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Clinical significance of serum intercellular adhesion molecule-1 detection in patients with hepatocellular carcinoma

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INTRODUCTION

Since the late 1980s, studies on the expression of intercellular adhesion molecule-1 (ICAM-1) in patients with malignancies have demonstrated that ICAM-1 may strongly express in two forms in such diseases: membranous one on the surface of tumor cells (membrane-bound ICAM-1) and soluble one in circulation (soluble ICAM-1, sICAM-1)[1,2]. Furthermore, increased expression of sICAM-1 in various malignant diseases, such as gastric cancer, colonic and pancr eatic cancer was reported by Tsujisaki *et al*[3], who found that th e incidence of positivity of sICAM-1 in the malignant diseases was significantl y higher than that in benign diseases. Therefore, the diagnostic value of detect ing sICAM-1 for some malignancies has been proposed[3]. The recent studies on detecting serum sICAM-1 in patients with hepatocellular carcinoma (HCC) have revealed that serum levels of sICAM-1 were well correlated to progr ession and prognosis of the disease[4-6], from which it has been conside red that sICAM-1 may be useful for monitoring the response to treatment[4]. However, whether sICAM-1 is a diagnostic marker is still controversial. Our recent study demonstrated that in HCC patients with normal or low levels of serum α-fetoprotein (AFP) measurement of sICAM-1 is of clinical value for detecting early HCC and its recurrence after hepatectomies[7-9]. To further evaluate the clinical significance of measur ing sICAM-1 in HCC, the serum levels of sICAM-1 in 134 patients with HCC were examined and the results were analyzed.

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MATERIALS AND METHODS

Patients

There were 134 patients with HCC, including 115 males and 19 females, aged from 12-80 years, median 49 years. The diagnosis of HCC for all patients was confirmed pathologically either by surgical resection of liver tumors or by liver biopsies. Tumor was less than 5 cm in diameter in 17 patients, less than 10 cm in 37 and more than 10 cm or with extrahepatic metastasis in 80 cases. Hepatitis B surface antigen (HBsAg) was positive in 112 cases and hepatitis C antibody positive in 10 patients. Surgical treatment was carried out in 68 patients, of whom 57 underwent tumor resection and 11 underwent laparotomy or selective catheterization of the hepatic artery. The rest of the patients were treated by transcatheter arterial embolization (TAE) or alcohol injection of tumors. As controls, serum levels of sICAM-1 were measured in 42 patients with chronic hepatitis B (CH), 40 with liver cirrhos is (LC) and 50 healthy blood donors.

Methods

Blood samples were collected early in the morning. The serum was immediately separated by centrifugation and frozen to -80℃. Concentrations of serum sIC AM-1 were measured with an enzyme-linked immunosorbent assay kit (Biosource Europe, Fleurus, Belgium). The quantitative determinations of serum AFP in patients with HCC was done by radio-immunoassay (RIA), using an AFP kit (Jiuding Biolo gical,Tianjin, China). The reference ranges of serum AFP concentration were classified as follows: above 200 μg/L, positive; 20 μg/L-200 μg/L, questionable positive; and below 20 μg/L, negative.

Statistical analysis

Data between groups were compared by Wilcox's Rank Sum test and Fisher test. $P<0.05$ means significance statistically.

RESULTS

The median of sICAM-1 in 134 patients with HCC was 1801 μg/L, which was significantly higher than

those in patients with CH (median = 462 μg/L), LC (median = 587 μg/L) and the healthy subjects (median = 305 μg/L) (Table 1). The compared analysis of serum levels of sICAM-1 and AFP in the HCC patients was shown in Table 2. Serum AFP concentration was positive in 85cases, negative in 22 and questionable positive in 27. The serum levels of sICAM-1, in the corresponding patients were 2018, 1370 and 1453 μg/L respectively. A correlated analysis of serum concentrations of AFP and sICAM-1 demonstrated that there was a close correlation between the two parameters in patients with AFP positive (r = 0.249, $P<0.05$). However, the correlation did not exist in patients with AFP negative or questiona ble positive. Although the serum concentrations of AFP in these two groups of patients were normal or in a low level, that of sICAM-1 in these patients all exceeded 1000 μg/L, the median values of which showed no significant difference compared with the median of the whole group of HCC patients ($P>0.05$). The ranges of serum levels of sICAM-1 in the pati ents with HCC are shown in Table 3. One hundred and seven patients (80%) had a sICAM-1 level higher than 1000 μg/L and 126 (94%) higher than 700 μg/L. There was no close correlation between the serum value of sICAM-1 and the tumor size among 134 patients with HCC (Table 4). The medians of serum levels of sICAM-1 in patients with different sizes of tumor showed no significant di fference ($P>0.05$).

Table 1 Concentrations of serum sICAM-1 in patients with HCC and c ontrol groups

Group	Number of patients	sICAM-1 (μg/L)[a]
Normal control	50	305
CH	42	462
LC	40	587
HCC	134	1801[b]

a median $P<0.01$ *vs* compared with other groups; [b]$P<0.01$ *vs* other groups each.

Table 2 Comparative analysis of serum levels of sICAM-1 and AFP in HCC patients

Group	Number of patients	sICAM-1 (μg/L)*	AFP (μg/L)*
AFP<20 μg/L	22	1370	11
AFP 20-200 μg/L	27	1453	89
AFP>200 μg/L	85	2018	31610

*median.

Table 3 Ranges of serum sICAM-1 concentration in 134 patients with HCC

sICAM-1 (μg/L)	Number of patients	(%)
330-690	8	6
700-990	19	14
1000-1990	72	54
>2000	35	26

Table 4 Serum concentrations of sICAM-1 and tumor size in 134 patie nts with HCC

Tumor size in diameter (cm)	sICAM-1 (μg/L)[a]	Number of patients
⩽5	1518[b]	17
⩽10	1769	37
>10	1897	80

a median; [b]$P>0.05$ *vs* others groups each.

DISCUSSION

One obvious phenomenon from the present study was that a much higher level of sICAM-1 was observed in our HCC patients than those reported by the others [4,6,12]. According to the following researches, we may explain the discrepancies: It has been known that ICAM-1 expression can be upregulated by several cytokines[10,11], of which interferon-gamma (INF-gamma) was the main cytokine trigger for ICAM-1 expression in a human hepatoplastoma cell line. In addition, hepatitis B virus-DNA- transfected cells expressed mem branous ICAM-1, the triggering mechanisms of which may be gene activation by virus genome or autocrine virus-induced hepatocellular cytokine production. Furthermore, the clinical research of relationship between serum levels of sICAM-1 and HCC showed that the high levels of sICAM-1 were closely related to the progression and prognosis of HCC[4,6,12]. In this study, the rate of hepatitis B infection was 84% (112/134) and 87% of the patients were in the middle or late stage of HCC (117/134). Thus it can beseen from our study that a high infectious rate of hepatitis B and a delayed dia gnosis of HCC in this group of patients may be the main reasons for the high expression of serum levels of sICAM-1.

However, with regards to the study on sICAM-1 and HCC, one more important point, which is still controversial and to be resolved is whether detecting sICAM-1 in patients with HCC is of clinical significance for early diagnosing the disease and detecting its recurrence after surgical resection. As the study results by Hyodo *et al*.[4] showed that there was no difference in serum le vels of sICAM-1 between their patients with HCC and liver cirrhosis. Based on this they declared that sICAM-1 is only a marker for progression and prognosis of the disease, but not a diagnostic marker for HCC. However, this conclusion was at odds with the observations from other reports[6,8,12], in which significantly higher serum levels of sICAM-1 in patients with HCC than those with LC, HC and healthy controls were demonstrated. The results of present study by the authors further confirmed the observations.

Moreover, the following results from the literatures seem to be more useful to resolve the controversial problem: enhanced expression of ICAM-1 on HCC ce ll surface exists in most patients with HCC (ranged from 80% to 96.2%)[5,13], which did not exist in peri-tumor and normal liver tissues. Regarding the association between membranous and soluble ICAM-1 expression, a highly consistent expression rate of the two forms of ICAM-1 was reported by Momosaki *et al*[5]. They found that in tumor lines, the consistent expression rate of the two forms ICAM-1 was 87.5% (present or absent conc omitantly). There were two forms of sICAM-1 in HCC patients: inflammation-associated sICAM-1 and HCC-specific circulating form of sICAM-1. The latter mainly came from HCC cells,

from which the membranous ICAM-1 were shed into the circulation continuously and became the important source of sICAM-1 [14]. In addition, recent studies by the authors[9] found that regardless of positive or negative serum AFP, after a radical resection of liver tumor, the sICAM-1 level would be decreased to the normal within 1-2 months postoperatively. However, in patients underwent non-radical resection due to vascular invasions of the liver or extrahepatic metastasis, the serum levels of sICAM-1 will maintain at a high level. It has been suggested from all of the studies mentioned above that the high level of serum sICAM-1 in HCC may originat e mainly from tumor itself. Thus we believe sICAM-1 in HCC patients may be a useful marker for detecting HCC and a monitor of recurrence after hepatectomy.

As the strong correlation between serum levels of sICAM-1 and AFP in patients with positive AFP was disclosed (Table 2), the clinical significance of sICAM-1 detection for diagnosing HCC will be focused on patients with normal or low levels of serum AFP. Serum AFP is still the best diagnostic marker for HCC. But AFP levels may be normal in 20%-40% of patients with HCC, depending on the severity of the disease [15]. In China about 30% of HCC patients can not be diagnosed by this serum marker, which results in delayed diagnosis and, consequently, hampers efforts to improve effective surgical treatment of the dis ease. Therefore, more sensitive serum markers are required for detecting HCC.

From the study, one of the interesting results was that there were 22 (16.4%) and 27 (20.2%) patients with HCC, whose serum levels of AFP were negative (median = 11 μg/L) and questionable positive (median = 89 μg/L). However, that of sICAM-1 in those patients were 1370 and 1453 μg/L respectively (Table 2), which showed no significant difference compared with the median level of total group of HCC(P>0.05). Furthermore, analysis of ranges of sICAM-1 levels in patients with HCC demonstrated that 80% of the patients had a high serum level of sICAM-1 exceeding 1000 μg/L. According to the study by Shimizu *et al*[6], sICAM-1 level above 1000 μg/L is a determinant for prognosis and progression of HCC, the proportion of patients with high levels of sICAM-1 (>1000 μg/L) in patients with HCC in our study was obviously highe r than that of AFP (>200 μg/L). As mentioned in our previou s studies the diagnosis of HCC should be strongly suspected when a patient with an uncertain intrahepatic lesion had a serum level of sICAM-1 higher than 1000 μg/L[7]. The results of the pre sent study further confirm our previous conclusion.

Another interesting finding from the study was that a significant correlation between serum level of sICAM-1 and tumor size of HCC was not observed (Table 4). The median of sICAM-1 concentration in 17 patients with tumor diameter less than 5 cm was 1518 μg/L, among them 4 being negative, 8 questionable positive and 5 positive for AFP. In addition, a tumor recurrence was diagnosed in 4 of the 17 patients after 1-3 hepatectomies during the postoperative follow-up. The median of tumor size in the 4 cases was only 2.8 cm whe n recurrence was confirmed, however, the median of serum level of sICAM-1 in the same patients was 1378 μg/L. It was strongly suggested by our observation that measurement of sICAM-1 is of clinical significance in detecting early HCC and monitoring its recurrence postoperatively when tumor is small in diameter, particularly for patients with normal or low serum concentrations of AFP.

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