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Reversing the poor prognosis of primary light-chain amyloidosis with cardiac involvement

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New York Heart Association (NYHA) functional class, brain natriuretic peptide (BNP), and C-reactive protein (CRP) levels are known risk factors for increased mortality in patients with primary light-chain (AL) amyloidosis [1]. However therapeutic options to overcome a poor prognosis have been limited. Approved in January 2021, daratumumab (Dara) with cyclophosphamide, bortezomib, and dexamethasone (CyBorD) demonstrated improved hematologic and organ responses in patients with newly diagnosed AL amyloidosis [2]. Here, we present the clinical image of a 63-years-old man with primary AL amyloidosis presenting with a rapidly progressive heart failure [3].

The patient was diagnosed with acute heart failure (NYHA III). In addition, the patient had a history of hypertension, diabetes, and renal failure (estimated glomerular filtration rate, 50 ml/min/1.73m^2). The electrocardiogram demonstrated, depression of 1 mm of ST segments with inverted T waves in I, avL, V1-V6 leading to coronary angiography, which was normal. On echocardiography, red flags for cardiac amyloidosis were found: myocardial granular sparkling and thickening of the left (LV), and right ventricle (Figure 1B), significant enlargement of both atria, LV ejection fraction 50%, and a restrictive filling pattern with low mitral annulus velocity in TDI (< 5 cm/s) [4]. The global longitudinal strain (GLS) was abnormal (-10.4%) with apical sparing (Figure 1A), and scintigraphy with technetium-99m-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid was negative for ATTR amyloidosis. Myocardial volume overload was confirmed by significantly elevated cardiac biomarkers, NT-proBNP (Figure 1E), and hs-troponin I (45.6 ng/L). AL amyloidosis (kappa light chain) was diagnosed, Mayo stage III (Figure 1C).

In January 2021, the patient received treatment with Dara-CyBorD as part of an Emergency Drug Access scheme. The hematologic response was immediate and followed by a gradual decline in the NT-proBNT, by 60% from its peak (Figure 1E). The treatment was interrupted after two cycles due to SARS-CoV-2 infection. After recovery, the patient received maintenance treatment with Dara-Bort. Granulocyte colony-stimulating factor-based (G-CSF) stem cell mobilization failed, and a second attempt with plerixafor plus G-CSF plus cytarabine was successful. In August 2021, the patient received high-dose chemotherapy (MEL140) followed by autologous stem cell transplantation. The therapy led to deepening of response (complete response, CR) (Figure 1E, G) and minimal residual disease (MRD) was undetectable. Renal function was stable, whereas further cardiac improvement was observed after a maximum deterioration (GLS -6.11%; Figure 1E) as a decrease in GLS to baseline levels (Figure 1D vs. 1F). The patient returned to full-time work.

Historically, the median overall survival in Mayo cardiac stage III AL amyloidosis was seven months, with 42% of patients dying before first response evaluation [3]. Dara-CyBorD remarkably improved hematologic response and organ involvement [2]. The treatment, interrupted and modified, reversed the poor prognosis. Consolidative stem cell transplant therapy became possible and resulted in MRD-negativity associated with improved cardiac function after CR [5].

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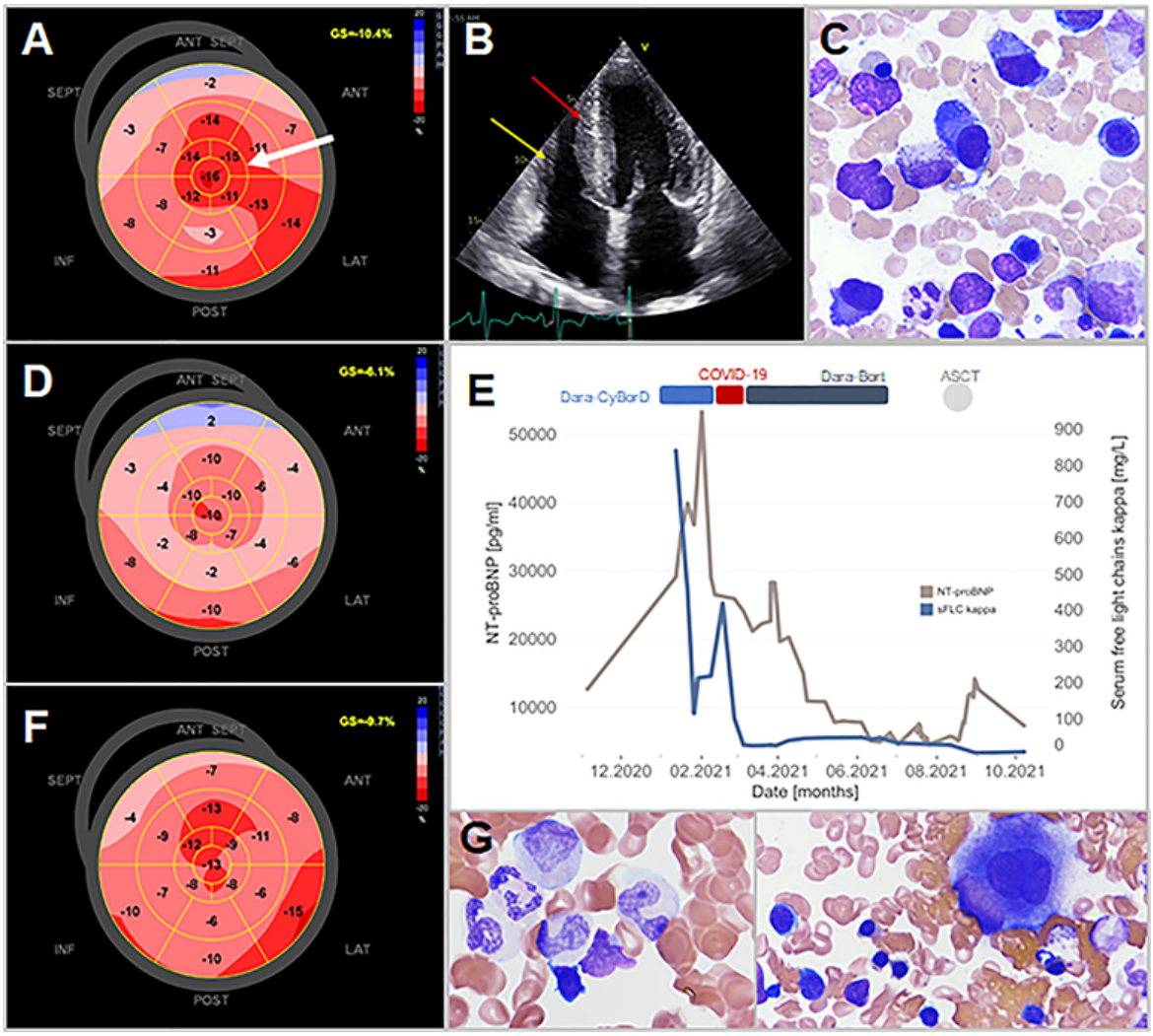

Figure 1 Clinical data during the treatment course. Top panels A-C presents data before treatment: **(A)** Severe LV longitudinal systolic dysfunction with apical sparing (white arrow): global longitudinal strain (GLS) = -10.4 % **(B)** LV hypertrophy with typical myocardial granular sparkling (red arrow) and RV wall thickening > 5mm (yellow arrow) **(C)** Bone marrow aspirate smear showing plasma cells before treatment (× 1000, Wright's staining) **(D)** The period during hematologic treatment showing significant deterioration of longitudinal LV function: Very low GLS = - 6.1% **(E)** Changes in the concentration of NT-proBNP and serum-free light chains (sFLC) during the treatment course. Bottom panels F and G present data after complete remission: **(F)** Improvement of LV longitudinal function: GLS -9.6%. **(G)** Bone marrow aspirate smears showing normal hematopoietic cells in remission (× 1000 and × 400, Wright's staining)