	0.032*

LNM, lymph node metastasis. *means $P<0.05$.

of CD133 and clinicopathological factors, the expression of MMP-9; Kaplan-Meier analysis was used to determine the OS; the log-rank test was used to compare survival outcomes between patient subgroups, the Cox-regression model was used to perform multivariate analysis. All the analysis was performed using the SPSS 20.0 software and $P<0.05$ was considered statistically significant.

Results

Expression of CD133 and its relationship with clinicopathological factors and the expression of MMP-9

The representative positive staining of CD133 was shown in **Figure 1**, the immunopositivity for CD133 was mainly observed in the cytoplasm and on the membrane of ICC cells. Among the 70 patients, 32 (45.7%) cases got the positive staining. The patients were subdivided into two groups according to the status of the immunohistochemistry and clinicopathological factors between two groups were compared as shown in the **Table 1**. Chi-square analysis showed that positive expression of CD133 was significantly correlated with lymph node metastasis ($P=0.009$), tumor differentiation ($P=0.018$) and tumor stage ($P=0.010$). Other factors including gender, age, HBV, AFP, CEA, CA-199, satellite, tumor size and vascular invasion showed no significant correlation with the expression of CD133.

The representative positive staining of MMP-9 which was mainly expressed in the cytoplasm was also shown in **Figure 1**, 34 (48.6%) patients had the positive staining. Among the 18 patients with lymph node metastasis, 13 cases had the MMP-9 positive staining, and 20 of 32 patients with CD133 positive had the MMP-9 positive staining. The expression of MMP-9 was significantly related with the CD133 expression ($P=0.032$) and lymph node metastasis ($P=0.020$) as shown in **Table 2**.

Univariate and multivariate analysis for prognosis of patients with ICC

Thirteen potential prognostic factors were analyzed for their risk on the survival of patients with ICC. In univariate survival analysis, Kaplan-Meier method was used to calculate the cumulative survival curve and the differences in survival were accessed by the log-rank method. The results were shown in **Table 3**. CD133, vascular invasion, lymph node metastasis and tumor staging were significant risk factors for the overall survival. All these four factors significant in univariate analysis entered multivariate analysis based on the Cox proportional hazard model. The results were also shown in **Table 3**, only CD133 and tumor staging were significant independent risk factors for the overall survival.

Patients with CD133 positive had a significant shorter survival than those with CD133 negative ($P=0.002$); The 3-year survival rates of patients with CD133 positive and negative were 21.2% and 60.1%, respectively. Patients with higher tumor staging had a significant shorter survival than those with lower tumor staging ($P=0.003$); The 3-year survival rates of patients with high and low tumor staging were 24.8% and 57.4%, respectively, as shown in **Figure 2**.

Discussion

Clinical interest in improving early diagnosis and overall survival has been generated due to the increasing incidence of intrahepatic cholangiocarcinoma. The identification of accurate molecular markers in prediction of survival and even for the strategy of therapy is necessary. Because of the lack of the effective adjuvant treatment modalities, curative surgical resection is considered to be the only potential treatment [23]. But R0 resection (resection of the gross and microscopic disease) was found to improve survival only in patients without regional lymph node metastasis [24, 25], and the overall 3- and 5-year survival rates are still

Table 3. Univariate and multivariate analysis of prognostic factors for overall survival in ICC

	Univariate analysis		Multivariate analysis	
	P-value	RR	95% CI	*P*-value
Gender (Male vs. Female)	0.555	-	-	-
Age (years) (≤60 vs. >60)	0.723	-	-	-
HBV (positive vs. negative)	0.607	-	-	-
AFP (ng/ml) (≤7.0 vs. >7.0)	0.310	-	-	-
CEA (ng/ml) (≤10 vs. >10)	0.361	-	-	-
CA-199 (U/ml) (≤39 vs. >39)	0.058	-	-	-
Satellite (Absent vs. Present)	0.755	-	-	-
Tumor size (cm) (≤5 vs. >5)	0.138	-	-	-
CD133 (positive vs. negative)	0.002*	1.957	1.097-3.491	0.023*
Vascular invasion (Absent vs. Present)	0.015*	1.820	0.946-3.502	0.073
Differentiation (Well/Moderate vs. Poor/undifferentiation)	0.101	-	-	-
LNM (Absent vs. Present)	0.042*	0.790	0.353-1.770	0.567
Staging (I/II vs. III/IV)	0.003*	2.171	1.069-4.409	0.032*

HBV, hepatitis B virus; CEA, carcinoembryonic antigen; AFP, alpha fetoprotein; CA-199, carbohydrate antigen 199; LNM, lymph node metastasis. *means $P<0.05$.

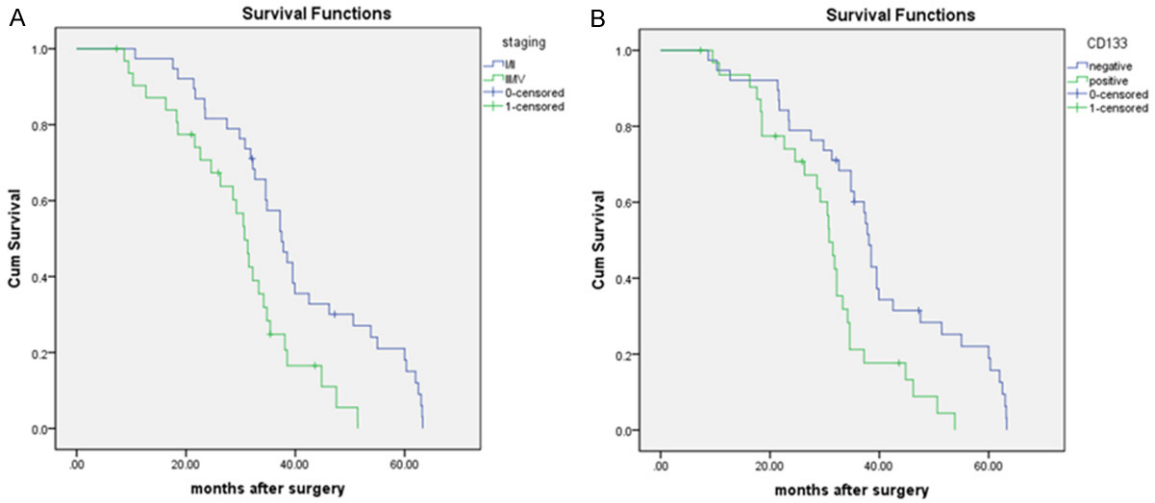

Figure 2. Survival curves for patients with ICC. The cumulative survival rate is significantly lower in patients with high tumor staging than those with low tumor staging (P=0.003) (A). The cumulative survival rate is significantly lower in patients with CD133 positive than those with negative (P=0.002) (B).

unfavorable. The limited treatment options present great challenges and many potential markers have been tested even though the specific mechanisms are still unknown [26-28].

In the present study, 32 of 70 (45.7%) ICC patients got CD133 positive expression. We demonstrate that patients with CD133 positive have a higher chance of lower tumor differentiation, this may be in accordance with the hypothesis of cancer stem cell, because CD133 has been accepted as a member of markers for cancer stem cells which have the abilities to self-renew, differentiate, and be tumorigenic and chemoresistant [29]. Leelawat et al. [15] found that the CD133 positive cells had a higher invasive ability compared with CD133 negative cells *in vitro*, this is in accordance with our result that CD133 positive patients got a higher rate of lymph node metastasis. The specific mechanism is unknown, but it may be related with MMP-9 that promotes the dissolution of extracellular matrix because the rate of MMP-9

positive is significantly higher in patients with CD133 positive than those with CD133 negative. This report confirms the relation between CD133 and MMP-9 for the first time, but further research is needed to clarify the mechanism.

Regarding the prognostic value of CD133, we found that CD133 was related to poor prognosis and was an independent prognostic indicator in ICC. The 3-year survival rates of patients with CD133 positive and negative were 21.2% and 60.1%, respectively. The same result has also been found in other cancers, e.g., pancreatic cancer [11], hepatocellular carcinoma [12] and colorectal cancer [13, 14]. Shimada et al. [16] also found that CD133 expression was a potential prognostic indicator in ICC. But Fan et al. [17] found that the median survival was 4 months for CD133 negative patients and 14 months for CD133 positive ones, CD133 negative expression correlated with poor prognosis while CD133 positive expression predicted a favorable outcome. The reason that caused these different outcomes was unknown, further investigation with more samples is needed.

In recent years, many mechanisms about the relationship between CD133 and carcinogenesis have been investigated. In pancreatic ductal adenocarcinoma, CD133 overexpression resulted in decreased epidermal growth factor (EGF) expression, increased telomerase reverse transcriptase expression, and increased Akt phosphorylation [30]. IL-6 signaling could promote DNA repair while protecting CD133 positive cells from apoptotic death in lung cancer [31], the similar result was found that interleukin-6/signal transducer and activator of transcription 3 (IL-6/STAT3) signaling induced expression of CD133 through functional cooperation with NF-κB and hypoxia-inducible factor 1 alpha (HIF-1α) during liver carcinogenesis [32]. And another signal pathway of CD90-integrin-mTOR/AMPK-CD133 has been confirmed in promoting liver carcinogenesis [33]. In the present study, we demonstrated that CD133 was correlated with MMP-9, but the specific signal pathway is needed to be clarified in further research.

In conclusion, we found that CD133 expression was correlated with tumor differentiation, lymph node metastasis, tumor staging and the expression of MMP-9, and also a potential indicator for overall survival. Thus CD133 could be a useful biomarker and therapeutic target in ICC, though the mechanisms are needed to be investigated in further study.

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Disclosure of conflict of interest

None.

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