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Color ultrasound-guided fine-needle cutting biopsy for the characterization of diffuse liver damage in critical bone marrow transplanted patients

MARCO PICARDI,* PIETRO MURETTO,° GENNARO DE ROSA,* CARMINE SELLERI,* AMALIA DE RENZO,* MARCELLO PERSICO,# BRUNO ROTOLI*

*Division of Hematology, Federico II University Medical School; #Hepatology Unit, II University, Naples; °Pathology Unit, San Salvatore Hospital, Pesaro, Italy

Correspondence: Prof. Bruno Rotoli, Divisione di Ematologia, Nuovo Policlinico, via S. Pansini 5, 80131 Naples, Italy. Phone:international +39.081.7462068. Fax: international +39.081.7462165. E-mail: rotoli@unina.it

Background and Objectives. The optimal method for liver biopsy in patients with simultaneous bone marrow and liver impairment has not yet been established. New approaches (e.g. imaging-guided methods) for this procedure are needed. In spite of coagulopathy, immunosuppression, anemia or ascites, we histologically characterized liver damage in a series of bone marrow transplanted patients using color-Doppler ultrasonography, which permits very keen visualization (and assessment) of hepatic parenchyma and vessels, and a fine needle for percutaneous biopsy.

Design and Methods. We performed percutaneous liver biopsy using a Menghini-type automatic very fine cutting needle (1.2 mm, 18G) under color ultrasound guidance in 16 bone marrow transplanted adult patients consecutively seen in our units from 1998 to 2001. The patients had clinically defined diffuse serious liver damage; liver biopsy was performed between 3 and 10 months after allogeneic (n= 11) or autologous (n= 5) transplantation.

Results. Fifteen patients tolerated the procedure well and had no discomfort, while one patient developed intrahepatic hemorrhage. All liver biopsies were suitable for histologic examination and informative, revealing the specific etiology of liver damage: graft-versus-host disease in six patients, drug toxicity in five, hepatitis C virus acute reactivation in two, and in one each vanishing bile duct syndrome, nodular regenerative hyperplasia and hemochromatosis. Biopsy detected potentially injurious concomitant factors, e.g., occult intrahepatic hepatitis B virus infection and reactivation. Histology radically changed the presumptive clinical diagnosis in 10 of the 16 patients and led to successful treatment changes in six.

Interpretation and Conclusions. Percutaneous biopsy with a small cutting needle under color ultrasound guidance carries a low risk of complications and provides reliable information regarding liver histology in critically ill patients, in the early stage after bone marrow transplantation. We suggest including this imaging-guided mini-invasive procedure to the standard work-up of post-transplant liver damage.

Key words: percutaneous liver biopsy, color ultrasound scan, liver damage, bone marrow transplant.

Liver complications are a serious clinical problem in patients with hematologic malignancies undergoing bone marrow transplantation (BMT). Morbidity and mortality due to hepatic failure appear to have a significant impact on survival of transplanted patients.[1,2] A variety of factors may induce liver damage, a combination of which may occur simultaneously or sequentially in the same patient.[1,2] The etiology of liver damage is evaluated nowadays by non-invasive studies, while histology is reserved for occasional cases, especially when serious bone marrow impairment co-exists.[3,4] We investigated the role of color ultrasound-guided percutaneous biopsy using a fine cutting needle with automatic aspiration, for etiologic diagnosis of liver damage in patients after BMT for hematologic malignancies, and compared the histologic diagnosis with the presumptive clinical diagnosis.

Design and Methods

Over the last 4 years, sixteen consecutive patients who had undergone BMT presented with severe or life-threatening liver damage, in the absence of focal lesions (Table 1). Their median serum transaminase level was 635 U/L [(range 90-3396; upper normal limit (UNL)= 40)], total bilirubin 10 mg/dL (1.6-50; UNL= 1), alkaline phosphatase 535 U/L (100-900; UNL= 275) and glutamyl-transpeptidase 720 U/L (47-2000; UNL= 50). Two patients had grade II hepatic encephalopathy. Except three who had shown mild hypertransaminasemia (2.5 × normal value), all patients had had normal liver function tests before their transplant. For allo-transplanted patients, graft-versus-host disease (GvHD) prophylaxis was cyclosporin A (for 6 months) and short-course methotrexate.[5] Evaluation before biopsy included history, physical examination, serum bilirubin, liver enzyme determination, iron status, search for viral markers, blood count, prothrombin time (PT) and partial thromboplastin time, fibrinogenemia, and color-Doppler ultrasound scans.[6-9] The clinical

Table 1. Patients' characteristics at the time of biopsy.

Pt	Age (years), sex	Disease, BMT	Preparative regimen*	Months from BMT	Platelet count ($\times 10^9$/L)	Viral status	Drugs in use
1	45, M	AML, Allo	BU-CY	7	80	negative	PDN 50, CsA 100
2	55, M	CML, Allo	BU-CY	5	80	HBsAb+	PDN 75, CsA 300, FLC 300
3	37, M	CML, Allo	BU-CY	9	80	negative	PDN 100, CsA 300, FLC 300
4	40, M	AML, Allo	BU-CY	6	80	negative	PDN 25, CsA 300
5	30, M	AML, Allo	BU-CY	6	45t	negative	PDN 50, CsA 150
6	20, F	ALL, Allo	BU-CY	6	60	negative	PDN 25, CsA 100
7	30, F	AML, Allo	BU-CY	8	60	HBsAb+/cAb IgG+	PDN 75, CsA 150
8	21,F	CML, Allo	BU-CY	3	45t	negative	MPD 60, CsA 150, ITRA 300, ACY 1500
9	38, M	CML, Allo	BU-CY	10	40t	negative	MPD 625, CsA 300, FLC 300, ACY 1500, TPN
10	55,M	NHL, Allo	THIO-CY	5	20t	HBsAb+/eAb+/cAb IgG+	MPD 625, CsA 100, ITRA 200, ACY 1500, TPN
11	27, M	HL, Allo	BU-CY	5	80	HBsAb+	PDN 25, CsA 300, CLA 1000, ITRA 400, CYC 1500
12	40, F	AML, Auto	BU-CY	7	80	negative	none
13	38, F	HL, Auto	BEAM	7	80	negative	none
14	35, M	NHL, Auto	THIO-CY	3	60	HBsAb+/eAb+/cAb IgG+	none
15	52, M	AML, Auto	BU-CY	7	60	HCV-Ab+/RNA+	none
16	44, M	HL, Auto	BEAM	4	60	HCV-Ab+/RNA+	none

*Allo= allogeneic BMT from HLA-identical sibling, Auto= autologous, CML= CML in chronic phase, NHL= aggressive NHL; PDN= prednisone mg/day, CsA= cyclosporin A mg/day, FLC= fluconazole mg/day, MPD= methylprednisolone mg/day, ITRA= itraconazole mg/day, ACY= acyclovir mg/day, TPN= total parenteral nutrition, CLA= clarythromycin mg/day. *According to standard doses (references #8 and #27); = patients who received platelet transfusion.*

diagnosis of liver damage, which was determined via these non-invasive studies, was subsequently compared with the histologic diagnosis. We considered contraindications to biopsy massive ascites, bile duct dilation or absolute absence of patient co-operation.[10] A platelet transfusion (single-donor pheresis unit) was administered on the day of the procedure if the platelet count was less than 50×10^9/L. For patients with PT < 50%, coagulation factors (Protromplex, Immuno AG, Wien, Austria, 5-10 U/kg i.v.) were administered on the day before biopsy. Vitamin K, broad-spectrum antibiotics and tranexamic acid were given to all patients the day before, the day of and the day after the procedure. A Hitachi instrument equipped with color-Doppler (EUB 525, Tokyo, Japan), a 2.5/3.5 MHz broad band curvilinear probe and puncture adaptor was used. After informed consent, a pre-biopsy color ultrasound map of intrahepatic vascularization was obtained using a large-size color box and parameters adjusted for slow-flow detection (1.5 Hz CF, 100 Hz band filter, high color persistence).[11,12] The information related to intrahepatic angioarchitecture was used to select the target zone for biopsy: the needle was preferably directed through relatively hypoperfused tissue, to avoid intervening vessels. After fasting and during slight inspiration, the procedure was carried out with an aseptic technique (sterile cover of the probe and sterile gel; Parker laboratories, Fairfield, NJ, USA) and cutaneous anesthesia, by two members of the hematology staff, using a 1.2 mm (18G) diameter Menghini cutting needle 150 mm in length with automatic aspiration (Biomol HS-Hospital; Rome, Italy). After biopsy, the patients remained in a supine position for 1 hour with monitoring of vital signs every 15 minutes; then abdominal ultrasound scan was repeated to look for procedure-related complications. In all cases, a repeat blood count was performed the next day.[13] Histopathologic examination was performed in a single Pathology Unit (S. Salvatore Hospital, Pesaro, Italy) and was blind to the patient's clinical conditions. Biopsies were considered diagnostic if a minimum of three portal spaces were present to permit evaluation of fibrosis and necrotic-inflammatory changes.[14,15] The histologic sections were analyzed according to standard methods;[2,16] in addition, immunoperoxidase staining for HBsAg and HBcAg, and *in situ* hybridization for HBV-DNA were carried out using standard procedures.

Results

At the time of the biopsy, all patients had abnormal blood count: neutrophils ranged between 0.8 and 2.4×10^9/L (median 1.2), lymphocytes 0.2-2.0×10^9/L (median 1.0), hemoglobin 7.5-11 g/dL (median 10) and platelets 20-80×10^9/L (median 60). Four patients had mild to moderate ascites. Eleven patients were receiving steroids and CsA. Four patients received single-donor pheresis units

Table 2. Clinical and histologic diagnoses, and changes in therapeutic approach following liver biopsy.

Pt.	*Clinical diagnosis*	*Histological diagnosis*	*Change in treatment*	*Patient outcome (months from biopsy)*
1	GvHD	GvHD	increase steroids and CsA	liver function normalization in 8 weeks (40+)
2	GvHD	drug toxicity	discontinue drugs in use	liver function normalization in 10 weeks (38+)
3	GvHD	NRH	discontinue drugs in use	no liver function improvement (30+)
4	GvHD	GvHD	increase steroids and CsA	liver function normalization in 7 weeks (28+)
5	GvHD	GvHD	increase steroids and CsA	liver function normalization in 9 weeks. Died of leukemia relapse (25)
6	GvHD	GvHD	increase steroids and CsA	liver function improvement. Died of leukemia relapse (18)
7	GvHD	GvHD and occult HBV infection	increase steroids, introduce lamivudine *	liver function improvement (18+)
8	GvHD	drug toxicity	discontinue drugs in use	liver function improvement (18+)
9	GvHD	drug toxicity	discontinue drugs in use	liver function improvement. Died of leukemia relapse (2)
10	GvHD	drug toxicity and occult HBV infection	none	expired for acute liver failure two days after biopsy
11	drug toxicity	GvHD	introduce steroids and CsA	liver function normalization in 8 weeks (28+)
12	drug toxicity	drug toxicity	none	liver function normalization in 10 weeks (22+)
13	lymphoma involvement	VBDS	introduce UDCA	liver function improvement (8+)
14	lymphoma involvement	hemochromatosis and occult HBV reactivation	introduce lamivudine*	liver function improvement. Died of lymphoma relapse (2)
15	HCV+ cirrhosis and drug toxicity	HCV+ active chronic hepatitis	none (§)	no liver function improvement (18+)
16	HCV+ cirrhosis and drug toxicity	HCV+ active chronic hepatitis	none (§)	no liver function improvement (4+)

*GvHD= chronic GvHD, NRH= nodular regenerative hyperplasia, VBDS= vanishing bile duct syndrome; UDCA= ursodeoxycholic acid 15 mg/kg/day orally. *100 mg/day orally; (§) the patient refused α-interferon and ribavirine treatment.*

the day of the biopsy (one for each patient) and two of them received additional pheresis units during and the day after the procedure (Table 1). A single patient (n# 10) received coagulation factor concentrate pre-biopsy, having a PT 40%.

Biopsy-related procedure and complications

In 14 patients the liver biopsy was performed in a day-hospital regimen; the remaining 2 were in-patients because of acute liver failure, and biopsy was carried out directly at the patient's bedside. The biopsy was performed 7 to 14 days (median 8) after the onset of signs of liver dysfunction not responding to medical management. The average time required for the procedure (including color ultrasound study) was about 35 minutes; the cutting needle crossed at least 5 cm of the right (12 cases) or left (4 cases) hepatic lobe by a sub-costal approach. Except a single case, neither major nor minor complications were observed during or after the biopsy; no patient required a surgical intervention and no biopsy-related peritoneal bleeding, peritonitis, sepsis or pain requiring analgesics occurred. All day-hospital patients left the hospital after 3 hours and maintained telephone contact for 24 hours; no biopsy-related hospitalization was needed for any of them. One of the in-patients (#10), who had a pre-biopsy total bilirubin 50 mg/dL and transaminase 1500 U/L developed abdominal pain, tachycardia and hypotension two hours after the biopsy. Ultrasound scan detected a large intrahepatic hematoma in the right lobe, without evidence of intraperitoneal hemorrhage; blood count showed severe anemia (6 g/dL) and thrombocytopenia (30×10^9/L). Intravenous fluids, three units of blood and two single-donor pheresis units were promptly administered. Two days later an aggravation of liver failure (grade IV encephalopathy) occurred and the patient died, despite resolution of the anemia. A *post-mortem* was not performed.

Histologic features

Histologic results were obtained 4 to 6 days (median 5) after biopsy. In all patients a single pass produced diagnostic tissue considered sufficient

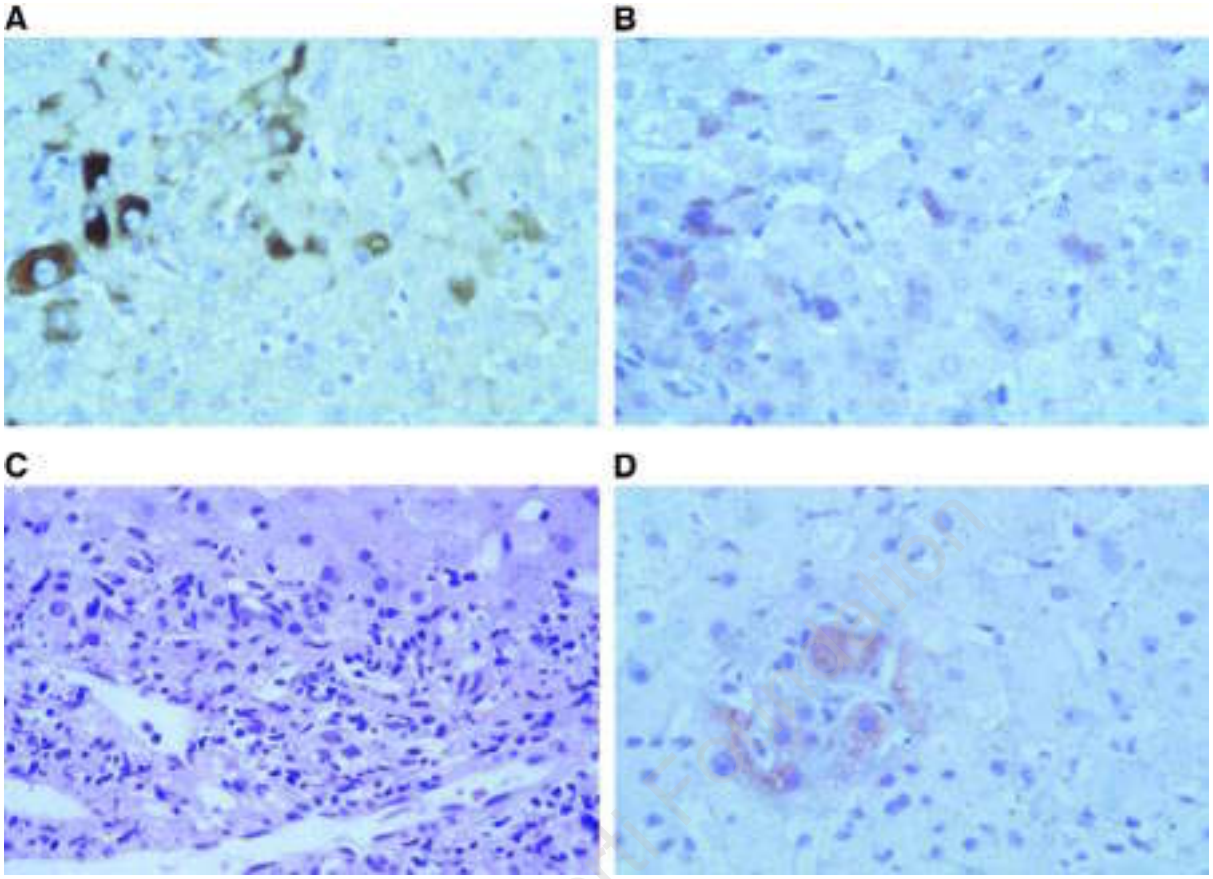

Figure 1. Representative histologic findings obtained after bone marrow transplant by fine-needle liver biopsy. (A) Intracytoplasmic HBsAg (immunoperoxidase staining) and (B) HBV-DNA (*in situ* hybridization) in a case of occult HBV reactivation; (C) lymphocyte infiltration in a portal space with cytolysis, lymphocyte satellitosis and bile ductule degeneration in a case of severe GvHD; (D) intracytoplasmic HBV-DNA suggesting an occult HBV infection in the same patient as in (C).

for histology. The samples obtained measured about 1 mm in diameter and ranged in length from 20 to 30 mm (median 25). All liver biopsies were informative, establishing the specific etiology of liver damage in all patients and completely or partially changing the presumptive clinical diagnosis in 11 of them (69%) (Table 2). Six patients had chronic GvHD, involving skin and lungs in 4 of them and limited to the liver in two. Five patients were suffering from direct drug toxicity demonstrated by the presence of typical toxic alterations (steatosis, binucleated hepatocytes and cholestasis) in the absence of signs of inflammation (portal space infiltration or fibrosis, bile duct proliferation). The two HCV-Ab$^+$ patients showed active chronic hepatitis characterized by portal space inflammation and fibrosis, and moderate hepatocyte necrosis related to acute reactivation of HCV infection (serum HCV-RNA: 0.25 copies $\times 10^{-6}$/mL, in both patients). One patient showed mild vanishing bile duct syndrome characterized by loss of interlobular bile ducts in about 30% of portal spaces, without evidence of infiltration by the basic disease (Hodgkin's lymphoma). One patient had developed nodular regenerative hyperplasia. One patient had active chronic hepatitis characterized by portal space inflammation, fibrosis and moderate hepatocyte necrosis related to severe iron overload. As a concomitant abnormal finding, liver biopsy detected an intrahepatic reservoir of HBV in three serum HBsAg-negative patients who had had only one previous viral contact (Table 1). In particular, two of them had occult HBV infection (intracytoplasmic HBV-DNA in about 30% of hepatocytes), while the other showed occult viral reactivation (intracytoplasmic HBsAg and HBV-DNA in about 40% of hepatocytes) (Figure 1).

Patients' outcome

Changes in therapeutic approach following biopsy and outcome for each patient are shown in Table 2. Altogether, in 12/16 patients the results of the histologic examination led to treatment modification which was followed by signs of improved or normalized liver function in eleven.

Discussion

We tested the feasibility, associated risk and diagnostic accuracy of an imaging-guided mini-invasive procedure used to assess the specific etiology of liver damage in a small series of critically ill patients in the early phase post-BMT. The procedure was easily and quickly carried out directly in the hematology unit by members of the hematology staff trained in diagnostic ultrasonography. Despite the reported significantly increased risk of percutaneous biopsy-related complications,[10,17,18] this occurred in only one case. Intrahepatic hematoma is a severe but non-fatal complication of percutaneous biopsy; conservative medical management is generally sufficient for recovery.[10,13,19] However, in our patient there was strict time-relationship between biopsy-related hematoma/anemia/hypotension and fatal liver failure. We cannot exclude that the biopsy played a role as a co-factor in precipitating the hepatic deterioration in this patient with underlying life-threatening liver disease related to non-viral (drug toxicity) and viral (occult HBV infection) agents.[20] Given the small number of patients, we cannot make absolute conclusions regarding safety, but we would like to underline the low incidence of complications and the excellent tissue samples obtained,[21] which were successful and informative in all instances. About 70% of presumptive clinical diagnosis were corrected by the histologic diagnosis; in most cases the biopsy-guided therapeutic changes led to improvement or normalization of liver function. Chronic GvHD presented itself as acute hepatitis in patients under tapering immunosuppression or receiving no immunosuppression, as already reported in other series.[22] Drug toxicity due to immunosuppressants, antimicrobials, transfusions or total parenteral nutrition was a frequent cause of damage, particularly after allogeneic BMT. Clinically significant liver damage related to acute HCV reactivation occurred in two non-cirrhotic HCV-infected patients, suggesting a more aggressive behavior of the virus when significant alteration of the immune response is induced in the host.[23] The intrahepatic presence of HBV genome in absence of signs of viral activity in the serum in three cases is intriguing; further dedicated studies are warranted in order to investigate a link between an occult intrahepatic HBV reservoir and triggering of hepatocellular injury.[20,24]

In conclusion, our study confirms that correct diagnosis and therapeutic management of a transplanted patient with serious liver damage should be guided by histologic assessment,[10,16,22] in order to avoid mistaken diagnoses and unnecessary, empirical and potentially injurious treatments. We suggest adding our imaging-guided mini-invasive procedure to the standard diagnostic work-up of post-BMT liver damage. Other more invasive, complex and expensive procedures used to obtain hepatic tissue, such as transjugular or laparoscopic biopsy,[25,26] should be limited to patients in the very early post-transplant phase and/or with very severe coagulopathy unresponsive to transfusion of hemoderivatives.[18]

Contributions and Acknowledgments

MP and BR conceived and drafted the study. PM, GDR, CS, ADR, and MP are listed in order of the amount of data they contributed.

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Disclosures

Conflict of interests: none.

Redundant publication: no substantial overlapping with previous papers.

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PEER REVIEW OUTCOMES

Manuscript processing

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What is already known on this topic

Nowadays, liver damage in critically ill patients after BMT may be evaluated by a transjugular or laparoscopic biopsy. These invasive methods are complex, expensive and not exempt from complications.

What this study adds

This study shows that percutaneous biopsy with a small cutting needle under ultrasound guidance is a good method to obtain hepatic tissue samples in these patients.

Potential implications for clinical practice

This mini-invasive procedure permits a correct diagnosis to be established in most cases and consequently an adequate therapeutic approach to be adopted.

Enric Carreras, Associate Editor