Venoocclusive Liver Disease After Bone Marrow Transplantation: Findings at Duplex Sonography

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Ascites, thickening of the gallbladder wall, and reversal of portal flow are documented sonographic findings in venoocclusive disease of the liver. The frequency and specificity of these findings and their relationship to the severity of this disease have not been studied. In an attempt to clarify these issues, 65 patients who had bone marrow transplantations were prospectively studied with serial B-scans and duplex color Doppler sonography. For all patients, assessment included liver size and texture, thickening of the gallbladder wall (>10 mm), and presence of ascites. Doppler flow velocity profiles were obtained from the portal vein, hepatic veins, and inferior vena cava. The hepatic artery resistive index (RI) was calculated. Twenty volunteers were also studied to establish normal flow values. Nineteen patients had documented venoocclusive disease, nine had hepatic graft-vs-host disease (GVHD) (five after proved venoocclusive disease), two had hepatitis, and 40 had no clinical or biochemical evidence of liver injury after bone marrow transplantation. Ascites (n = 16), thickening of the gallbladder wall (n = 8), hepatomegaly (n = 8), and altered liver texture (n = 3) were not distinguishing features of venoocclusive disease. Mean hepatic artery RI was as follows (ranges are in parentheses): control group, 0.69 (0.58–0.76); venoocclusive disease patients, 0.81 (0.75–0.87); GVHD patients, 0.69 (0.63–0.71); all other patients after bone marrow transplantation, 0.66 (0.61–0.71). The RI values in venoocclusive disease were significantly elevated, but an incremental rise in RI with increasing severity of the disease was not seen. Abnormalities in portal vein flow were seen in only two patients: In one with fatal venoocclusive disease, reversed portal flow developed, and in one with GVHD, portal vein thrombosis developed. Contrary to previous reports, no correlation between abnormalities in portal flow and venoocclusive disease was seen. Flow velocities in the hepatic veins and the inferior vena cava were not significantly different from values in the volunteer group.

These results suggest that a significant elevation of the hepatic artery RI may be a sensitive index of liver damage related to venoocclusive disease after bone marrow transplantation and an important distinguishing sonographic feature.

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Venoocclusive disease of the liver results from intensive conditioning chemotherapy and radiotherapy in patients undergoing allogenic or autologous bone marrow transplantation [1–3]. The disease typically becomes manifest in the first 2 weeks after transplantation and includes weight gain caused by fluid accumulation, tender hepatomegaly, and elevated levels of bilirubin. Other liver enzymes, especially aspartate aminotransferase and alkaline phosphatase, may also be elevated. In the transplantation patient, differentiation of venoocclusive disease from other causes of liver dysfunction, particularly hepatic graft-vs-host disease (GVHD), may be difficult, because such entities may be associated with similar biochemical abnormalities. A definitive diagnosis is important because the treatment of each condition is considerably different. Treatment of hepatic venoocclusive disease is mainly supportive and involves fluid and sodium restriction, natriuresis, the use of albumin infusions, and reduction in the dose of cyclosporine. Conversely,

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treatment of acute GVHD involves increased immunosuppression with high-dose glucocorticoids, cyclosporine, and various monoclonal antibodies against T cells. Distinction between venoocclusive disease and GVHD can generally be made histologically; however, liver biopsy in these patients is associated with an increased risk of bleeding complications because of severe thrombocytopenia or coagulation abnormalities.

Several reports [1, 2, 4–7] have described the results of gray-scale and Doppler sonography in patients with hepatic venoocclusive disease. A variety of sonographic features has been recognized, including ascites, thickening of the gallbladder wall, and reversal of portal venous flow. However, the frequency of these findings and their relationship to the severity of venoocclusive disease have not been investigated. Moreover, no studies have yet established whether these abnormalities are also seen in patients with hepatic GVHD.

In an attempt to clarify the distinguishing gray-scale and Doppler findings in hepatic venoocclusive disease, we prospectively performed serial B-scans and duplex color Doppler sonography on 65 patients before and after bone marrow transplantation.

Subjects and Methods

From February 1990 to March 1991, 65 recipients of bone marrow transplants were prospectively studied with serial B-scans and duplex color Doppler sonography of the abdomen. All examinations were performed by using an Acuson 128 (Mountain View, CA) unit with a 3.5-MHz transducer for imaging and Doppler evaluation. All patients fasted a minimum of 8 hr before the study. Sixty-two patients had a pretreatment baseline sonogram, and all 65 patients had gray-scale and Doppler assessment in the third week after transplantation. Additional sonographic studies were performed in those patients in whom biochemical evidence of hepatic venoocclusive disease developed (bilirubin ≥60 μmol/l; this bilirubin level was selected in an effort to differentiate hepatic venoocclusive disease from mild GVHD). Initial sonograms were obtained within 24 hr of tests that showed elevated levels of bilirubin. Two scans per week were obtained until either the hepatic abnormality resolved or the patient died. Venoocclusive disease was clinically graded according to criteria of Bearman et al. [8], which are based on the degree of biochemical hepatic dysfunction (bilirubin >34 μmol/l) and fluid overload (weight gain >2.5% from baseline).

Each sonographic examination included a full gray-scale assessment of the abdomen with particular attention to liver size and texture. Features noted included thickening of the gallbladder wall (>10 mm), dilatation of the biliary ducts, and ascites. Doppler flow-velocity profiles were obtained in the main portal vein; right and left portal vein branches; right, middle, and left hepatic veins; and the inferior vena cava. All Doppler data were obtained with the patient supine. The presence and direction of flow were recorded, and the peak flow velocity in each vessel was measured by using a 3.5-MHz transducer and a 30–60° angle of insonation. Flow in the hepatic artery was assessed at the point where the artery courses over the main portal vein. An absolute peak systolic velocity in the hepatic artery was not measured. Instead, the hepatic artery resistive index (RI) was calculated; this parameter is independent of the angle of insonation. The RI was calculated several times during each study, and an average value was recorded. Statistical analysis of the RI values for the different patient groups included paired t-test analysis for baseline vs maximum values in patients with venoocclusive disease, and unpaired t-test analysis for maximum values in patients with venoocclusive disease vs maximum values for other disease groups.

Twenty control subjects also were studied in order to establish normal Doppler flow values in the portal and hepatic venous systems and to determine a normal range for the hepatic artery RI.

Results

All 20 control subjects had continuous pulsatile flow within the main portal vein and its right and left branches (Fig. 1A). The mean peak portal vein velocity was 51 cm/sec (range, 15–88 cm/sec). The inferior vena cava and hepatic veins showed phasic velocity profiles reflecting hemodynamic changes in the right atrium (Fig. 1B). The mean peak velocity in the inferior vena cava was 81 cm/sec (range, 44–118 cm/sec), and the mean peak velocity in the hepatic veins was 38 cm/sec (range, 16–61 cm/sec). The mean hepatic artery RI for the control group was 0.69 (range, 0.58–0.76).

Venoocclusive disease of the liver developed in 19 of the bone marrow transplantation patients (Table 1). The diagnosis was based on histologic findings in 10 cases and on clinical and biochemical findings in nine. Hepatic GVHD developed in nine patients and was histologically proved in eight. In five

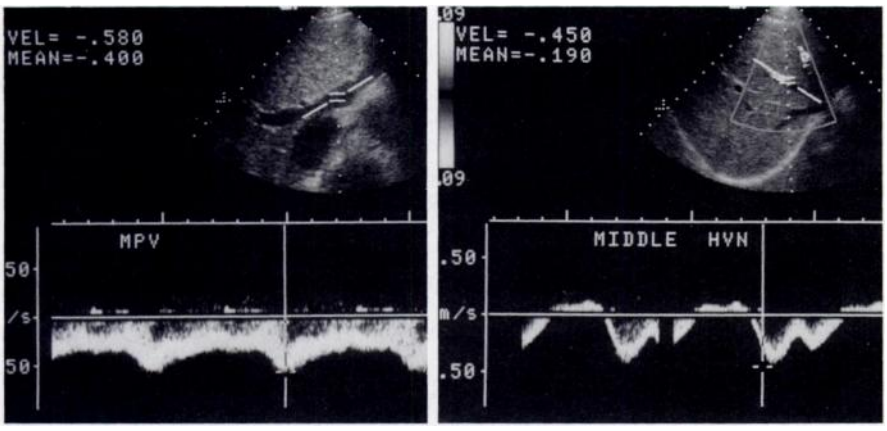

Fig. 1.—Control subject.
***A*, Spectral waveform shows normal continuous pulsatile flow in main portal vein. Peak and mean portal vein velocities are indicated.**
***B*, Spectral waveform shows a normal phasic velocity profile in middle hepatic vein. Peak and mean hepatic vein velocities are indicated.**

patients, GVHD developed after proved venoocclusive disease. In two patients with elevated levels of liver enzymes, hepatitis was found by liver biopsy; 40 recipients of bone marrow transplants showed no clinical or biochemical evidence of liver dysfunction.

Thickening of the gallbladder wall (>10 mm) developed in eight patients after bone marrow transplantation. This occurred in two patients with venoocclusive disease, two with GVHD, the two with hepatitis, and two with normal liver function. Ascites was detected in 16 patients, and all patients with thickening of the gallbladder wall had ascites. Ascites was detected in six patients with venoocclusive disease only, three with venoocclusive disease and subsequent GVHD, three with GVHD only, the two with hepatitis, and two with normal liver function. Hepatomegaly (n = 8) and altered liver texture (n = 3) were not specific to any disease state. No case of biliary dilatation was found.

The mean maximum hepatic artery RI for all patients with venoocclusive disease was 0.81 ± 0.037 (range, 0.75–0.87) (Table 1). An increase in RI above the initial baseline value was seen in 18 of 19 bone marrow transplant recipients in whom venoocclusive disease developed (Fig. 2). In each case, the increase in RI was detected within 24 hr of tests that showed a biochemical abnormality. In the 19th patient, poor signal quality prevented an adequate measurement of the RI. In 11 of 19 patients, the RI subsequently returned to values observed before bone marrow transplantation, and this change corresponded with resolution of the hepatic dysfunction. In seven of 19 patients, all of whom died, the last RI value obtained was elevated. The RI values in patients with venoocclusive disease were significantly higher than baseline RI values in those same patients ($p < .01$) and significantly higher than RI values in the control group ($p < .01$), in patients with isolated GVHD ($p < .01$), in patients without liver dysfunction after bone marrow transplantation ($p < .001$), and in the two patients with hepatitis ($p < .01$). However, an incremental rise in mean RI was not found with increasing clinical severity of venoocclusive disease. No significant difference was found in the mean hepatic artery RI between the group with pathologic proof of venoocclusive disease (n = 10) and the group with biochemical and clinical evidence of venoocclusive disease (n = 9). GVHD subsequently developed in five patients with histologically proved venoocclusive disease; all five had a significantly elevated hepatic artery RI during the course of venoocclusive disease, but RI values in all these patients returned to normal and remained so during the course of GVHD.

Normal flow velocities were seen in the hepatic veins and inferior vena cava in all patients during this study. We found no significant difference in the mean peak velocity flow values

TABLE 1: Hepatic Artery Resistive Index in Control Subjects and in Patients Before and After Bone Marrow Transplantation

Group	No. of Subjects	Baseline RI Mean ± SD (Range)	Maximum RI Mean ± SD (Range)
Controls	20	0.69 ± 0.043 (0.58–0.76)	—
Venoocclusive disease			
Grade I	5 (1)		0.80 ± 0.053 (0.75–0.87)
Grade II	8 (3)		0.82 ± 0.041 (0.77–0.86)
		0.68 ± 0.042 (0.55–0.71)	
Grade III	3 (1)		0.78 ± 0.031 (0.75–0.81)
Grade IV	3 (0)		0.80 ± 0.016 (0.79–0.83)
Graft-vs-host disease	9	0.64 ± 0.037 (0.58–0.70)	0.69 ± 0.030 (0.63–0.71)
Hepatitis	2	0.69 ± 0.028 (0.67–0.71)	0.66 ± 0.028 (0.64–0.68)
No liver dysfunction	40	0.66 ± 0.022 (0.57–0.69)	0.66 ± 0.019 (0.61–0.71)

Note.—RI = resistive index. Figures in parentheses after number of subjects indicate number of patients with subsequent graft-vs-host disease. Clinical grading of venoocclusive disease was done according to Bearman et al. [8].

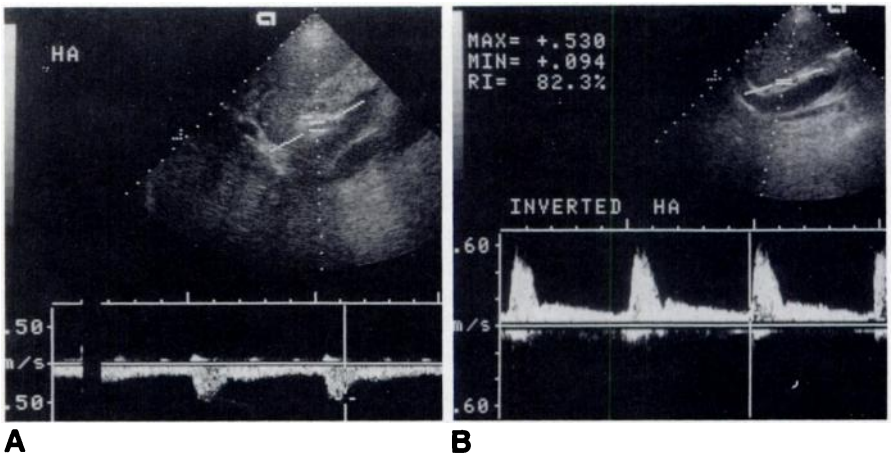

Fig. 2.—Recipient of bone marrow transplant.
***A*, Spectral analysis shows calculated baseline resistive index (RI) was normal (0.65) before conditioning chemotherapy/radiotherapy.**
***B*, Spectral analysis 8 days after bone marrow transplantation shows RI increased significantly to 0.82. Patient had biopsy-proved grade II venoocclusive disease.**

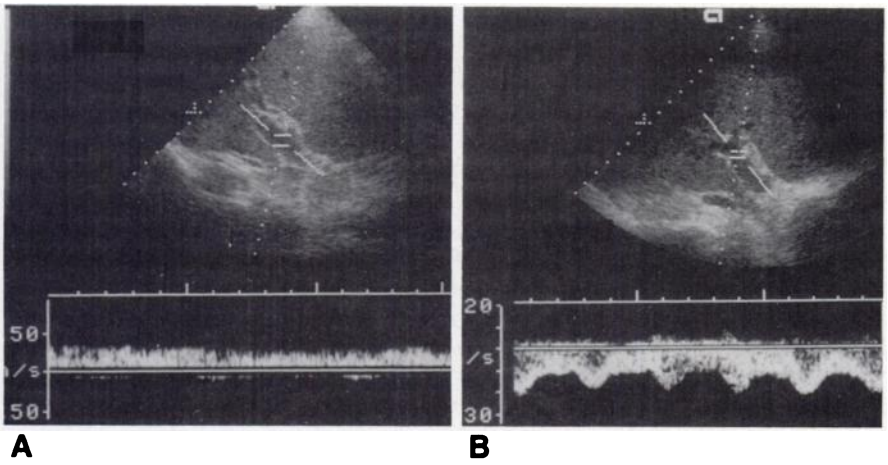

Fig. 3.—Patient with biopsy-proved grade IV venoocclusive disease after bone marrow transplantation.

***A*, Spectral analysis shows normal antegrade portal venous flow 7 days after bone marrow transplantation.**

***B*, Spectral analysis shows reversed portal venous flow 20 days after bone marrow transplantation. Patient subsequently died.**

between control subjects and the various groups of patients. The hepatic vein mean peak velocity was 49 cm/sec (range, 13–86 cm/sec), and the inferior vena cava mean peak velocity was 103 cm/sec (range, 26–180 cm/sec) for the combined patient groups. Normal portal venous flow was seen in 63 of 65 recipients of bone marrow transplants. In these patients, the mean peak portal vein velocity was 52 cm/sec (range, 13–90 cm/sec). Altered portal venous flow was seen in only two of the 65 recipients of bone marrow transplants. In one patient with fatal venoocclusive disease, a progressive decrease and eventual reversal of portal flow was seen (Fig. 3); this change was accompanied by a rise in RI from a baseline 0.68 to 0.82 at the onset of clinical venoocclusive disease. The RI remained elevated until the patient's death. The second patient had chronic hepatic GVHD but normal findings on serial sonographic examinations until the acute onset of massive ascites. Despite sonographic evidence of portal vein thrombosis at that time (Fig. 4A), neither a significant change in hepatic function nor any elevation in the hepatic artery RI occurred (Fig. 4B).

Discussion

Real-time sonography is frequently used in recipients of bone marrow transplants to detect the presence of ascites, to assess causes of liver dysfunction, and to determine the presence or absence of hepatic and portal vein thrombosis. The role of Doppler spectral analysis remains controversial. The pathogenesis of venoocclusive disease is thought to involve endothelial damage leading to activation of the coagulation cascade, fibrin deposition, and eventually fibrous obliteration of the terminal hepatic venules [3, 4, 9]. The hemodynamic changes occurring as a consequence of this vascular damage may, in theory, be detectable with Doppler sonography. Moreover, since GVHD mainly affects small bile canaliculi and does not cause vascular damage, it is unlikely to cause alteration in flow characteristics.

In this study, we found that an elevated hepatic artery RI after bone marrow transplantation was highly suggestive of hepatic venoocclusive disease. None of our patients had an elevated RI in the absence of venoocclusive disease. This association between altered hepatic arterial flow and venoocclusive disease has not been previously reported. We are unable to explain the strong association between an elevated hepatic artery RI and hepatic venoocclusive disease; no correlation exists between the hepatic artery RI and liver transplant rejection [10].

In our series, an abnormality in portal vein velocity was seen in only one of 19 patients with venoocclusive disease: In this patient, portal vein flow reversed 20 days after transplantation, and the patient subsequently died. Although changes in portal flow in venoocclusive disease have been reported [4, 5, 7], the frequency of these abnormalities has not been studied prospectively. Brown et al. [4] reported changes in portal flow in six of six patients with proved venoocclusive disease. Kriegshauer et al. [7] detected portal flow reversal in one case of fatal venoocclusive disease. In a study by Morris et al. [5], two of three children had reversed portal flow. The severity of venoocclusive disease in these patients was not indicated. Our observations suggest that detectable alteration of portal flow occurs infrequently even with severe (grade IV) venoocclusive disease. Portal velocity profiles were not useful in our series in distinguishing mild, moderate, or severe venoocclusive disease from GVHD. Moreover, contrary to the report by Ralls [11], our two patients with altered portal flow did not have increased systolic velocity in the hepatic artery or altered hepatic artery RI.

We cannot definitely identify the mechanism responsible for the elevated hepatic artery RI in the absence of detectable change in portal flow, a phenomenon that occurred in all but one of our 19 patients with venoocclusive disease. Possibly, endothelial damage occurring in venoocclusive disease causes an increase in resistance to flow in the hepatic artery before the development of portal hypertension. Alternatively, Doppler imaging within the portal veins may not detect small or early rises in portal pressure, and the elevated RI might result from elevated presinusoidal pressure associated with an expanded intravascular volume. However, we think that volume overload is not a sufficient explanation for these findings. First, although salt and water retention are prominent features of venoocclusive disease, most of the retained fluid is located in the extravascular space. The RI remained ele-

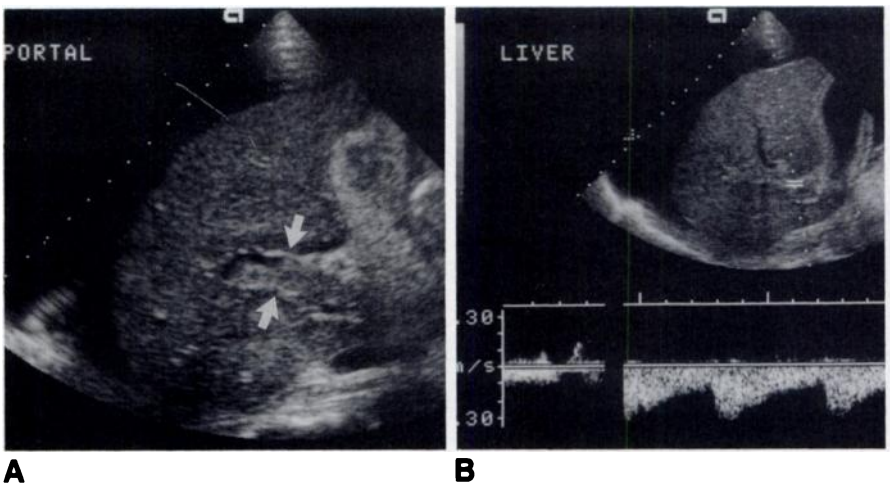

Fig. 4.—Patient with histologically proved graft-vs-host disease after bone marrow transplantation.

***A*, Sonogram shows ascites, abnormal liver texture, and portal vein thrombosis (*arrows*).**

***B*, Spectral analysis shows a normal hepatic artery waveform despite the presence of portal vein thrombosis. The calculated resistive index was normal (0.67).**

vated in six of our venoocclusive disease patients after diuretic therapy and clinical evidence of intravascular volume depletion. Moreover, RI values were normal in two patients who had severe GVHD and marked intravascular fluid overload.

Other parameters assessed in this study were not useful as distinguishing features of venoocclusive disease. Thickening of the gallbladder wall and the presence of ascites were seen both in venoocclusive disease and in other causes of hepatic dysfunction with equal frequency.

Differentiation of venoocclusive disease from GVHD may be difficult. In our experience, reversal of portal flow is an uncommon event that may occur in fatal venoocclusive disease. Elevation of the hepatic artery RI is a more sensitive index of liver damage related to venoocclusive disease and was the only distinguishing sonographic feature in our study. However, clinical grading of venoocclusive disease does not correlate with any incremental rise in the RI value.

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