CORRESPONDENCE

Antibody-Associated Reversal of ATTR Amyloidosis–Related Cardiomyopathy

TO THE EDITOR: Cardiac transthyretin amyloidosis (also called ATTR amyloidosis cardiomyopathy or ATTR-CM) is a progressive disease and a cause of fatal heart failure resulting from extracellular myocardial accumulation of plasma transthyretin. Advances in imaging techniques and comparison of the results of imaging with those of histologic analysis of endomyocardial-biopsy specimens have led to the validation of imaging-based diagnosis of ATTR-CM (without an endomyocardial biopsy)[1] and have also been associated with a recent upsurge in the number of patients with a diagnosis of ATTR-CM.[2]

Disease progression caused by continuous interstitial deposition of ATTR amyloid is quantifiable through estimation of extracellular volume on cardiac magnetic resonance imaging,[3] and it is associated with worsening systolic and diastolic function detected on echocardiography, decreasing voltage detected on electrocardiography, decreasing exercise capacity, and increasing serum levels of N-terminal pro–B-type natriuretic peptide.[4] No therapy has been found to reverse the disease process.

Here, we report clinical, exploratory, and potentially mechanistic findings in three male patients who were 68, 82, and 76 years of age and who had ATTR-CM–associated heart failure that resolved spontaneously, with reversion to near-normal cardiac structure and function. Each patient had a characteristic hypertrophic phenotype and Perugini grade 2 cardiac uptake on technetium-99m–labeled 3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy. Grades on the Perugini scale, which is used to visually compare tracer uptake in the myocardium with that in the bones, range from 0 (no cardiac uptake and normal bone uptake) to 3 (strong cardiac uptake with little or no bone uptake). At follow-up, each patient reported a reduction in symptoms, although they had not received any new or potentially disease-modifying treatments. None of the patients had had recent vaccinations, notable infections, or any clinical suggestion of myocarditis. Clinical recovery was corroborated by substantial improvement or normalization of findings on echocardiography, serum biomarker levels, and results of cardiopulmonary exercise tests and scintigraphy (Fig. 1A). Serial cardiac magnetic resonance imaging scans confirmed near-complete regression of myocardial extracellular volume, coupled with remodeling to near-normal cardiac structure and function without scarring (Fig. 1A).

A retrospective, in-depth analysis of case records, serial echocardiograms, serum biomarker levels, and the 6-minute walk distance in 1663 patients with ATTR-CM who underwent follow-up at the National Amyloidosis Centre in London did not identify any other patients who had signs of spontaneous recovery. Patient 3 had undergone an endomyocardial biopsy that contained a highly uncharacteristic infiltrate of

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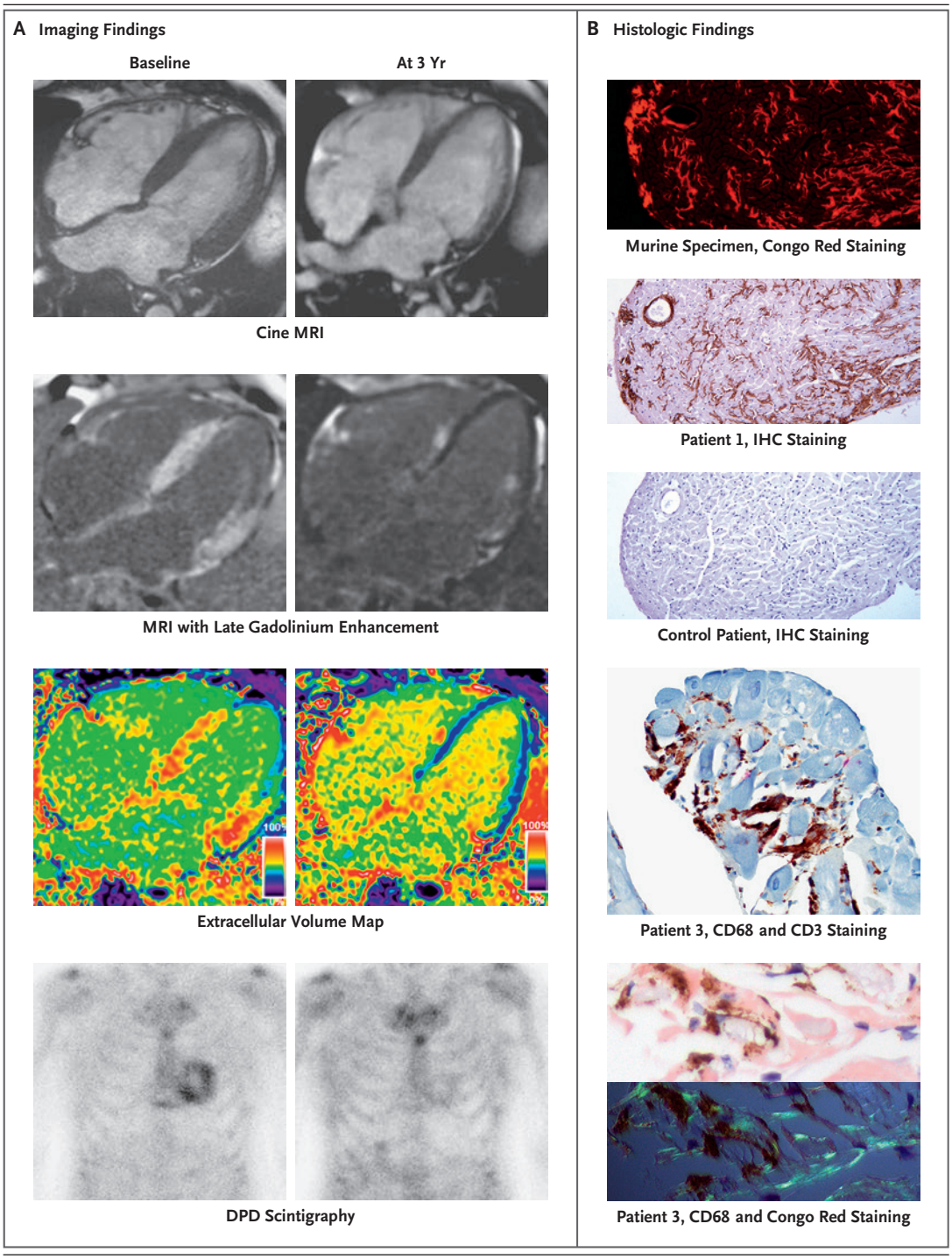

macrophages and giant cells surrounding the amyloid deposits (Fig. 1B).[5] These findings prompted histologic review of the endomyocardial biopsies performed in 286 of 1663 patients with ATTR-CM, and none of the biopsy specimens revealed such myocardial inflammation. Mass spectrometry of amyloid material from the endomyocardial-biopsy specimen obtained from Patient 3 showed transthyretin, IgG, and complement C3 (see Fig. S4 in the Supplementary Appendix, available with the full text of this letter at NEJM.org).

We investigated the possibility that the three patients had had an antiamyloid immune re-

Figure 1 (facing page). Imaging and Histologic Findings in Patients with Antibody-Associated Cardiac Amyloid Regression.

Panel A shows imaging findings at baseline and at the 3-year follow-up visit in Patient 1. Cardiac cine magnetic resonance imaging (MRI) in a long-axis view was performed to evaluate ventricular wall thickness and mass. MRI with late gadolinium enhancement in a long-axis view and the extracellular volume map show near-complete regression of myocardial extracellular volume, coupled with remodeling to near-normal cardiac structure and function without scarring. Technetium-99m–labeled 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) scintigraphy shows a decrease in cardiac tracer uptake from grade 2 (more than bone uptake) to grade 1 (less than bone uptake), as graded with the Perugini scale, which ranges from 0 (no cardiac uptake and normal bone uptake) to 3 (strong cardiac uptake with little or no bone uptake). Panel B shows histologic findings. The top three images show serial sections of human transthyretin amyloid (also called ATTR amyloid)–containing transgenic mouse heart. The top section is stained with Congo red to show amyloid distribution. The next two sections show immunohistochemical (IHC) findings with serum obtained from Patient 1 and with serum obtained from a typical control patient who had transthyretin amyloidosis cardiomyopathy (each sample at 1:2000 dilution). The serum samples were used as the primary reagent and were probed with an antihuman IgG secondary antibody. An endomyocardial-biopsy specimen obtained from Patient 3 was immunostained for CD68 (a macrophage marker) and CD3 (a lymphocyte marker) or stained with Congo red. In the bottom image, a specimen examined with bright-field microscopy (upper half of the image) or polarizing microscopy (lower half of the image) showed a CD68 multinucleate giant cell (brown in the upper half of the image) that appeared near amyloid deposits (green in the lower half of the image).

sponse, and we identified high-titer circulating polyclonal IgG antibodies to human ATTR amyloid in each of the patients. These antibodies bound specifically to ATTR amyloid deposits in tissue sections from mice (Fig. 1B) and humans and to synthetic ATTR amyloid fibrils. No such antibodies were present in 350 consecutive patients with ATTR-CM who had a typical clinical course.

The cause and clinical significance of the anti-ATTR amyloid antibodies are intriguing and presently unclear. However, the clinical recovery of these patients establishes the unanticipated potential for reversibility of ATTR-CM and raises expectations for its treatment.

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