

CONCISE REPORT

Thrombocytopenia in Venocclusive Disease After Bone Marrow Transplantation or Chemotherapy

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Hepatic venocclusive disease (VOD) is a frequent complication of bone marrow transplantation (BMT). Analysis of 13 cases observed during a 3-year period in our BMT center shows that VOD is associated with a constant peripheral thrombocytopenia and refractoriness to platelet transfusion. These signs appear in the very early stage of VOD, five to ten days before the classical signs, painful hepatomegaly and sudden weight gain. Analysis of platelet consumption, frequency of platelet transfusion and platelet recovery, and examination of known causes of peripheral thrombocytopenia (mainly allo- and autoimmunization, disseminated intravascular coagulation [DIC] and splenomegaly) lead to the conclusions that this association is not coincidental. The exact mechanism of platelet consumption in VOD is unknown.

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HEPATIC venocclusive disease (VOD), was originally described by Bras in 1954¹ in Jamaican children treated with herbal medicinal teas containing pyrrolizidine alkaloids. *Senecio*, *Crotalaria*, and *Heliotropum* plants were found to be responsible for micro-epidemics of VOD in the Caribbean, India, Egypt, Hong Kong, Afghanistan, Mexico, and Arizona.²⁻⁵ Alcohol was also shown to be a causative factor of VOD.^{6,7} VOD was later described following treatment by cytarabine, 6-thioguanine, and azathioprine.⁸⁻¹¹ Noteworthy is the high incidence of this disease after bone marrow transplantation. Twenty percent of the patients undergoing allogeneic bone marrow transplantation eventually develop VOD, with a 75% average mortality rate.¹²⁻¹⁵ Most cases occurred after the usual conditioning regimen with cyclophosphamide and total body irradiation. Isolated cases following autologous bone marrow graft have also been reported in patients prepared with mitomycin, DTIC, and nitrosourea.¹⁶⁻²⁰

Between July 1982 and April 1985 we observed 13 cases of VOD. In addition to the clinical features classically described, ie, sudden painful hepatomegaly with postsinusoidal intrahepatic portal hypertension, we noticed that these patients were deeply thrombocytopenic and developed an early refractoriness to platelet transfusion. This association does not seem purely coincidental and we present these observations.

MATERIALS AND METHODS

Thirteen patients were diagnosed as having VOD. Nine of the cases followed allogeneic bone marrow transplantation for acute myeloblastic (2 cases) and lymphoblastic (5 cases) leukemia, chronic myeloid leukemia (1 case), and aplastic anemia (1 case). In the latter, preventive treatment of graft-versus-host disease involved use of cyclosporine; in the other patients, the treatment regimen used was methotrexate at days 1, 3, 6, and 11, and then weekly. In two cases VOD followed autologous bone marrow transplantation for acute leukemia and T-lymphoblastic lymphoma. The last two cases were observed after chemotherapy for relapsing leukemia, one myeloblastic and one lymphoblastic. Clinical characteristics and conditioning regimen used for the bone marrow transplantation are summarized in Table 1.

The diagnosis of VOD was confirmed either by transjugular liver biopsy or by postmortem examination in 10 patients: at least two of these three signs—central or sublobular vein occlusion, without thrombosis; congestion of centrilobular sinusoids; centrilobular fibrosis—were found. In the three remaining cases the diagnosis was

based on the criteria defined by Shulman: clinical association of a 1.5 kg weight gain in 24 hours and concomitant sudden development of a painful hepatomegaly within the month following transplantation¹² and by echography (Table 2).

The 9 patients with VOD following allogeneic bone marrow transplantation were compared with all the patients who underwent allogeneic transplantation in our institution. In the two groups we analyzed and compared the following factors:

(1) Platelet consumption: number of platelet units, either random or single-donor platelet concentrates transfused during the 3 months following transplantation.

(2) Frequency of platelet transfusion: analysis concerned the first, second, and third platelet transfusion after bone marrow graft and was expressed as the number of days between those platelet transfusions.

(3) Platelet recovery was calculated in cases of transfused single-donor platelet concentrates as follows:

$$R = \frac{\text{observed increment} \times \text{blood volume}}{\text{number of platelets infused}} \times 100$$

Blood volume was evaluated according to Nadler.²¹ In all cases platelet count after transfusion was performed 16 to 18 hours after the end of the transfusion.

Since February 1984 we have studied the recovery after single-donor platelet concentrate transfusion. Therefore 23 patients could be analyzed for platelet transfusion recovery: 7 with VOD and 16 without VOD. Patients were considered refractory when the recovery was less than 25%. The mean recovery value in non-HLA immunized patients without fever of more than 38 °C and splenomegaly is 56 ± 15% (extreme values 38 to 80). HLA alloimmunization was assessed by standard microlymphocytotoxicity test on a panel of 18 lymphocytes at least once a week. Coagulation tests included prothrombin time and assay of vitamin K dependent factors, partial thromboplastin time, fibrinogen, fibrinogen degradation products, and soluble complexes. Statistical analysis was performed using Student *t* test and the chi-square test.

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Table 1. Clinical Status of Patients With VOD

Name	Diagnosis	Status	Treatment	GVH	Cause of Death	Survival Duration Following Therapy
1. JOI	T-ALL	2nd CR	BCNU/VP 16/AraC/CPM TBI/Allo BMT	0	VOD/CMV	79
2. MOS	T-ALL	1st CR	CPM/TBI/Allo BMT	2	—	670+
3. BRI	cALL	Relapse	VP 16/AraC/CPM TBI/AlloBMT	2	VOD	50
4. DJE	cALL	3rd CR	VP 16/AraC/CPM TBI/AlloBMT	0	VOD	22
5. AZI	ALL	1st CR	CPM/TBI/AlloBMT	0	VOD/IP	59
6. BAH	cALL	Relapse	PDN/VCR/Aspa	—	VOD/Leukemia	81
7. VAN	T-NHL	PR	Busulfan/CPM/AutoBMT	—	Lymphoma	172
8. EZZ	AML	1st CR	CPM/TBI/AlloBMT	0	VOD/IP	55
9. BOZ	AML	1st CR	CPM/TBI/AlloBMT	0	VOD	90
10. FAK	AML	2nd CR	CPM/TBI/AutoBMT	—	—	348+
11. BOU	AML	Relapse	HD/AraC/Amsa	—	VOD/leukemia	24
12. DUP	CML	CP	CPM/TBI/AlloBMT	0	VOD	21
13. ABO	AA		CPM/TAI/AlloBMT	0	VOD	17

Abbrev: ALL, acute lymphoblastic leukemia; T, type T; c, common; T-NHL, T-lymphoblastic lymphoma; AML, acute myeloblastic leukemia; AA, aplastic anemia; CP, chronic phase; CR, complete remission; PR, partial remission; TBI, total body irradiation; TAI, thoracoabdominal irradiation; BMT, bone marrow transplantation; VOD, veno-occlusive disease; CMV, cytomegalovirus; IP, interstitial pneumonia; GVH, graft-versus-host disease.

RESULTS

In all 13 observations there existed a thrombocytopenia, refractory to platelet transfusion. Amidst our allogeneic bone marrow transplant patients the number of platelet units required was significantly greater in those developing VOD ($P < 0.05$). Both groups received an average of 6 ± 2 units of single donor platelets; a mean of 37 pooled random donor units were transfused per patient in the control group and 300 units in patients developing VOD. Platelet requirement persisted a long time after the bone marrow repopulation in VOD patients.

Transfusion ineffectiveness occurred soon after transplantation, often after the first transfusion. The interval between the first and the third transfusions was 5 ± 1 days in VOD patients and 7 ± 2 days in other patients. This difference is statistically significant ($P < 0.05$). No significant difference

exists in the recovery at the first transfusion between the two groups ($P < 0.1$). Transfusional recovery remains stable between the first, second, and third transfusions in the control group; however, it sharply drops in patients developing VOD (Fig 1). This difference is statistically significant from the second transfusion onward ($P < 0.02$). Considering together the second and third platelet transfusions after bone marrow transplantation, 9 out of 9 VOD patients have a recovery value less than 25% while only 5 out of 18 do in the control group.

The ineffectiveness of platelet transfusion is a very early symptom of VOD. It was noted at day 6 ± 2 after bone marrow transplantation, while the clinical diagnosis of VOD was made at day 15 ± 5 .

Four patients out of 9 (44%) with VOD had anti-HLA antibodies, either prior to or after transplantation. Among the 34 transplanted patients without VOD, 12 (35%) were

Table 2. Criteria of VOD Diagnosis in 13 Patients

	Centrilobular		Congestion of Sinusoid	Liver Biopsy	Days After Therapy*	Echography	Sushepatic Block
	Venocclusion	Fibrosis					
1. JOI	+	+	+	Transjugular	D + 22	+	+
2. MOS	—	+	+	Transparietal	D + 100	+	ND
3. BRI	ND	ND	ND	ND	ND	+	ND
4. DJE	+	+	+	Autopsy	D + 22	+	ND
5. AZI	ND	ND	ND	ND	ND	+	ND
6. BAH	+	+	+	Transjugular	D + 21	+	+
7. VAN	ND	ND	ND	ND	ND	+	ND
8. EZZ	+	+	+	Autopsy	D + 55	ND	ND
9. BOZ	+	+	+	Autopsy	D + 90	ND	ND
10. FAK	—	+	+	Autopsy	D + 62	ND	ND
11. BOU	+	+	+	Autopsy	D + 24	ND	ND
12. DUP	+	+	+	Autopsy	D + 21	ND	ND
13. ABO	+	+	+	Autopsy	D + 17	ND	ND

Clinical features of VOD are initially diagnosed with sudden weight gain and painful hepatomegaly. All patients develop prominent ascitis and jaundice. Biopsies were performed in 10 cases out of 13 for histologic confirmation. Hepatomegaly was confirmed with echography: normality of three sushepatic veins and ascitis were identified in the three remaining patients.

*Days of liver biopsy after therapy.

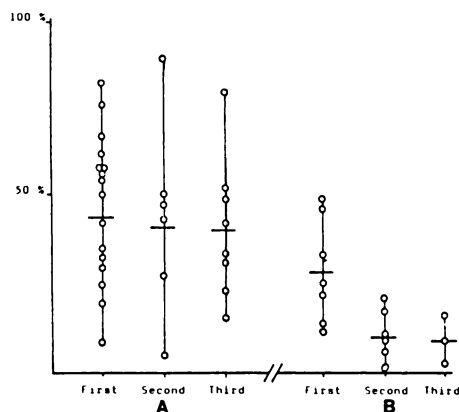


Fig 1. Platelet recovery after transfusion of single-donor platelet concentrates in patients undergoing bone marrow transplantation. (A) Patients without VOD; (B) Patients with VOD.

found to be HLA-immunized in the same conditions. This difference is not significant.

In 4 VOD patients to whom single-donor platelet concentrates from bone marrow donor were transfused, platelet recovery was poor; in three cases the recovery calculated as mentioned previously was 34%, 14%, and 0%, respectively. In the fourth patient, the lifespan was studied by chromium 51-labelled platelets from his bone marrow donor. The platelet half-life was 12 hours; destruction had no preferential site and no splenic or hepatic sequestration was identified.

Coagulation studies performed during the entire period show three different abnormalities. A vitamin K deficiency, almost constant during the first 15 days, is easily corrected with addition of parenteral vitamin K. This deficiency was not more frequent or more intense in either group. In all VOD patients except patient no. 9 a significant rise of FDP is observed. This elevation remains stable during the disease. Factor VIII/von Willebrand activity is elevated in three patients with VOD (680%, 700%, 300%). This elevation was always observed at least 2 times for each patient. Bidimensional chromatography, however, showed no abnormal migratory pattern.

DISCUSSION

Peripheral thrombocytopenia with refractory transfusion was found in all 13 cases of VOD. The exact mechanism involved remains unclear. Peripheral destruction is evidenced by the short life-span (<12 h) of the platelets of the marrow donor as calculated by either transfusion recovery at 16 to 18 h or chromium 51-labelled platelets. The presence of morphologically normal megakaryocytes in the bone marrow smears corroborates this feature. Anti-HLA alloimmunization cannot be held solely responsible since it occurred with the same frequency in both patient groups. Moreover, the ineffectiveness of bone marrow donor platelets, observed in all the 4 cases tested, cannot be explained by an HLA alloimmunization.

We did not look for a specific antiplatelet alloimmunization in this series. These antibodies are responsible for poor

platelet transfusion recovery. We think that they are probably not involved in our observation of VOD patients, however, for their occurrence has been shown to be less than 20% in a series of patients undergoing therapeutic aplasia.²² An autoimmune phenomenon could be suspected; however, it usually appears later after bone marrow transplantation.²³ In our experience, low platelet count invalidates reliability of search for IgG-coated platelets to study autoimmunization.²⁴ Spleen size was not increased and VOD occurred in a splenectomized patient with the same picture of refractory thrombocytopenia. Splenic or hepatic sequestration was not found in Cr51-labelled platelets.

FDP rise could account for a DIC mechanism in platelet consumption. This rise, however, is never observed before the clinical onset of VOD, while platelet refractoriness is observed earlier. Moreover, when the FDP level rises, there is neither concomitant consumption of coagulation factors II, V, and VIII, nor presence of soluble complexes. Thus, the FDP rise cannot be related, at least in the course of the VOD, to a DIC phenomenon and is more likely an early sign of hepatic deficiency.

The concentration of factor VIII/von Willebrand activity was very high. Migration patterns were normal. We have not, however, followed the evolution of the multimers in the surviving patients and multimers could be coated on the platelet in active phase. We cannot, therefore, definitively exclude for the thrombocytopenia a mechanism similar to that described in thrombotic thrombocytopenic purpura or uremic hemolytic syndrome.^{25,26}

Few studies in the literature have reported platelet counts during VOD. We have reviewed 9 cases in which this was mentioned: three after 6-thioguanine,^{9,10} one during the course of cirrhosis,⁷ and one after absorption of Senecio² had depressed platelet counts. Normal counts are seen in pulmonary VOD occurring in pregnancy,²⁷ and in VOD after conditioning with DTIC¹⁹; however, the pathologic description is ambiguous, because centrolobular venous thrombosis was present. In the case of Berk et al.,¹⁴ the patient died at the 25th day after allogeneic bone marrow transplantation and had a low platelet count, but no information was provided about the frequency of transfusion. Finally, one patient with VOD following autologous bone marrow transplantation reported by Cahn²⁰ was refractory to transfusion; however, this was ascribed to platelet alloimmunization.

In summary, we retrospectively analyzed 13 cases of VOD occurring after chemotherapy, or autologous or allogeneic bone marrow transplantation. Peripheral thrombocytopenia with refractory transfusion was observed in all cases. The mechanism of refractory thrombocytopenia remains unclear. Nine patients with VOD after allogeneic bone marrow transplantation are compared with the group of allogeneic grafted patients as control. This association is not coincidental, as a significant difference in transfusion requirements exists between patients developing VOD and control patients. Refractoriness to transfusion was noted early in the course of events before establishing the diagnosis of VOD. Low recovery (<25%) at the second and subsequent transfusions should be considered, therefore, as a predictive factor for VOD.

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