# Functional Asplenia in Patients with Chronic Graft-versus-Host Disease: Concise Communication

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**Liver/spleen images were performed with technetium-99m sulfur colloid in 53 patients who had undergone bone-marrow transplantation. The spleen was not seen in the images in five out of the ten patients with chronic graft-versus-host disease (GVHD). None of the five had a history of splenectomy. In two of these patients, anatomical presence of the spleen had been documented earlier by scintigram. The spleen was visible in all seven patients with acute and in all 36 patients without GVHD. Neither the differences in methods of treating the patients before bone-marrow transplantation nor the time lapse between transplantation and the liver/spleen image correlated with the observed effect among these three groups of transplant patients. We conclude that there is a high association between chronic GVHD and functional asplenia.**

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Allogeneic bone-marrow transplantation has been used increasingly for the management of patients with hematological malignancies or aplastic anemia (*1*). Two types of immunologic rejections occur: rejection of the grafted bone marrow by the host, and graft-versus-host disease (GVHD). Acute GVHD develops approximately 2 mo after transplantation and is believed to result from a direct cytotoxic reaction of donor cells against host alloantigens (*2*). Chronic GVHD develops 3 mo to 12 mo after transplantation (*3,4*), and in such patients an increased frequency of infections constitutes a major cause of morbidity and mortality (*4,5*).

Spleen imaging has been widely used for the evaluation of splenic size and the detection of disorders of the spleen. Nonvisualization of the spleen may indicate either anatomical or functional asplenia. Functional asplenia was first described in patients with sickle cell disease, in whom the spleen is anatomically present but functionally unable to accumulate radiocolloids (*6*). It has since been described in a variety of other conditions (*7–14*).

Recently we observed a bone-marrow transplant patient who had nonvisualization of his spleen on the liver/spleen image using Tc-99m sulfur colloid. There was no history of splenectomy, and an image done with Ga-67 citrate 4 mo before had revealed normal uptake of Ga-67 by the spleen. These findings suggested the possibility of functional asplenia. We thus undertook a retrospective study to determine the frequency of functional asplenia in patients with bone-marrow transplantation.

## METHODS

From November 1976 to July 1981, 300 patients with various hematological disorders were treated with bone-marrow transplantation at our hospital. Of these, 53 patients had liver/spleen images performed within 1 mo to 12 mo after transplantation. Thirty-five patients were male and 18 were female, age ranged 2.5 to 42 yr. The liver/spleen studies were done to evaluate liver and spleen for the presence of abscesses or metastases.

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**TABLE 1. Tc-99m SULFUR COLLOID SPLEEN IMAGES IN PATIENTS WITH BONE-MARROW TRANSPLANTATION**

| | Spleen scan | | | |
|---|---|---|---|---|
| | Uptake ↑ | Normal uptake | Uptake ↓ | Absent function |
| Acute GVHD | 2 (1)* | 5 (1) | — | — |
| Chronic GVHD | — | 4 (2) | 1 | 5 |
| No GVHD | 7 (2) | 29 (3) | — | — |
| Total | 9 (3) | 38 (6) | 1 | 5 |

* Numbers in parentheses indicate number of patients with enlarged spleen.

For the liver/spleen study, 5mCi (185.2 MBq) of Tc-99m sulfur colloid was injected intravenously. Imaging was performed 30 min after injection using a wide-field-of-view scintillation camera equipped with a low-energy, high-resolution, parallel-hole collimator. Eight views were obtained in each patient: anterior, posterior, both laterals, anterior and posterior obliques. The size of the spleen was gauged according to the criteria of Larson et al. (*13*). The intensity of the activity in the liver was used as a reference to determine whether tracer uptake in the spleen was increased, normal, or decreased.

## RESULTS

As shown in Table 1, nine of the 53 patients who had liver and spleen images performed 1–12 mo after a bone-marrow transplantation showed increased uptake of Tc-99m sulfur colloid by the spleen; one had markedly reduced splenic uptake; and five gave no splenic image. All five patients with absent splenic function, and also the patient with markedly reduced splenic uptake, were in the group of patients who developed chronic GVHD. None of these patients had a history of splenectomy.

We considered the possibility that a difference in methods of treatment of the patients before transplantation, or the delay between transplantation and liver/spleen imaging, could account for the difference in the spleen-image patterns in these three groups of bone-marrow transplant patients. As shown in Table 2, a larger proportion of patients (70%) who developed chronic GVHD had received total-body irradiation (1200 rad delivered in 4 days) as a part of the preparation for bone-marrow transplantation; more patients (40% compared with 30% for acute GVHD, and 22% for patients without GVHD) in this group had their liver/spleen images performed between 5–8 mo after transplantation. However, a sizable number of patients who did not develop any GVHD also received total-body irradiation (19 patients), and had spleen studies performed within this period (eight patients). None of the functionally asplenic patients received total nodal radiation therapy (including the spleen) before the liver/spleen study.

The following two patients are examples.

**Patient 1.** This 14-yr-old white female was admitted to our oncology center in February 1979 with a diagnosis of severe aplastic anemia of 6 mo duration. After preparation with cyclophosphamide and total-body irradiation, she received a bone-marrow transplantation from a genotypically HLA-identical sibling on March 1, 1979. The early posttransplant course was unremarkable and complete engraftment was demonstrated. On April 25, 1979, a Ga-67 citrate study was performed in search of a source of infection. There was normal Ga-67 uptake by the spleen (Fig. 1A). In June 1979, she was readmitted with diffuse interstitial pneumonia. She subsequently developed chronic persistent hepatitis, cutaneous chronic GVHD with poikiloderma and systemic sclerosis requiring imuran and prednisone therapy. A liver/spleen study done at this time (August 8, 1979) failed to show the spleen (Fig. 1B).

In July 1981, she was again admitted with *Streptococcus pneumoniae* sepsis and markedly worsened chronic GVHD. Her infection cleared with appropriate antibiotics, but the chronic GVHD could not be controlled despite the institution of procarbazine, cyclophosphamide, and cyclosporin A. A repeat liver/spleen study done on August 25, 1981, showed no change from the previous study (Figs. 1B compared with 1C). She was

**TABLE 2. METHODS OF PREPARATION FOR BONE-MARROW TRANSPLANTATION AND DELAY BETWEEN TRANSPLANTATION AND SPLEEN IMAGE**

| | Acute GVHD | Chronic GVHD | No GVHD |
|---|---|---|---|
| Methods of preparation* | | | |
| Bu, Cy | 3 | 3 (1)† | 13 |
| Cy, TBI | 1 | 7 (4) | 14 |
| Cy, Dox | | | 1 |
| CDV, TBI | | | 2 |
| Cy | 2 | | 3 |
| Cy, Dox, TBI | | | 3 |
| Procarb, ATG, TBI | 1 | | |
| Duration | | | |
| 1–4 mo | 5 | 3 (3) | 22 |
| 5–8 mo | 1 | 4 (1) | 8 |
| 9–12 mo | 1 | 3 (1) | 6 |

* Bu = busulfan; Cy = cyclophosphamide: TBI = Total-body irradiation; Dox = doxorubicin; CDV = cytoxan, doxorubicin, vincristine; Procarb, procarbazine; ATG, antithymocyte globulin.

† Numbers of parentheses indicate number of patients with no splenic visualization in image.

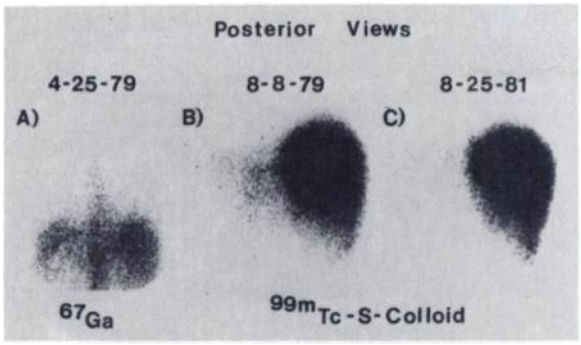


**FIG. 1.** (A) Gallium-67 citrate image; (B) and (C) Posterior Tc-99m sulfur colloid liver/spleen images from Case 1. Note that spleen was normal in Ga-67 study but was absent in both Tc-99m sulfur colloid images.

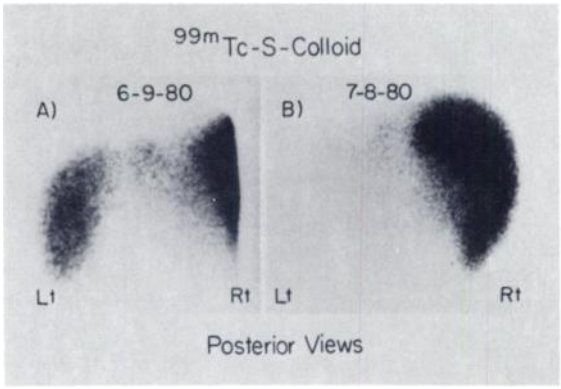


**FIG. 2.** Tc-99m sulfur colloid liver/spleen images (a and b) from Case 2.

then treated with total lymphoid irradiation, with marked improvement of her chronic GVHD. In April 1982, after 3 mo of apparent well-being, she developed fatigue and weakness. She was seen at a local hospital and died a few hours after the onset of the symptoms. No autopsy was performed.

*Comment.* This patient had a normal Ga-67 spleen image shortly after bone-marrow transplantation. She developed chronic GVHD 3 mo later and a liver/spleen study showed functional asplenia, which lasted for at least 2 yr.

**Patient 2.** This 13-yr-old boy, with acute lymphocytic leukemia in second remission, was admitted to our oncology center for bone-marrow transplantation. After preparation with cyclophosphamide and fractionated total-body irradiation, he received a genotypically HLA-identical bone-marrow graft on March 21, 1980.

His early posttransplant course was complicated by multiple bacterial infections, but the marrow engrafted with good hematological recovery except for a mild persistent thrombocytopenia. Three months later he developed chronic GVHD, with poikiloderma, chronic active hepatitis, and malabsorption. A liver/spleen study done at this time (June 9, 1980) showed normal splenic function (Fig. 2A). Because of his persistent thrombocytopenia, he tolerated the therapy with imuran and prednisone poorly, requiring the discontinuation of imuran. A repeat liver/spleen study 1 mo later (July 12, 1980) failed to show the spleen (Fig. 2B). Under high doses of methylprednisolone have chronic GVHD stabilized, but frequent infectious complications occurred. His chronic GVHD resolved over the ensuing 2 yr, and currently he is doing well on prophylactic antibiotics.

*Comment.* This patient developed functional asplenia approximately 1 mo after the diagnosis of chronic GVHD.

## DISCUSSION

In this study we found a marked association between the development of chronic GVHD and functional asplenia in patients with bone-marrow transplantation. Of the ten patients who developed chronic GVHD and had liver/spleen studies performed, five had nonvisualization of the spleen. None of these five had a history of splenectomy. Anatomical presence of the spleen was documented by scintigram in two of these patients. Unfortunately, because of the retrospective nature of this study, information on the red-cell abnormalities (Howell-Jolly bodies, nucleated red cells, etc.) that may indicate the presence of asplenia (*6*) was not available in most patients. Thus, we were unable to establish clearly that in the other three patients, functional asplenia developed after bone-marrow transplantation. However, it is unlikely that these patients had congenital asplenia, since this is rare and is usually associated with congenital cardiovascular, pulmonary, and abdominal anomalies (*14,15*). Thus, these five patients most likely had functional asplenia. A functioning spleen was observed in all patients who developed acute GVHD or none at all. Neither the difference in methods of preparation for bone-marrow transplantation, nor the delay between transplantation and the time of liver/spleen images, correlated with the observed difference in the spleen-image patterns among these three groups of patients.

Functional asplenia may result from vascular occlusion, leading to infarction or hypoxia, or be due to hypofunction of splenic macrophages (*11,12*). In some cases, the cause of functional asplenia is uncertain; in some, the functional asplenia is transient and reversible (*7,11,18*). Although the most common cause of functional asplenia is sickle-cell disease, it has been described in a variety of conditions: other hemoglobinopathies (*7,8*), splenic-artery occlusion (*9*), splenic-vein thrombosis (*9*), metastatic breast carcinoma (*10*), chronic aggressive hepatitis (*11*), retained splenic thorotrast (*13*), celiac sprue (*13*), cyanotic congenital heart disease (*14*), and mixed immunological disorders (*11*).

The pathogenesis of functional asplenia in patients with chronic GVHD is not clear. We did not have the opportunity to examine the spleen microscopically in any

of these patients. It is also unclear whether the functional asplenia in this condition is reversible. It is possible that functional asplenia may contribute to the increased frequency of infections in patients with chronic GVHD. A more detailed prospective study will be necessary to answer these important questions.

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