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**THE AUTHORS REPLY:** We believed that retrospective analyses<sup>1</sup> and small prospective studies<sup>2</sup> linking a high frequency of ventricular pacing to increased risks of atrial fibrillation and heart failure in patients with sinus node disease, though compelling, did not meet the highest level of clinical evidence necessary to broadly inform changes in clinical practice. Furthermore, conventional dual-chamber pacing, despite a high frequency of “forced” ventricular pacing,<sup>1</sup> had not been proven inferior to any alternative pacing strategy.<sup>3</sup> Accordingly, our study was designed to definitively test the hypothesis that high-frequency ventricular pacing, despite continuous atrioventricular synchronization, may increase the risk of atrial fibrillation in patients with sinus-node disease, as compared with the best available techniques for reducing ventricular pacing when the trial was initiated in 2002. Now that it has been established that less ventricular pacing is better, perhaps additional studies will be necessary to establish the best approach. Newer pacing strategies developed

specifically to achieve this goal, such as “managed ventricular pacing,” have been shown to reduce the frequency of ventricular pacing to 5% or lower in more than 90% of patients, without the functional limitations of dynamic or fixed long atrioventricular intervals.<sup>3-5</sup>

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## Multiple Autoimmune Diseases after Autologous Stem-Cell Transplantation

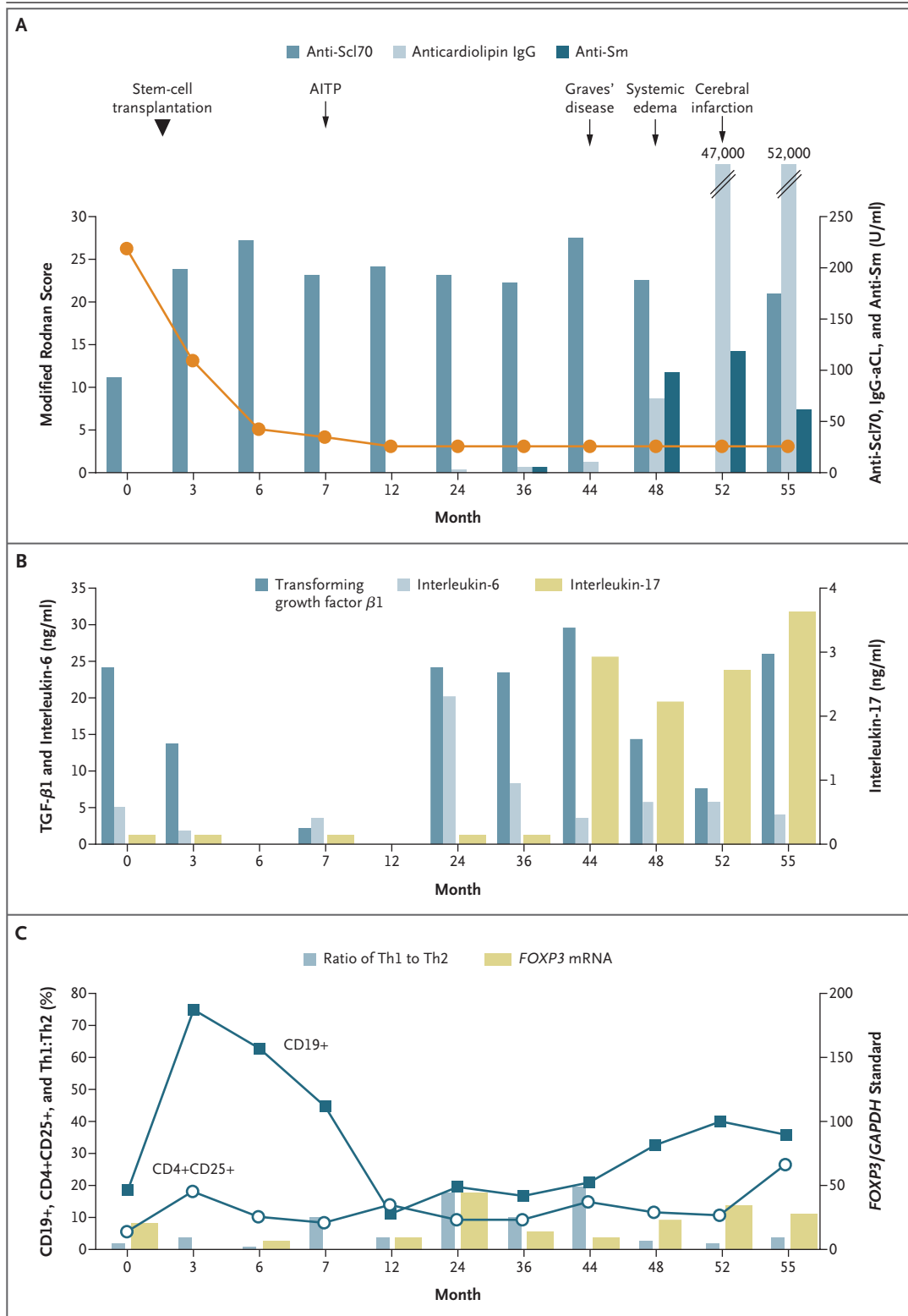
**TO THE EDITOR:** Hematopoietic stem-cell transplantation can be an effective treatment in patients with refractory systemic sclerosis.<sup>1</sup> We report on a 19-year-old woman with systemic sclerosis who underwent CD34+-selected autologous hematopoietic stem-cell transplantation in March 2001. Before the transplantation, the physical and laboratory findings showed no evidence

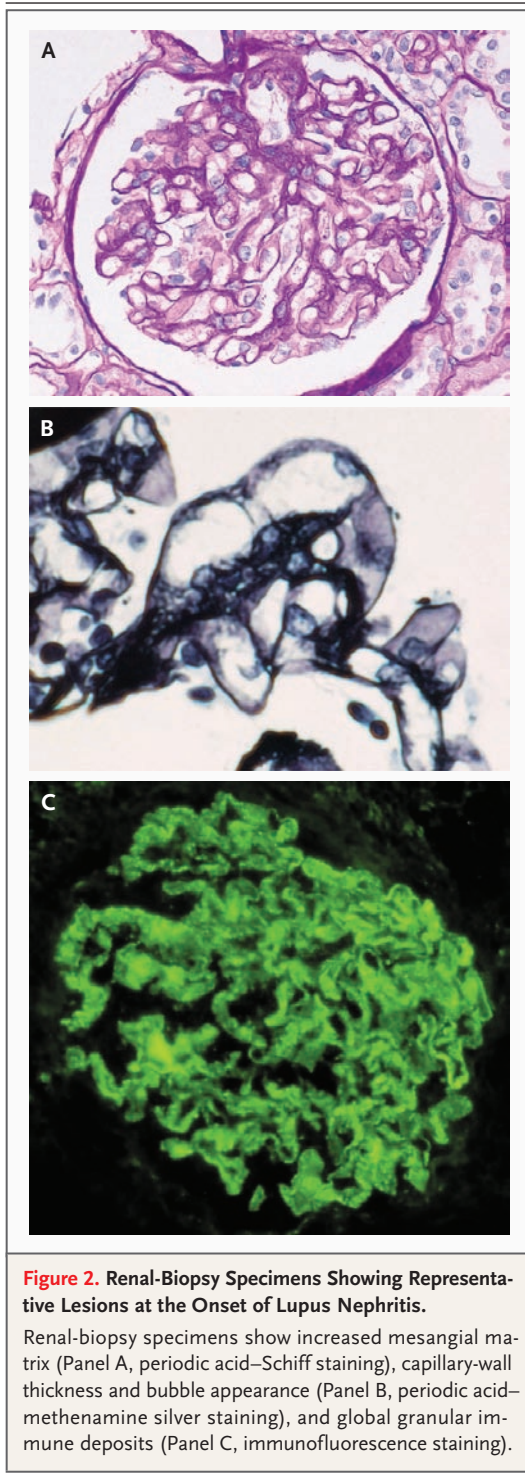
of any other autoimmune diseases. After written consent was obtained from the patient, CD34+ hematopoietic stem cells were transplanted according to a method used for systemic sclerosis.<sup>1</sup> The dermal sclerosis improved immediately after transplantation, but thrombocytopenia and Graves' disease developed.

In June 2005, the patient was admitted to the

### Figure 1 (facing page). Clinical and Laboratory Findings after CD34+-Selected Autologous Hematopoietic Stem-Cell Transplantation.

Panel A shows the association between clinical events (including the onset of autoimmune thrombocytopenia [AITP], Graves' disease, systemic edema, and cerebral infarction) and changes in titers of each autoantibody. At the onset of edema, a serum sample from the patient contained anti-Sm, anti-Scl70, and anticardiolipin IgG antibodies (IgG-aCL), in addition to anti-DNA autoantibodies and lupus anticoagulant. The solid line indicates the modified Rodnan total skin thickness score (ranging from 0 to 51, with higher values indicating more thickness). Normal ranges for these levels are as follows: anti-Sm, 0 to 5.9 U per milliliter, anti-Scl70, 0 to 18.9 U per milliliter; and IgG-aCL, <1.3 U per milliliter. Panel B shows serum levels of interleukin-17, transforming growth factor  $\beta$ 1 (TGF- $\beta$ 1), and interleukin-6. Normal ranges for these levels are as follows: TGF- $\beta$ 1, 30.95 to 38.65 ng per milliliter; interleukin-6, 0.54 to 1.10 ng per milliliter; and interleukin-17, not detected. Panel C shows changes in T cells, including the ratio of interferon- $\gamma$ -producing CD4+ T cells (Th1) and interleukin-4-producing CD4+ T cells (Th2) and FOXP3 messenger RNA (mRNA) on peripheral-blood mononuclear cells. The solid squares indicate levels of CD19+ cells, and the circles indicate levels of CD4+CD25+ cells. Normal ranges are as follows: ratio of Th1 to Th2, 7.22 to 47.52; FOXP3 mRNA, 57.10 to 175.19 copies per glyceraldehyde-3-phosphate dehydrogenase (GAPDH) standard; CD19+, 9.24 to 17.01%; and CD4+CD25+, 5.66 to 10.24%. Calculations were made with the JMP statistical software package, version 5.0 (SAS Institute).





**Figure 2. Renal-Biopsy Specimens Showing Representative Lesions at the Onset of Lupus Nephritis.**

Renal-biopsy specimens show increased mesangial matrix (Panel A, periodic acid–Schiff staining), capillary-wall thickness and bubble appearance (Panel B, periodic acid–methenamine silver staining), and global granular immune deposits (Panel C, immunofluorescence staining).

hospital because of fever and edema. Blood tests revealed proteinuria (11.4 g per day) and new autoantibodies in the serum (Fig. 1A). On the sixth hospital day, paralysis developed on the left side as the result of a right cerebral infarction. Systemic lupus erythematosus with membranous-type lupus nephritis (Fig. 2) and the antiphospholipid-antibody syndrome were diagnosed; the patient was treated with prednisolone, warfarin, and cyclosporine. She is currently in clinical remission and is back at work.

During the early phases of immune reconstitution, residual lymphocytes undergo proliferation and expansion, a process controlled by regulatory T cells.<sup>2,3</sup> These cells, defined by the phenotype CD4+CD25+FOXP3+, are important in the prevention of autoimmunity. Interleukin-17–producing helper T (Th17) cells may play a role in the induction of autoimmunity.<sup>4,5</sup> In our patient, the level of serum interleukin-17, released mainly by Th17 cells, was elevated at the onset of the systemic lupus (Fig. 1B). Levels of FOXP3 messenger RNA, a marker of regulatory T cells, were reduced, suggesting a deficiency of such cells (Fig. 1C). The findings in our patient suggest a role of both regulatory T cells and Th17 in the development of systemic lupus.

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