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Case Reports

Pericardiectomy and Mechanical Mitro-Aortic Valve Replacement in a Young Patient With Erdheim-Chester Disease

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Abstract

Erdheim-Chester disease is a rare histiocytosis that primarily affects the skeletal system, but cardiovascular manifestations occur in 75% of cases and are associated with a poor prognosis. Given the small number of cases, the evolution and management of the disease are uncertain. Therefore, it is important to report and share Erdheim-Chester cases. This report presents the case of a young patient with constrictive pericarditis and mitral valve regurgitation resulting from Erdheim-Chester disease.

Keywords: Erdheim-Chester disease; pericarditis, constrictive; pericardiectomy; mitral valve; aortic valve

Case Report

Presentation and Physical Examination

A 38-year-old woman was admitted with a 3-week history of abdominal distension, polyarthralgia, New York Heart Association class III dyspnea, orthopnea, runny nose, and cough. On admission, she was stable, eupneic, and apyretic, with a regular heart rate of 100/min. There was no evidence of edema or jugular venous distention, but a new 3/6 systolic murmur was heard at the aortic cusp accompanied by bibasal pulmonary hypoventilation and palpable hepatosplenomegaly. A 12-lead electrocardiogram showed sinus tachycardia without other abnormalities. Laboratory findings included anemia (hemoglobin 94 g/L), absence of leukocytosis, an elevated C-reactive protein level of 40 mg/L, abnormal liver function tests, and normal kidney function. In addition, a COVID-19 test was positive. A thoracoabdominal computed tomography (CT) scan revealed cardiomegaly, bilateral hilar adenopathies, bilateral pleural effusions, and significant hepatosplenomegaly.

She was admitted to a COVID-19 unit, where transthoracic echocardiography revealed a low normal left ventricular ejection fraction (LVEF) estimated at 50% to 55%, moderate to severe aortic valve regurgitation, mild to moderate mitral valve regurgitation, mild pericardial effusion without signs of constrictive pericarditis, and bilateral pleural effusions. In addition, transesophageal echocardiography (TEE) did not identify a specific mechanism for the regurgitation except for moderate thickening of both valve leaflets. At that time, it was concluded that the patient had heart failure resulting from aortic and mitral valve regurgitation of unknown origin. After improvement with medical treatment that included loop diuretics, she was discharged home.

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After discussion at the Heart Team meeting, a decision was made to perform elective mechanical aortic valve replacement and mitral valve repair. The patient was readmitted to the hospital only a few days later, however, because of retrosternal pain. Transthoracic echocardiography showed a decrease in LVEF to 40% to 45% and stable pericardial effusion. Immunologic tests, including rheumatoid factor and antineutrophil cytoplasmic antibody tests, were negative. With a presumptive diagnosis of pericarditis secondary to COVID-19 infection, she was discharged home on treatment with colchicine and ibuprofen.

One week later, she was admitted for cardiogenic shock with hypotension, tachycardia, and transient loss of consciousness. She was immediately transferred to the intensive care unit. Transthoracic echocardiography revealed an LVEF of 30% to 35% with severe aortic valve regurgitation, moderate to severe mitral valve regurgitation, discrete pulmonary and tricuspid valve regurgitation, and noncompressive pericardial effusion. A cardiac CT scan showed no significant coronary lesions. Preoperative coronary angiogram was not performed. Given the patient's critical condition, urgent surgery was indicated.

Medical History

The patient, originally from Haiti, was known to have glucose-6-phosphate dehydrogenase (G6PD) deficiency and α thalassemia, but she had no relevant cardiovascular risk factors. Her only treatments were ibuprofen and folic acid.

Differential Diagnosis

Because of her Haitian origin, rheumatic heart disease was initially suspected, but she had lived in Switzerland since childhood and had no history of streptococcal infection. In addition, the various echocardiograms did not reveal the typical rheumatic valve changes, and there was no evidence of arthritis, chorea, erythema marginatum, or subcutaneous nodules.

A comprehensive infectious/parainfectious workup that included blood tests and broad-range polymerase chain reaction testing on pericardial fluid was negative for tuberculosis; *Coxiella burnetii*; Whipple disease; Legionella; HIV; hepatitis A, B, and C viruses; Epstein-Barr virus; cytomegalovirus; human herpesvirus 6; influenza; chlamydia; and mycoplasma.

Ankylosing spondylitis can be associated with pericarditis, valvulopathies, and aortitis and is characterized by erosive sacroiliitis. A positron emission tomography/CT scan, however, did not show hypermetabolism, the human leukocyte antigen-B27 test was negative, and the patient did not show signs of enthesopathy (psoriasis, uveitis, or arthritis). There was no evidence of connective tissue disease, antiphospholipid antibody syndrome, or Libman-Sacks endocarditis.

Biopsy samples obtained during valve replacement finally demonstrated the characteristic histopathology of Erdheim-Chester disease (ECD) with CD68+/CD1a–/S100– histocytes surrounded by fibrosis (Fig. 1). Positron emission tomography/CT scans showed hypermetabolic foci in the aortic cross and segments of the descending aorta as well as hepatosplenomegaly and mediastinal hypermetabolic splenomegaly (Fig. 2). A next-generation sequencing genetic panel was negative for *NRAS, PIK3CA, BRAF, KRAS, MAP2K1, MAP2K2,* and *ARAF* alterations. Despite the absence of skeletal involvement on bone scintigraphy and supportive genetic alterations, the diagnosis of ECD with cardiovascular manifestations was made based on clinical and histologic findings.

Technique

The patient was taken to the operating room, and preoperative TEE confirmed the presence of severe aortic and mitral valve regurgitation, mitral valve annulus dilatation, and limited leaflet motion (Carpentier I and IIIb). The LVEF was moderately reduced, the aortic root appeared normal, and moderate tricuspid valve regurgitation was noted (Fig. 3).

Key Points

- The indications for cardiac surgery in the management of cardiac manifestations of ECD remain unclear, but cardiac surgery has been shown to be beneficial in selected cases.
- Biopsies of affected organs are crucial for the diagnosis of ECD.
- Medical management of ECD should be patient oriented. Cardiac side effects of ECD treatment must be considered when cardiac involvement is present.

Abbreviations and Acronyms

CT	computed tomography
ECD	Erdheim-Chester disease
LVEF	left ventricular ejection fraction
POD	post-operative day
TEE	transesophageal echocardiogram

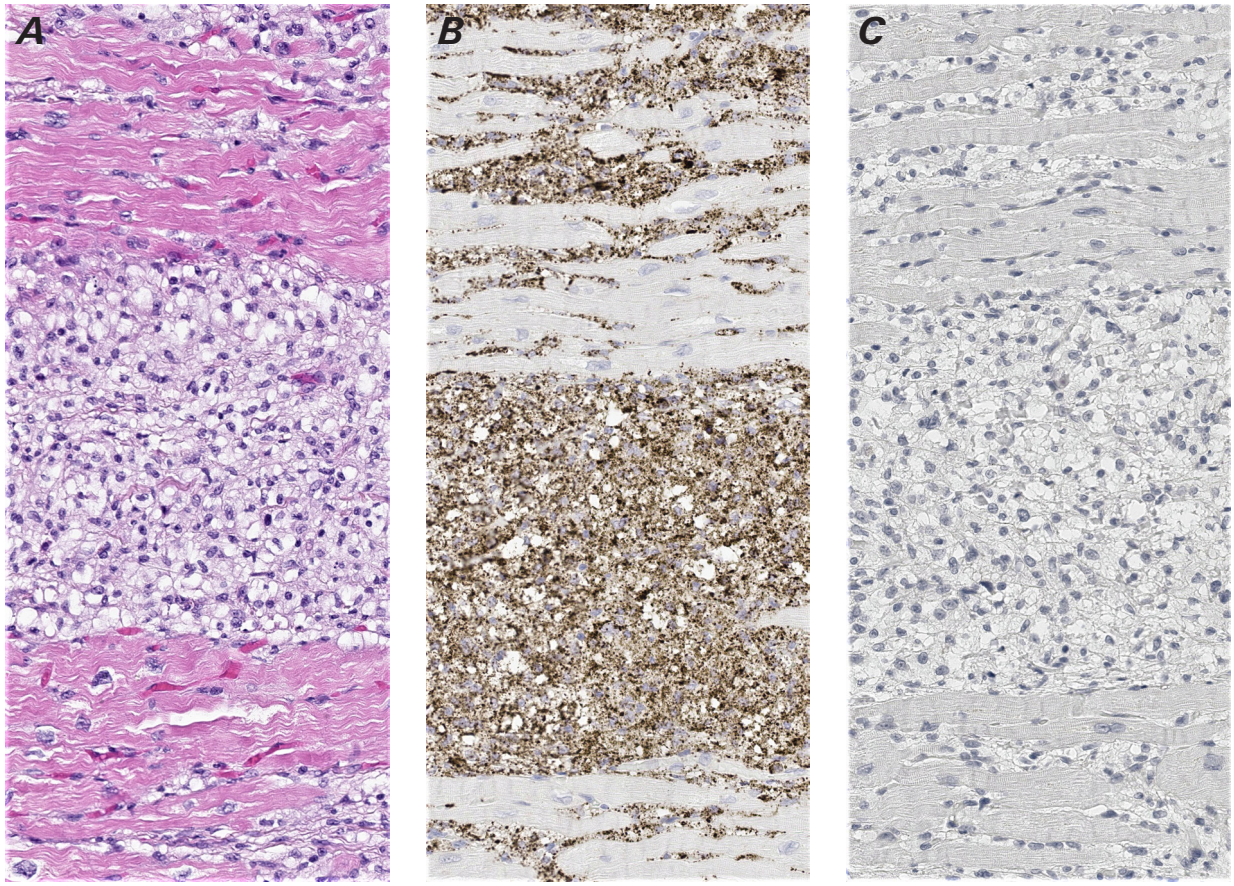

Fig. 1 Histology results from myocardial biopsy. **A**) Inflammatory infiltration (H&E, ×38); (**B**) histiocytosis with CD68-positive cells (blue) on immunostaining (×38); (**C**) histiocytosis with CD1-negative cells on immunostaining (×38).

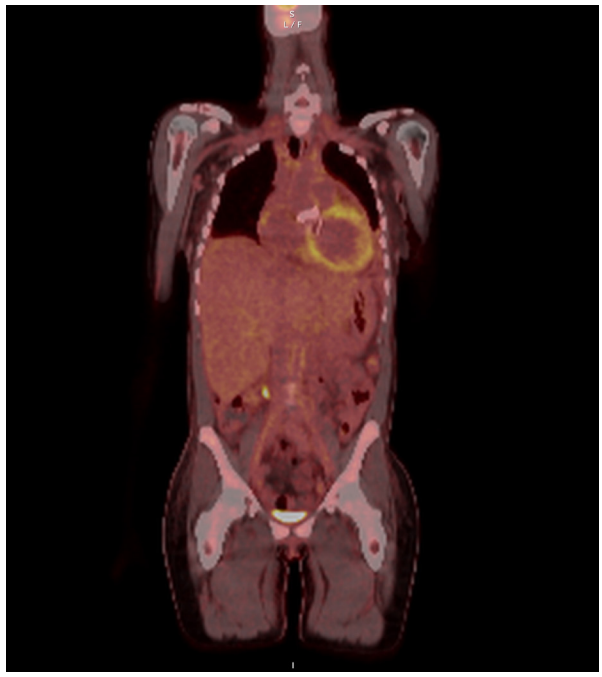

Fig. 2 Thoracoabdominal positron emission tomography/computed tomography scan showing hypermetabolic activity along the pericardium, the aortic cross to the left common carotid artery, and the descendant thoracic aorta. Also shown is the presence of hypermetabolic, mediastinal, cardiophrenic, and internal mammary artery adenomegalies as well as a nutmeg liver appearance caused by congestive hepatopathy.

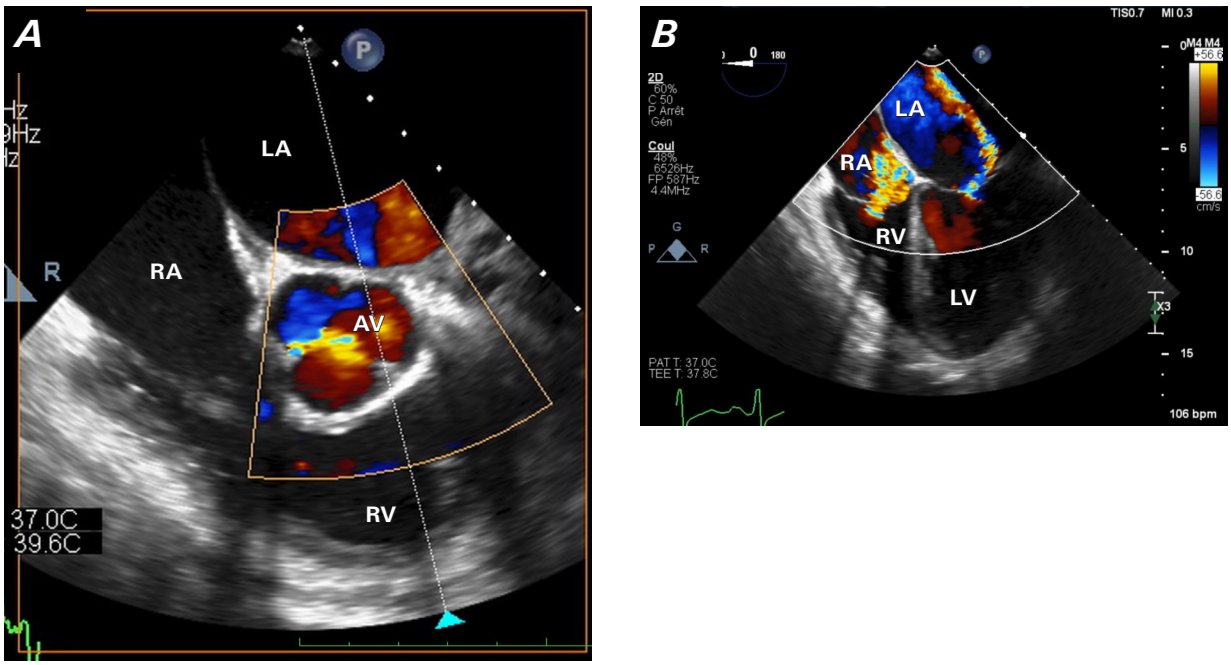

Fig. 3 Perioperative transesophageal Doppler echocardiogram. **A**) Midesophageal aortic valve short-axis view shows the aortic valve with severe regurgitation, especially between the noncoronary and right coronary leaflet commissure. **B**) Midesophageal 4-chamber view shows severe mitral valve regurgitation, with annulus dilatation, restricted leaflet movement (Carpentier I and IIIb), and discrete tricuspid valve regurgitation.

AV, aortic valve; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

After sternotomy, a thick, sticky constrictive pericarditis was observed (Fig. 4). Complete pericardiectomy was performed. Pericardial fluid, visceral, and left parietal pericardial specimens were sent to pathology. Right atrial myocardial biopsies were performed because of the swollen appearance of the myocardium. The aortic root was dilated using the Nicks procedure. The aortic valve was replaced with a 22-mm mechanical prosthesis, and the mitral valve was replaced with a 33-mm mechanical prosthesis. Both native valves were sent for analysis. The left appendix was ligated. Total cardiopulmonary bypass time was 3 hours, 51 minutes, and aortic clamp time was 2 hours, 12 minutes.

Weaning from cardiopulmonary bypass was not possible because of severely reduced LVEF and biventricular dysfunction. Peripheral venoarterial femorofemoral extracorporeal membrane oxygenation was initiated. A massive transfusion protocol was initiated for hemorrhagic shock. The chest was left open with packing. The final postoperative TEE showed a severely reduced LVEF with global hypokinesia.

On postoperative day (POD) 1, LVEF was estimated at 5%, with a pulsed pressure of 4 mm Hg, and an intra-aortic balloon pump was inserted through the femoral artery. A second look with sternal closure was performed on POD 3. Transesophageal echocardiography showed an improved LVEF of 25%, with satisfactory valvular surgical results. Levosimendan treatment was initiated, allowing for the withdrawal of adrenergic support and intra-aortic balloon pump ablation on POD 4. Successful withdrawal of extracorporeal membrane oxygenation was performed on POD 6. The patient was transferred to the cardiology unit on POD 11. All 4 basic therapies for congestive heart failure with reduced ejection fraction were initiated and progressively titrated along with loop diuretics and maintenance of oral anticoagulation. The patient was discharged on POD 55. The last in-hospital transthoracic echocardiogram showed an LVEF of 25% to 30% with no prosthetic valve dysfunction. Severe tricuspid valve regurgitation, moderate pulmonary valve regurgitation, and the absence of pericardial effusion were also noted. The patient was enrolled in the outpatient cardiovascular

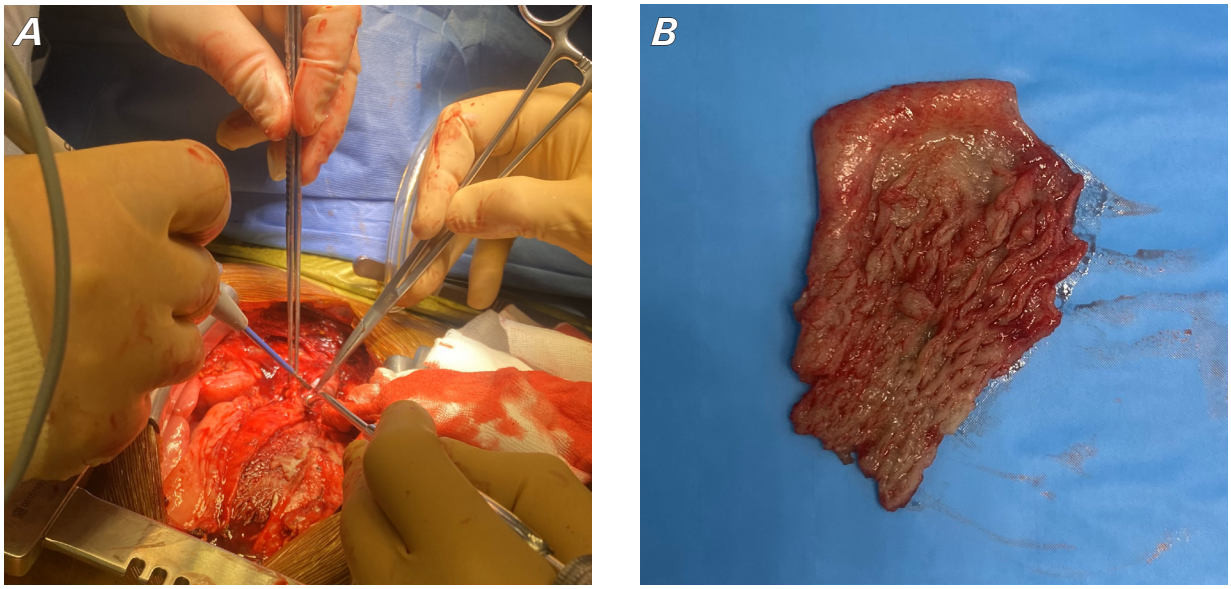

Fig. 4 A) Intraoperative photograph of the pericardiectomy procedure. Note the thickness of the pericardium. **B**) Photograph of perioperative findings: a piece of removed visceral pericardium. Note its thickness.

rehabilitation program and followed up by the clinical immunology team.

Outcome

Heart failure management was further optimized, and the patient improved clinically. Immunosuppressive therapy consisting of sirolimus was initiated. No specific treatment for ECD was initiated because of the absence of *BRAF/MAPK* variation.

Latest Follow-Up

At the last follow-up visit by the cardiology team 10 months after surgery, the patient reported no limiting cardiovascular symptoms. Her LVEF had improved to 45%, with well-functioning prosthetic valves and residual moderate tricuspid valve regurgitation. Her current medication includes rapamycin, acenocoumarol, low-dose carvedilol, sacubitril/valsartan, spironolactone, dapagliflozin, and torasemide.

Discussion

Erdheim-Chester disease is a rare form of non–Langerhans cell histiocytosis, with approximately 800 cases published since 1930.[1] It predominantly affects men, with the highest incidence occurring in patients between 40 and 50 years of age.[1-3]

Although it primarily affects large bones, ECD can also present with extraskeletal manifestations, including involvement of the nervous system, retro-orbital tissues, pulmonary system, liver, spleen, retroperitoneum, skin, and cardiovascular system. The prognosis in cases with multisystemic manifestations remains poor, with a mortality rate of 60% at 32 months after diagnosis, mainly because of cardiopulmonary causes.[1-3]

Erdheim-Chester disease affects the cardiovascular system in 75% of patients, with pericardial infiltration being the most common manifestation. It may also present as myocardial inflammation; pseudotumoral lesions in the right atrium; and valvular disease, particularly aortic and mitral valve regurgitation.[3-8]

Diagnosis is mainly based on clinical and radiologic findings (depending on the organs involved) and histopathology. For cardiac involvement, initial evaluation may include exercise tolerance test and TEE, but cardiac magnetic resonance imaging scanning is superior for characterizing cardiac infiltrations and is recommended for diagnosis and follow-up.[1,8]

Whenever possible, biopsies of affected organs should be performed. Histology is characterized by the presence of lipid-laden histocytes with surrounding fibrosis, along with the immunohistochemical markers CD68+, CD1–, and S100– without the presence of Birbeck granules. Genetic alterations in the BRAF and MAPK

pathway can be supportive but are not essential for diagnosis.[1]

Treatment and prognosis of this disease show large interindividual variability. The latest guidelines (2020) recommend symptomatic treatment and the introduction of corticosteroids to reduce inflammation but not as monotherapy. The role of cardiac surgery depends on the clinical presentation of the patient. Pericardiectomy is the most common intervention for constrictive pericarditis, with the goal of relieving symptoms and preventing recurrent pericardial effusion.[5,6] For patients with *BRAF* V600E alteration and cardiac or neurologic disease or end-organ dysfunction, BRAF inhibitor therapy with tyrosine kinase inhibitors, vemurafenib, or dabrafenib should be used as first-line therapy.[1,9,10] For patients with cardiac or neurologic involvement but without genetic alterations, empiric treatment with MEK inhibitors (cobimetinib, trametinib, binimetinib, and selumetinib) should be considered.[1]

Tyrosine kinase inhibitors should be used with caution because of potential cardiovascular adverse events, such as hypertension, left ventricular dysfunction, venous thromboembolism, atrial arrhythmia, and QT interval prolongation on electrocardiogram.[11] Given this patient's reduced LVEF, she would probably not have been treated with these agents even if she had *ARAF-1*–positive alteration.

Because of their antiproliferative and immunosuppressive properties, mammalian target of rapamycin inhibitors such as sirolimus, also known as rapamycin, are used in several diseases, including malignant tumors and rheumatic diseases, and for the prevention of allograft rejection. Gianfreda et al[12] reported promising results with sirolimus in combination with prednisone in patients with ECD. A positive response to sirolimus monotherapy was shown in 3 consecutive patients with ECD, with subjective clinical improvement and radiologically documented regression of organ involvement. Treatment has been well tolerated, but the correct dose, duration, and prognosis are uncertain. Each case should be discussed by a multidisciplinary team, and individualized decisions should be made.

Conclusion

Erdheim-Chester disease is a rare but striking disorder. Cardiac involvement is common and associated with a poor prognosis resulting from the elusive diagnosis, lack of knowledge about its onset and evolution, and lack of effective treatment. Few cases have been described in the literature, underscoring the importance of sharing this clinical case.

Article Information

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References

1. Goyal G, Heaney ML, Collin M, et al. Erdheim-Chester disease: consensus recommendations for evaluation, diagnosis, and treatment in the molecular era. *Blood.* 2020;135(22):1929-1945. doi:10.1182/BLOOD.2019003507
2. Mazor RD, Manevich-Mazor M, Shoenfeld Y. Erdheim-Chester disease: a comprehensive review of the literature. *Orphanet J Rare Dis.* 2013;8:137. doi:10.1186/1750-1172-8-137
3. Estrada-Veras JI, O'Brien KJ, Boyd LC, et al. The clinical spectrum of Erdheim-Chester disease: an observational cohort study. *Blood Adv.* 2017;1(6):357-366. doi:10.1182/BLOODADVANCES.2016001784
4. Chahine J, Alzubi J, Alnajjar H, Ramchand J, Chetrit M, Klein AL. Erdheim-Chester disease: a rare but important cause of recurrent pericarditis. *Curr Cardiol Rep.* 2020;22(8):75. doi:10.1007/s11886-020-01307-z
5. Lin J, Tang SQ, Chen JC, Zhang YH, Zhang Q. Erdheim-Chester disease: an unusual etiology of recurrent massive pericardial effusion. *Can J Cardiol.* 2020;36(11):1832.e11-1832.e13. doi:10.1016/j.cjca.2020.04.040

6. Quinaglia-Silva T, Medina F, Ramos CD, Coelho-Filho OR. Cardiac involvement in Erdheim-Chester disease. *Circ Cardiovasc Imaging.* 2018;11(12):e008531. doi:10.1161/CIRCIMAGING.118.008531
7. El-Andari R, Baghaffar A, O'Connell A, et al. Pericardiectomy for constrictive pericarditis in a young patient with Erdheim-Chester disease. *JACC Case Rep.* 2022;4(14):862-867. doi:10.1016/J.JACCAS.2022.03.024
8. Ponsiglione A, Puglia M, Barbuto L, et al. Cardiac involvement in Erdheim-Chester disease: MRI findings and literature revision. *Acta Radiol Open.* 2015;4(9):2058460115592273 doi:10.1177/2058460115592273
9. Abla O. Management of ECD: the era of targeted therapies. *Blood.* 2020;135(22):1919-1920. doi:10.1182/BLOOD.2020005803
10. Aziz SN, Proano L, Cruz C, et al. Vemurafenib in the treatment of Erdheim Chester disease: a systematic review. *Cureus.* 2022;14(6):e25935. doi:10.7759/CUREUS.25935
11. Glen C, Tan YY, Waterston A, et al. Mechanistic and clinical overview cardiovascular toxicity of BRAF and MEK inhibitors: *JACC: CardioOncology* state-of-the-art review. *JACC CardioOncol.* 2022;4(1):1-18. doi:10.1016/J.JACCAO.2022.01.096
12. Gianfreda D, Nicastro M, Galetti M, et al. Sirolimus plus prednisone for Erdheim-Chester disease: an open-label trial. *Blood.* 2015;126(10):1163-1171. doi:10.1182/BLOOD-2015-01-620377