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EDITORIAL COMMENT

# Light-Chain Cardiac Amyloidosis

## A Heart With 2 Very Different Ventricles?*

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Amyloidosis is a generic term that refers to the deposition of a substance called amyloid in the extracellular matrix of body tissues. This substance is constituted from the accumulation of insoluble fragments of a certain type of protein. The most distinctive pathological characteristic of amyloid deposits is its staining with Congo red and the acquisition of an apple-green birefringence under polarized light. This characteristic is common to all types of amyloid, so other techniques (e.g., immunohistochemistry or mass spectrometry) are necessary to show the responsible protein (1).

In humans, 36 proteins can lead to the formation of amyloid material (2), but only 5 of them are associated with significant cardiac involvement: apolipoprotein A, fibrinogen, serum amyloid protein A, light chains, and transthyretin (TTR). The last 2 are the cause of light-chain (AL) and transthyretin (ATTR) amyloidosis, the 2 main types of this disease that affect the heart (3).

AL is included in a group of blood malignances called monoclonal gammopathies or plasma cell dyscrasias. These disorders are characterized by inappropriate proliferation of a single clone of plasma cells that produce large amounts of a single class of immunoglobulin. In the case of AL, tumor cells only elaborate the variable domain of 1 type of light chain (λ in 75% of cases), which is the precursor protein for the formation of amyloid material (4).

Heart involvement predicts poor prognosis in AL, and biomarkers of cardiac injury are considered valid predictors of survival. Thus, one of the most commonly used prognostic classification models (the revised Mayo staging system) includes both biomarkers, together with the serum-free, light-chain levels (5). In addition, cardiac involvement limits the use of traditional treatment options, and these patients are often ineligible for autologous stem cell transplant (SCT) due to high treatment–related mortality. Regimens that include proteasome inhibitors (e.g., bortezomib, ixazomib) are currently the standard for upfront therapy in these cases because of their superior response rates over other regimens. Other novel agents such as daratumumab (a humanized monoclonal antibody that targets CD38) are promising for the treatment of patients with AL cardiac amyloidosis ($CA_{AL}$). Based on data from early phase studies, this drug appears to be a safe and well-tolerated alternative (6).

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In this issue of *JACC: Case Reports*, Poller et al. (7) present a case of advanced $CA_{AL}$ in which they performed a multimodal approach to monitor the response to treatment. Upon diagnosis, the patient was classified as Mayo stage III, and quantitative immunohistology on endomyocardial biopsy suggested the existence of intense myocardial inflammation. As the same investigators previously reported (8), this predicted a poor prognosis, and the patient was considered not eligible for SCT. In this context, as we previously discussed, bortezomib is the best treatment option. In addition, the investigators enrolled the patient in the phase III VITAL (The VITAL Amyloidosis Study, a Global Phase 3, Efficacy and Safety Study of NEOD001 in Patients With AL Amyloidosis) (NCT02312206) (9), and she was assigned to receive NEOD001, a humanized immunoglobulin-G1 κ monoclonal antibody that

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neutralizes soluble light-chain aggregates and promotes the clearance of insoluble amyloid material via macrophage signaling and phagocytosis. The authors assume that the investigators did not consider other therapeutic options (e.g., heart transplantation) due to a significant extracardiac organ involvement that contraindicated it, although they did not make a specific mention about this condition.

The main observation in this case was the favorable response of the left ventricle to treatment, which was accompanied by a transient improvement in the patient's clinical situation. The investigators related this improvement to the observed reduction of myocardial inflammation and amyloid deposits. Although the mechanism of cardiac dysfunction in AL is not completely understood, the available evidence points toward it as not being the only consequence of the distortion of tissue architecture caused by accumulation of amyloid deposits in the extracellular space (10). Light chains may induce cardiomyocyte dysfunction and death (a process called proteotoxicity) through an increase in oxidative stress and an inflammatory response. This case exemplifies the potential usefulness of monitoring myocardial inflammation in this disease to establish prognosis and guide therapy, including the use of immunomodulatory drugs (8). Regarding the reduction of amyloid deposits, the patient was treated with a fibril directed therapy, the antibody NEOD001. This pharmacological group can accelerate the removal of amyloid fibrils from affected tissues and may have a central role in the treatment of AL. NEOD001 was tested in a phase IIb study PRONTO (Global Phase 2b Study of NEOD001 in Previously Treated Subjects With Light Chain [AL] Amyloidosis; NCT02632786) and failed to meet the primary endpoint of cardiac response. Because of that, the phase III VITAL study was stopped prematurely, and development of the drug has been discontinued. Although the experience with NEOD001 could be daunting, other antibodies such as anti-serum amyloid P are still promising.

As opposed to the left ventricle, the right ventricle showed progressive deterioration despite treatment, and the patient died due to refractory right heart failure 15 months after diagnosis. It is well known that right ventricular dysfunction is an adverse prognostic predictor in AL (11) and in other heart failure etiologies. This divergent response of both ventricles was highlighted by the investigators and is certainly interesting. However, although the investigators tried to give an explanation for this finding by suggesting a mechanism of amyloid-induced microvascular dysfunction, a single case might not be enough to establish a consistent hypothesis. More evidence is needed. Undoubtedly, this individual observation can be the basis for future research.

Finally, the investigators reflected on the need for invasive hemodynamic monitoring in cases in which development of pulmonary vascular disease and increased pulmonary artery pressure was suspected. In the authors' opinion, the attitude should be the same as in other heart failure etiologies, with the purpose of evaluating heart transplantation candidacy. The authors have serious doubts that the intensification of antiplasma cell therapies would be enough in that context, as stated by the investigators.

In conclusion, the case published by Poller et al. (7) is illustrative of AL amyloidosis with advanced cardiac involvement and suggests that there might be an opposite response of both ventricles to treatment. The authors encourage the investigators to continue their research in the field.

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