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ORIGINAL ARTICLE

Thrombocytosis in Liver Transplant Recipients: Prevalence, Natural History, and Impact

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The prevalence, natural history, and implications of reactive thrombocytosis after liver transplantation (LT) are unknown. Prospectively collected data from July 2000 to February 2006 were analyzed. Post–LT thrombocytosis was defined as a platelet count of $>450 \times 10^3/\mu L$ lasting for >7 days and starting within 8 weeks of transplantation. In patients who survived >8 weeks, graft and patient outcomes were compared with liver transplant recipients who survived >8 weeks and did not develop any thrombocytosis. Post-LT thrombocytosis was seen in 92 (14.7%) of 627 patients. The median onset was on day 13 (range, days 1-44) and the peak platelet count was seen on day 17 (range, days 3-110). The median duration of thrombocytosis was 25 days (range, 7-1,253 days), with a median peak platelet count of $625 \times 10^3/\mu L$ (range, $472\text{-}1{,}381 \times 10^3/\mu L$). Seronegative fulminant hepatic failure was the indication for transplantation in 18% of patients with post-LT thrombocytosis compared with 3% of controls ($P < 0.001$). There was a lower proportion of patients transplanted for hepatitis C–related cirrhosis in the thrombocytosis group (10% vs. 18%, $P = 0.04$). The occurrence of hepatic arterial thrombosis was similar in the 2 groups (5% vs. 4%, $P =$ NS). None of the 4 patients with platelet count higher than $1{,}000 \times 10^3/\mu L$ developed thrombotic complications. Post-LT thrombocytosis is more often associated with seronegative fulminant hepatic failure, and there is a negative association with hepatitis C–related cirrhosis. Post-LT thrombocytosis does not increase the risk of hepatic artery thrombosis, and patients without thrombotic complications should not be treated. ***Liver Transpl 13:1598-1602, 2007.*** © **2007 AASLD.**

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Thrombocytopenia is common in patients with cirrhosis of liver who are listed for liver transplantation (LT). Traditionally, this has been attributed to hypersplenism resulting from portal hypertension.[1] However, a direct correlation between portal pressure, spleen size, and platelet count has not been demonstrated.[2] Moreover, normalization of portal pressure after radiological or surgical shunting does not seem to affect the absolute platelet count.[3] Thrombopoietin (TPO) is a major regulator of platelet production and megakaryocyte maturation. Recently, it has been suggested that diminished production of TPO and increased degradation of TPO by sequestered platelets are fundamental in the development of thrombocytopaenia.[4]

On the first day after LT, the platelet count decreases further because of hemodilution and platelet consumption. This is likely the consequence of profound changes in coagulation with hyperfibrinolysis during graft reperfusion and in the early period after LT.[5] As TPO production increases, the peripheral platelet count rises after a lag period and returns to the pre-LT level by day 6. Thereafter, the platelet count continues to rise and is usually within the normal laboratory range approximately 2 weeks after LT. In some patients, the platelet count may continue to rise, and there are anecdotal reports of thrombocytosis after LT.[6] However, the prevalence, natural history, and implications of thrombocytosis after LT are unknown. In this study, we aimed to establish the prevalence and natural history of thrombocytosis after LT and to correlate this with patient and graft outcomes.

PATIENTS AND METHODS

Prospectively collected data of consecutive adult LT recipients transplanted at our hospital from July 2000 to February 2006 were analyzed.

Abbreviations: LT, liver transplantation; TPO, thrombopoietin; PLTT, post–liver transplantation thrombocytosis; HAT, hepatic artery thrombosis; SNFHF, seronegative fulminant hepatic failure; IL, interleukin.

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Inclusion Criteria

All patients who developed post-LT thrombocytosis (PLTT) were included. PLTT was defined as a platelet count of >450 $\times$ $10^3/\mu L$ lasting for >7 days and starting within 8 weeks after LT.

Exclusion Criteria

Patients with a high platelet count before LT and those with prior splenectomy were excluded.

Parameters Studied

The age, gender, diagnosis, date, type of LT, and cold ischemia time were recorded. The day of onset of thrombocytosis, peak platelet count attained, and duration of thrombocytosis were noted. The white cell count, serum bilirubin, aspartate transaminase, alkaline phosphatase, and international normalized ratio of prothrombin time at the time of the peak thrombocytosis were recorded. A note was made of the cytomegalovirus status of the donor and recipient, and we also recorded the requirement for continuous venovenous hemofiltration. The use of aprotinin and aspirin, if prescribed, was recorded. In those who survived >8 weeks, episodes of hepatic artery thrombosis (HAT), portal vein thrombosis, and hepatic venous outflow tract obstruction were noted. Duration of stay in the intensive care unit, total hospital stay, episodes of rejection, graft failure at 3 months, and deaths from 2 to 3 months were also noted.

Controls

The outcomes were compared with LT recipients who survived >8 weeks and who did not develop thrombocytosis.

Statistical Analysis

Statistical analysis was performed by SPSS version 15.0 (SPSS, Chicago, IL). Categorical variables were compared by the χ^2 test with appropriate corrections and continuous variables by the Mann-Whitney test.

RESULTS

A total of 638 adults underwent LT during the study period. Of these, 11 patients, 7 with a high platelet count before LT and 4 who had undergone splenectomy, were excluded. None of the patients were transplanted for Budd-Chiari syndrome or with an underlying prothrombotic disorder. The median platelet count before LT was 161 $\times$ $10^3/\mu L$ (range, 41-446 $\times$ $10^3/\mu L$). Post-LT thrombocytosis was seen in 92 (14.7%) of 627 patients. The median onset of PLTT was on day 13 (range, days 1-44), and 58% of these cases were noted on days 10-15 after LT (Fig. 1). The peak platelet count was seen on day 17 (range, days 3-110). The median duration of PLTT was 25 days (range, 7-1,253 days), with a median peak platelet count of 625 $\times$ $10^3/\mu L$ (range, 472-1,381 $\times$ $10^3/\mu L$). In 4 patients, the platelet count was >1,000 $\times$ $10^3/\mu L$. A total of 117 patients with a one-off value of platelet count of >450 $\times$ $10^3/\mu L$ were excluded. Ninety patients with PLTT and 371 patients with no thrombocytosis survived 8 weeks and were included in the analysis.

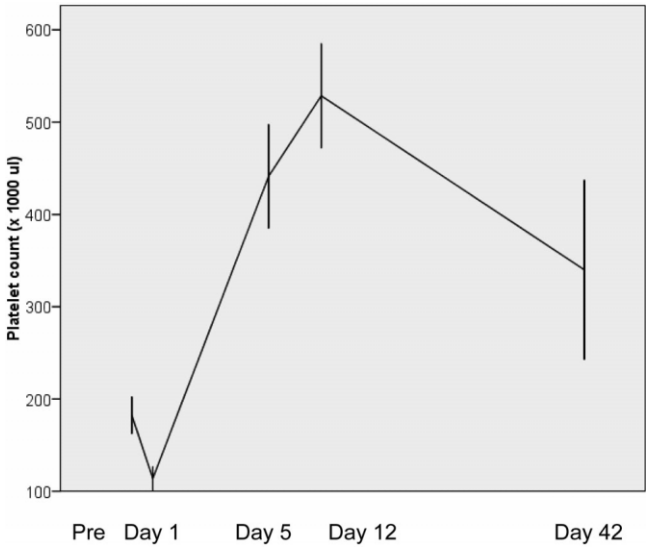

Figure 1. Temporal profile of patients with post–liver transplantation thrombocytosis showing mean values (with standard error bars) at onset, peak, and duration.

The demographics and laboratory parameters of the test and control populations are shown in Table 1. The 2 groups did not differ statistically significantly in terms of age, gender, type of LT, cold ischemia time, use of aprotinin, presence of hepatocellular carcinoma, cytomegalovirus status (both donor and recipient), and the use of continuous venovenous hemofiltration. Seronegative fulminant hepatic failure (SNFHF) was the indication for transplantation in 18% of patients with PLTT compared with 3% of the controls ($P < 0.0001$). There was a negative association with patients transplanted for hepatitis C–related cirrhosis (10% vs. 19%, $P = 0.04$).

The white cell count at the time of peak platelet count was statistically significantly higher in patients with PLTT ($P < 0.001$). However, the duration of stay in the intensive care unit and total hospital stay were similar in the 2 groups (Table 2). The occurrence of hepatic arterial thrombosis was similar in the 2 groups (5% vs. 4%, P = NS). The median peak platelet count in the 4 patients with HAT was 736 $\times$ $10^3/\mu L$ (range, 623-920 $\times$ $10^3/\mu L$). No patients in either group developed portal vein thrombosis or hepatic venous outflow obstruction. Episodes of acute rejection requiring treatment were observed in 33% of patients with PLTT and 36% of the controls (P = NS). Graft failure and death at 12 weeks were similar in the 2 groups.

DISCUSSION

Thrombocytosis may occur as the result of a wide variety of causes (Table 3). Transient thrombocytosis may occur after administration of epinephrine as a result of mobilization of the extravascular platelet pool.[7] Most cases of thrombocytosis are reactive. In a study of 777

TABLE 1. Demographics and Laboratory Parameters of Patients With Post–Liver Transplantation Thrombocytosis and Controls

Parameter	PLTT	Control	*P* value
Number	90	371	. . .
Platelet count ($\times 10^3/\mu L$), peak (range)	633 (472–1,381)	312 (68–449)	. . .
Age (yr) (range)	53 (20–72)	52 (16–73)	NS
Male sex, n (%)	50 (55%)	201 (54%)	NS
Diagnosis			
Alcoholic liver disease	10 (11%)	53 (14%)	NS
Autoimmune hepatitis	Nil	22 (6%)	NS
Cryptogenic cirrhosis	9 (10%)	25 (7%)	NS
Hepatitis C–related cirrhosis	9 (10%)	70 (19%)	0.04
Hepatitis B–related cirrhosis	3 (3%)	18 (5%)	NS
Paracetamol overdose	4 (4%)	10 (3%)	NS
Seronegative FHF	16 (18%)	11 (3%)	<0.0001
Subacute hepatic failure	5 (5%)	1 (0.4%)	0.001
Primary biliary cirrhosis	13 (14%)	80 (22%)	NS
Primary sclerosing cholangitis	8 (9%)	36 (10%)	NS
Other	13	45	. . .
Hepatocellular carcinoma	14 (14%)	72 (19%)	NS
Split liver transplantation	6 (7%)	32 (9%)	NS
Cold ischemia time	593 (244–970)	606 (201–1,115)	NS
Aprotinin use	37 (41%)	150 (40%)	NS
Donor CMV positive	41 (46%)	180 (48%)	NS
Recipient CMV positive	47 (52%)	241 (65%)	0.02
CVVH	19 (21%)	80 (21%)	NS
Hb at peak platelets	9.9 (7.3–12.7)	9.9 (6.4–15.3)	NS
WCC at peak platelets	13.6 (4.2–33.2)	10.6 (2.6–55.3)	<0.001
S bilirubin at peak	24 (3–217)	30 (6–495)	0.005
AST at peak	26 (10–197)	32 (6–2,302)	0.05
Alkaline phosphatase at peak	569 (169–2,496)	688 (37–4,521)	0.05
INR at peak platelets	1.1 (0.9–1.5)	1.1 (0.9–2.3)	NS

Abbreviations: PLTT, post–liver transplantation thrombocytosis; FHF, fulminant hepatic failure; CMV, cytomegalovirus; Hb, hemoglobin; AST, aspartate aminotransferase; INR, international normalized ratio of prothrombin time.

TABLE 2. Length of Hospital Stay, and Graft and Host Outcomes in Patients With Post–Liver Transplantation Thrombocytosis and Controls

Parameter	Patients	Controls	*P* value
Days in intensive care unit (range)	3 (1–26)	3 (1–97)	NS
Days in hospital (range)	11 (3–54)	12 (1–133)	NS
Hepatic artery thrombosis (n)	4	13	NS
Portal vein thrombosis	0	0	. . .
Hepatic venous outflow tract obstruction	0	0	. . .
Treated acute rejection episodes, n (%)	30 (33%)	142 (38%)	NS
Graft failure at 8–12 weeks, n (%)	4 (4%)	15 (4%)	NS
Death at 8–12 weeks, n (%)	1 (1%)	7 (2%)	NS

sequential patients with platelet counts of >500,000/μL, 21% of thrombocytosis cases were caused by infection, 18% by tissue damage, 13% by chronic inflammation, and 19% by rebound after bleeding, iron deficiency, or cancer chemotherapy.[8] Malignancy, splenectomy, and myeloproliferative disorders accounted for <5% each. In another study of patients with platelet counts of >1,000,000/μL, reactive thrombocytosis accounted for 82% and myeloproliferative disorders 14% of patients, and 4% were of uncertain etiology.[9] Infection was the most common cause of reactive thrombocytosis (31%), followed by postsplenectomy status (19%), malignancy (14%), and trauma (14%).

The pattern of occurrence of thrombocytosis 12 days after LT suggests that overcorrection of platelet count as a result of excessive production of TPO is the most likely mechanism, rather than the surgery itself. Even though the white cell count was higher than in patients

TABLE 3. Causes of Thrombocytosis

Physiological
Exercise
Parturition
Epinephrine
Primary
Myeloproliferative syndrome
Secondary (reactive)
Infection
Inflammatory disease
Neoplasm
Rapid blood regeneration after hemorrhage and hemolysis
Rebound after recovery from thrombocytopenia
Asplenia (anatomic or functional)
Postsurgical
Iron deficiency

with PLTT, the typical and consistent timing of thrombocytosis without an increase in length of stay in the intensive care unit or total hospitalization suggests little role for infections. In fact, a characteristic leukocytosis occurring 7-14 days after transplantation, unaccompanied by fever, in the absence of documented infections or rejection and resolving spontaneously without antibiotics has been described.[10] The platelet count of these patients was statistically significantly higher than those of postoperative ($P < 0.01$) or infectious leukocytosis ($P < 0.05$), suggesting excessive production from the bone marrow. It has been demonstrated that TPO concentration is low in patients with cirrhosis of liver with thrombocytopenia and that it is then restored after orthotopic LT.[11,12] Increased thrombopoiesis after LT has also been demonstrated.[13]

We have shown that the occurrence of PLTT is far higher in patients who are transplanted for SNFHF compared with patients with other indications. What could be the explanation for this phenomenon? Is it that patients with fulminant hepatic failure, as a group, are systemically more unwell than those with cirrhosis of liver at the time of LT, and thus they have an acute inflammatory response? There is evidence in mice that interleukin (IL)-1 and tumor necrosis factor increase megakaryocytopoiesis through production of IL-6.[15] Administration of recombinant IL-6 increases megakaryocyte counts and size in humans and treatment with anti–IL-6 results in progressively diminished platelet counts that return to normal several days after the infusion is discontinued.[16] However, PLTT was not observed more frequently in our patients transplanted for other causes of fulminant hepatic failure (e.g., drug overdose or hepatitis B). It seems, therefore, that PLTT is a phenomenon seen most often in patients transplanted for SNFHF, a group that is also prone to develop other hematological complications—for example, aplastic anemia. Post-LT aplastic anemia has been described in 23% of children and young adults transplanted for SNFHF.[17] It has been demonstrated that patients who go on to develop aplastic anemia after LT may have evidence of bone marrow dysfunction before LT in the form of lower white cell count and lower platelet count compared with controls.[18] If so, can the presence of PLTT predict patients with SNFHF who do not develop aplastic anemia? When we looked at the records of only 3 adults with this background, none of them had PLTT. Possibly, a much larger study in children might answer this question.

Having addressed the issues of prevalence, natural history, and mechanism of PLTT, the next question was whether the high platelet count was detrimental or beneficial to the graft and patients. We have demonstrated that the risk for HAT, portal vein thrombosis, and hepatic venous outflow obstruction was not increased in patients with PLTT compared with controls. Of 4 patients who developed HAT in patients with PLTT, the development of HAT preceded the development of thrombocytosis in 1 patient. Moreover, aspirin was initiated postoperatively in all 4 patients, which implies concern about vascular anastomosis. In a multivariate analysis of 21 patients diagnosed over 10 years at our hospital, thrombocytosis was not a risk factor for early HAT[19]; however, only platelet counts on day 1 and day 3 were studied. In another study of 31 patients with delayed HAT, no donor or recipient risk factor was found at our institution.[20]

Is there a need to start antiplatelet therapy for PLTT? It is known that even though patients with reactive thrombocytosis may have platelet counts as high as those of patients with myeloproliferative disorders, hemorrhage and thrombosis are unusual, occurring in <5% of patients.[21] Reactive thrombocytosis resolves when the underlying disease is treated and additional therapy is rarely required. Platelets play an important role in regeneration of the liver. In a study of hepatocytes from male BLB/c mice, the effect of platelet contact on hepatocyte proliferation was examined.[22] Statistically significant increment of DNA synthesis of hepatocytes, as indicated by 3-H thymidine uptake, was demonstrated compared with controls ($P < 0.001$), thus indicating that direct contact with platelets induces hepatocyte regeneration and platelets contain a substance that promotes hepatocyte regeneration.

In another study, thrombocytosis produced by intraperitoneal injection of TPO 5 days before 70% hepatectomy in male BLB/c mice resulted in increased liver weight/body weight ratio and higher mitotic index 48 hours after liver resection compared with controls with normal or low platelet counts.[23] Electron microscopy revealed translocation of platelets into the space of Disse and direct contact with hepatocytes within 5 minutes of hepatectomy. Platelets contain several growth factors in alpha granules. It has been demonstrated that increment of platelets by TPO accelerated the production of growth factors such as platelet-derived growth factor and hepatocyte growth factor, which induced early phosphorylation of transcriptional factors after hepatectomy to promote liver regeneration.[24] Platelets also carry 95% of the serotonin in blood, a potent stimulator of hepatocyte mitosis. In thrombocytopenic mice, a serotonin agonist was shown to reconstitute hepatocyte proliferation.[25] Two days after hepatectomy, a 3-fold to 4-fold upregulation in the

expression of 5-HT2A and 5-HT2B receptors was observed, and antagonists of these receptors inhibited liver regeneration. The inhibition of platelet function by clopidogrel reduced hepatocyte proliferation in partially hepatectomized mouse livers, but the effect was less pronounced than the thrombocytopenic model. Levels of serum bilirubin and aspartate aminotransferase were far lower in our patients with PLTT. However, hepatocyte regeneration cannot be offered as an explanation because the alkaline phosphatase level was also lower in this group compared with controls. Better liver function did not translate into improved graft and patient survival at 12 weeks, and no reasonable explanation can be offered with the available data.

We reviewed the pattern of prescribing low-dose aspirin at our unit in 33 patients with PLTT. Five patients were already receiving aspirin because of concerns with vascular anastomosis, 7 (21%) were prescribed aspirin after onset of PLTT, and 21 (64%) were not prescribed any treatment. It may be important to resist the temptation of starting ant-platelet therapy for PLTT in the light of these data. Symptomatic patients may benefit from platelet apheresis and hydroxyurea therapy until symptoms resolve and platelet count is controlled. In 2 patients with reactive thrombocytosis and portal vein thrombosis after LT with platelet counts of $>1{,}000 \times 10^3/\mu L$, rapid control of platelet count was achieved by platelet apheresis.[26] In all 5 of our patients with HAT, the platelet count was $<1{,}000 \times 10^3/\mu L$.

Our study has demonstrated for the first time the prevalence and natural history of PLTT. Thrombocytosis after LT is more often associated with SNFHF, and there is a negative association with hepatitis C–related cirrhosis. Patients with PLTT are not at increased for HAT, and there is no indication for treatment without evidence of thrombotic complications.

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