Acute heart failure and bradyarrhythmia in a young male—what hides beneath the surface?: a case report

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Background
Muscular dystrophies (MDs) are characterized by early-onset muscular atrophy and weakness, with frequent cardiac involvement. Myocardial dysfunction and conduction system involvement are often rapidly progressive despite medical and device therapy, and may even precede muscular symptoms, posing a challenge to diagnosis.

Case summary
We report a case of a young male admitted to a cardiac intensive care unit due to ‘de novo’ acute heart failure (HF) and atrial flutter with a slow ventricular response. Careful evaluation of past medical history revealed the presence of neuromuscular symptoms since childhood, disregarded throughout adult age. Diagnostic workup allowed to establish a diagnosis of non-dilated hypokinetic cardiomyopathy secondary to Emery-Dreifuss MD, due to lamin A/C (LMNA) gene mutation. Our patient was treated with neurohormonal modulation therapy and a cardiac resynchronization therapy defibrillator (CRT-D) was implanted, but due to worsening advanced HF, cardiac transplantation was needed.

Discussion
Association of skeletal muscle and cardiac symptoms should always raise the suspicion for an underlying MD, since the consequences of a missed diagnosis are often dramatic. A timely diagnosis is crucial to prevent sudden death due to arrhythmias in these patients and to delay the progressive course of cardiomyopathy.

Learning points
• Muscular dystrophies (MDs) are commonly associated with heart involvement and muscular symptoms often precede cardiovascular manifestations.
• Identifying ‘red flag’ signs and symptoms, such as neuromuscular involvement, advanced conduction disorders, and arrhythmias in early ages may help to diagnose MDs.
• Lamin A/C mutation in Emery-Dreifuss is associated with early-onset cardiomyopathy and significant risk of sudden death due to both bradyarrhythmia and ventricular arrhythmias.

Introduction
Muscular dystrophies (MDs) are rare disorders, usually characterized by early onset of muscular atrophy and weakness, frequently noticeable in the first two decades of life.1,2 Cardiac involvement is more unpredictable, however, ranging from absence of any cardiac abnormalities to early-onset heart failure (HF), conduction disorders or even sudden death, sometimes even before muscular symptoms are recognized.2,3 Muscular dystrophies diagnosis may prove difficult due to heterogeneous presentation, as patients often have mild and ignored muscular symptoms for several years, allowing the
Cardiologist to be the physician establishing the link between peripheral muscular and cardiac symptoms.

**Timeline**

| Month 0 | First hospitalization due to ‘de novo’ acute heart failure, B profile CRT-D implantation and neurohormonal therapy initiation |
| Month 1 | Genetic test result revealing mutation variant c.136A>G p.(Ile46Val) in LMNA gene |
| Month 5 | Initiation of therapy with nepriysin inhibitor sacubitril/valsartan (previously on angiotensin-convert ing enzyme-inhibitor therapy) |
| Month 6 | Clinically stable in New York Heart Association Class II. No ventricular arrhythmias (VAs) detected. Biventricular pacing rate of 98%. Thrombus resolution confirmed |
| Month 12 | Hospitalization due to acute heart failure (HF), profile C. History of syncope at home. ICD interrogation confirmed appropriate therapy for VA |
| Month 14—Month 20 | Four episodes of hospitalization due to acute HF, profile C, requiring inotropic support. Left ventricular ejection fraction (LVEF) decline (LVEF 30%) despite medical/device therapy |
| Month 20 | Cardiac catheterization and cardiopulmonary exercise test undertaken after inotropic cycle |
| Month 21 | Orthotopic cardiac transplantation (class INTERMACS 4) |
| Month 24 | Cardiac rehabilitation program. First months of follow-up after cardiac transplantation without significant complications |

**Case presentation**

A 32-year-old male was admitted to the emergency department due to mild effort fatigue, paroxysmal nocturnal dyspnoea, and right epigastric discomfort. He denied syncope, chest pain, or recent infection history.

Past medical history was remarkable for orthopaedic surgeries to the elbow and Achilles’ tendon during adolescence, for relief of contractures. Family history was unremarkable. Patient denied chronic medication, tobacco, alcohol, or illicit drug use. He was a professional table tennis player.

Emergency department examination revealed bradycardia of 42 b.p.m., normal blood pressure, and no respiratory distress signs. There was significant jugular venous distension. Cardiac auscultation was irregular, without murmurs, and pulmonary auscultation was normal. There was no peripheral oedema nor signs of hypoperfusion.

Blood analysis revealed normal hemogram, serum electrolyte, renal function, troponin I, and C-reactive protein levels, with elevated liver enzymes, lactate dehydrogenase, and brain natriuretic peptide (Table 1).

Electrocardiogram (ECG) showed atrial fibrillation (40–45 b.p.m.), anterior and inferior QS pattern, and low QRS voltage in the frontal plane (Figure 1A). Remarkably, a previous ECG recorded 2 years earlier exhibited sinus rhythm, a long PQ interval of 320 ms with anterior and inferior QS pattern (Figure 1B). Chest X-ray revealed cardiomegaly and mild pleural effusion (Supplementary material online, Figure S1).

Bedside echocardiography demonstrated bi-atrial dilatation, normal left ventricle (LV) dimension and wall thickness, a slightly reduced ejection fraction (LVEF)—45%—due to global hypocontractility, preserved right ventricle dimension, and systolic function. No significant valvular abnormalities were detected. Interestingly, almost perfect visualization of the left atrial appendage revealed a heterogeneous and echogenic mass, with a larger diameter of 20 mm, presumably corresponding to thrombus (Figure 2 and Supplementary material online, Figure S2a–c).

Therapy with intravenous diuretics and anticoagulation with enoxaparin were initiated, with improvement of clinical status.

Laboratory tests for cardiomyopathy aetiological diagnosis did not reveal significant abnormalities (Table 1).

Cardiac magnetic resonance imaging (MRI) was performed, confirming bi-atrial dilatation, normal LV dimension, and a reduced LVEF (37%) due to global hypocontractility. Extensive areas of multifocal and circumferential late gadolinium enhancement (LGE) of non-ischaemic type (predominantly intramural in the basal and mid segments) were identified, as well as diffuse bi-atrial LGE. Subtle hypersignal in the T2-weighted sequences was also reported (Figure 3 and Supplementary material online, Figure S3a–e). Metabolism/perfusion $^{18}$FDG and $^{13}$N-ammonia positron emission tomography (PET) scan was undertaken, revealing diffuse cardiac $^{18}$FDG uptake, associated with focal areas of reduced perfusion, assessed by $^{13}$N-ammonia (mainly lateral left ventricular segments). There was no significant extracardiac $^{18}$FDG uptake (Supplementary material online, Figure S4a–c).

Due to the association of muscular symptoms, Neurology consultation was pursued. Humeroperoneal muscle weakness and wasting were clearly recognized, as were contractures of elbow flexors and Achilles’ tendons. Spine rigidity with limitation of neck flexion was also present (Figure 4A and B and Supplementary material online, Figure S5). Patient confirmed that muscular symptoms had begun in the second decade of life. Laboratory tests taken 6 years ago revealed mildly increased creatine kinase.

After multidisciplinary discussion with Neurology, a diagnosis of Emery-Dreifuss muscular dystrophy (EDMD) with associated cardiomyopathy was presumed. Genetic testing for LMNA and EMD mutations was requested and a decision to implant a CRT-D was made. The procedure underwent without any complications and patient was discharged asymptomatic, anticoagulated with warfarin and medicated with maximally tolerated neurohormonal modulation therapy.

At 6-month follow-up, patient was stable in New York Heart Association Class II, without re-hospitalizations for HF nor ventricular arrhythmia (VA) episodes. Left atrial appendage thrombus resolution was confirmed. Genetic testing results confirmed the presence of mutation variant c.136A>G p.(Ile46Val) in heterozygosity in the LMNA gene, classified as a variant of uncertain significance. Genetic counselling consultation was scheduled for cascade genetic testing of relatives and
a diagnosis of cardiomyopathy secondary to EDMD was established. Participation in competitive sports was strongly discouraged.

In subsequent months of follow-up, substantial deterioration of clinical status ensued, with multiple hospitalizations due to HF requiring inotropic therapy support and several episodes of appropriate ICD shocks due to VAs. Repeat echocardiogram showed substantial decrease in LVEF, estimated at 30%, despite neurohormonal therapy titration and adequate biventricular pacing therapy.

Right heart catheterization and cardiopulmonary exercise testing revealed objective indicators of advanced HF with poor prognosis (Table 1). Advanced HF consultation was pursued and orthotopic cardiac transplantation was undertaken 21 months after initial diagnosis, with a favourable clinical course so far.

Explanted heart histopathologic analysis revealed diffuse interstitial fibrosis with myocyte cytoplasmic vacuolation, predominantly in subepicardial layers, no significant inflammatory infiltrate, no evidence of multinucleated giant cells nor granulomas.

**Discussion**

Emery-Dreifuss muscular dystrophy is a rare inherited dystrophy with an estimated incidence of 3 per million. This disease belongs to the so-called ‘envelopathies’, since it results from mutations that disrupt the normal stability of the nuclear membrane and chromatin condensation.1–3 Most cases of EDMD result from X-linked mutations in EMD gene (EDMD type 1), encoding the protein emerin, and autosomal dominant (EDMD type 2) or recessive (EDMD type 3) mutations in LMNA gene, encoding lamin A/C.2–4

Diagnosis is based on clinical findings, family history, and genetic testing.5 Family history was unremarkable in our patient, which is not infrequent, since up to 65% of EDMD cases due to LMNA mutation are caused by sporadic ‘de novo’ mutations.2,5 Indeed, cascade genetic testing confirmed the absence of the mutated variant in first degree relatives of this patient. The typical clinical triad is characterized by contractures first recognized in early childhood, humeroperoneal muscle weakness, and atrophy and cardiac involvement after the second decade of life. Skeletal muscle symptoms in EDMD2 are often less typical than in EDMD1 and may have a later onset and a milder or slower course.2,4,6

Cardiac involvement in EDMD2 is more variable and more difficult to predict than in EDMD1, being associated with earlier and more aggressive course, culminating in a dilated (sometimes restrictive) cardiomyopathy with decreased LVEF.2,4,7 Neurohormonal modulation therapy constitutes the main treatment of left ventricular dysfunction, although specific data on the efficacy of this therapy in EDMD is lacking.8 Heart transplantation constitutes an option for end-stage HF, if muscular symptoms are not severe and incapacitating. Multidisciplinary evaluation and tailored treatment decision

| Table 1 | Results from diagnostic and prognostic tests undertaken on admission and throughout follow-up |
|---------|--------------------------------------------------------------------------------------------------|
| Admission blood analysis | • Blood count: hemoglobin: 14.6 g/dL; leucocytes: 8.6 × 10⁹/L; platelets: 199 × 10⁹/L  
  • Coagulation: aPTT: 25.6 s  
  • Kidney function and ionogram: creatinine: 0.6 mg/dL; sodium: 143 mEq/L; potassium: 4.1 mEq/L  
  • Liver enzymes: AST: 348 UI/L; ALT: 841 UI/L; GGT: 167 U/I  
  • Total CK: 765 UI/L; LDH: 1228 U/I  
  • C-reactive protein: 1.16 mg/dL  
  • Troponin I 0.23 ng/mL; BNP: 433 pg/mL |
| Analytic tests for aetiological diagnosis | • Erythrocyte sedimentation rate: 4 mm/h  
  • Normal serum ACE, ferritin, ceruloplasmin, thyroid hormone, cortisol, and vitamin levels  
  • Negative panel for autoimmune antibodies  
  • Normal urine 24 h calcium, protein, and light chain secretion  
  • Negative plasma and urine immunofixation |
| Right heart catheterization | • mPAP 42 mmHg  
  • PCWP: 36 mmHg  
  • PVR: 1.2 Wood units  
  • Cardiac index: 1.8 L/min/m² |
| Cardiopulmonary exercise test | • RER: 1.1  
  • Peak VO2: 11.8 mL/kg/min (on low dose beta-blocker)  
  • VE/VCO2 slope: 41  
  • Peak PETCO2 29 mmHg  
  • Presence of oscillatory breathing pattern  
  • Two episodes of non-sustained ventricular tachycardia |

ACE, angiotensin-converting enzyme; ALT, alanine aminotransferase; aPTT, partial thromboplastin time; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; CK, creatine kinase; GGT, gamma-glutamyl transferase; LDH, lactate dehydrogenase; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RER, respiratory exchange ratio
considering expected progression of myopathic deterioration after heart transplant are essential. Post-transplant survival appears to be similar compared to other cardiomyopathy aetiologies, although data regarding this issue are scarce.\(^2,3,8-10\)

Conduction defects are common, being associated with sudden death due to bradyarrhythmia in early ages. Pacing therapy is sometimes advocated as prophylactic therapy when milder conduction disorders or bradycardia appear.\(^1,2\) LMNA-associated EDMD (EDMD type 2) is specially characterized by a high risk of life-threatening malignant VAs, which may precede the development of cardiomyopathy.\(^12,13\) Risk factors associated with VA include non-sustained ventricular tachycardia, male gender, LVEF <45%, and non-missense mutations.\(^1,14\) An implantable cardioverter defibrillator is often required for primary prevention of sudden death, due to increased arrhythmic risk associated.

Other common cardiac complication includes thrombus formation, due to atrial fibrillation/flutter and atrial standstill, increasing the risk for cerebral emboli and stroke.\(^1,3,11\)

![Figure 1](image1.png)  
**Figure 1** (A) Electrocardiogram showing atrial fibrillation with slow ventricular response, QRS broadening, and anterior and inferior QS pattern. (B) Electrocardiogram recorded 2 years before cardiac symptoms onset, showing sinus rhythm, first degree atrioventricular block (PQ: 320 ms), and both low P wave and QRS voltage in frontal plane. There is also anterior and inferior QS pattern with loss of R waves in precordial leads.

![Figure 2](image2.png)  
**Figure 2** Echocardiogram apical four-chamber view showing biatrial dilation, normal left ventricle chamber size, and a large mass in left atrial appendage.
Cardiac MRI features in EDMD are also scarcely described in literature. In type 2 EDMD, earlier cardiac involvement has reportedly been associated with none or minimal fibrosis, despite the presence of decreased systolic function, contrary to what is seen in other MDs, like Becker or Duchenne. The presence of diffuse and extensive fibrosis in this patient questions these findings, however. We cannot properly explain the diffuse 18FFDG uptake/perfusion defects on the PET scan and the subtle T2-sequence hypersignal on cardiac magnetic resonance imaging, but we hypothesize that they might represent either false-positive results or associated non-specific inflammatory activity (as described in rare cases of arrhythmogenic and hypertrophic cardiomyopathy), as the clinical picture was not compatible with inflammatory cardiomyopathy, including sarcoidosis (no extracardiac involvement, no granulomas detected in histological analysis).

Our patient had symptoms, laboratorial, and electrocardiographic abnormalities suggestive of muscular and cardiac involvement since infancy/adolescence that remained largely uninvestigated. These subtle signs were clear 'red flags'. An earlier referral and diagnosis might have had a possible impact delaying the course of cardiomyopathy.
Emery-Dreifuss muscular dystrophy is a rare muscular disorder whose signs and symptoms can be first identified in early infancy. Left unrecognized, this disease might lead to extensive cardiac involvement, presenting with HF and life-threatening arrhythmias in early adulthood. This case highlights the importance of early diagnosis in this type of disorders and specific considerations to bear in mind when managing EDMD patients.

**Conclusion**

Emery-Dreifuss muscular dystrophy is a rare muscular disorder whose signs and symptoms can be first identified in early infancy. Left unrecognized, this disease might lead to extensive cardiac involvement, presenting with HF and life-threatening arrhythmias in early adulthood. This case highlights the importance of early diagnosis in this type of disorders and specific considerations to bear in mind when managing EDMD patients.
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