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CASE REPORT

INTERMEDIATE

CLINICAL CASE

Curative Pericardiectomy in Interpheron-Resistant Severe Pericardial Erdheim-Chester Disease

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ABSTRACT

Erdheim-Chester disease is a rare clonal non-Langerhans cell histiocytosis with multisystemic involvement. It affects bones, large vessels, and retroperitoneum. Cardiac involvement is one of the main mortality predictors.[1] We present an unusual case that debuted with cardiac tamponade and pericardial constriction requiring pericardiectomy for definitive control. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2022;4:1534–1541) © 2022 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/).

HISTORY OF PRESENTATION

A 48-year-old farmer with hypertension consulted for diaphoresis, epigastric pain, and edema for the previous 2 months. He was afebrile and normotensive and did not present lymphadenopathies, other skin lesions, arterial murmurs in the extremities, or abnormal superficial temporal arteries examination.

LEARNING OBJECTIVES

- To be able to suspect Erdheim-Chester disease when typical cardiovascular findings are found.
- To summarize therapeutic options, including the possibility of pericardiectomy in case of cardiac constriction.

Examination revealed xanthelasmas (**Figure 1**), muffled heart sounds, and mild peripheral edema.

In chest X-ray, cardiomegaly was patent (**Figure 2**), electrocardiography showed sinus tachycardia and low voltages, and on transthoracic echocardiography (TTE), preserved biventricular systolic function, without valvular heart disease, and cardiac pendular motion within a massive pericardial effusion (PE) with hemodynamic compromise were found. An evacuating pericardiocentesis was performed and a mononuclear exudate without malignant cells was found. The Quantiferon-TB Gold test was positive. Blood tests showed normal renal and lipid profile and elevated acute-phase reactants. Urine sediment examination was normal. With the suspicion of complicated idiopathic acute pericarditis, treatment with ibuprofen and colchicine was started.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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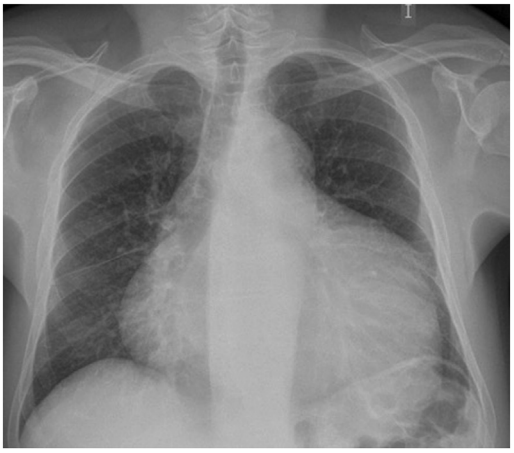
FIGURE 2 Cardiomegaly

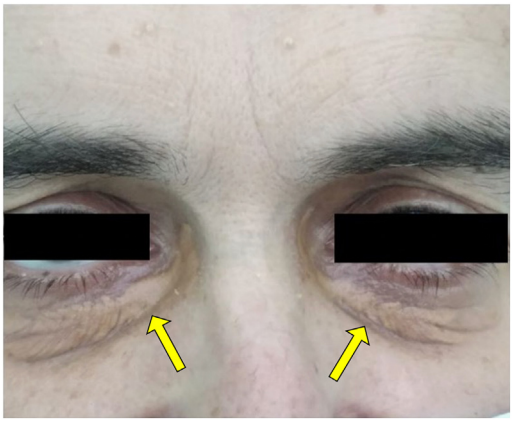


A new TTE showed recurrence of severe PE effusion without signs of cardiac tamponade and a possible aneurysmal dilatation of the ascending aorta. The patient was transferred to our acute cardiac care unit. On admission he was asymptomatic, afebrile, eupneic, mildly tachycardic and hemodynamically stable. An aortic computed tomographic (CT) scan revealed a soft tissue encasement of the aorta from the arch and supra-aortic arteries to the iliac (Figure 3), in the retroperitoneum and both renal cells, causing right chronic obstructive uropathy and renal atrophy.

DIFFERENCIAL DIAGNOSIS

We were facing a patient with severe PE with hemodynamic compromise, periaortitis, a retroperitoneal mass and previous tuberculous exposure. A chronic fibroinflammatory disease, mainly IgG4-related disease, was suspected.[2]

FIGURE 1 Xanthelasmas



INVESTIGATIONS

Blood tests including urea and uric acid, urine cultures, and serologic tests, specifically against syphilis, human immunodeficiency virus, and *Coxiella burnetii*, were negative. Also, antinuclear antibodies and antineutrophil cytoplasmic antibodies, rheumatoid factor, blood angiotensin-converting enzyme, and HLA-B51 and B-27 haplotypes were negative. Serum IgG4 levels were normal. With these results, the retroperitoneal mass, and the absence of recurrent orogenital ulcers, a negative pathergy test, pulmonary disease, extremities vascular claudication, or cranial and polymyalgia rheumatica-like symptoms, we excluded infectious aortitis and primary or secondary large-vessel vasculitis. The diffuse periaortic distribution and the absence of malignancy in the pericardial fluid cytology did not suggest malignant lymphoid or mesenchymal neoplasm, either.

A core needle biopsy of the retroperitoneal mass was performed, revealing mesenchymal tissue and mild inflammation with lymphocytes and IgG4-negative plasma cells. Abundant fibrin and isolated nests of foamy macrophages were observed. No necrotizing granulomas were found. Zielh-Neelsen staining and mycobacterial culture were negative.

MANAGEMENT AND CLINICAL COURSE

While completing the study, the persistence of severe PE and the suspicion of an inflammatory disease determined that high-dose glucocorticoids and isoniazid/pyridoxine were added to colchicine. In the follow-up TTEs, persistence of the PE was observed, so a surgical procedure with pericardial window and biopsy was performed.

The pericardium presented intense fibrosis rich in collagen and chronic inflammatory infiltrate without a significant increase in IgG4-positive plasma cells and nests of mononuclear histiocytes, some of them xanthomized, around the small vessels. These findings were similar to those found in the retroperitoneal mass. A systemic hystiocytosis was suspected. Positive histiocyte staining for CD68, CD163, factor XIIa, fascina, and, in small quantity, for S100 and CD4 and negativity for langerin, CD1a, and CD123 led to a diagnosis of Erdheim-Chester disease (ECD)[1] (Figure 4). Molecular cell study for the BRAF V600E mutation (Cobas 4800) was positive.

ABBREVIATIONS AND ACRONYMS

CT = computed tomography

ECD = Erdheim-Chester disease

MRI = magnetic resonance imaging

PE = pericardial effusion

pegIFN-α = pegylated interferon-alpha

PET = positron emission tomography

TTE = transthoracic echocardiography

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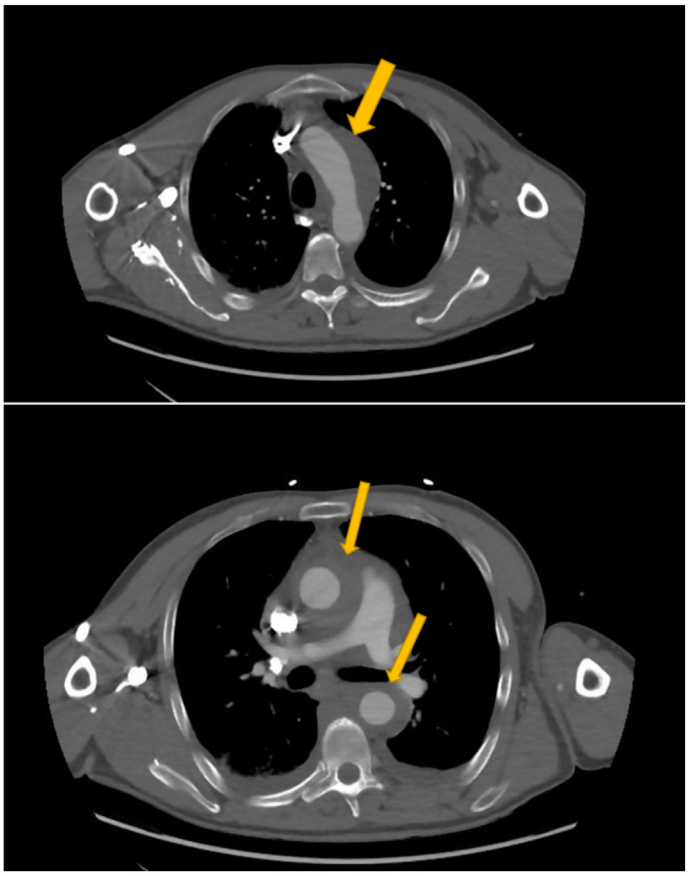
FIGURE 3 Aortic Computed Tomographic Scan



Showing periaortic fibrosis ("coated aorta").

An extension study confirmed long bones and vertebral, testicular, retroperitoneal, and periaortic involvement (Figure 5). Cardiac magnetic resonance imaging (MRI) showed mild biventricular systolic dysfunction, probably related to the limitation in diastolic expansion due to severe PE, and thickening of pericardium (up to 4 mm), right atrium, interatrial septum, and right atrioventricular groove around the right coronary artery (Figure 6). Central nervous system involvement was ruled out by brain MRI.

Medical treatment was modified with reduction of steroids until withdrawal and initiation of high-dose subcutaneous pegylated interferon alpha (pegIFN-α; 180 MU weekly) in addition to alendronic acid for bone pain relief. After several weeks of well tolerated treatment, and despite PE being moderate and well tolerated, TTE showed data of pericardial constriction (Video 1, Figure 7). Therefore, a sternotomy and interphrenic pericardiectomy were performed (Videos 2 to 4). The constrictive physiology resolved and the patient was discharged on pegIFN-α therapy. Post-surgical body positron emission tomography (PET)-CT showed metabolic activity in the mediastinum, retroperitoneum, and bone structures (Figure 8).

DISCUSSION

ECD is a clonal systemic proliferation of non-Langerhans histiocytic cells, generally mononuclear and xanthomized, with occasional giant multinucleated Touton cells, accompanied by important fibrosis and chronic reactive inflammation. Histiocytic cells have a typical immunophenotype (as mentioned above), which differentiates from other systemic histiocytosis, and carry the BRAF V600E mutation or NRAS signaling pathway mutations in 50% and 4% of cases, respectively.[3]

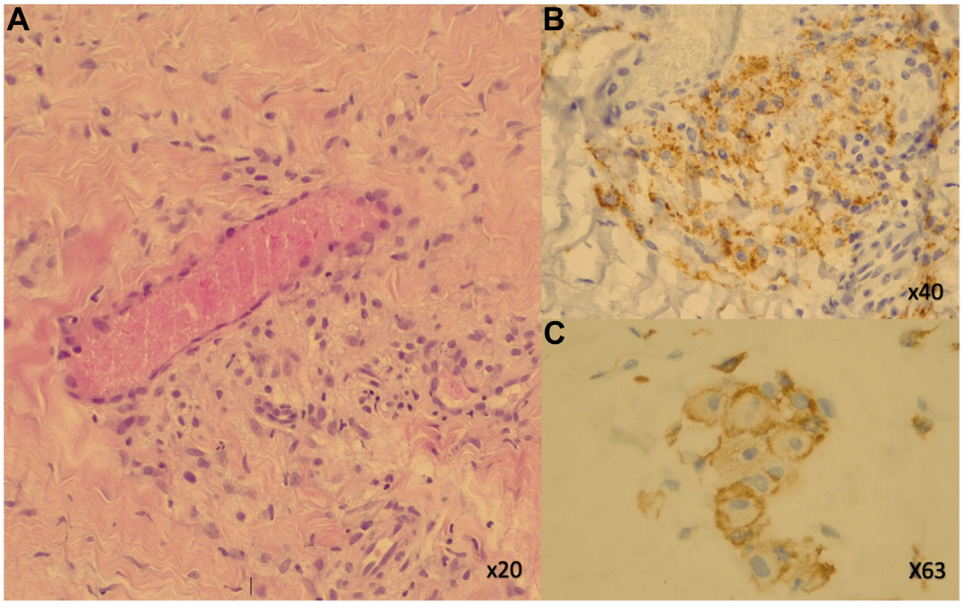
Cardiac involvement in ECD is described in up to 57% of patients[4] and after CNS involvement is one of the most important independent predictors of mortality,[1] being cause of death by this disease in 30% of cases. Therefore, it is recommended to actively rule out this affectation by means of MRI, CT, or PET-CT.

In a series of 37 patients with cardiac involvement,[1] pericardial infiltration by foamy histiocytes was described in 44%, myocardial infiltration in 31%, and pseudotumoral infiltration of the right atrium in 30%; 56% of them presented periaortic fibrosis, with the appearance of a "coated aorta," as with our patient. Likewise, 24% of patients developed PE, with thickening of the pericardium in 14%. To date, only 18 patients with ECD whose clinical presentation was severe or recurrent PE have been reported in the literature.[5-7]

Owing to its multiorgan involvement, ECD must be included in a wide differential diagnosis: sclerotic lesions in long bones, large-vessel involvement, retroperitoneal, intracranial, and orbital pseudotumoral masses, PE, or infiltrative cardiomyopathy. In the particular case of PE, the coexistence of involvement in other territories should suggest a systemic disease.

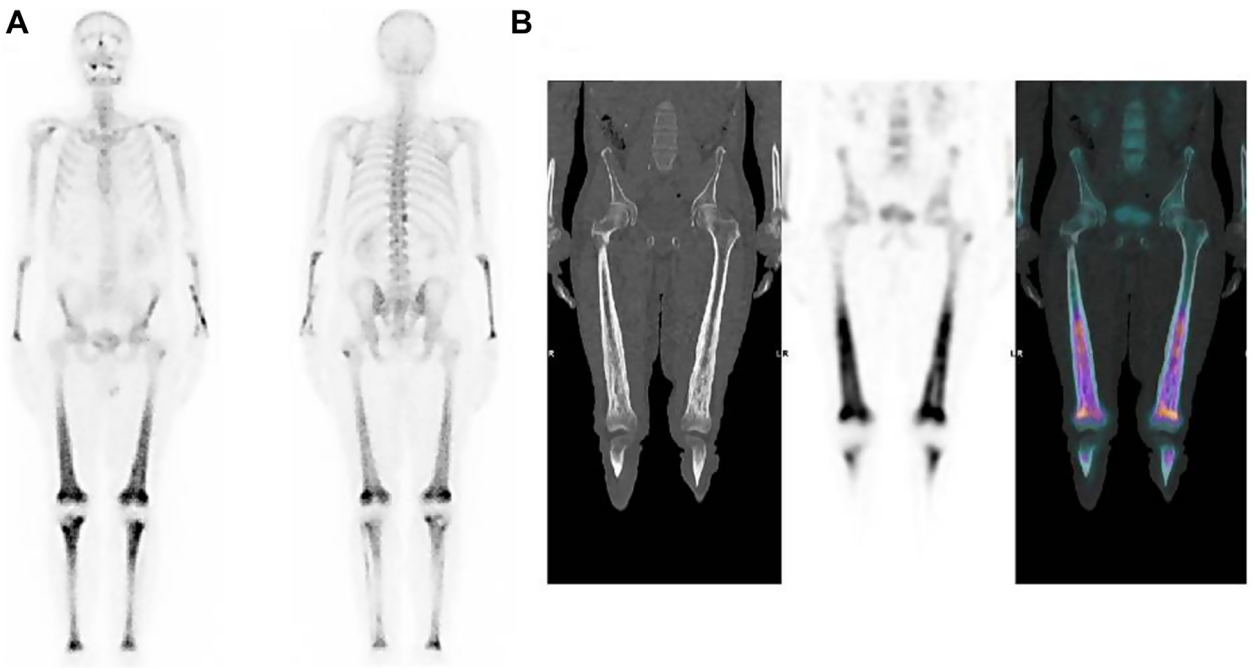
In asymptomatic ECD patients, without cardiac or CNS involvement and with nonprogressive disease, observation is recommended. Today, first-line treatment of ECD is IFN-α or pegIFN-α therapy, away from corticosteroids and cytostatics.[8] Arnaud et al[9] described in a cohort of IFN-treated patients, especially with cardiac or neurologic involvement, better

FIGURE 4 **Pericardial Biopsy**



(A) Hematoxylin and eosin staining: perivascular histiocytic infiltrate. **(B)** CD68 staining. **(C)** CD163 staining.

FIGURE 5 **Full-Body Bone Scintigraphy and Single-Photon Emission Computed Tomography-Computed Tomography of Lower Limbs**



(A) Pathologic increase in radiopharmaceutic uptake in the appendicular skeleton, predominantly in the middle and distal thirds of both femurs, the proximal and distal thirds of both tibias, and both radii. **(B)** Corticomedullary sclerosis in both femurs.

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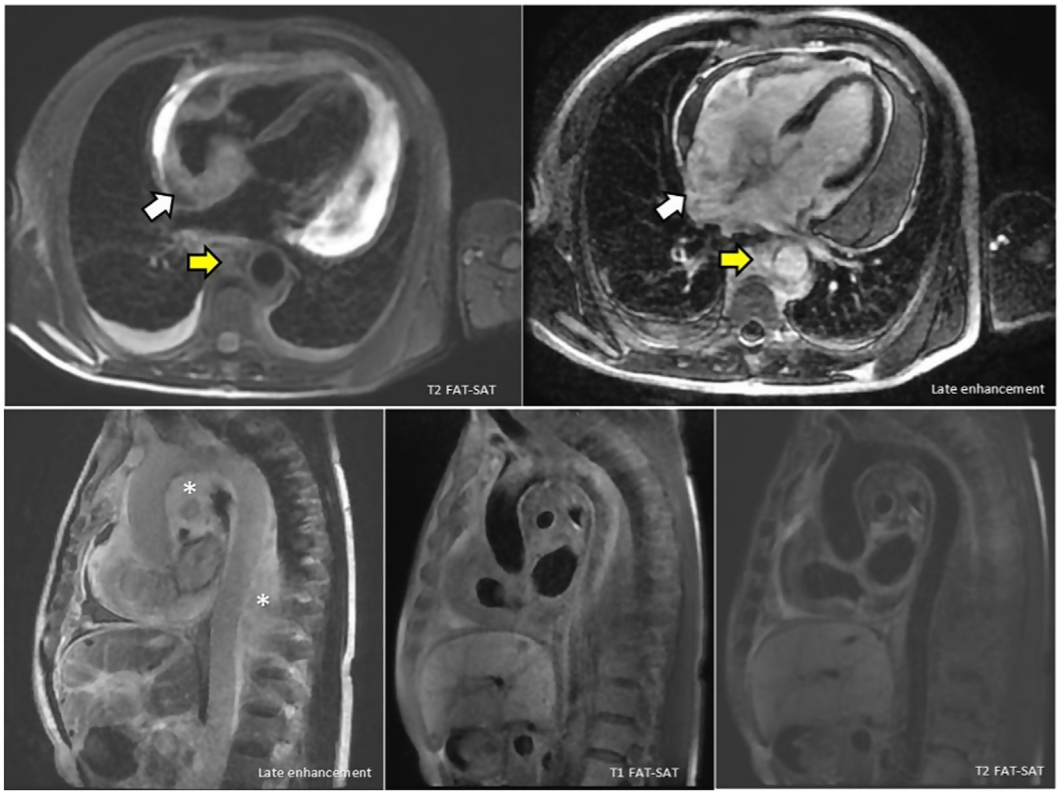
FIGURE 6 Magnetic Resonance Imaging



Pericardial thickening, left atrial infiltration **(white arrows)** and periaortic fibrosis **(yellow arrows and asterisks)**.

survival than control subjects. Response of ECD to therapy based on interleukin (IL)-1, IL-6, or tumor necrosis factor receptor antagonists has also been described.

In case of intolerance or lack of response to IFN-α therapy, changing to or addition of new targeted molecular therapies, mainly BRAF signaling pathway inhibitors, is the second-line most accepted therapy. Owing to the increasing identification of cell-cycle regulation gene mutations in ECD, further targeted molecular therapies could be applicable for refractory patients.[8]

Regarding the specific management of pericardial involvement, according to the latest ESC guidelines,[10] the cornerstone for the treatment of constrictive pericarditis is surgery with pericardial resection. However, it is recommended to use imaging techniques such as CT or cardiac MRI to differentiate patients with transient or chronic forms of constrictive pericarditis, because in the former, intensive anti-inflammatory or immunosuppressive treatment could prevent pericardiectomy.

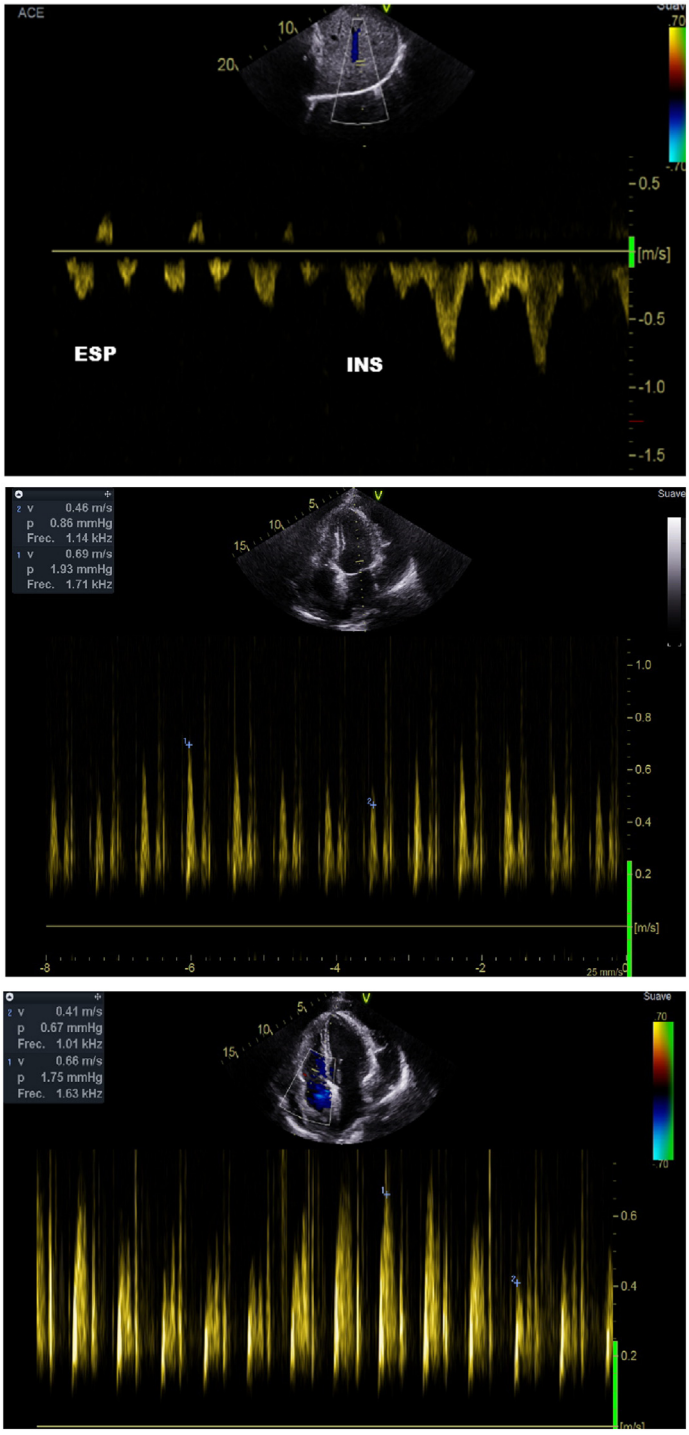
In a systematic review of 33 ECD patients with pericardial involvement, in only 2 cases was a pericardiectomy performed, and the indication was not cardiac constriction but PE. There is only 1 case report of ECD where the indication for pericardiectomy was cardiac constriction.[7]

In our patient, the partial response to pegIFN-α therapy for at least 2 months, the failure of the surgical pericardial window, and the development of constrictive semiology made interphrenic pericardiectomy mandatory, which was successful.

FOLLOW-UP

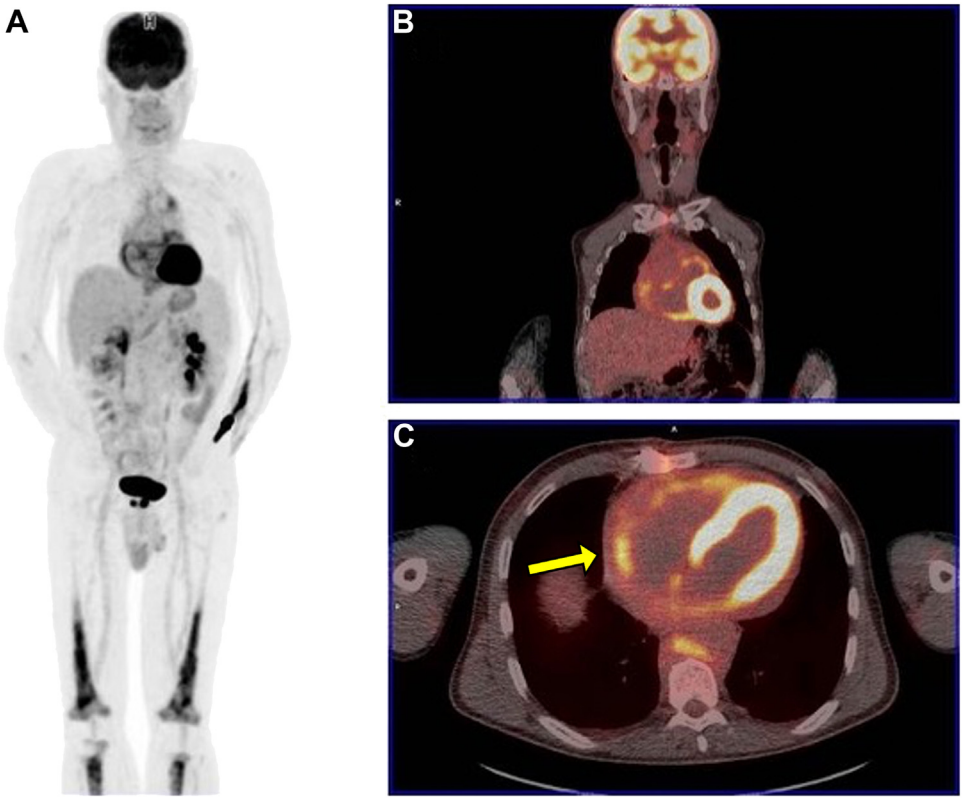
Two and 5 months after discharge, the patient was asymptomatic and presented mild pericardial effusion, without hemodynamic repercussion, and normal ventricular function. A cardiac MRI performed 8 months after discharge showed persistence of mediastinal and perivascular fibrous tissue but disappearance of PE, normal biventricular function, and absence of active inflammation.

FIGURE 7 **Transthoracic Echocardiography**



Hepatic vein diastolic reversal with **(top)** expiration, **(middle)** transmitral, and **(bottom)** transtricuspid flow variation.

FIGURE 8 Positron Emission Tomographic Computed Tomography With ^{18}F-Fluorodeoxyglucose



(A) Hypermetabolism in sclerotic lesions in the distal third of both femurs and the proximal third of both tibias compatible with infiltration. **(B, C)** Soft tissue hypermetabolism in the anterior mediastinum surrounding the ascending and descending thoracic aorta, with mild pericardial effusion.

CONCLUSIONS

ECD is a rare clonal non-Langerhans cell histiocytosis, with frequent cardiovascular involvement. This entity must be suspected when recurrent PE or typical "coated aorta" are present along with multisystemic findings. When pericardium is affected and cardiac constriction develops, pericardiectomy could be a feasible option.

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REFERENCES

1. Haroche J, Cluzel P, Toledano D, et al. Cardiac involvement in Erdheim-Chester disease. *Circulation*. 2009;119:e597–598.

2. Wallace ZS, Naden RP, Chari S, et al. The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-related disease. *Arthritis Rheumatol*. 2020;72:7–19.

3. Emile J-F, Abla O, Fraitag S, et al. Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. *Blood*. 2016;127:2672–2681.

4. Arnaud L, Gorochov G, Charlotte F, et al. Systemic perturbation of cytokine and chemokine networks in Erdheim-Chester disease: a single-center series of 37 patients. *Blood*. 2011;117:2783–2790.

5. Sanchez-Nadales A, Anampa-Guzman A, Navarro-Motta J. Erdheim-Chester disease with extensive pericardial involvement: a case report and systematic review. *Cardiol Res*. 2020;11:118–128.

6. Palazzuoli A, Mazzei MA, Ruocco G, Volterrani L. Constrictive pericarditis in Erdheim-Chester disease: an integrated echocardiographic and magnetic resonance approach. *Int J Cardiol*. 2014;174:e38–41.

7. Ding F, Chahine J, Deshwal H, et al. Mysterious quad of constrictive pericarditis, recurrent pleural effusions, bone involvement and interstitial lung disease. *Oxf Med Case Rep*. 2019;2019:omz015.

8. Emile J-F, Charlotte F, Amoura Z, Haroche J. BRAF mutations in Erdheim-Chester disease. *J Clin Oncol*. 2013;31:398.

9. Arnaud L, Hervier B, Néel A, et al. CNS involvement and treatment with interferon-α are independent prognostic factors in Erdheim-Chester disease: a multicenter survival analysis of 53 patients. *Blood*. 2011;117:2778–2782.

10. Adler Y, Charron P, Imazio M, et al. 2015 ESC guidelines for the diagnosis and management of pericardial diseases: the Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC). Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2015;36:2921–2964.

KEY WORDS aorta, cardiac magnetic resonance, cardiovascular disease, constrictive, echocardiography, imaging, MR sequences, nuclear medicine, pericardial effusion

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