Extracorporeal Membrane Oxygenation as Bridge-to-Decision in Acute Heart Failure due to Systemic Light-Chain Amyloidosis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEFG 1,2   Jennifer Mancio Silva
ACDE 1,2   Ricardo Fontes-Carvalho
BD 3   Dília Valente
B 3   Cristiana Almeida
B 4   António José Cruz
B 5   David Tente
ABCD 6   Henrique Coelho
BD 1   Marco Oliveira
BCDE 1   Aníbal Albuquerque
CDEFG 1   Vasco Gama Ribeiro

1 Department of Cardiology, Centro Hospitalar de Vila Nova de Gaia e Espinho, Vila Nova de Gaia, Portugal
2 Department of Physiology and Cardiothoracic Surgery, Medical School of Porto, Porto, Portugal
3 Department of Internal Medicine, Centro Hospitalar de Vila Nova de Gaia e Espinho, Vila Nova de Gaia, Portugal
4 Department of Internal Medicine, Centro Hospitalar Entre-Douro e Vouga, Santa Maria da Feira, Portugal
5 Department of Pathology, Centro Hospitalar de Vila Nova de Gaia e Espinho, Vila Nova de Gaia, Portugal
6 Department of Haematology, Centro Hospitalar de Vila Nova de Gaia e Espinho, Vila Nova de Gaia, Portugal

Corresponding Author: Jennifer Mancio Silva, e-mail: pdccv0104593@med.up.pt
Conflict of interest: None declared

Patient:	**Female, 58**
Final Diagnosis:	**Acute hear failure**
Symptoms:	**Dispnoea • edema • fatigue**
Medication:	**—**
Clinical Procedure:	**Bone marrow biopsy • endomyocardial biopsy • abdominal subcutaneous fat biopsy under ECMO support**
Specialty:	**Cardiology**

Objective: Rare disease

Background: Cardiac amyloidosis results from the amyloid deposition in heart tissue, either in the context of a systemic disease or as a localized form. Several pro-amyloid proteins can produce amyloid deposits in the heart. Each of these amyloidoses has characteristic clinical (cardiac and extracardiac) features, and a specific diagnosis and treatment.

Case Report: A 58-year-old woman who presented with acute heart failure and echocardiographic findings strongly suggestive of infiltrative cardiomyopathy needed percutaneous veno-arterial extracorporeal membrane oxygenation (ECMO) as bridge-to-decision. Amyloid deposition was found on endomyocardial and bone marrow biopsies. Bone marrow plasma cell infiltrate with acute renal lesion and hypercalcemia confirmed the diagnosis of multiple myeloma-associated systemic light-chain amyloidosis (AL). Refractory shock with multi-organic failure syndrome persisted and no improvements in left ventricular function and structure were seen. After extensive discussion by a multidisciplinary team, and with the patients' family, she was not considered eligible for high-dose chemotherapy and/or autologous stem cell transplantation, heart transplantation, or sequential heart with autologous stem cell transplantation. The patient died a few hours after ECMO withdrawal. During the 14 days of ECMO support no major bleeding or thrombotic complications occurred.

Conclusions: The clinician must consider a diagnosis of cardiac amyloidosis in patients with heart failure, a restrictive type of cardiomyopathy with ventricular hypertrophy in the absence of valve abnormalities, or uncontrolled arterial hypertension. Although developments in chemotherapy have greatly improved the outcomes in AL amyloidosis, the prognosis of patients with severe cardiac involvement remains very poor. ECMO is potentially a reliable bridge-to-diagnosis and bridge-to-decision in these patients. An experienced ECMO team, careful patient selection, and rigorous management protocols with objective criteria to wean or stop ECMO are needed.

MeSH Keywords: Amyloidosis • Cardiomyopathy, Restrictive • Extracorporeal Membrane Oxygenation • Heart Failure • Shock, Cardiogenic

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Background

In the setting of acute heart failure (HF) of unknown etiology where the patient has refractory shock, veno-arterial ECMO can serve as a bridge-to-diagnosis and potentially as destination therapy. In such patients the most import objective is to exclude potentially reversible causes of HF such as acute myocarditis, Takotsubo syndrome, acute coronary syndrome, or drug intoxication and consider heart transplantation [1]. Use of ECMO can buy valuable time in this clinical setting [2,3]. However, there are no rigorous management protocols with objective criteria to initiate and wean or stop ECMO.

We report a case of multiple myeloma-associated light-chain amyloidosis with severe cardiac involvement presenting with acute and rapidly deteriorating heart failure where full evaluation was not possible and in whom death would occur without ECMO support. The cardiac amyloidosis diagnostic workup and the AL amyloidosis-specific treatment options are highlighted. We also discuss the venoarterial (VA) ECMO indications, the appropriate patient selection, and the concept of ECMO futility.

Case Report

A 58-year-old woman was admitted to the Emergency Department complaining of dyspnea and peripheral edema. She reported a 6-month history of symmetric lower-limb edema, dyspnea on exertion, orthopnea, and paroxysmal nocturnal dyspnea.

Her medical history was unremarkable except for arterial hypertension and schizophrenia. Medication included ramipril and sulpiride. There were no known drug allergies. The patient was a single housewife without children. She did not smoke and rarely drank alcohol. There was no family history of cardiac disease.

On physical examination the patient was not in distress. Axillary temperature was 36.3°C, blood pressure 90/65 mmHg, and pulse 101 beats per minute, the respiratory rate 24 breaths per minute, and oxygen saturation 94% while breathing room air. The sclerae were anicteric, mucous membranes were moist, and the oropharynx was clear. The neck was supple, with no lymphadenopathy or thyromegaly. Carotid pulses were normal, without bruits. Jugular turgescence was markedly visible at 45° neck elevation. There was dullness on percussion over the right lung base, with no breath sounds; the lungs were otherwise clear on auscultation. The apex beat was not palpable, and there was no right ventricular heave. Cardiac auscultation was normal. The abdomen was distended but not tender, with a fluid wave. The liver was enlarged, and the spleen was not palpable. Pitting edema involved the legs, perineum, and abdominal wall, and there was mild bilateral upper-limb edema. Distal pulses were palpable. Changes associated with chronic venous stasis were present in the lower extremities. Neurologic examination was unremarkable.

Blood analysis revealed mildly raised creatinine and urea, decreased albumin with raised ionized calcium (6.7 mg/dL; normal range 4.6–5.4); NT-pro-BNP was markedly high (17719 pg/mL, normal <100 pg/mL) and troponin I was 0.07 ng/dL (normal<0.01ng/dL); transferrin saturation was low (9.9%). Urinalysis showed non-nephrotic proteinuria. Laboratory results are presented in Table 1.

The anteroposterior chest x-ray depicted a severely enlarged cardiac silhouette, ingurgitated hilar and interstitial pulmonary vasculature, and right pleural effusion (Figure 1).

The admission electrocardiogram showed normal sinus rhythm with first-degree AV block (PR 280 ms), low QRS voltage (<5 mm), leftward axis deviation, poor R-wave progression, and diffuse nonspecific T-wave changes (Figure 2). During electrical monitoring, periods of paroxysmal atrial fibrillation were noted.

Transthoracic echocardiography (Figure 3A–3D) showed: a) left and right ventricular hypertrophy (interventricular septum of 17 mm and right ventricular free wall of 7 mm); b) severe bi-atrial enlargement (left atrium of 52 mL/m^2 and right atrium of 48 mL/m^2) with normal ventricular chambers; c) severely depressed left and right ventricular systolic function (left ventricular ejection fraction [LVEF] of 16%, mean tissue Doppler mitral S'velocity: 4 cm/s; tricuspid annular plane systolic excursion [TAPSE]: 8 mm and tricuspid S'velocity by tissue Doppler: 6 cm/s); d) elevated left ventricular filling pressures (mean E/e' ratio of 19); d) absence of significant valvular disease or significant respiratory variation in mitral E velocity; e) and normal pericardium with minimum pericardial effusion. On the left atrial appendage, a highly mobile thrombus was visible.

At this point the clinical and echocardiographic data strongly indicated restrictive cardiomyopathy due to an infiltrative process; amyloidosis is the most common cause of this condition [3–5].

On the 2nd day of hospitalization, the patient had a cardiac arrest with ventricular fibrillation. Return of spontaneous circulation was achieved after 10 minutes of advanced life support. She recovered without neurological deficits but hemodynamic instability persisted. Inotropic and vasopressor support with dobutamine and norepinephrine was required. Current guidelines based on expert opinion recommend dopamine or dobutamine as first-line agents, with moderate hypotension (systolic blood pressure 70 to 100 mm Hg) and norepinephrine as the preferred therapy for severe hypotension (systolic blood pressure <70 mm Hg) [6]. We preferred small combined doses of inotropes and vasopressors over a single agent used at higher doses

Table 1. Laboratory results.

Variables	On admission	7th day after admission	14th day after admission	Normal range
Blood sample analysis				
Haematological counts				
Haemoglobin(g/dL)	13.6	10.5	8.7	12.0–16.0
Haematocrit (%)	49	28.5	26.4	40–52
White cell count (per mm³)	13390	35510	44760	3.8–10.6
Platelets count (per mm³)	340000	99000	84000	150000–440000
Biochemical parameters				
Creatinin (mg/dL)	1.5	2.6	3.6	0.7–1.2
Urea (mg/dL)	102	308	290	1–50
Sodium (mmol/L)6	138	143	148	136–145
Potassium (mmol/L)	3.8	4.1	4.4	3.4–4.5
Ionized calcium (mmol/L)	6.8			4.4–5.4
ALT (U/L)	194	360	16	1–37
AST (U/L)6	191	280	<5	1–41
LDH (U/L)	480	654	50	240–480
Bilirrubin (mg/dL)	0.85	1.6	2.0	0.1–1.1
INR (International Normalization Ratio)	1.3	1.8	3.2	<1
Pro-BNP (pg/mL)	17702		26092	0–334
T-cTn (ng/mL)	0.950		1.86	0.000–0.014
TSH (uUI/mL)	4.75			0.27–4.2
Protein imunoelectroforesis				
Total protein (g/dL)	4.8	3.9	3.7	6.0–8.2
Albumin (g/dL)	2.4	2.5	1.9	2.9–4.9
Alfa 1 (g/dL)	0.6			8.4–13.1
Beta (g/dL)	0.6			8.4–13.1
Gama (g/dL)	0.3			11.1–18.8
Immunoglobulines				
IgA (mg/dL)	59			114–457
IgG (mg/dL)	331			793–1590
IgM (mg/dL)	21			29–228
Kappa/Lambda free light chain relation	1.93			1.35–2.70
Serum proteins Electroimmunofixation				
Two bands with monoclonal characteristics corresponding to Kappa light chain				
Urine sample analysis				
Volume (mL/day)	1000			
Proteins (g/L)	0.59			<0.14
Kappa light chains (mg/mL)	64			
Lambda light chains (mg/mL)	<0.4			
Urine proteins Electroimmunofixation				
One band with monoclonal characteristics corresponding to Kappa light chain				

ALT – alanine aminotransferase; AST – aspartate aminotransferase; LDH – lactate dehydrogenase; TSH – thyroide stimulating hormone; I-cTn – I-type cardiac troponine; Pro-BNP – pro-B-type natriuretic peptide; Ig – immunoglobulin.

Figure 1. Chest X-ray at presentation. Antero-posterior chest-X ray incidence showed a normal cardiothoracic index with mild hilar ingurgitation and right pleural effusion.

to avoid dose-related adverse effects. Despite optimal medical treatment, deterioration of respiratory, renal, and hepatic function occurred (Table 1) and mechanical ventilation and peripheral veno-arterial extracorporeal membrane oxygenation (ECMO) were started. Cannulation of the right femoral vein and artery using 23 and 17 French catheters, respectively, was performed and the ECMO (Quadrox PLS oxygenator and Rotaflow RF 32, Maquet Cardiopulmonar AG, Maquet Gmbh® & Co., Germany) was set at a flow rate of 5 L/min (3000 rotation per minute).

The confirmation of the diagnosis of cardiac amyloidosis requires the demonstration of amyloid deposits on tissue biopsy. Since typical echocardiographic signs were present, amyloid deposition could be demonstrated first in other tissues that are more accessible than cardiac tissue; therefore, endomyocardial biopsy was not performed at this initial stage.

On the 4th day of hospitalization, abdominal fat tissue aspirate was performed. No amyloid deposition was demonstrated (negative for Congo red staining). A renal biopsy was the next step but no amyloid deposits were found. Thus, we decided to perform the endomyocardial biopsy.

Cardiac catheterization was performed; coronary angiography excluded obstructive coronary artery disease and 4 fragments of the interventricular septum obtained. The histological examination showed no signs suggesting myocarditis, granulomas, or iron deposition (Figure 3E) and confirmed amyloid deposits – positive staining with both Congo red in the few small vessels walls represented in the myocardial specimen (Figure 3F). It was not possible to determine the subtype of the amyloid material (Immunoglobulin AL, Amyloid A, or transthyretin) by immunohistochemistry. In these cases, AL amyloidosis must be ruled out. To do this, serum protein electrophoresis and serum and urine immunofixation were performed.

Two bands with monoclonal characteristics matching Kappa light-chains were detected on both serum and urine immunofixation (Table 1). Bone marrow aspirate (Figure 3H) and biopsy showed abundant amyloid deposits (Figure 3G) and plasma cells infiltrate (16%) with Kappa light-chain antibody restriction (Figure 3I–3L). These findings in combination with the acute renal lesion at presentation and hypercalcemia confirmed the diagnosis of multiple myeloma-related systemic AL amyloidosis.

Refractory shock with multi-organic failure syndrome persisted and no improvements in left ventricular function and structure were seen. After extensive discussion, the patient was not considered eligible for high-dose chemotherapy and/or autologous stem cell transplantation, heart transplantation, or sequential heart with autologous stem cell transplantation, and continuation of ECMO was considered futile. After discussion with the patient's family, ECMO support was stopped and the patient died a few hours later. During the 14 days of ECMO support, no major bleeding or thrombotic complications occurred.

Discussion

In our case, the main differential diagnosis at presentation was restrictive cardiomyopathy due to an infiltrative process. Both the left and right ventricular were thickened and there was no secondary cause for this hypertrophy (e.g., uncontrolled
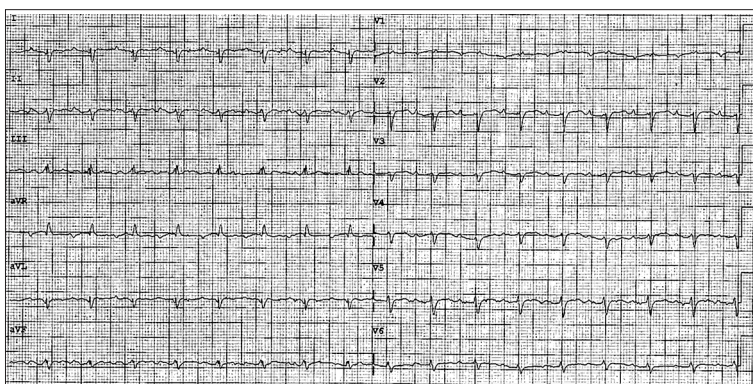
Figure 2. Electrocardiogram at presentation. Electrocardiogram showed sinus rhythm, first-degree atrioventricular block, and a low QRS voltage (<5 mm).
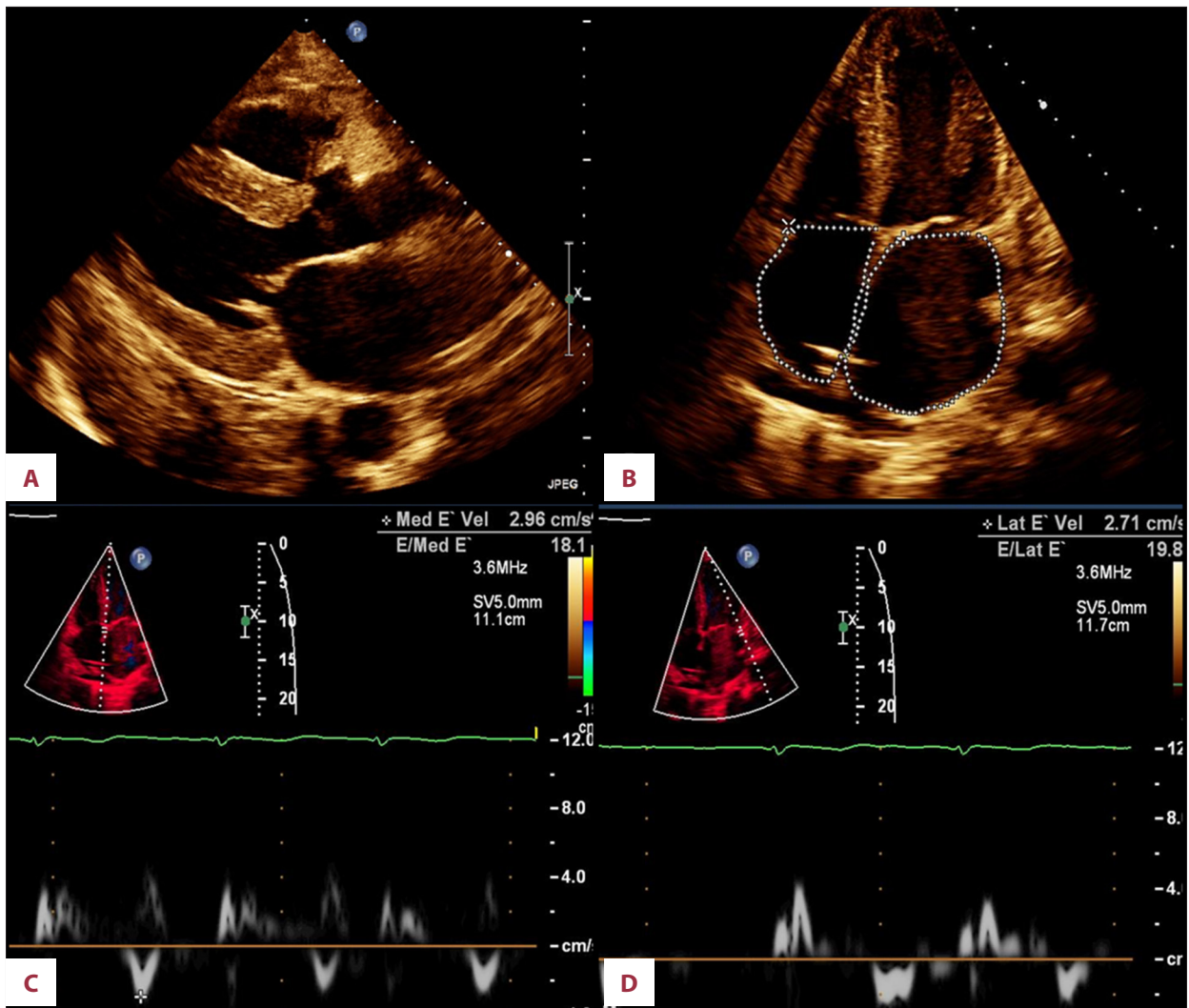
Figure 3 (A–D). (**A–D**) Transthoracic echocardiogram. (**A**) Parasternal long-axis view showing concentric left ventricular thickening, increased myocardial echogenicity, normal left ventricular cavity size, and a small pericardial effusion; (**B**) Apical view showing biatrial enlargement, normal right and left ventricular cavity sizes, with severely depressed systolic biventricular function (left ventricular ejection fraction of 16% and tricuspid annular plane systolic excursion of 8 mm); (**C and D**) Tissue Doppler velocities recorded at septal and lateral sides of the mitral annulus showing reduced systolic velocities (S'), and markedly reduced early and late diastolic velocities with elevated left ventricle filling pressures (septal E/E' ratio of 18.1 and lateral E/E'ratio of 19.8).

hypertension, aortic stenosis, pulmonary hypertension) [3,4]. Constrictive pericarditis could explain the biventricular heart failure with a restrictive pathophysiology, but this diagnosis would not explain the ventricular thickening and reduced septal e' velocities [3]. Myocardial infiltration can occur from different pathophysiological mechanisms, but amyloid protein deposition is the most common process in the Western world [4,5]. Confirmation of the diagnosis of cardiac amyloidosis and the definitive characterization of the type of amyloidosis is critical for prognostic and treatment purposes, but it is laborious and time-consuming work that evolves a multidisciplinary team.

We decided to initiate mechanical circulatory support (MCS) based on her poor clinical evolution and on medical team's judgment of a potentially reversible condition. There are only a few small series and observational studies available in the literature addressing the issue of MCS management [1,2]. In our patient, we expected a good neurologic outcome because she had in-hospital cardiac arrest with return of spontaneous circulation in less than 20 minutes, and there was no previous neurologic damage, nor was there a history of malignancy or irreversible organ failure. ECMO was chosen over other modalities of MCS based on biventricular dysfunction presence, and greater experience of our center with ECMO [1].
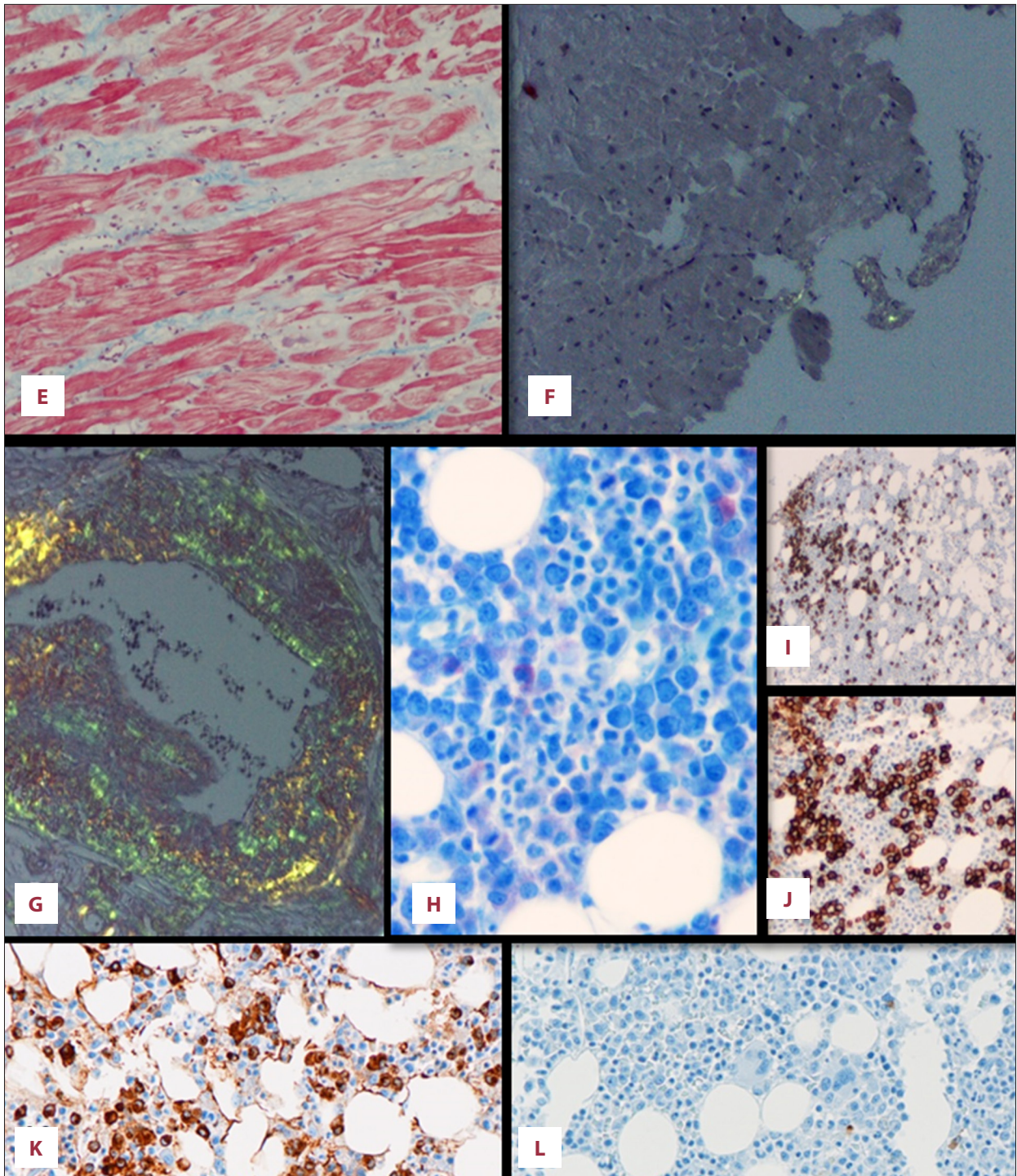
Figure 3 (E–L). (**E and F**) Histology of myocardial biopsy. (**E**) Myocyte degenerative changes with cellular derangement and interstitial fibrosis. No findings suggestive of myocarditis or granulomas were found; (**F**) Positive Congo red reaction confirming myocardial amyloid deposits. The apple-green or bottle-green staining with Congo-red observed under polarized light characteristic of Congo-red amyloid material is inside the circle. (**G–L**) Histology of bone marrow biopsy. Bone marrow sample showing apple-green or bottle-green staining with Congo-red observed under polarized light (**G**) and significant interstitial and focal infiltration by plasma cells, often with asynchronous maturation (**H** ×400, Giemsa, center and left), with positivity for anti-CD38 and anti-CD138 antibodies (**I and J**). Plasma cells showed kappa light-chain antibody restriction (**K** ×200, Kappa Light-Chain) relatively to lambda light-chain (**L** ×200, Lambda Light-Chain).

In our case there were typical echocardiographic signs of infiltrative cardiomyopathy, thus amyloid deposition was analyzed first in abdominal fat and renal biopsies. Abdominal fat tissue aspirate sensitivity is high (84–88%) and it is more feasible and safer than endomyocardial biopsy. Some authors have used salivary gland biopsy with excellent results, even in patients with a negative abdominal fat biopsy. Our biopsies of fat and renal tissues were negatives for Congo red staining, but our suspicion for cardiac amyloidosis persisted and a cardiac biopsy was performed. Four endomyocardial samples ensure 100% sensitivity for the detection of the disease. Once the presence of amyloid deposition has been confirmed, the next step is the amyloid type identification [4]. Amyloidosis may be acquired or familial and its type is classified according the underlying mechanism of pro-amyloid protein synthesis as AL amyloidosis (due to immunoglobulin light-chain), secondary-reactive (due to serum amyloid A), hereditary-familial (due to transthyretin, apolipoprotein AI, or apolipoprotein AII), or acquired-senile (due to transthyretin). Cardiac amyloidosis can result from any type of amyloidoses, but when the heart is severally affected, as in the case reported, the differential diagnosis is essentially restricted to transthyretin-associated amyloidosis (senile or late-onset familial amyloidosis) or AL amyloidosis [5,6]. It has been demonstrated that the combination of an abnormal kappa/lambda ratio and a positive immunofixation reaction has a sensitivity of 99% for diagnosing AL amyloidosis [6,7]. In these cases, bone marrow biopsy gives the final answer as to which plasma cells disorder (PCD) is producing the paraprotein. According to the 2010 International Myeloma Working Group diagnostic criteria, multiple myeloma is defined by the following 2 criteria: (1) serum monoclonal protein ≥3 g/dL and/or clonal bone marrow plasma cells ≥10%, and (2) presence of end-organ damage such as lytic bone lesions, anemia, hypercalcemia, or renal failure that can be attributed to PCDs [7]. At the time of diagnosis, we found clonal bone marrow plasma cells at 16%, renal failure, and hypercalcemia, which established the definitive diagnosis of multiple myeloma.

ECMO support gave us time to confirm the etiology and to plan and discuss treatment and prognosis. In our patient the therapeutic alternatives would be high-dose chemotherapy with melphalan and autologous stem cell transplant or a bortezomib plus dexamethasone combination [7–10]. None of these options were considered to be suitable by the multidisciplinary team, taking into account the following reasons: i) bortezomib and melphalan have high cardiotoxicity and are associated with worsening fluid retention and congestive heart failure [8]; ii) in patients with severe cardiac involvement (decompensated heart failure, an ejection fraction less than 40%, or systolic blood pressure less than 90 mmHg), high-dose chemotherapy with autologous stem cell transplantation do not improve survival [4,9]; and iii) pharmacological treatment does not remove preexisting amyloid deposits and, therefore, would

not significantly improve cardiac function. On the other hand, heart transplantation was contra-indicated due to the possibility of other organ system involvement and recurrence of amyloidosis in the graft, since systemic amyloid deposition was already present. Heart transplantation in amyloidosis has been performed almost exclusively in cases with isolated cardiac involvement [10]. In patients with severe cardiac involvement who are not eligible for chemotherapy and/or autologous stem cell transplantation, some centers recommend sequential heart and autologous stem cell transplantation [10]. If patients do not present outcome-limiting organ dysfunction, early heart transplant can be performed followed by high-dose chemotherapy with melphalan and autologous stem cell support [9,10]. However, there is no evidence from randomized controlled trials to support this strategy.

In the clinical vignette, the interruption of ECMO was decided based on the proposals of Lazzeri et al. [2], which recommends stopping ECMO when: i) there is evidence of brain death (based on serial neurological assessment by means of electroencephalogram and somato-sensory evocated potentials evaluation); ii) in the absence of recovery signs or therapeutic options that could improve the prognosis; and/or iii) the patient is not considered eligible for heart transplant.

Modern medical technology allows support of human life for an indeterminate period. This has led to difficult legal and moral discussions concerning medical futility and transitions from aggressive treatment to palliative care. This article takes a closer look at ethical concerns that intensive care units physicians face while performing weaning or assistance on ECMO. In our case, ECMO was considered *medical futility*. The patient was terminally weaned off the ECMO, and although we were not euthanizing the patient, we were deciding to remove equipment that will most likely always lead to death. Futility in medicine is an ancient concept. Hippocrates clearly stated that physicians should "refuse to treat those who are overmastered by their disease, realizing that in such cases medicine is powerless" [11]. *Medical futility* is defined as a clinical action serving no useful purpose in attaining a specified goal for a given patient [12,13]. In our case, the action – ECMO – effectively delivers blood and oxygen. However, the goals of cardiac function recovery or heart transplantation cannot be effectively achieved with any of the treatment options for which the ECMO was serving as a bridge to. We explained to the patient's family that ECMO would not give her a chance to recover. If the goal of aggressive treatment is to prevent bodily death, ECMO would be not futile, as we can achieve this goal. On the other hand, if the intention of aggressive treatment is to return the patient to independent living or prevent imminent death, ECMO serve no useful purpose and are futile. ECMO might even be considered maleficent or harmful if the goal of treatment is to allow a more peaceful and dignified death.

Conclusions

The clinician must consider a diagnosis of cardiac amyloidosis in patients with heart failure, a restrictive type of cardiomyopathy with/without ventricular hypertrophy in the absence of valve abnormalities or uncontrolled arterial hypertension. The main types are transthyretin-associated amyloidosis (senile or late-onset familial amyloidosis) or AL amyloidosis. Confirmation of amyloid type is now possible in most cases through a combination of immunohistochemistry, DNA analysis, and proteomics. Although developments in chemotherapy have greatly improved the outcomes in AL amyloidosis, the prognosis of patients with severe cardiac involvement remains very poor. ECMO is potentially a reliable bridge-to-diagnosis and bridge-to-decision in these patients. Recent technological developments allow for longer ECMO support, if required. An experienced ECMO team, careful patient selection, and rigorous management protocols with objective criteria to wean or stop ECMO are needed. ECMO futility cannot be determined without succinctly stating goals for ECMO support. Negotiating care when either the physician or family believes treatments are futile is a delicate process built upon respecting both patient and professional values. In the end, respect of persons and beneficent approaches can lead to ethically and morally viable solutions.

Statement

Competing interests

No conflicts to disclose.

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