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EDITORIAL COMMENT

Amyloid Cardiomyopathy*

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The retrospective study by Kristen et al. (1) in this issue of the *Journal* brings attention to cardiac amyloidosis as an often underrecognized cause of restrictive cardiomyopathy and highlights the differences between immunoglobulin light-chain (LC) and transthyretin (TTR) amyloidosis. There are, however, a number of different types of amyloidosis that can affect the heart, and with present and newly emerging forms of therapy, a definitive diagnosis is required (2). Immunoglobulin LC amyloidosis and TTR amyloidosis are the most common types of amyloidosis that cause cardiomyopathy, but apolipoprotein AI, apolipoprotein AII, and even secondary amyloidosis (amyloid A) have been reported to give clinically significant cardiac involvement.

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The diagnosis of amyloidosis is often delayed until patients develop end-stage organ involvement, and treatment options are limited. Classically described features, such as low voltage on the electrocardiogram despite evidence of left ventricular hypertrophy on echocardiography, are supportive of an infiltrative myopathy but are not sufficient to make a specific diagnosis. Other tests including serum and urine electrophoresis with immunofixation, serum free light-chain concentrations, echocardiography with strain, cardiac magnetic resonance, and radionuclide imaging are useful, but tissue biopsy remains the gold standard to diagnose cardiac amyloidosis when diagnostic uncertainty exists (3-6).

Even though the diagnosis of amyloidosis is confirmed by Congo red-stained deposits on biopsy, it is necessary to determine the specific type of amyloidosis to plan therapy and venture a prognosis. The pattern of amyloid deposition in a cardiac biopsy may be suggestive of 1 type of amyloidosis, but characterization of the amyloid subunit protein by immunohistochemistry or mass spectroscopy plus clinical correlation are recommended to make a definitive diagnosis (7-9) (**Figures 1 to 4**).

To judge the importance of the amount of amyloid in a cardiac biopsy requires attention to certain aspects of both transthyretin (ATTR) and AL amyloidosis. Restrictive cardiomyopathy is a feature of ATTR caused by many of the TTR mutations. Although there is considerable variation in the degree of cardiac involvement and the rate of progression of amyloid deposition in the heart, the amount of amyloid found in a random endocardial biopsy would not be expected to be of much prognostic value, because clinically significant cardiac dysfunction that would lead to a heart biopsy for diagnosis is far past the time frame of early diagnosis. With hereditary TTR cardiomyopathy and wild-type TTR cardiomyopathy, which may differ with respect to rate of progression, prognostication is best left to serial measures of cardiac parameters on echocardiography and magnetic resonance imaging (3,10). This is of particular importance for wild-type TTR cardiomyopathy, which is being seen with increasing frequency by practicing cardiologists.

Immunoglobulin AL amyloidosis presents even more vagaries that need to be kept in mind. Every case of immunoglobulin AL amyloidosis is unique. The primary cause of AL is a plasma cell dyscrasia, which generates light-chain protein capable of forming amyloid fibrils (11). Thus, it depends on which plasma cell clone is selected, for whatever reasons, to expand and produce a monoclonal protein. We know that certain subtypes of light-chain

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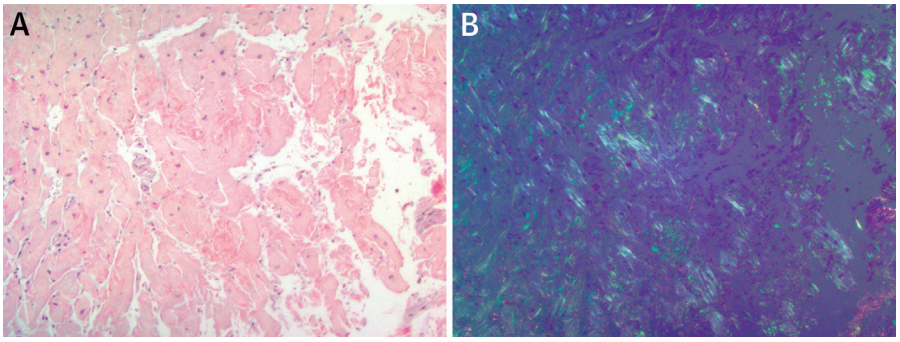
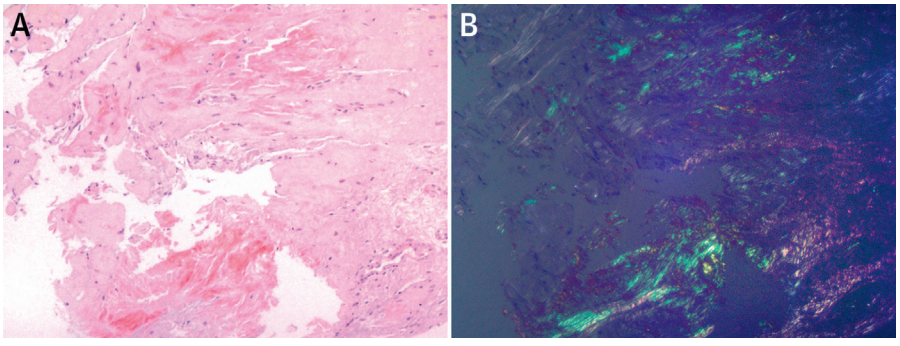
FIGURE 1 Endomyocardial Biopsy From a Patient With ATTR Val122Ile Showing Mainly an Interstitial Pattern of Deposition



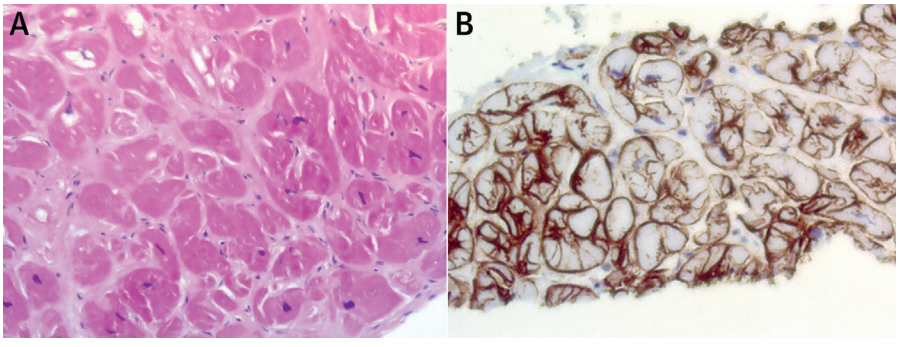
(A) Congo red bright light. **(B)** Same section as **A** viewed with crossed-polars. Original magnification ×100. ATTR = transthyretin amyloid.

FIGURE 2 Endomyocardial Biopsy From a Patient With ATTR Wild-Type Showing Nodular Pattern of Amyloid Deposition



(A) Congo red with bright light. **(B)** Same section as **A** viewed with crossed-polars. Original magnification ×100. ATTR = transthyretin amyloid.

FIGURE 3 Endomyocardial Biopsy From a Patient With AA Amyloidosis Showing Interstitial Deposition of Amyloid



(A) Endomyocardial biopsy from a patient with amyloid A (AA) amyloidosis with interstitial amorphous eosinophilic deposits. Original magnification ×200. **(B)** Myocardial biopsy from same patient as **A** showing interstitial deposits stained positive for AA. Immunohistochemistry with mouse monoclonal antihuman AA and goat antimouse immunoglobulin G/diaminobenzidine. Original magnification ×200.