

CASE REPORT

Mysterious quad of constrictive pericarditis, recurrent pleural effusions, bone involvement and interstitial lung disease

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Abstract

Erdheim–Chester disease (ECD) is a rare multisystemic non-Langerhans cell histiocytic neoplasm. The rarity of the disease and heterogenous clinical presentations often leads to delayed diagnosis. Historically, ECD lacked effective treatment and the prognosis was poor. Following the recent discovery of frequent BRAF-V600E mutation in patients with ECD, vemurafenib, a selective BRAF V600 kinase inhibitor has been approved for BRAF-mutated ECD patients. The prognosis of ECD has dramatically improved with early recognition of the disease and available treatment. ECD affects nearly every organ system. Cardiac involvement with pericardial effusion is common but rarely with constrictive physiology or requiring pericardiectomy. We present a case of a 56-year-old woman with recurrent pericarditis with constrictive physiology along with pleural effusion and interstitial lung disease that was diagnosed with ECD 3 years after initial presentation. The patient's symptoms were relieved with pericardiectomy and targeted therapy.

INTRODUCTION

Erdheim–Chester disease (ECD) is a rare form of non-Langerhans cell histiocytosis characterized by infiltration of CD68 (+), CD1a (-), S100 (-) histiocytes to the bones and various organs, resulting in heterogeneous clinical manifestations [1]. The most common symptom is bone pain caused by symmetric osteosclerosis from histiocytic infiltration [1, 2]. More than half of the patients have extraosseous manifestations [2]. Cardiac involvement with pericardial effusion is common but rarely with constrictive physiology or

requiring pericardiectomy. Here we report a unique case of recurrent pericardial effusion with constrictive physiology, along with interstitial lung disease, which successfully attained stabilization and symptom relief following total pericardiectomy and initiation of vemurafenib, a selective BRAF V600 kinase inhibitor.

CASE REPORT

A 56-year-old female presented with unresolving symptoms of exertional dyspnea, chest pain and cough. Three years earlier

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she presented with recurrent pericarditis, and pleural effusions with mild interstitial lung infiltrates. Pericardiocentesis revealed scant mesothelial cells and lymphocytes. A video-assisted thoracoscopic (VATS) lung biopsy was reported at the outside hospital as non-diagnostic, with non-specific acute and chronic inflammation with mild to moderate interstitial fibrosis without granulomas or a neoplasm. She was empirically treated with prednisone 10 mg once daily for 15 days with some subjective relief. She underwent an abdominal surgery for small bowel obstruction 2 years ago and the mesentery peritonium biopsy was reported at the outside hospital as non-specific inflammation.

She remained stable from the cardiopulmonary standpoint until 6 months ago. She was once again admitted to the outside hospital for acute onset of pleuritic chest pain, shortness of breath and orthopnea and the physical examination revealed jugular venous distention, hypotension, and tachycardia. Echocardiogram showed moderate pericardial effusion with signs of early tamponade and constrictive physiology. A pericardial window was attempted but failed because of thick pericardial adhesions. Cytology of the pericardial fluid showed non-specific chronic pericarditis with fibrinoid exudates. She was again treated with prednisone 60 mg twice a day (2 mg/kg/day) and furosemide 20 mg once daily with subjective improvement.

She presented to our institution for a second opinion for her ongoing dyspnea and cough. Laboratory workup revealed leukocytosis with white blood cell count of $24 \times 10^3/\mu\text{l}$, and N terminal-pro B-type Natriuretic Peptide (NT-pro BNP) of 358 pg/ml (normal is below 125 pg/mL). We reviewed the chest and abdominal computed tomography (CT) performed at the outside hospital, which showed bilateral smooth septal thickening of the lungs, pleural effusion, pericardial effusion, an infiltrative opacity surrounding the kidneys and sclerotic densities within the ribs and thoracic spine (Fig. 1a–c). A skeletal survey did not report any bony abnormalities. The patient had right and left heart catheterization and echocardiogram, which were non-diagnostic. A cardiac MRI showed a small pericardial effusion with severe, diffuse, circumferential pericardial thickening

consistent with active pericarditis but no ongoing constrictive physiology. It also showed moderate, diffuse pleural enhancement bilaterally (Fig. 2a–c).

The patient underwent total pericardiectomy for symptomatic relief along with a right lung biopsy, at the same time that the microscopic slides of the patient's 3-year prior lung and peritoneal specimens, were received for review from the outside hospital. The pericardium and the visceral pleura of the lung in all samples were thickened by fibrosclerosis with a mixed infiltrate of lymphocytes and plasma cells and many large histiocytes, highlighted with immunohistochemical stains for CD 68. Stains for S100 and CD1a were negative. The same infiltrate involved the perivascular regions of the lung parenchyma. The morphologic findings were consistent with ECD. The proliferating histiocytes were positive for BRAF V600E immunohistochemical stain (Fig. 3a–e). A screening MRI of the brain was performed to evaluate for the possibility of neurologic involvement, which was negative. A whole-body technetium bone scan revealed an intense symmetrically increased uptake involving the maxillae, bilateral distal femurs, entire tibiae, and fibulae, as well as the radii and ulnae.

The multidisciplinary team with members of hematology/oncology, cardiology and pulmonology advised to slowly taper off prednisone, add colchicine 0.3 mg twice a day, and start treatment with a selective BRAF V600 kinase inhibitor, vemurafenib. Treatment with vemurafenib was started with half of the recommended dose, 480 mg twice a day, due to the patient's significant multiple comorbidities that raised concerns for adverse events, with the intention to gradually escalate to a full dose depending on tolerability. Her symptoms began to improve with increased exercise tolerance at time of discharge. The patient was advised to follow closely with physicians at her home country and follow with specialists at our institution in 6 months. On a follow-up phone call three months after initiation of vemurafenib, she was doing well without shortness of breath. She tolerated vemurafenib (480 mg twice a day) without significant side effects. Her prednisone dose was decreased to 20 mg once daily.

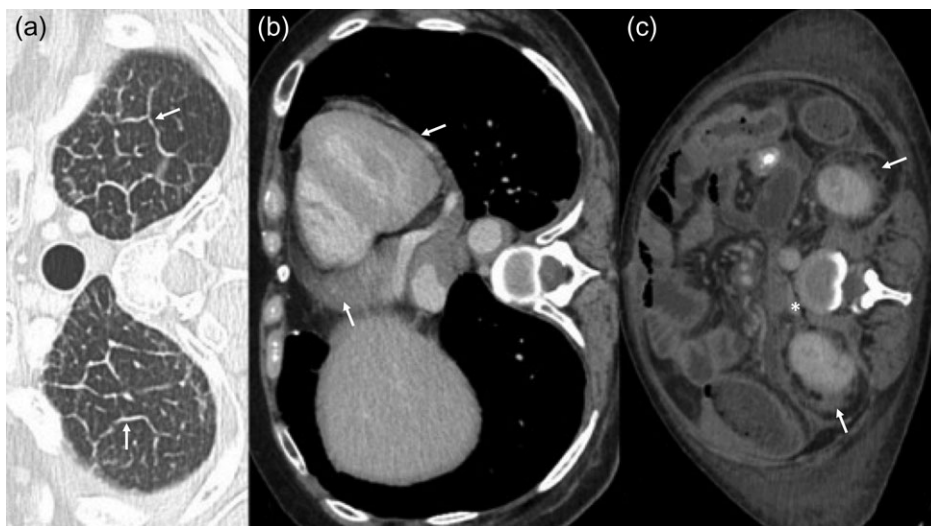


Figure 1: (a) Interlobular septal thickening (arrows) on the high-resolution CT scan of the chest; (b) severe soft tissue thickening of the pericardium (arrows) with enhancement on the contrast enhanced CT scan of the chest; (c) abnormal soft tissues around retroperitoneal structures (kidneys) (arrows) without encasement or displacement of IVC (*) and ureters (unlike retroperitoneal fibrosis) on the CT scan of the abdomen.

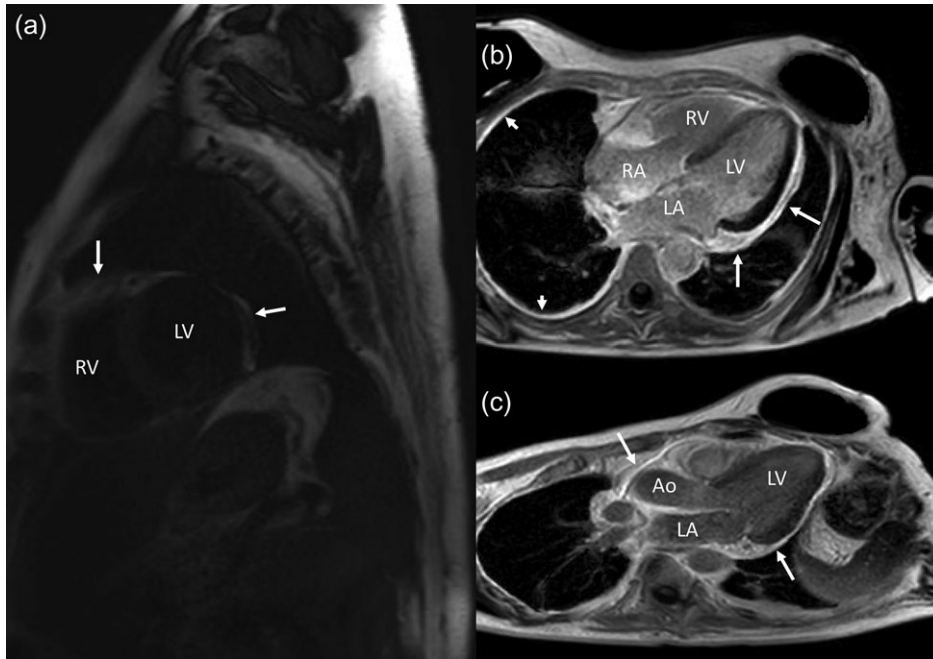


Figure 2: Cardiac MRI (a) There is circumferential increased pericardial signal intensity (arrows) on T2-weighted short-tau inversion recovery (STIR) consistent with edema likely reflective of pericardial inflammation; On 4-chamber (b) and 3-chamber (c) delayed enhancement imaging, there is severe, circumferential pericardial enhancement (long arrows), along with diffuse pleural enhancement (short arrows) diffuse pleural enhancement. This constellation of findings is consistent with active pleuro-pericarditis. LV: left ventricle; RV: right ventricle; LA: left atrium; RA: right atrium; Ao: aorta.

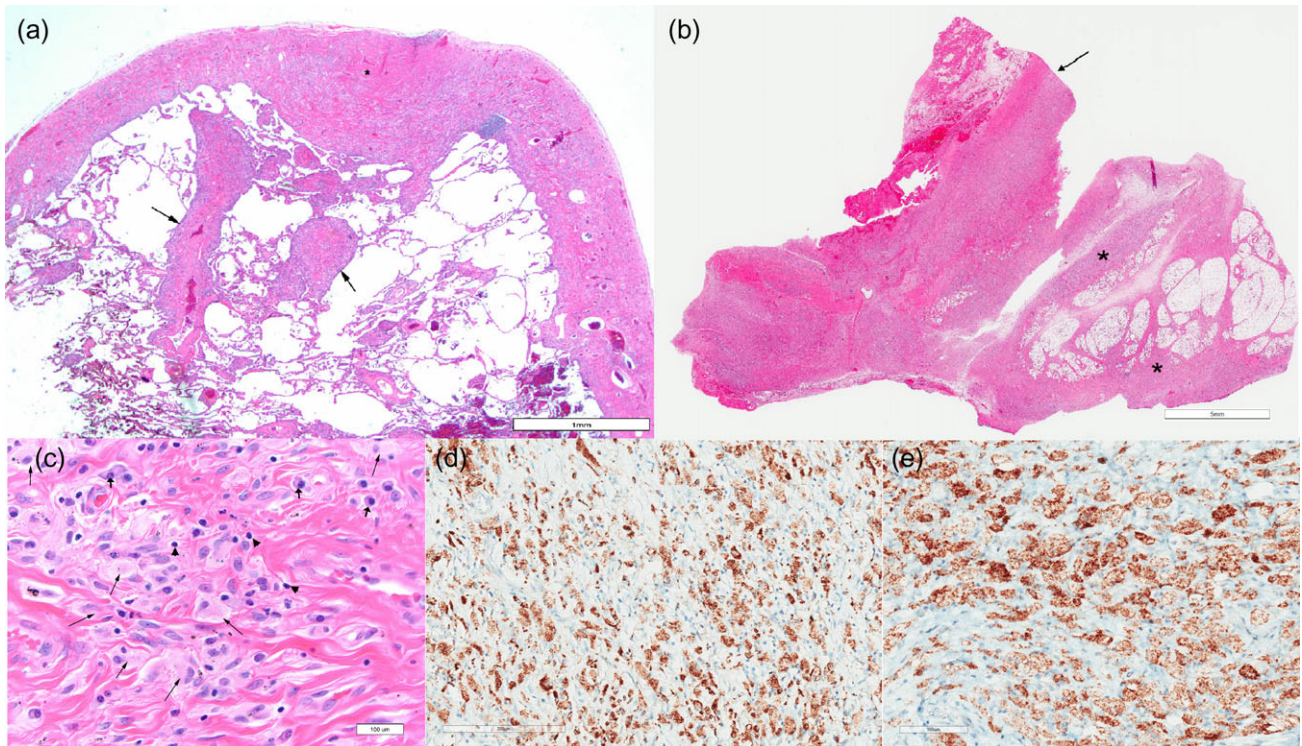


Figure 3: (a) Lung with fibrotic surrounding of the pleura (*) and perivascular regions (arrows). Tissue was obtained from the video-assisted thoracoscopic (VATS) lung biopsy in 2015 at the outside hospital. H&E, 2x, ruler 1 mm. (b) Thickened pericardium (arrows) and pericardial fat with fibrosis of the interlobular septa (*). H&E, 0.4x, ruler 5 mm. (c) Higher magnification of pleura showing infiltrate of plump, large histiocyte with pale eosinophilic cytoplasm and indistinct cell borders (long arrows). Scattered plasma cells (short arrows) and lymphocytes (arrowheads) present with the histiocytic infiltrate. H&E, 40x, ruler 100 μ m. (d) Histiocytic infiltrate positive for histiocytic marker CD68. 20x, ruler 200 μ m. (e) Histiocytic infiltrate positive for an immunohistochemical stain for BRAF V600, indicating the presence of a mutation of the BRAF gene. 20x, ruler 100 μ m.

DISCUSSION

ECD is a non-Langerhans cell clonal neoplasm derived from monocyte-macrophage lineage [1]. It is named after the cardiologist William Chester and his Viennese pathology mentor Jakob Erdheim who reported the first two cases in 1930 as 'Lipoid granulomatosis' [3]. ECD primarily affects adults between their fifth and seventh decades of life with a slight male predilection [1].

Common clinical and radiological features include skeletal involvement (>90%) with bilateral symmetric cortical osteosclerosis of the diaphyseal and metaphyseal regions in the long bones with sparing of the epiphyses, which is nearly pathognomonic for ECD [1, 2]. This is best visualized by technetium bone scan, less sensitively by positron emission tomography (PET) and is often missed on plain films [4]. The central nervous system (CNS) manifestations include central diabetes insipidus and orbital infiltration with exophthalmos [1]. Its renal involvement is often referred to as 'hairy kidney' due to perinephric infiltration of histiocytes, and retroperitoneal infiltrates [1, 2]. The pulmonary presentations include interstitial lung disease (ILD) of varying severity and pleural thickening [1]. Distinctive features of thoracic CT scan of ILD are smooth thickening of interlobular septa and visceral pleura associated with reticulation and ground-glass opacities with a predilection for the upper lung zones [5].

The cardiovascular involvement is present in up to 70% of patients with ECD, and the common manifestations are peri-aortic fibrosis leading to 'coated aorta', pseudotumor of the right heart and pericardial involvement [6]. The latter can be seen in the form of pericarditis, asymptomatic pericardial effusion to life-threatening, rapid, recurrent pericardial tamponade. Recurrent pericardial effusions with tamponade caused by ECD, however, are extremely rare [7]. Mishra et al. reported a patient who continued to experience clinical deterioration despite multiple pericardiocentesis and pericardial window [7]. Only two cases of ECD with constrictive pericarditis have been reported in the literature [8, 9]. This is the first case with initial presentation of recurrent pericarditis with a constrictive physiology that required pericardiectomy.

Due to diverse manifestations and rarity of the disease, clinical and histopathologic diagnosis can be extremely challenging, and our patient was not an exception whose diagnosis was missed on initial lung biopsy reviewed at an outside institution 3 years prior to consultation in our institution. The definitive diagnosis of ECD is established by biopsy of clinically involved tissues, usually skin, bone, retroorbital, retroperitoneal, lung or pericardium [1]. The histopathologic findings include infiltration by histiocytes with foamy/eosinophilic cytoplasm admixed with reactive inflammatory cells associated with varying degrees of fibrosis. The histiocytes are positive for CD68 and negative for CD1a and S100 [1, 4]. Cytology from pericardiocentesis is usually non-diagnostic [7-9]. Tissue sampling is also necessary for the evaluation of BRAF mutations with immunohistochemical stain or genetic testing.

Following the discovery that over 50% of ECD patients carry the oncogenic mutation of BRAF V600E, ECD has been recognized as an inflammatory myeloid neoplasm [2]. BRAF is a well-known human gene that encodes a protein called B-raf, which regulates the mitogen-activated protein kinase (MAPK) signaling pathway that affects cell division and differentiation [4]. Based on the phase 2 VE-BASKET, a non-randomized, open-label, multicenter, multi-histology basket trial for patients with nonmelanoma cancers harboring BRAF V600 mutation (NCT01524978) [10], vemurafenib, a selective BRAF V600 kinase

inhibitor, in November 2017 became the first Food and Drug Administration (FDA) approved drug to treat ECD patients. In the VE-BASKET trial, a total of 22 patients with ECD were enrolled in this study and the confirmed objective response rate (ORR) at week 8 by Response Evaluation Criteria in Solid Tumors (RECIST) was 54.5% (95% CI, 32.2-75.6%). Two-year progression-free survival (PFS) was 83% (95% CI, 66-100%) and 2-year overall survival (OS) was 95% (95%CI, 85-100%) [10].

The prognosis of ECD has been historically poor. In the case series reported by Veyssier-Belot C et al., only 43% of patients (15 out of 37 patients) with ECD diagnosed between 1972 through 1994 survived after a mean follow-up of 32 months [1]. However, recent reports of long term survival are promising. In a cohort of 165 ECD patients seen at least once in a French tertiary center between 1981 and 2016 with a mean follow-up of 63 months, the 5-year survival rate was 82.7%. The estimated median survival time was 13.5 years and 34% of them received targeted therapy [2]. The significantly improved survival rate could be due to early diagnosis of ECD with increased physician awareness and targeted therapy [2]. CNS, retroperitoneal or lung involvement were associated with a poor prognosis, whereas response to interferon-alpha treatment or targeted therapy were associated with a better prognosis [2]. Previous studies also reported poor prognosis of ECD patients with cardiovascular involvement [6].

In summary, we report a case of a 56-year-old woman with recurrent symptomatic pericardial and pleural effusions, along with multisystemic involvement and a missed diagnosis of ECD for 3 years. Our case was unique as the patient developed constrictive physiology requiring pericardiocentesis. Clinical stabilization was achieved with pericardiectomy and initiation of vemurafenib.

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CONFLICT OF INTEREST STATEMENT

None declared.

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CONSENT

Patient's consent has been obtained.

GUARANTOR

Allan L. Klein MD (corresponding author).

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