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Letters to the Editor

Evidence of a Graft-versus-Hodgkin Lymphoma Effect in the Setting of Extensive Bone Marrow Involvement

Although a graft-versus-malignancy effect is well documented in many hematologic malignancies [1], the issue of whether a graft-versus-Hodgkin lymphoma (HL) effect does exist has been the subject of considerable controversy [2]. Responses to donor leukocyte infusions (DLIs) are often viewed as the gold standard to establish a graft-versus-HL effect. DLI response rates (complete plus partial responses) reported in the literature in patients not receiving concomitant salvage chemotherapy are in the 30%-40% range [3,4]. Achievement of a complete response after DLIs is associated with the development of acute or chronic GVHD (aGVHD, cGVHD) [3]. In these cases, objective documentation of disease progression by biopsy or disease regression by imaging or other diagnostic studies is not usually provided. Moreover, it is not clear whether responses can be achieved even in patients with disseminated, high-volume disease (eg, extensive marrow involvement), or primarily in patients with localized, low-volume tumor burden.

A 26-year-old man was diagnosed with stage IIB "bulky" HL in November 2003. He failed to respond to ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), and achieved a partial response to ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin). In October 2004, he underwent BEAM (carmustine, etoposide, cytarabine, melphalan) high-dose chemotherapy and autologous peripheral blood stem cell transplantation (PBSCT). In January 2005, restaging revealed disease progression and he received salvage chemotherapy with COPP (cyclophosphamide, prednisone, procarbazine, vincristine) for 3 cycles, leading to a partial response.

On May 5, 2005, the patient underwent an unmanipulated matched unrelated donor marrow transplant. His conditioning regimen included fludarabine, melphalan, and thymoglobulin. He was treated as part of an institutional review board (IRB)-approved protocol, and he provided written informed consent.

He achieved 100% donor-derived engraftment by peripheral blood chimerism studies and an initial complete remission with his day 30 restaging (July 2005). Around that time he also developed limited, biopsy-proved, steroid-responsive cutaneous GVHD. He subsequently reported low back pain, and in November 2005, a 2-deoxy-2-[18F]fluoro-D-glucose (FDG) positron emission tomography/computed tomography (PET-CT) study showed a hypermetabolic hypodense lesion in the marrow of the right sacral ala. A pelvic magnetic resonance imaging study in February 2006 showed an infiltrative process involving the right

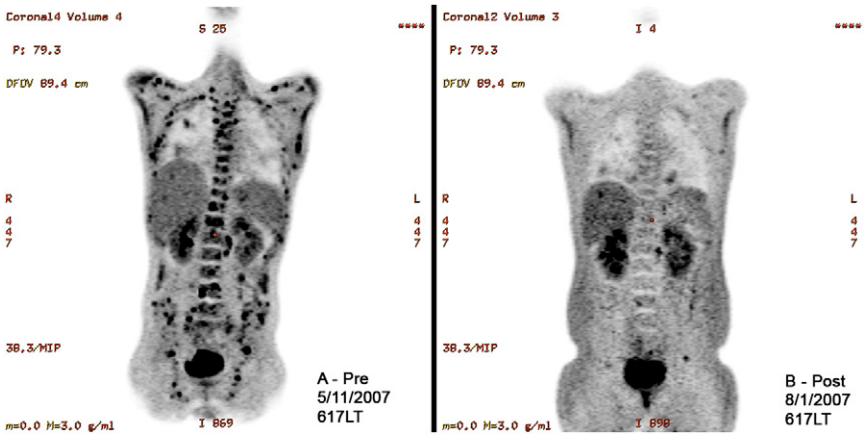

Figure 1. (A, left) This displays the May 11, 2007, positron-emission tomography (PET)-computed tomography (CT) scan showing recurrent disease with multiple, extensive PET-positive lesions throughout the skeleton, and retroperitoneal adenopathy. (B, right) This shows the August 1, 2007, PET-CT study showing complete resolution of the multifocal osseous as well as nodal lesions. PET scans were acquired following the intravenous injection of 16.9 mCi of 2-deoxy-2-[18F]fluoro-D-glucose (FDG), and noncontrast enhanced CT scans were acquired for attenuation, correction and, diagnosis.

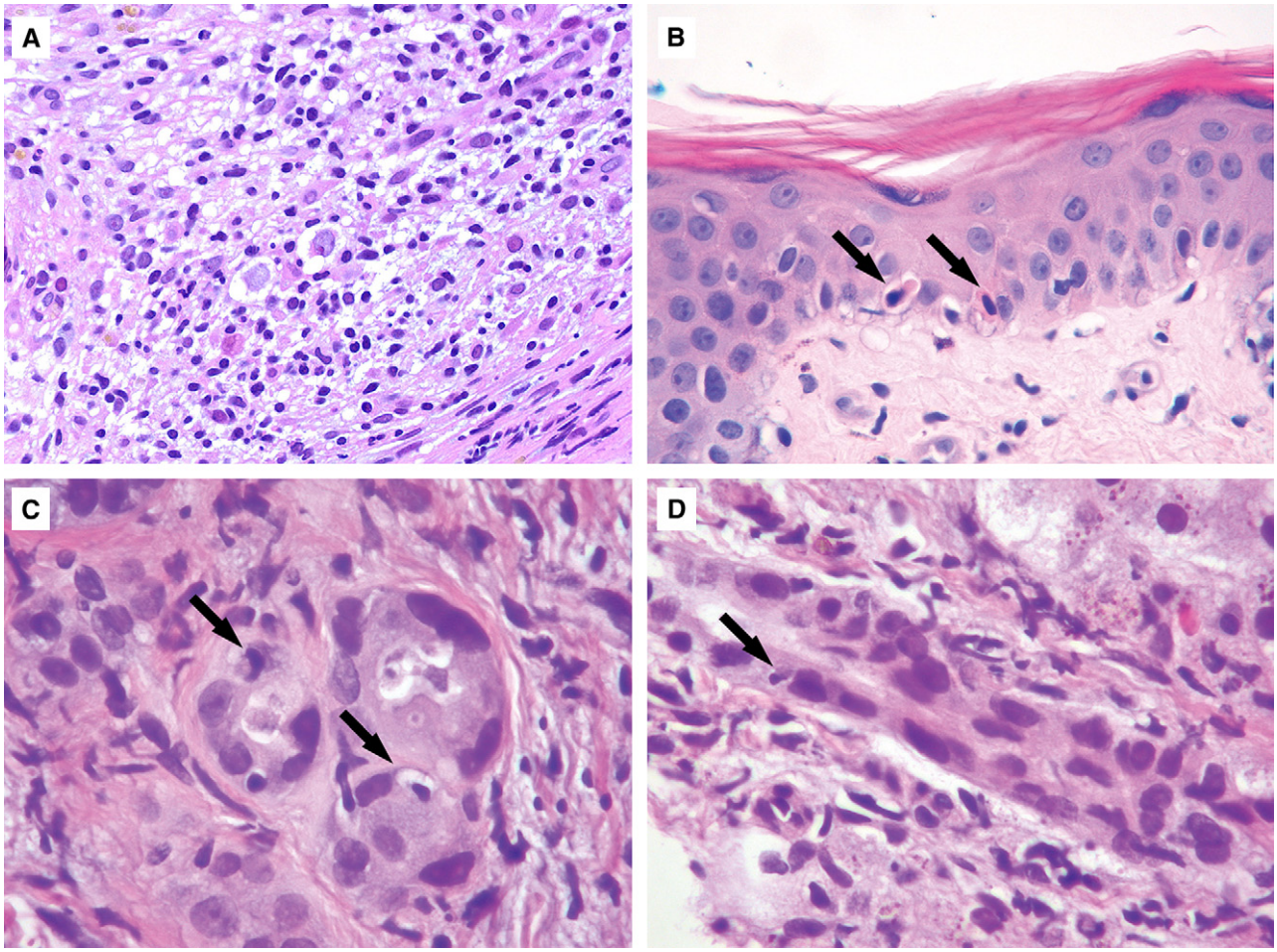

Figure 2. Bone marrow biopsy (A) showing Hodgkin cells (center) in a background of small lymphocytes, histiocytes, and marrow fibrosis. Original hematoxylin & eosin (H&E), ×500 magnification. Skin biopsy (B) showing necrotic keratinocytes (arrows) indicating cutaneous GVHD (original H&E stain, ×400 magnification). Transjugular liver biopsy (C and D) showing bile-duct damage with necrotic cholangiocytes (arrows) consistent with hepatic graft-versus-host disease (original H&E stain, ×400 magnification).

sacrum and the posterior right ilium, as well as probable involvement of L3 and L5. A biopsy of the right sacral-based mass in February 2006 revealed recurrent HL, establishing a reliable correlation between FDG PET imaging and histologic findings.

The patient received 2 courses of pentostatin, followed by a first DLI on May 4, 2006. The $CD3^+$ cell dose infused was 5×10^6 $CD3^+$ cells/kg. This was followed by mild, steroid-responsive skin GVHD but no disease response. An FDG PET-CT scan in mid-June 2006 documented marrow involvement with multiple hypermetabolic osseous lesions involving ribs, thoracic and lumbar spine, bilateral iliac bones, and sacrum.

Shortly thereafter, the patient was treated with 2 cycles of hyperfractionated cyclophosphamide, followed by a second DLI with $2\times$ 10^7 $CD3^+$ cells/kg (August 31, 2006). He then developed abdominal pain and profuse watery diarrhea, and was found to have biopsy-proved gastrointestinal GVHD. He required high-dose methylprednisolone (MP), tacrolimus, infliximab, budesonide, and pentostatin for GVHD treatment. Restaging in October 2006 revealed a complete response, with resolution of his multiple PET-positive marrow-based lesions.

In mid-May 2007 he again was diagnosed with recurrent disease with multiple FDG PET-positive osseous lesions throughout the skeleton and retroperitoneal adenopathy. Maximal standardized uptake values (SUVs) varied with the location of the skeletal lesions, ranging from 5.7 to 12.6 (Figure 1A). A bone marrow biopsy confirmed marrow involvement with HL (Figure 2A). Although the patient was being considered for investigational salvage agents, he developed a skin rash and jaundice (serum total bilirubin peaking at 13.3 mg/dL). A skin biopsy (June 20) showed GVHD (Figure 2B), and a transjugular liver biopsy (June 22) showed bile-duct damage consistent with GVHD and no evidence of lymphoma infiltration (Figure 2C and D). The patient was started on MP (200 mg intravenously daily), tacrolimus, and

extracorporeal photopheresis. His jaundice and his skin rash resolved, and an MP taper was started. Three weeks later (July 24, 2007) his MP dose was down to 32 mg/day. On August 1, 2007, a follow-up FDG PET-CT scan on that day showed dramatic and complete resolution of the tracer uptake in the multifocal marrow-based lesions as well as resolution of his retroperitoneal adenopathy. The lytic lesions in the marrow demonstrated interval calcification in keeping with response to treatment (Figure 1B). At that time, he was receiving low-dose MP (8 mg/day), tacrolimus (1 mg every other day), and weekly extracorporeal photopheresis. A follow-up bone marrow biopsy (August 17, 2007) showed a hypocellular marrow and no evidence of HL infiltration. At that time the patient's MP dose had been further reduced to 4 mg/day. At his latest follow-up (October 2, 2007), his HL remains in clinical remission. His MP dose remains 4 mg/day, and his tacrolimus dose is 0.5 mg every other day.

We believe this case provides vivid, objective documentation that a powerful graft-versus-HL effect exists even in patients with disseminated and extensive disease (including marrow involvement), albeit overlapping in this case with severe skin and hepatic GVHD. Although it cannot entirely be ruled out that steroid therapy started for GVHD may have contributed to the most recent response, this patient was known to have advanced, highly refractory disease. Such a rapid and generalized response to single-agent methylprednisolone is unlikely. In addition, his methylprednisolone dose was quite low at the time of his FDG PET-CT restaging and repeat marrow biopsy, and his overall clinical course supports the presence of a graft-versus-HL effect. The immunologic mechanisms underlying this effect are not clear. Whether and how this effect can be harnessed and modulated in a more selective and clinically useful fashion deserves further study.

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Paolo Anderlini, MD
Department of Stem Cell Transplantation and Cellular Therapy
The University of Texas M.D. Anderson Cancer Center
Houston, Texas

Nancy Swanston
Department of Nuclear Medicine
The University of Texas M.D. Anderson Cancer Center
Houston, Texas

Ashif Rashid
Department of Pathology
The University of Texas M.D. Anderson Cancer Center
Houston, Texas

Carlos Bueso-Ramos
Department of Hematopathology
The University of Texas M.D. Anderson Cancer Center
Houston, Texas

Homer A. Macapinlac
Department of Nuclear Medicine
The University of Texas M.D. Anderson Cancer Center
Houston, Texas

Richard E. Champlin
Department of Stem Cell Transplantation and Cellular Therapy
The University of Texas M.D. Anderson Cancer Center
Houston, Texas

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Allogeneic Hematopoietic Stem Cell Transplantation for Peripheral T Cell Lymphomas; Evidence of Graft-Versus-T Cell Lymphoma Effect

T cell non-Hodgkin lymphomas (TNHL) are an uncommon and heterogeneous group of lymphoid malignancies characterized by a poor prognosis. They usually present with advanced-stage disease and high International Prognostic Index (IPI) score [1]. Patients with TNHL treated with conventional-dose chemotherapy alone in general have