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CASE REPORT

ADVANCED

CLINICAL CASE

Extranodal Rosai-Dorfman Disease Presenting as a Pericardial Mass and Constrictive Pericarditis

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ABSTRACT

Rosai-Dorfman disease is a rare, idiopathic disorder of histiocyte proliferation. We describe a case of a 59-year-old woman who presented with heart failure symptoms from a large pericardial mass causing constrictive pericarditis. Pathologic findings including immunohistochemistry suggested the diagnosis. She was treated with corticosteroids and improved clinically. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2019;1:643–7) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

A 59-year-old female patient presented to our clinic with progressive dyspnea on exertion for the past 2 years, particularly worse for the past few months. She also reported productive cough, wheezing, and symptoms suggestive of worsening of her long-term acid reflux disease. On physical examination, her vital signs were normal and she exhibited minimal jugular venous distension, clear lung fields, normal heart tones, no murmurs, a normal abdominal examination, and no lower extremity edema.

LEARNING OBJECTIVES

- Understand the approach to work-up of intrapericardial masses.
- Review the differential for "benign" intrapericardial masses based on immunohistochemistry.
- Summarize therapeutic options for RDD.

PAST MEDICAL HISTORY

The patient had a history of hypertension, type 2 diabetes mellitus, asthma, gastroesophageal reflux disease, prior rheumatic fever, and cutaneous squamous cell carcinoma excised from the left shoulder 1 month prior.

DIFFERENTIAL DIAGNOSIS

Initial diagnostic considerations included reflux asthma syndrome, chronic obstructive pulmonary disease, congestive heart failure, valvular heart disease, and carcinoid heart disease.

INVESTIGATIONS

An echocardiogram demonstrated nonspecific thickening of the right ventricular free wall and features of constrictive pericarditis (**Figures 1A to 1C**, Videos 1 and 2). A noncontrast computed tomography of the

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Informed consent was obtained for this case.

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ABBREVIATIONS AND ACRONYMS

FDG = fluorodeoxyglucose

RDD = Rosai-Dorfman disease

chest demonstrated a masslike density of the anterior pericardium (Figure 2). Subsequent cardiac magnetic resonance imaging demonstrated an intrapericardial mass (6.9 × 2.3 cm) involving the pericardium overlying the right ventricular free wall, with encasement of the right coronary artery, ascending aorta, and aortic arch (Figures 3A to 3C, Video 3).

The patient underwent open surgical biopsy, which demonstrated fibrosis, fat necrosis, and chronic inflammation. Immunohistochemical staining showed significantly increased plasma cells in the infiltrate, as well as increased IgG and IgG4, suggesting IgG4-related disease. A lymph node biopsy demonstrated a reactive infiltrate. She continued to report worsening heart failure symptoms and was sent to a referral facility for a second opinion. There, fluorodeoxyglucose (FDG) positron emission tomography demonstrated avid pericardial mass uptake (Figure 4). A repeat computed tomography-guided needle biopsy demonstrated fibrosis and a dense lymphohistiocytic infiltrate (Figures 5A to 5D). The infiltrate was positive for CD163 and S100 and negative for BRAF. There were also scattered IgG reactive plasma cells, 20% of which were IgG4 reactive. Serum levels of IgG and IgG4 were within normal limits. There was evidence of emperipolesis, which is histiocytic engulfment of lymphocytes and plasma cells.

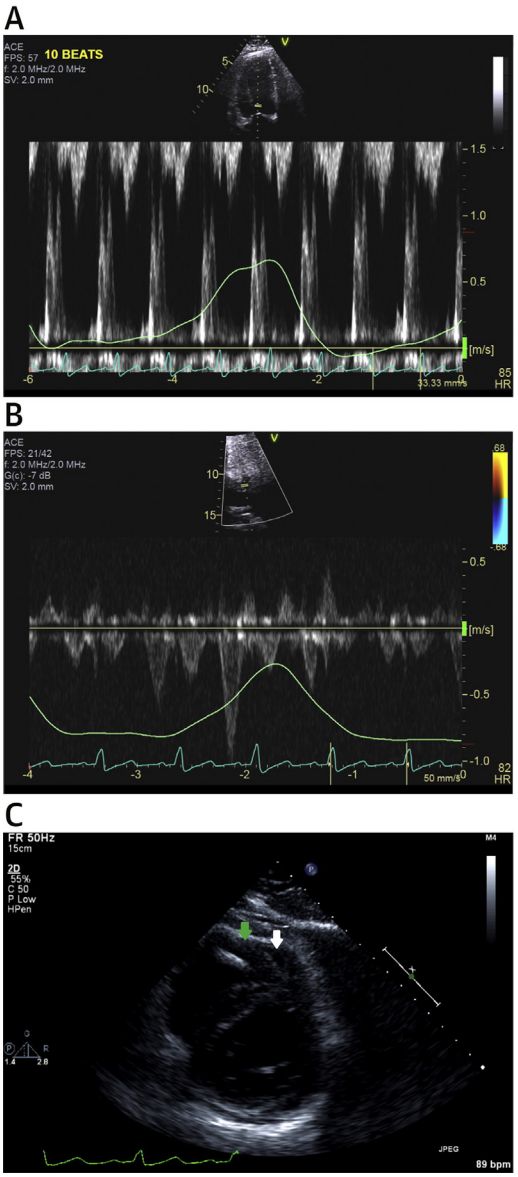
MANAGEMENT AND CLINICAL COURSE

The previous findings included features to suggest an immune-mediated process including IgG4-related disease and the rare histiocytosis. The observed immunohistochemical pattern and emperipolesis suggested a diagnosis of sinus histiocytosis with massive lymphadenopathy, or Rosai-Dorfman disease (RDD). Owing to progressive weight loss and class III heart failure symptoms, the decision was made to offer therapy. After consideration of multiple possible treatment modalities, the patient ultimately opted for an extended course of prednisone.

DISCUSSION

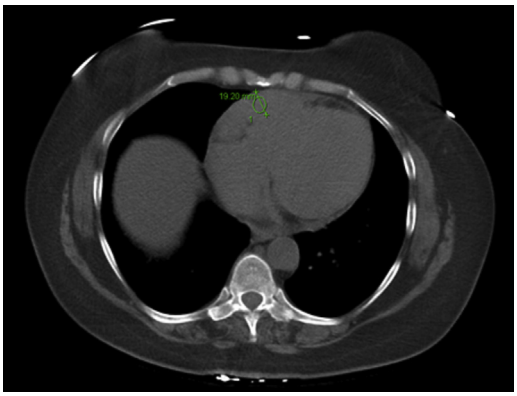
RDD is classified as a non-Langerhans-type histiocytosis and was first described in the 1960s (1,2). It is also known as sinus histiocytosis with massive lymphadenopathy due to its most common dominant clinical finding, but cardiac involvement including structural infiltration has been described (3). Although the exact etiology of RDD remains unclear, mitogen-activated protein kinase pathway alterations have been reported in 33% of RDD patients—this suggests a potential clonal origin at least in a subset of these patients (4). Cardiac involvement by RDD is

FIGURE 1 Pericardial Constriction by Echocardiography



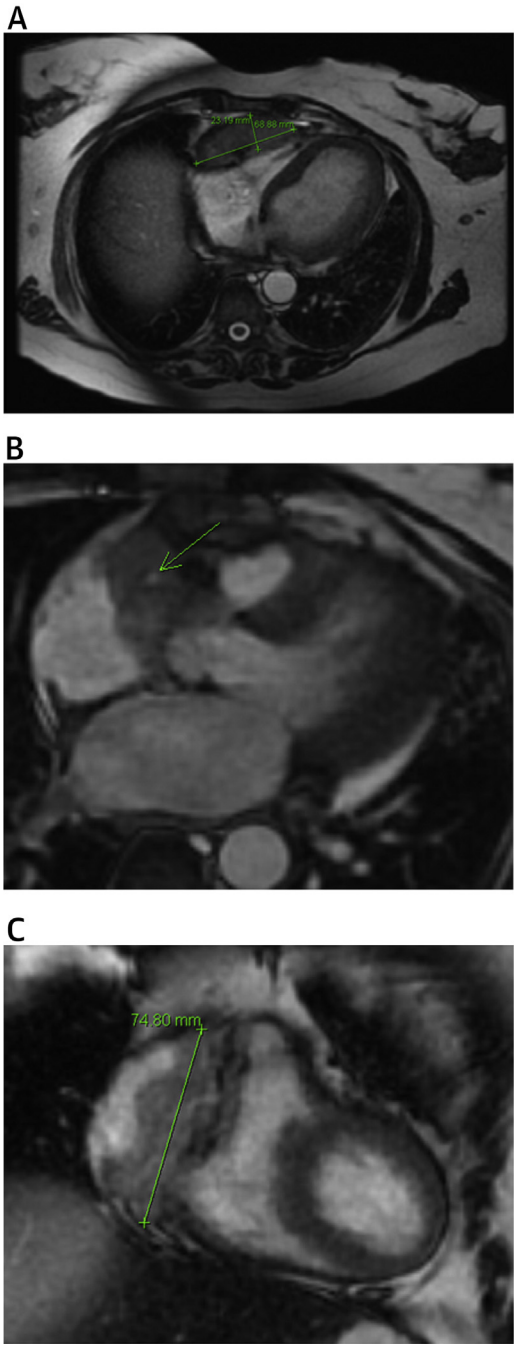
(A) Mitral inflow pulsed wave Doppler, 10-beat acquisition with respirometer, demonstrating respirophasic flow variation. **(B)** Hepatic vein pulsed wave Doppler, 10-beat acquisition with respirometer, demonstrating expiratory flow reversal. **(C)** Echocardiogram from parasternal window, short axis, right ventricular free wall thickening **(green arrow)** and hypoattenuation **(white arrow)**. See Videos 1 and 2.

FIGURE 2 Pericardial Mass by Computed Tomography



Noncontrast chest computed tomography demonstrating pericardial thickening versus mass-like density measuring up to 19 mm.

FIGURE 3 Extent of Mass by Cardiac MRI

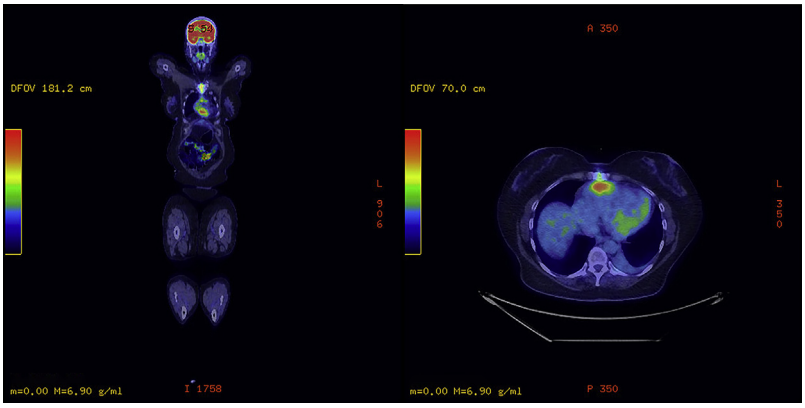


(A) Cardiac magnetic resonance imaging (MRI) with contrast demonstrating intrapericardial mass along right ventricular free wall, measuring 23 × 69 mm. **(B)** Cardiac MRI with contrast demonstrating intrapericardial mass encasing proximal right coronary artery **(green arrow)**. **(C)** Cardiac MRI with contrast demonstrating extent of mass along right ventricle. See Video 3.

considered rare, and a high index of suspicion is required to entertain the diagnosis. In a Mayo Clinic study of 55 patients with RDD, only 2 (4%) had involvement of the cardiovascular system (5). In this case, the diagnosis was supported by the histopathological findings. Also in the differential was Erdheim-Chester disease, another rare non-Langerhans cell histiocytosis that can also present with pericardial involvement and stain CD163-positive, but it is usually S100-negative and *BRAF* mutation-positive (6). Similarly, while IgG4-related disease can manifest with pericardial involvement, the IgG4-positive fraction of plasma cells in the infiltrate seen in the present case did not meet criteria for primary IgG4-related disease, nor were there elevated IgG and IgG4 levels in the serum (7). The IgG4+ plasma cell content observed in the biopsy specimens may reflect an associated secondary process in this particular case.

The management of cardiac RDD needs to be highly individualized. Consensus recommendations for therapy for RDD in general range from close observation to steroids and chemotherapeutic agents and radiotherapy or surgery in certain cases (8). When the disease process leads to complex structural infiltration and mechanical obstruction, noninvasive management of obstruction with adjuvant radiation has been described (9). Various groups have reported good clinical outcomes with surgical management in cases of distinct cardiac masses (3). Medical therapy alone for such patients has also been described (10). Therapeutic options include corticosteroids, various

FIGURE 4 Pre-Treatment Functional PET Imaging



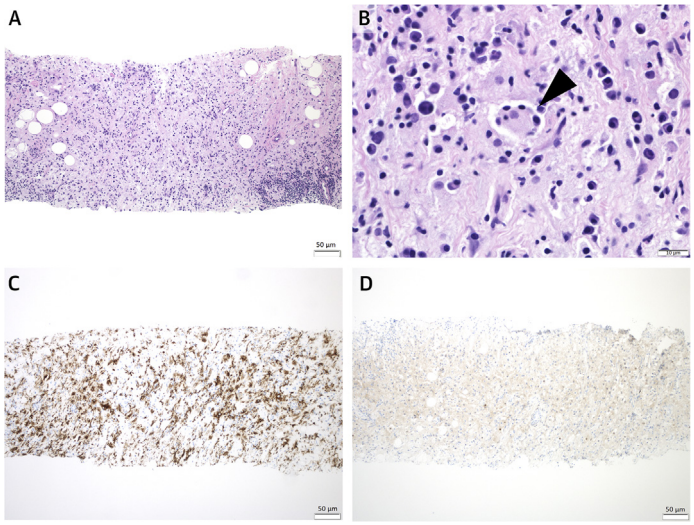
Fluorodeoxyglucose positron emission tomography scan before therapy demonstrating increased metabolic activity in the mass **(red and yellow)** (**left** = whole body coronal plane, **right** = cardiac mass in axial plane).

combinations of chemotherapeutic agents, and targeted agents (in patients with applicable genetic mutations). Targeted agents include the tyrosine kinase inhibitor imatinib and the mitogen-activated protein kinase kinase inhibitor cobimetinib. The latter in particular is a key inhibitor of the RAF-RAS signaling pathway that has shown promise in early studies of *BRAF* mutation histiocytosis (8).

FOLLOW-UP

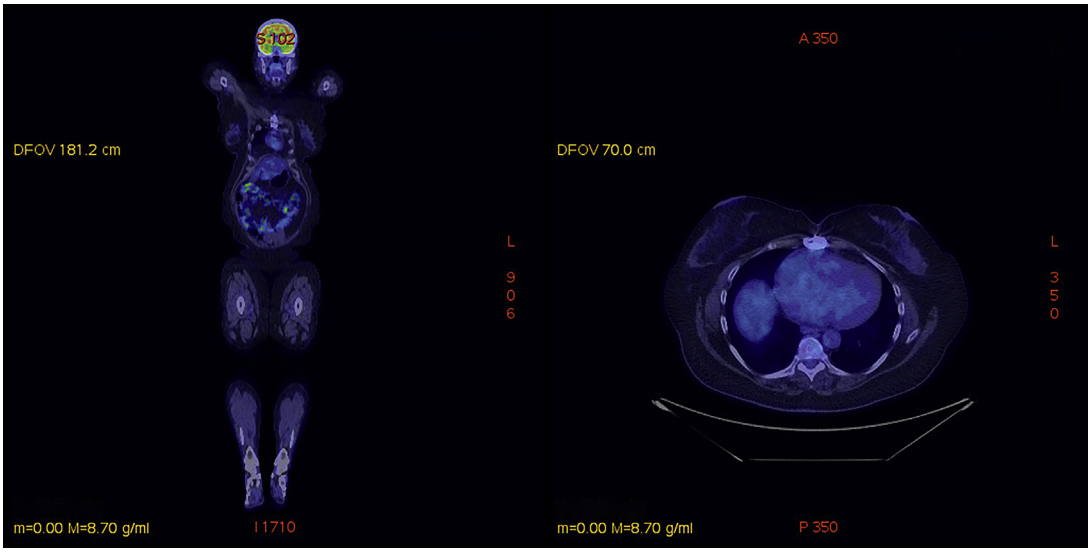
Follow-up FDG positron emission tomography after 2 months of therapy demonstrated a decreased density of soft tissue infiltration and a reduced FDG avidity, suggesting a positive response to steroid therapy (**Figure 6**). She was gradually tapered off prednisone from a 60-mg/day initial

FIGURE 5 Post-Treatment Functional PET Imaging



(A) Histopathologic findings of the biopsied mass showing a dense lymphohistiocytic infiltrate infiltrating the epicardial fibroadipose tissue. **(B)** Histopathologic findings of the biopsied mass showing emperipolesis **(black arrowhead)**. **(C)** Histopathologic findings of the biopsied mass showing histiocytes highlighted by staining the tissue with immunohistochemical antibodies directed against CD163. **(D)** Histopathologic findings of the biopsied mass showing rare cells expressing S100 protein **(brown dots)**.

FIGURE 6 Histologic Specimens From Biopsied Mass



Fluorodeoxyglucose-positron emission tomography scan after prednisone therapy demonstrating reduced uptake in pericardial mass, consistent with a favorable response.

dose over the course of 12 months. Her symptoms markedly improved and her follow-up echocardiogram showed resolution of constrictive physiology.

CONCLUSIONS

RDD is a condition characterized by nonclonal proliferation of histiocytes. In rare cases, it can present with pericardial infiltration without clinically apparent nodal involvement. Although idiopathic in etiology, it can be treated conservatively with steroids, which may be most beneficial in the setting of extensive infiltrative disease.

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KEY WORDS cardiac, constriction, corticosteroids, heart failure, sinus histiocytosis

APPENDIX For supplemental videos, please see the online version of this paper.