Circulation: Cardiovascular Imaging

CARDIOVASCULAR IMAGES

Hypersensitivity Myocarditis Following Deferasirox Administration

Andrea Frustaci, MD; Romina Verardo, PhD; Giancarlo Labbadia, MD; Vito Menafra, MD; Nicola Galea, MD; Matteo Antonio Russo, MD

Hypersensitivity myocarditis is an underestimated disease that if recognized by endomyocardial biopsy can completely recover following withdrawal of the culprit drug and steroid administration for few weeks/few months or if undiagnosed may bring to death, accounting for 0.47 % of large autopsy series.[1]

A 73-year-old woman, receiving regular blood transfusion for 2 years as affected by myelodysplasia and under treatment with deferasirox (14 mg/kg daily; 2 tablets of 360 mg/die) in the last 2 months due to the registration of high levels of ferritin (1000 µg/L) was admitted because of acute heart failure. She was on treatment only with deferasirox and previously the patient presented normal ECG and at echocardiogram normal cardiac parameters with a left ventricular (LV) ejection fraction of 64%. Cardiac magnetic resonance suggested myocardial iron deposition (Figure S1) that was confirmed at histology with metachromatic perinuclear granules after Perls' staining (Figure S2) and at ultrastructural examination of LV endomyocardial biopsy tissue (Figure S3). At admission, the woman was afebrile, dyspnoeic even at rest (New York Heart Association class 4), and showed ECG sinus tachycardia (118 bpm) with frequent supraventricular ectopic beats and elevation of ST-segment in the anterior leads (Figure S4A). An echocardiogram showed a normal-sized (LV end-diastolic diameter of 54 mm) but diffusely hypokinetic LV (ejection fraction 32 %; in the Figure S4C).

Cardiac magnetic resonance study confirmed a normal LV cavity with marked reduction of systolic function (LV ejection fraction: 35.6%, Video S1) and pericardial effusion. T2-weighted images and on T1/T2 maps revealed a diffuse edematous LV involvement, more prominent at the midapical region (Figure 1, Video S1). After gadolinium administration, only thin subepicardial striae of late enhancement have been detected on mid-basal lateral wall.

Abnormal hematochemical exams included increased troponin I (3.0 µg/L; normal values <0.030) and leucocytosis (11.2×10^3 /mm3) with elevated eosinophil count (500/mm^3).

To investigate the cause of heart failure, the patient underwent an invasive cardiac study including coronary with LV angiography and LV endomyocardial biopsy.

Coronary arteries were normal and endomyocardial samples were processed for histology, electron-microscopy, and real-time polymerase chain reaction for the most common cardiotropic viruses, including adenovirus, Epstein Barr Virus, herpes virus 1/2, Herpes Human Virus Simplex 6, Parvovirus B19, enterovirus, influence virus A/B. Histology showed an active myocarditis with extensive inflammatory infiltrates including lymphocytes, macrophages, and mostly degranulated eosinophils associated with focal necrosis of the adjacent myocytes (Figure 2). Negative was the polymerase chain reaction for tested viral genomes. Clinical profile, histology, negative polymerase chain reaction for viral agents, and hypereosinophilia following the administration of a single drug suggested the diagnosis of hypersensitivity myocarditis to deferasirox. The patient withdrew the drug and received prednisone 1 mg/kg daily for 3 weeks and then tapered until steroid withdraw.

The patient improved progressively with recovery of LV function (ejection fraction at 2-dimensional-echo

Key Words: autopsy ■ biopsy ■ deferasirox ■ hypersensitivity ■ myocarditis

Correspondence to: Andrea Frustaci, MD, Department of Cardiovascular, Respiratory, Nephrologic, Anesthesiologic and Geriatric Sciences, La Sapienza University, Viale del Policlinico 155, 00161, Rome, Italy. Email biocard@inmi.it

Supplemental Material is available at: https://www.ahajournals.org/doi/suppl/10.1161/CIRCIMAGING.121.013702.
For Sources of Funding and Disclosures, see page 130.

Circulation: Cardiovascular Imaging is available at www.ahajournals.org/journal/circimaging

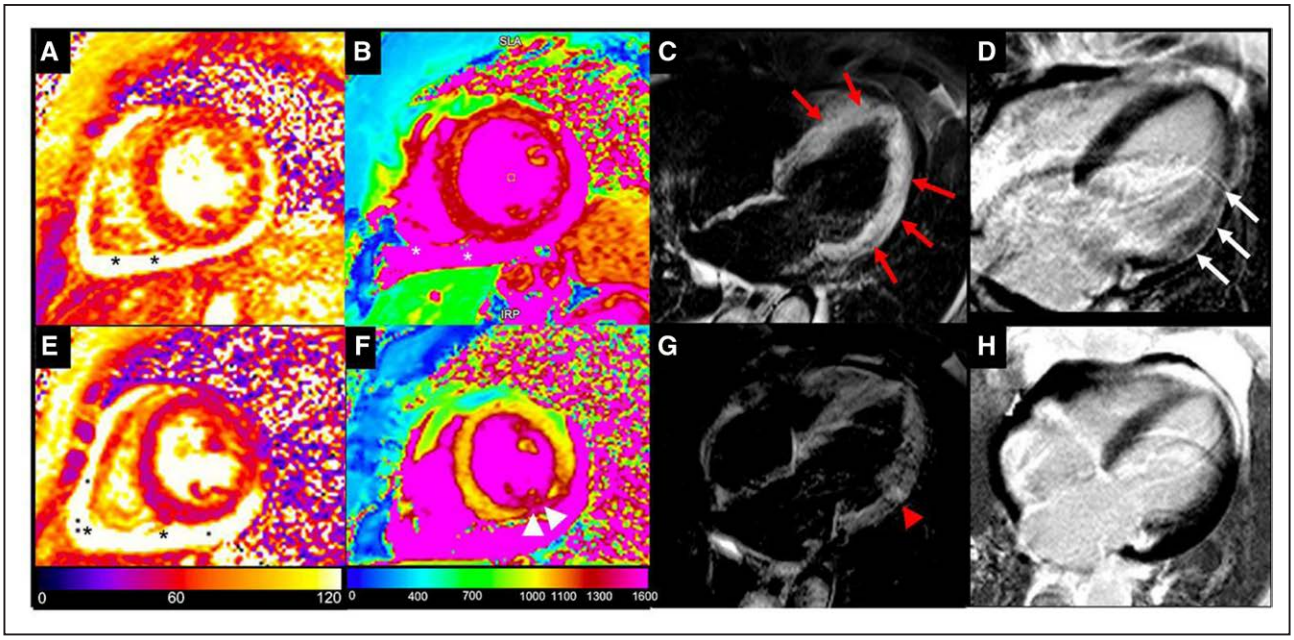

Figure 1. Cardiac magnetic resonance in a 73-y-old woman with deferasirox-induced hypersensitivity myocarditis.
A–**D**, Cardiac magnetic resonance performed during the acute presentation for the clinical suspicion of myocarditis. Myocardial T2 (**A**) and T1 (**B**) maps show respectively marked increase of native T2 (global T2 value: ≈62 ms, normal range <49.9 ms) and T1 (global native T1: ≈1300 ms, normal range <1027 ms), also confirmed on STIR T2 weighted image acquired on horizontal long-axis view (**C**) which shows hyperintensity of lateral wall and septum, reflecting myocardial edema (red arrows). Abundant pericardial effusion was also detected (asterisk). Late gadolinium–enhanced image show thin subepicardial striae of myocardial enhancement at the level of the lateral wall on the mid-basal planes (white arrows). **E**–**H**, The corresponding images acquired at 1-mo follow-up demonstrate the reduction and normalization of T2 map (**E**, global T2 value: 47 ms), reduction of normal myocardial T1 value (**F**, global native T1: 1060 ms) with a focal area of increased T1 value within the midventricular inferolateral left ventricular wall (arrowheads). Almost complete resolution of myocardial edema (only a small hyperintense area persists on lateral wall, red arrowhead) and persistence of thin striae of enhancement are detected respectively on STIR T2-weighted (**G**) and late gadolinium enhancement (**H**) images.

68%, see Figure S4D). Cardiac magnetic resonance exam acquired at 1-month follow-up demonstrated restoration of normal LV contractile function (LV ejection fraction 68%), pericardial effusion disappearance, and myocardial edema solution (Figure 1, Video S1).

Drug-related myocarditis is as subtle as a potentially devastating entity that is difficult to identify in life.

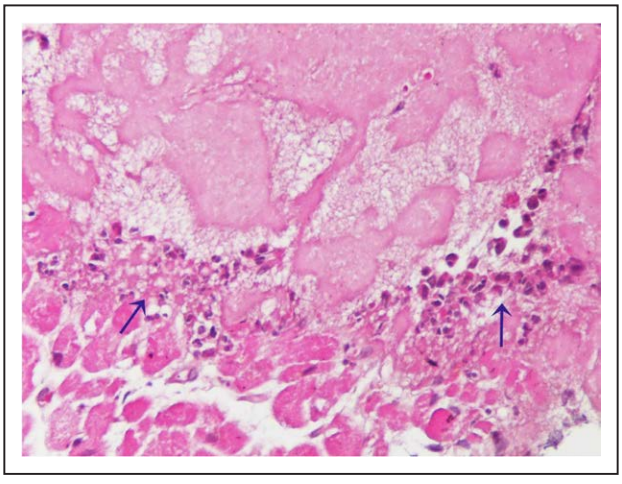

Figure 2. Eosinophilic myocarditis.
Extensive eosinophilic myocarditis (arrows) with interstitial edema and necrosis of cardiomyocytes adjacent to inflammatory infiltrates. hematoxylin and eosin (magnification ×400).

Major clinical characteristics include sudden cardiac deterioration and/or electrical instability occurring 2 to 6 weeks after the introduction of a single or a new drug. These manifestations are typically associated with elevation of markers of myocardial necrosis and increase in eosinophilic count, of particular significance in those subjects with no history of allergic diseases.

Mechanism of a drug inducing myocardial hypersensitivity includes a stable drug deposition in the myocardium and the formation of a new antigen with the drug conjugating as hapten to cell membrane molecules.

Endomyocardial biopsy is the gold standard for the diagnosis as it shows the presence of eosinophilic myocarditis and allows through polymerase chain reaction to exclude possible infectious agents.

Proper disease recognition may result in a complete cardiac recovery even in the condition of a severe cardiac compromise thanks to the effects of steroids on reduction of eosinophil production and stabilization of eosinophil membrane preventing crystalloid degranulation and release of toxic agents as the cationic protein that causes endothelial and cardiomyocyte damage as well as activation of factor X promoting endocardial thrombosis.

ARTICLE INFORMATION

Affiliations

Department of Cardiovascular, Respiratory, Nephrological, Anesthesiologic and Geriatric Sciences, Sapienza University, Rome, Italy (A.F., G.L., V.M., N.G.). Cellular and Molecular Cardiology Lab, IRCCS L. Spallanzani, Rome, Italy (R.V.). Department of Internal Medicine A and Metabolic Bone Diseases, Rome, Italy (G.L., V.M.). MEBIC Consortium, San Raffaele University and IRCCS San Raffaele, Rome, Italy (M.A.R.).

Source of Funding

Funded partially by Italian Health Ministry (IRCCS L. Spallanzani and IRCCS San Raffaele Roma - Ricerca Corrente No. 2020/1) and by Fondazione Roma (MEBIC No. 18/6/2019).

Disclosures

None.

Supplemental Materials

Figure S1–S4
Video S1

REFERENCE

1. Fenoglio JJ Jr, McAllister HA Jr, Mullick FG. Drug related myocarditis. I. Hypersensitivity myocarditis. *Hum Pathol.* 1981;12:900–907. doi: 10.1016/s0046-8177(81)80195-5