Fulminant Myocarditis Unmasking Adult-Onset Still's Disease and Desmoplakin Truncation

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A 24-year-old man with no documented allergies, cardiovascular risk factors, except for obesity and smoking habit, and no family history of sudden cardiac death or cardiomyopathies, was admitted to the emergency department with a 7-day history of fever (38 °C–40 °C), associated with general discomfort, painful submandibular and cervical lymphadenopathy, dyspnea, hypotension, diaphoresis. The patient reported home initiation of antibiotic therapy. Patient was transferred to cardiac intensive care unit with clinical signs of pulmonary congestion, his invasive radial blood pressure was 85/45 mm Hg, jugular venous pressure was 8 mm Hg, heart rate was 125 bpm, respiratory rate was 44 breaths/minute, the temperature was 37.6 °C, SpO_2 was 96% with O_2 therapy with nasal cannulas (5 L/minute, FiO_2 40%). Arterial and venous blood gas analysis showed respiratory alkalosis, hypoxemia, lactate 2.3 mmol/L, SVO2 79%. ECG showed sinus tachycardia (115 beats/minute), low QRS voltages in peripheral leads, diffuse repolarization abnormalities (Figure 1A).

Transthoracic echocardiogram revealed a severe impairment in left ventricular ejection fraction (30%) and global longitudinal strain (Figure S1A; Video S1). Right ventricular function was preserved. Moderate to severe functional mitral and tricuspid regurgitation (3+/4+) with a pulmonary artery systolic pressure of 33 mm Hg was observed. Inferior vena cava was dilated with reduced inspiratory collapse. A mild pericardial effusion was present. Supportive inotropic therapy was promptly initiated with continuous infusion of dobutamine plus broad-spectrum antibiotic therapy.

Laboratory tests showed neutrophilic leukocytosis (WBC 47.93×10^3/μL with 94% neutrophils; N.V. 4.5–11), high-sensitivity troponin I concentration of 568 pg/mL (N.V. 40.8–115.1), NT-proBNP level of 53.000 pg/mL (N.V. 0–125), ferritin level of 4325 ng/mL (N.V. 30–400), hsC-reactive protein level of 27 mg/dL (N.V. <1), ALT (alanine transaminase) level of 280 IU/L (N.V. 10–49) and AST (aspartate transaminase) level of 266 IU/L (N.V. 0-34), and a creatinine level of 1.5 mg/dL (N.V. 0.6–1.1; Figure 1B; Table S1). Nasopharyngeal swab assessing a full panel of respiratory viruses and SARS-CoV-2 by RT-PCR were negative except for human rhinovirus and enterovirus. Culture and serology test results excluded active bacterial and viral infections.

Right heart catheterization performed during dobutamine infusion showed a pulmonary artery wedge pressure of 15 mm Hg, a mean pulmonary artery pressure of 18 mm Hg, cardiac index of 4.2 L/min/m^2, right atrium pressure of 10 mm Hg, systemic vascular resistance of 646 dyn·s·cm^{-5}, suggesting a mixed shock status.

Right ventricle endomyocardial biopsy was performed showing a diffuse active and florid lymphocytic myocarditis (Figure 2).

Contrast enhanced CT scan showed pulmonary alveolar edema, cardiomegaly, mild basal pleural effusion, hepatomegaly with hepatic steatosis, splenomegaly

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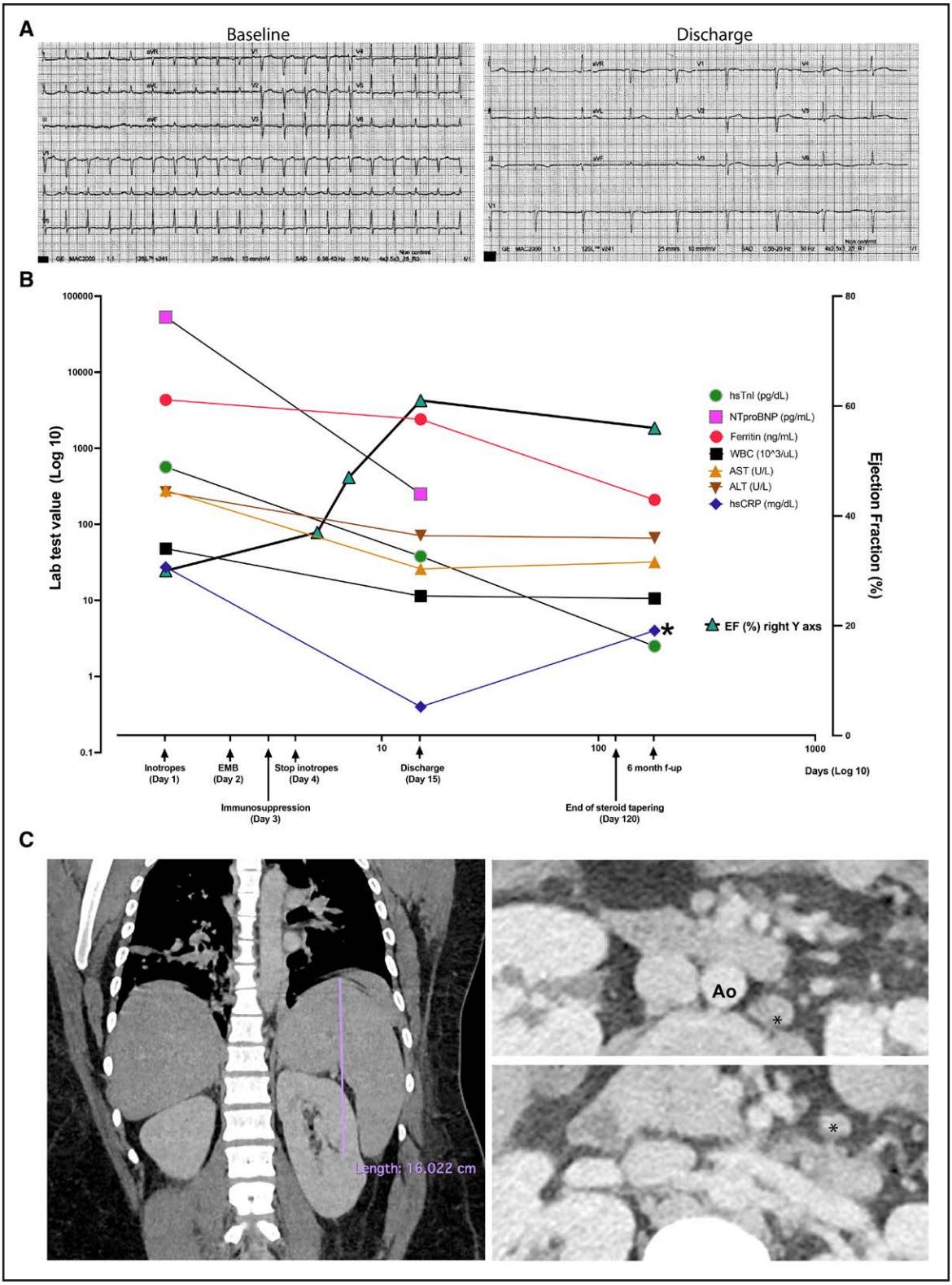

Figure 1. Clinical course of the disease.
A, ECG at baseline and discharge. **B**, Timeline of laboratory tests and ejection fraction. **C**, Representative computed tomography scan images showing splenomegaly (left) and aortic (right-top) and mesenterial (right-bottom) enlarged lymph nodes. *CRP at follow-up was measured in a different laboratory and was not high sensitivity with normal value <5 mg/dL. ALT indicates alanine transaminase; Ao, aorta; AST, aspartate transaminase; EF, ejection fraction; EMB, endomyocardial biopsy; hsCRP, high-sensitivity C-reactive protein; hsTnI, high-sensitivity troponin I; NTproBNP, N-terminal prohormone of brain natriuretic peptide; and WBC, white blood cell.

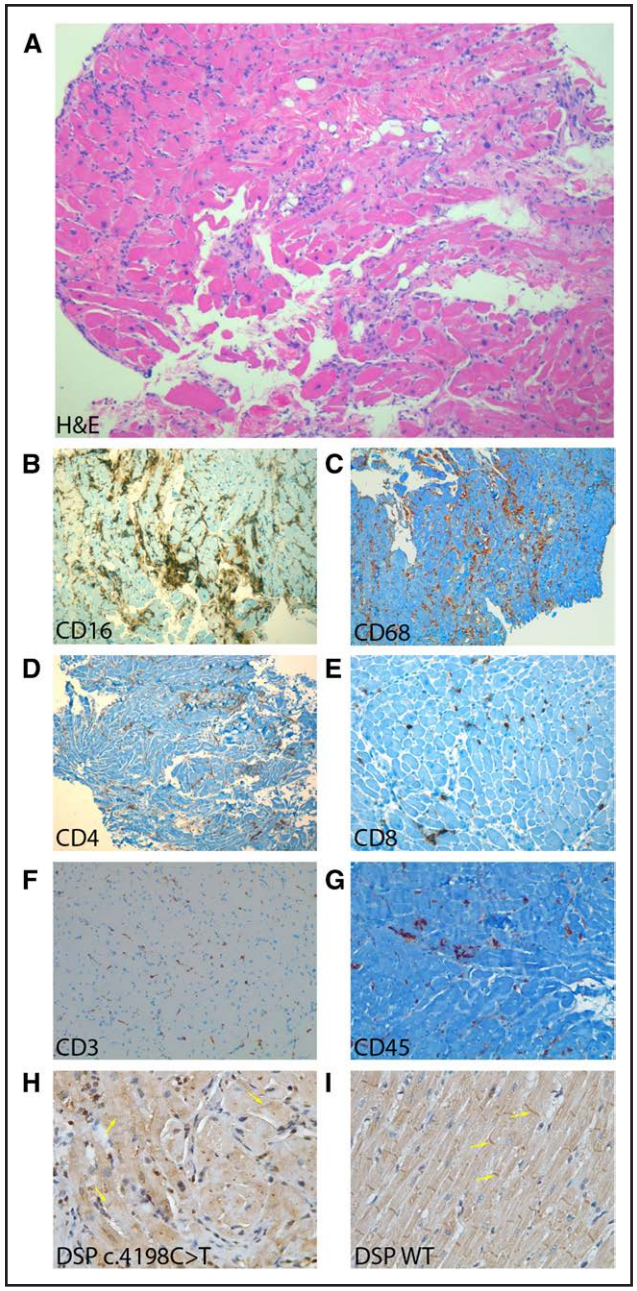

Figure 2. Endomyocardial biopsy histology.
A, Hematoxylin and eosin stain (10X) showing severe lymphocytic myocarditis without areas of fibrofatty replacement; immunohistochemistry showing (**B**) intense myocardial infiltration of $CD16^+$ cells, a common marker of macrophages, natural killer (NK) cells and neutrophils, that, as shown in **C**, are mainly represented by $CD68^+$ cells suggesting a macrophagic infiltrate. **D**, CD4 T Helper lymphocytes ($CD4^+$, 10X) and (**E**) spotty CD8 suppressor lymphocytes ($CD8^+$, 20X) are also represented as confirmed by CD3 (**F**) and CD45 (**G**) positive cells. **H**, Mutant desmoplakin (c.4198C>T) immunohistochemical staining (anti-DSP Ab, 40X) revealed a smoother and fainter signal when compared with the wild-type control (**I**). DSP indicates desmoplakin.

(craniocaudal length 16 cm), lymphadenopathy in the left lumbar aortic area (Figure 1C).

Sequential organ failure assessment score was 7.

Adult-onset Still's disease (AOSD) was diagnosed according to Yamaguchi's criteria,[1] presenting 2 major, neutrophilic leukocytosis and fever >39 °C lasting >1 week and 5 minor criteria including recent development of significant lymphadenopathy, splenomegaly, sore throat, abnormal liver function test, negative tests for infectious and rheumatological diseases.

High-dose corticosteroid therapy was initiated (1000 mg of intravenous methylprednisolone per day for 3 consecutive days, followed by progressive tapering) with a prompt clinical improvement.

Laboratory tests, except for ferritin, were normalized (Figure 1B).

Transthoracic echocardiogram showed improvement in global longitudinal strain (−18.3%) and left ventricular ejection fraction (61%) with mild mitral and tricuspid regurgitation (Figure S1B; Video S2).

Predischarge cardiac magnetic resonance imaging showed normal biventricular geometry and contractility (left ventricular ejection fraction 74%; Video S3). T2-weighted STIR images (Figure 3) showed absence of myocardial edema in the LV; a limited area of LGE with subepicardial/intramyocardial distribution involving the inferolateral basal segment of the left ventricle was present (Figure 3).

Since we are performing a study in our department to characterize the genetic background of acute myocarditis, in particular, those with recurrency, the patient underwent DNA sequencing for 174 common cardiomyopathy-causing genes with next generation sequencing detecting heterozygous variant in the form of nonsense mutation c.4198C>T (p.Arg1400*) for desmoplakin (*DSP*) gene classified by ClinVar as pathogenic/likely pathogenic. At 6-month follow-up, the patient was asymptomatic with normal laboratory tests (Figure 1B) ECG, transthoracic echocardiogram (Figure S1C; Video S4), and cardiac magnetic resonance imaging (Figure 3; Video S5) and had discontinued corticosteroid therapy. Genetic testing has been extended to the patient's family members and is ongoing.

AOSD is a rare inflammatory disease, recently classified as polygenic inflammatory disorder; the diagnosis remains challenging and it has to meet Yamaguchi's criteria.[1]

Although the etiology is unknown, AOSD is considered a continuum of juvenile idiopathic arthritis, emphasizing the central role of inflammasome and cytokine storm (especially IL-1, IL-6, TNF-alpha). This uncontrolled inflammatory state can represent a life-threatening condition for the patients because of disseminated intravascular coagulation, macrophage activation, thrombotic microangiopathy and myocarditis. Cardiac involvement is most frequently represented by pericarditis, associated with pericardial effusion and chest pain while myocarditis is more common in young men and can represent the onset symptom.[2] While corticosteroids remain the

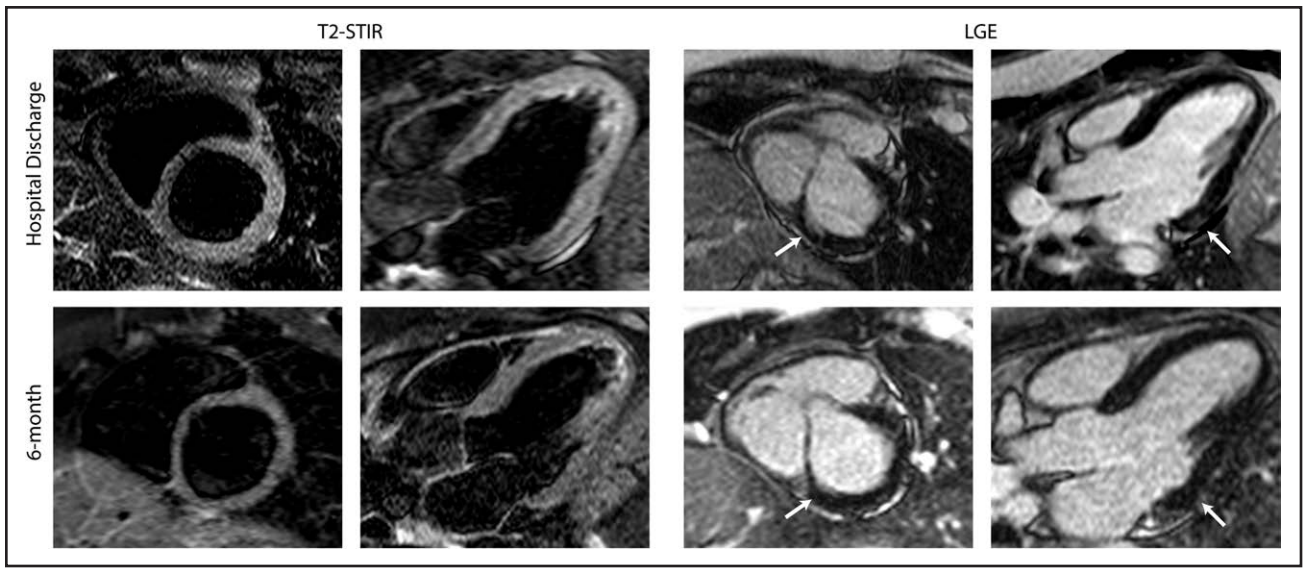

Figure 3. Cardiac magnetic resonance imaging.
T2-weighted short-TI inversion recovery (STIR) images in short-axis and 3-chamber view showing absence of edema in the left ventricle (LV) at discharge and at 6-month follow-up. Short-axis and 3-chamber view showing a limited area of late gadolinium enhancement (LGE) involving the inferolateral basal segment of the LV that is not present at 6 months (white arrow).

first-line therapy, biotherapies can be immediately evaluated, especially for patients with cardiac involvement that are often affected by an intense inflammatory storm. The subsequent finding of *DSP* gene's mutation has shed the light on a new scenario. *DSP* is a fundamental structural protein for anchoring intermediate filaments to desmosomes in cardiomyocytes, which ensures normal force transmission.

DSP mutations, in fact, can lead to development of a rare and distinct cardiomyopathy,[3] characterized by recurrent myocarditis (that can be the first sign of this disease), fibrosis and ventricular dysfunction (mainly of the left ventricle), which can facilitate the onset of ventricular arrhythmias.[4] We hypothesize that the presence of an unknown *DSP* mutation has promoted the unusual presentation of AOSD as fulminant myocarditis. *DSP* immunohistochemical signal in our case was reduced and less sharp when compared with wild-type control (Figure 3); however, routine endomyocardial biopsy histology is a major limitation in distinguishing *DSP*-related myocarditis thus genetic evaluation is crucial. Furthermore, no fibrofatty replacement was observed. Although the best therapeutic management of acute myocarditis in *DSP* cardiomyopathy is still a matter of debate, there are increasing evidence suggesting the role of immunosuppressive therapy, based on high-dose steroids. Our patient was hospitalized in shock and the correct diagnosis of AOSD was crucial as high-dose corticosteroid therapy was started causing a dramatic clinical improvement.

Clinical practice aimed at distinguishing between autoimmune or genetic and secondary forms is crucial to improve patient's outcome.

ARTICLE INFORMATION

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Disclosures

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