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Thrombocytosis and Hepatocellular Carcinoma

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Abstract

Background—Thrombocytopenia has been reported to be both a risk factor for hepatocellular carcinoma (HCC) development as well as a prognostic factor. Many HCCs also occur in presence of normal platelets.

Aim—To examine a cohort of HCC patients with associated thrombocytosis.

Methods—Records were examined of a cohort of 634 biopsy-proven and randomly presenting HCC patients without thrombocytopenia.

Results—In the total cohort, 52 patients were identified with thrombocytosis (platelet levels $>400 \times 10^9/L$) and compared with 582 patients with normal platelet values. The average tumor sizes were 13.1 versus 8.8 cm ($p < 0.0001$), and their total average bilirubin levels were 0.9 versus 1.5 ($p = 0.02$), comparing thrombocytosis patients versus normal platelet count HCC patients. These differences were even more pronounced in patients with HCC sizes >5 cm. Thrombocytosis patients were younger and had less cirrhosis, but similar percent with hepatitis B or C or alcohol consumption.

Conclusion—Thrombocytosis in association with HCC occurs in patients with larger tumor sizes and better liver function.

Keywords

HCC; Size; Thrombocytosis; Portal vein thrombosis

Introduction

Hepatocellular carcinoma (HCC) occurs most frequently in livers that have been chronically damaged due to hepatitis B or C, chronic alcohol ingestion, food contamination with mycotoxins such as aflatoxin B₁, ditch and pond water carcinogens such as microcystins, or a wide range of chronic metabolic disturbances. Most cases develop in association with liver fibrosis or cirrhosis, especially in the presence of hepatitis C, although chronic infection with hepatitis B can lead to HCC without cirrhosis and HCC in Africa is commonly

associated with massive tumors and less cirrhosis. HCC represents the fifth commonest human cancer and the third highest cause of death from cancer globally, due to the incidence and mortality rates being similar, and it is thought that 80 % of global HCC occurs in developing countries, in which chronic hepatitis B virus (HBV) infection as well as both food and water contamination by liver carcinogens occur [1–8].

The time interval from HBV or hepatitis C virus (HCV) infection till the development of HCC is often 20–50 years. Surveillance therefore offers the possibility of identifying early-stage HCCs, which are potentially resectable. A consequence of the liver fibrosis that can result from chronic viral hepatitis is portal hypertension, with associated splenomegaly that can cause thrombocytopenia. The latter has been considered to be a warning sign of impending HCC development in patients who are chronically infected with viral hepatitis [9–11]. Thrombocytopenia-associated HCC has recently been shown to be associated with smaller-size tumors [12, 13], although only 28 % of the patients had thrombocytopenia. In contrast, several reports have shown that large-size HCCs often have normal platelet counts [14–17], likely due to less portal hypertension. There is a large literature describing thrombocytosis with various cancer types [18–20], but only few reports on thrombocytosis in HCC, typically with larger tumors [21–24] as well as in hepatoblastoma [24–26]. The current report extends that literature, by describing the characteristics of 43 patients with HCC and thrombocytosis (blood platelets $>400 \times 10^9/L$), most of whom had very large HCCs, higher levels of serum alkaline phosphatase (ALKP) and gamma glutamyltranspeptidase (GGTP), and lower total bilirubin levels than a comparator 438 HCC patients with platelets in the normal range ($125\text{--}400 \times 10^9/L$).

Methods

Clinical Methods

On initial clinical presentation for evaluation, all HCC patients had: baseline complete blood count, and blood liver function tests, blood alpha-fetoprotein (AFP) levels, and hepatitis serology, physical examination, liver and tumor biopsy, and a triphasic helical computerized axial tomography (CAT) scan of the chest, abdomen, and pelvis. The data and CT descriptors were prospectively recorded and entered into an HCC database intended for follow-up and analysis. This analysis was done under a university institutional review board (IRB)-approved protocol for the retrospective analysis of de-identified HCC patient records.

Statistical Analysis

Means and standard deviations (SD) for continuous variables, and relative frequencies for categorical variables, were used as indices of centrality and dispersion of the distributions. χ^2 test was used for categorical variables and Wilcoxon rank-sum (Mann–Whitney) test for continuous variables.

The nonparametric test for trend, developed by Cuzick, across ordered groups of platelet count categories was used to evaluate whether the increase of platelets was associated with increase in the maximum tumor size. For survival evaluation between two categories of platelets, the Kaplan–Meier curve and relative Wilcoxon (Breslow) test were used.

An unconditional logistic regression model was used to evaluate the odds ratio on platelets $>400 \times 10^9/L$ for each parameter, treated as a continuous variable, in the total HCC cohort examined.

When testing the null hypothesis of no association, the probability level of α error, two tailed, was 0.05. All the statistical computations were carried out using STATA 10.0 statistical software (2007; StataCorp LP, College Station, TX, USA).

Results

Thrombocytosis in the Total HCC Cohort

The whole cohort of 634 HCC patients who did not have thrombocytopenia (platelets $<125,000 \times 10^9/L$ blood) was dichotomized according to normal platelet values or thrombocytosis ($125,000\text{--}400,000 \times 10^9$ versus $400,000 \times 10^9$ platelets/L). Results (Table 1) showed that 52 patients (8.2 % of the cohort) had thrombocytosis (median platelets 515.5; range 402–1,074). There was a statistically significant increase in tumor diameter in patients with thrombocytosis compared with other patients ($p < 0.001$) (median platelets 202.0 K; range 125–400 K). However, the tumor characteristics of number of tumor nodules or presence of portal vein thrombosis did not differ between the two HCC groups. Levels of the tumor marker alpha-fetoprotein (AFP) were slightly higher in the thrombocytosis group, but not significantly. However, levels of GGTP and ALKP were significantly increased in the thrombocytosis group. Conversely, levels of total plasma bilirubin were significantly decreased in the thrombocytosis group, consistent with better liver function than in the other patients. WBC was decreased in this group, possibly reflecting some level of hepatic fibrosis. A relationship between the maximum tumor size (diameter) and blood platelet counts in the total cohort is shown in Fig. 1, with significant increases in tumor size with increased platelet levels and a significant trend.

Comparison of Large Tumor HCC Patients, Dichotomized by Platelets

Large tumor size has a negative prognostic significance for HCC [14–17] as for many other tumor types. There were 481 patients with HCCs with largest tumor nodule ≥ 5 cm, and these were dichotomized according to platelet count (Table 2). The thrombocytosis group (median platelets 528.0 K; range 402–1,085 K) also had significantly larger tumors than the normal platelet group (median platelets 211.5 K; range 125–398 K), with $p < 0.0001$, as seen for the total cohort. AFP was higher, but not significantly, but both GGTP and ALKP were significantly higher in the thrombocytosis group with larger size tumors than in the normal platelet group, and total bilirubin levels were significantly lower in the thrombocytosis patients. Both in this cohort and in the total cohort, Hgb levels were significantly lower in the patients with thrombocytosis and larger tumors (Tables 1, 2), possibly reflecting anemia of chronic disease. The demographic characteristics of these larger HCC subsets showed some significant differences (Table 3). The gender ratio was similar in the two subsets, but the thrombocytosis patients were significantly younger and the percent of patients with cirrhosis was significantly lower in the thrombocytosis subset, consistent with their lower bilirubin levels (Tables 2, 3). However, there were no significant differences between the two subsets with respect to hepatitis B or C, alcohol consumption or smoking. Furthermore, survival between the large tumor size subsets was also similar despite differences in average tumor maximum diameters (Fig. 2), with the median overall survival being 9 months in each subset.

Comparison of Small Tumor HCC Patients, Dichotomized by Platelets

The 153 patients with tumors <5 cm were then also dichotomized according to presence or absence of thrombocytosis (Table 4). Only nine patients (5.8 % of small tumors) had thrombocytosis (median platelets 499.0 K; range 443–639 K). They had higher AFP, GGTP, and ALKP levels than the patients with similar small tumor size but with normal platelets (median platelets 170.5 K; range 125–400 K), as well as higher percent of patients with portal vein thrombosis (PVT) and lower bilirubin levels. However, only GGTP levels were significantly different and higher in the thrombocytosis patients. These patients also had higher WBC counts, likely due to absence of liver fibrosis. The tumor sizes and numbers of tumor nodules were similar in these two subsets. In order to ascertain whether there might be patterns amongst the patients with small HCCs that would predict who might develop

thrombocytosis-associated larger tumors, each of the two small size HCC subsets was compared with the large size thrombocytosis-associated patients from Table 2 (Table 4, two right-side columns). Comparison of the normal platelet small HCCs with the thrombocytosis-associated HCCs showed many significant differences amongst the parameters, in addition to tumor size. However, a similar comparison for the nine small tumor thrombocytosis-associated patients with the large tumor thrombocytosis-associated subset showed no significant differences in any parameter except tumor size, suggesting the possibility that HCCs of these patients might be potential precursors of the larger size thrombocytosis-associated HCCs. However, the small patient number in this subset limits interpretation. An unconditional logistic regression analysis was performed on each variable to platelet counts. Table 5 shows that an increase of hemoglobin was inversely associated with platelets $>400 \times 10^9/L$, with statistical significance [odds ratio (OR) = 0.73, $p < 0.001$]. An increase of ALKP and an increase in the amplitude of the maximum tumor diameter were positively associated with platelet values $>400 \times 10^9/L$, with statistical significance, respectively, of OR = 1.001, $p = 0.001$, and OR = 1.12, $p < 0.001$.

Discussion

Thrombocytosis has been reported long ago to be associated with many tumor types [18–20], and its presence even suggests the diagnosis of cancer in the absence of iron-deficiency anemia and benign inflammatory disease [20]. It can also be associated with primary liver malignancy [21–26]. Liver and liver tumors can synthesize thrombopoietin, a major factor in platelet production [26, 32, 33], and HCCs could thus induce the paraneoplastic thrombocytosis that has been reported. Conversely, platelets have been reported to interact with cancer cells and be involved in their growth enhancement [27–31], and antiplatelet therapy can antagonize experimental tumor growth [27]. Specifically with regard to HCC, platelets are known to produce multiple HCC growth stimulants [34–36], including vascular endothelial growth factor (VEGF) [34], platelet-derived growth factor (PDGF) [37–41], serotonin [42, 43], and fibroblast growth factor (FGF) and its receptors [44–46]. Each of these has been shown to be involved in human HCC and to be a potential target in experimental HCC therapeutics. They are also involved in hepatitis B-associated liver inflammation, and antiplatelet therapy can inhibit experimental HCC in a hepatitis B mouse model [47].

In the current report, we identified 52 patients among a large cohort of Western HCC patients who had thrombocytosis. Those patients had on average significantly larger tumors than other patients of the cohort with blood platelets in the normal range, their bilirubin values were significantly lower, and a lower percentage of them had cirrhosis, as several reports of large HCCs have shown [14–17]. Although noncirrhotic HCC patients have been reported to have less thrombocytopenia than cirrhotic HCC patients, thrombocytosis seems to be uncommon, with few reports in HCC. We also found thrombocytosis in nine patients of a cohort with small <5.0 cm tumors, and a higher percent of them had portal vein thrombosis than those small HCC patients without thrombocytosis. Possibly, they are precursors to the large tumors with thrombocytosis, as their other parameters were similar to those of patients with large tumors. We found a significant increase in tumor size with increasing platelet values and a significant trend (Fig. 1). Survival was similar for patients who had larger size HCCs, with and without thrombocytosis. The thrombocytosis patients had larger tumors but better liver function, and conversely in patients with platelets in the normal range, who had smaller tumors but worse liver function. Thus, the adverse prognostic effects of large HCC size in the $>400 \times 10^9/L$ platelet subcohort might have been balanced by excellent liver function in those patients with HCCs >5 cm (Table 2; Fig. 2), while the adverse effects of poor liver function in those patients with HCCs >5 cm and platelets $125\text{--}400 \times 10^9/L$ might have been balanced by the presence of smaller tumors.

Liver failure was not seen in patients with large tumors and thrombocytosis, indicating that they likely died of their cancer. This was much more variable in the patients with normal platelet levels, many of whom had elevated blood bilirubin levels (Tables 1, 2, 4). In those normal platelet patients, liver failure likely contributed to their causes of death.

Whether some HCCs produce large amounts of thrombopoietin, which contributes to the thrombocytosis, is not determined here. However, platelets are a source of several HCC growth factors and are involved in tumor interactions, tumor growth, tumor angiogenesis, and tumor cell protection from immune responses [48]. Thus, even in the absence of thrombocytosis, platelets in the normal range or their platelet-derived HCC growth factors might be rational targets for future therapies.

Abbreviations

HCC	Hepatocellular carcinoma
AFP	Alpha-fetoprotein
PVT	Portal vein thrombosis
Hgb	Hemoglobin
Plts	Platelets
WBC	White blood count
GGTP	Gamma glutamyltranspeptidase
PT	Prothrombin time
M	Mean
SD	Standard deviation
CAT	Computerized axial tomography
K	$\times 10^3$
Platelet units	$\times 10^9/L$
Bilirubin values	mg/dL

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Fig 1.

Comparisons of maximum tumor size amongst HCC patients in different platelet ranges, in the total cohort. Values are mean $\pm$ standard error of the mean. Kruskal–Wallis rank test: $p = 0.0001$. Test for trend (Cuzick): $p < 0.001$

Fig 2. Kaplan–Meier survival probability for HCC patients with or without thrombocytosis. $\S$ Wilcoxon (Breslow) test: $p = 0.59$

Table 1

Comparisons between platelet categories in the total HCC cohort

Parameter ^a	Platelet counts ($\times 10^9/L$)		<i>p</i> value [#]
	(125–400) (<i>n</i> = 582)	Plt >400 (<i>n</i> = 52)	
AFP (ng/mL)	45,807.2 $\pm$ 195,195.3	50,486.2 $\pm$ 181,562.4	0.67
GGTP (U/100 mL)	314.6 $\pm$ 325.0	393.0 $\pm$ 262.4	0.001
ALKP (U/100 mL)	244.3 $\pm$ 214.1	425.8 $\pm$ 545.9	0.001
Total bilirubin (mg/dL)	1.5 $\pm$ 2.4	0.9 $\pm$ 0.7	0.02
PT (s)	13.0 $\pm$ 2.2	12.8 $\pm$ 1.2	0.83
Albumin (g/L)	3.3 $\pm$ 0.6	3.4 $\pm$ 0.7	0.75
Hgb (g/dL)	12.5 $\pm$ 2.0	11.2 $\pm$ 1.9	<0.0001
WBC ($\times 10^9/L$)	9.1 $\pm$ 5.0	10.6 $\pm$ 5.6	0.01
Platelet counts ($\times 10^9/L$)	217.3 $\pm$ 68.8	544.5 $\pm$ 134.6	<0.0001
Max tumor size (cm)	8.8 $\pm$ 5.4	13.1 $\pm$ 7.0	<0.0001
Tumor number (no. of nodules)	3.4 $\pm$ 2.2	3.8 $\pm$ 2.1	0.20
PV thrombosis	41.9 %	46.8 %	0.52 ^{\$}

^a All values: mean $\pm$ standard deviation[#] Wilcoxon rank-sum (Mann–Whitney) test^{\$} χ^2 test

Table 2Comparisons between HCC patients with tumor sizes ≤ 5 cm, dichotomized by platelet counts

Parameter ^a	Platelet counts ($\times 10^9/L$)		p value [#]
	(125–400) (n = 438)	>400 (n = 43)	
AFP (ng/mL)	41,300.9 $\pm$ 9,341.2	71,437.73 $\pm$ 19,083.1	0.94
GGTP (U/100 mL)	316.1 $\pm$ 306.6	371.3 $\pm$ 243.8	0.03
ALKP (U/100 mL)	261.2 $\pm$ 232.4	435.2 $\pm$ 586.5	0.007
Total bilirubin (mg/dL)	1.5 $\pm$ 2.3	0.8 $\pm$ 0.6	0.007
PT (s)	13.1 $\pm$ 2.2	12.7 $\pm$ 1.1	0.80
Albumin (g/L)	3.4 $\pm$ 0.5	3.4 $\pm$ 0.7	0.51
Hgb (g/dL)	12.4 $\pm$ 1.9	11.1 $\pm$ 1.8	<0.0001
WBC ($\times 10^9/L$)	9.4 $\pm$ 5.4	10.2 $\pm$ 5.2	0.13
Platelet counts ($\times 10^9/L$)	223.7 $\pm$ 68.9	551.1 $\pm$ 145.1	<0.0001
Max tumor size (cm)	10.8 $\pm$ 4.7	15.3 $\pm$ 5.5	<0.0001
Tumor number (no. of nodules)	3.4 $\pm$ 2.1	3.9 $\pm$ 2.1	0.20
PV thrombosis	47.9 %	47.4 %	0.95 [§]

^a All values: mean $\pm$ standard deviation[#] Wilcoxon rank-sum (Mann–Whitney) test[§] χ^2 test

Table 3Demographic characteristics of HCC patients with tumor sizes ≥ 5 cm, dichotomized by platelet counts

Parameter ^a	Platelet counts ($\times 10^9/L$)		<i>p</i> value [§]
	(125–400) (<i>n</i> = 438)	>400 (<i>n</i> = 43)	
Sex (%)			0.20
Female	25.8	34.9	
Male	74.2	65.1	
Age (years)	62.0 $\pm$ 13.6	55.7 $\pm$ 13.9	0.008 [#]
Hepatitis (%)			0.72
None	57.9	65.0	
B	17.4	12.5	
C	16.4	17.5	
B and C	8.2	5.0	
Cirrhosis (%)			0.001
Negative	36.1	63.4	
Positive	63.9	36.6	
Alcohol (%)			0.55
No	34.1	39.4	
Sometimes	19.8	21.2	
Irregularly	10.3	15.1	
Everyday	35.7	24.2	
Smoking (%)			0.84
No	37.3	42.4	
Occasionally	10.6	9.1	
Smoker	52.0	48.5	

^aAll values: mean $\pm$ standard deviation[§] χ^2 test[#]Wilcoxon rank-sum (Mann–Whitney) test

Table 4

Comparisons between HCC patients with tumor sizes <5 cm, dichotomized by platelet counts

Parameter ^a	Platelet counts ($\times 10^9/L$)		p value [#]	p value [§]	p value ^Δ
	(125–400) (n = 144)	>400 (n = 9)			
AFP (ng/mL)	28,629.3 $\pm$ 20,685.0	62,056.0 $\pm$ 22,832.5	0.81	0.05	0.56
GGTP (U/100 mL)	278.3 $\pm$ 375.8	494.3 $\pm$ 334.3	0.02	0.0002	0.29
ALKP (U/100 mL)	192.7 $\pm$ 132.5	383.0 $\pm$ 320.7	0.19	<0.0001	0.80
Total bilirubin (mg/dL)	1.6 $\pm$ 2.6	1.2 $\pm$ 1.0	0.68	0.01	0.12
PT (s)	13.0 $\pm$ 2.4	13.3 $\pm$ 1.9	0.30	0.79	0.45
Albumin (g/L)	3.3 $\pm$ 0.7	3.4 $\pm$ 0.7	0.57	0.99	0.77
Hgb (g/dL)	12.5 $\pm$ 2.2	11.8 $\pm$ 2.0	0.32	0.0003	0.31
WBC ($\times 10^9/L$)	7.9 $\pm$ 3.4	12.3 $\pm$ 7.1	0.01	0.002	0.48
Platelet counts ($\times 10^9/L$)	197.8 $\pm$ 64.8	513.3 $\pm$ 59.6	<0.0001	<0.0001	0.70
Max tumor size (cm)	2.7 $\pm$ 1.0	2.5 $\pm$ 1.0	0.49	<0.0001	<0.0001
Tumor number (no. of nodules)	3.5 $\pm$ 2.2	3.7 $\pm$ 2.3	0.76	0.27	0.79
PV thrombosis	22.4 %	44.4 %	0.14 [§]	0.003 [§]	0.87 [§]

^a All values: mean $\pm$ standard deviation

[#] Wilcoxon rank-sum (Mann–Whitney) test

[§] χ^2 test

[§] Comparisons between patients with small tumors (<5 cm) and platelets (125–400 K) versus large tumors ($\geq$ 5 cm) and platelets (>400 K)

^Δ Comparisons between patients with small tumors (<5 cm) and platelets (>400 K) versus large tumors ($\geq$ 5 cm) and platelets (>400 K)

Table 5

Unconditional logistic regression analysis of platelet counts on each variable

Parameter	OR (SE)	95 % CI	<i>p</i> value
AFP	1.00 (0.00001)	0.999–1.000	0.87
GGTP	1.001 (0.0004)	0.999–1.001	0.10
ALKP	1.001 (0.0004)	1.0001–1.002	0.001
Total bilirubin	0.69 (0.14)	0.46–1.03	0.07
PT	0.94 (0.08)	0.80–1.11	0.48
Albumin	1.06 (0.26)	0.66–1.71	0.81
Hgb	0.73 (0.06)	0.63–0.85	<0.001
WBC	1.04 (0.02)	1.001–1.091	0.04
Max tumor size	1.12 (0.03)	1.07–1.18	<0.001
Tumor number (no. of nodules)	1.08 (0.07)	0.95–1.23	0.23
PV thrombosis	1.22 (0.37)	0.67–2.22	0.52

Unconditional logistic regression analysis on each variable of platelet counts $>400 \times 10^9/L$, as odds ratio (OR) and 95 % confidence interval (CI), in the total HCC cohort ($n = 634$ patients); ($n = 582$ for platelets 125–400; $n = 52$, for platelets $>400 \times 10^9/L$)