An Unusual Case of Disseminated Erdheim-Chester Disease

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ABSTRACT

Introduction: Erdheim-Chester disease (ECD) is a rare non-Langerhans histiocytic multisystem disorder, deriving from mononuclear phagocytic cells. It is notoriously challenging to diagnose. Here we present a case of a patient with multisystem ECD.

Case Presentation: A 76-year-old female with a history of Hashimoto's thyroiditis who presented with persistent leukocytosis was found to have bilateral renal enlargement with a perinephric mass, a recurrent pericardial effusion, and bilateral pleural effusions. Following biopsies of several sites of involvement, a diagnosis of ECD was made.

Discussion: The existing literature on ECD is sparse, and no diagnostic criteria have been put forward due to widely differing presentations, although the most common is skeletal. Definitive diagnosis requires a tissue sample.

Conclusions: In presenting our clinical reasoning and approach, we hope to contribute to the existing body of literature on ECD, with the aim of ultimately having sufficient data to compile a diagnostic framework for other clinicians who encounter ECD.

INTRODUCTION

Erdheim-Chester disease (ECD) is a rare non-Langerhans histiocytic multisystem disorder; fewer than 1000 cases have been documented in the literature, and its exact prevalence is, therefore, unknown. While Langerhans cell histiocytosis is thought to be derived from Langerhans cells—specialized dendritic cells of the skin and mucosa—non-Langerhans histiocytosis derives from mononuclear phagocytic cells. ECD is notoriously challenging to diagnose, with up to 20% of primary presenting complaints being constitutional symptoms and no consistent diagnostic clinical factors having been identified. However, in patients presenting with suspicion for malignancy and with involvement of multiple organ systems, a differential diagnosis of ECD should continue to be entertained, especially if preliminary diagnostic evaluation is inconclusive.

CASE PRESENTATION

Our patient was a 76-year-old female with a past medical history significant for hypertension, asthma, and Hashimoto's thyroiditis, who transferred to our service in April 2021 for pericardiocentesis and drain placement due to recurrent pericardial effusions in the context of persistent leukocytosis and diarrhea.

Her symptoms began in January 2020, when she developed fatigue, nausea, and vomiting. A complete blood cell count (CBC) showed a white count of 14.1×10^3/uL, with mild neutrophilic leukocytosis. Given a low-normal mean corpuscular volume of 80 fL, she was thought to have a viral gastroenteritis; however, she reported persistence of her symptoms for weeks. A repeat CBC a month later demonstrated persistent neutrophilic leukocytosis, with a white count of 12×10^3/uL, along with thrombocytosis to 415×10^3/uL. Ferritin was elevated to 313 ug/L, and her iron panel was consistent with chronic inflammation; however, her antinuclear antibody, rheumatoid factor, and erythrocyte sedimentation rate were all within normal limits. In May, she was referred to hematology, and a more extensive workup was significant for a reticulocyte count elevated to 127×10^3/uL. She was BCR-ABL negative, and her leukocytosis was suspected to be secondary to her past infection.

In March 2021, she presented to the emergency department due to a month-long history of diarrhea, and she was admitted

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Figure 1. Pericardial Effusion on Transthoracic Echocardiogram

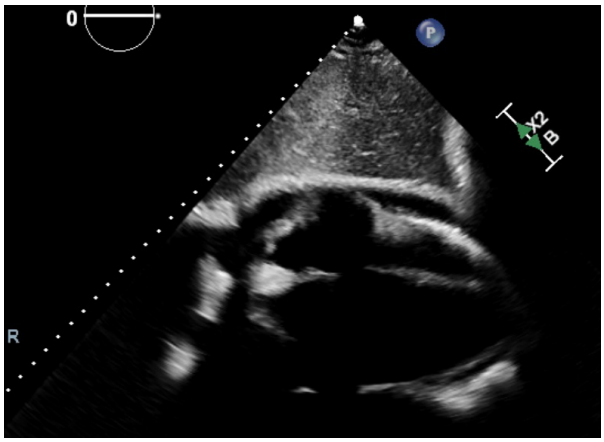


Figure 2. Diastolic Collapse of the Right Ventricle on Transthoracic Echocardiogram

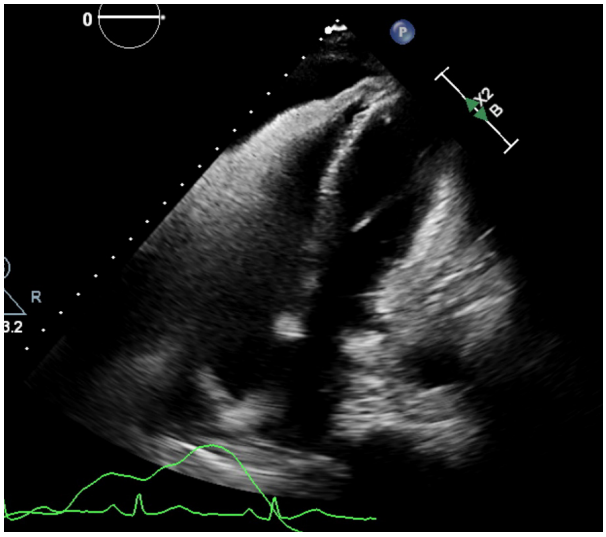


Figure 3. Fibrinous pericardial strand on Transthoracic Echocardiogram

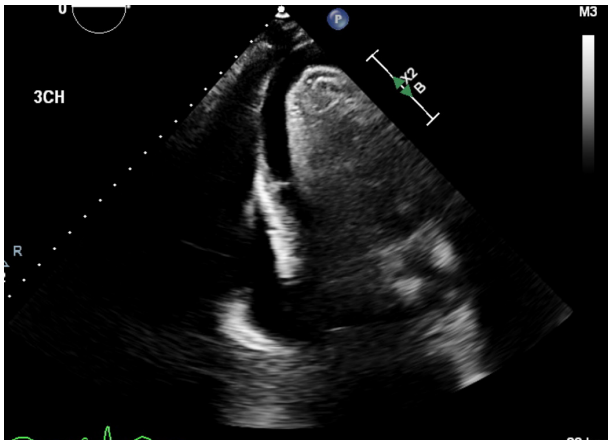
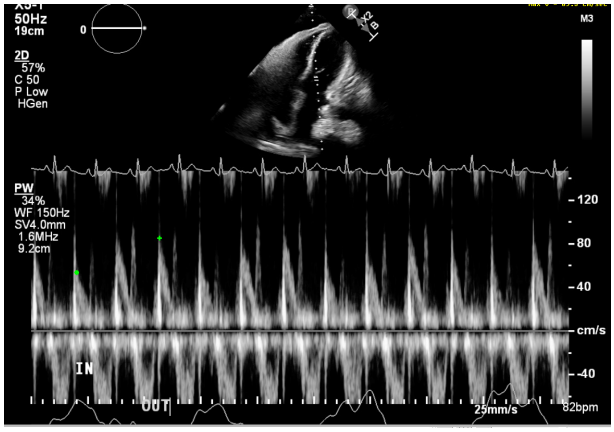


Figure 4. Respirophasic Variation of Mitral Inflow Velocity of More Than 25%.



for further workup. Her CBC showed stable persistent neutrophilia, monocytosis, mild anemia, thrombocytosis, and microcytosis. Computed tomography (CT) of the abdomen and pelvis revealed bilateral kidney enlargement with extensive perinephric at stranding concerning for pyelonephritis, glomerulonephritis, or neoplasm, as well as left periaortic lymph node enlargement or soft tissue swelling. On a repeat CT a few weeks later, obtained as she began to develop shortness of breath, a moderate pericardial effusion was identified, along with bilateral pleural effusions. A follow-up transthoracic echocardiogram (TTE) demonstrated a pericardial effusion (Figure 1) with diastolic collapse of the right ventricle (Figure 2), fibrinous stranding of the pericardium (Figure 3), and respirophasic variation of mitral valve inflow velocity of greater than 25% (Figure 4)—all findings consistent with constrictive pericarditis.

Cardiothoracic surgery performed a pericardiocentesis and placed a drain that was pulled 4 days later; however, repeat TTE demonstrated reaccumulation of pericardial fluid and resulting tamponade physiology, along with pleural effusion. Therefore, she underwent a pericardial window, a diaphragm biopsy, chest wall biopsy, and left lower lobe wedge resection. The following day, a CT-guided biopsy of her known perinephric mass was performed.

Her diaphragmatic and chest wall biopsy revealed pleural thickening with lymphohistiocytic infiltration; the left lower lobe resection similarly demonstrated pleural thickening and fibrosis with lymphohistiocytic infiltration into the lung parenchyma via interlobar septa. The perinephric mass biopsy demonstrated histiocytic proliferation and fibrosis; the foamy histiocytes were positive for CD163 and negative for S100 and CD1a. A diagnosis of ECD was made based on her biopsy results.

A nuclear medicine positron emission tomography (PET)/CT was obtained and was significant for numerous findings that were nonspecific but consistent with her new diagnosis: hypermetabolic perinephric soft tissue stranding along her aorta, heart, and pericardium; reticulonodular and ground glass opacities in

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the lungs suggestive of pulmonary involvement; trace bilateral pleural effusions with a hypermetabolic pleural-based nodule in the right lower lobe; hypermetabolic jejunal mesenteric adenopathy; 2 hypermetabolic peritoneal nodules; diffuse osseous uptake of radioactive tracer suspicious for reactive bone marrow; focal uptake in the right mastoid, with small-volume fluid in the mastoid air cells concerning for mastoiditis versus an additional focus of ECD involvement; and sclerotic hypermetabolic lesions in the sacrum and right humeral head.

She was discharged with close follow-up with medical oncology scheduled. She was started on steroid therapy and subsequently found to be *BRAF*-V600E positive, prompting initiation of vemurafenib therapy in addition to high-dose prednisone.

DISCUSSION

ECD is an extremely rare disease, with fewer than 1000 cases reported. Based on the current literature, it develops more commonly in males than females, with most cases presenting in the patient's fifth to sixth decade of life.[1] Originally termed "lipid granulomatosis" in 1930 by Jakob Erdheim and William Chester, it is characterized by the infiltration of lipid-laden histiocytes – identifiable by their foamy or eosinophilic cytoplasm – into bone and other organs or tissues.[2] The syndrome itself is a spectrum, and its presentation ranges from asymptomatic bony lesions or bone pain to pulmonary, neurological, cardiovascular, or even cutaneous manifestations. Whether this neoplastic disease is a malignant or a reactive polyclonal process remains a topic of debate, with the diagnostic process complicated by the lack of a codified diagnostic criteria.[1]

Based on currently available data, the most common presentation of ECD is skeletal, particularly with involvement of the long bones; diabetes insipidus, neurological, and constitutional symptoms are also common at presentation.[3] Endocrine abnormalities – especially involving the pituitary – are the next most common symptomatic presentations, often presenting with diabetes insipidus that may develop well before any other signs of disease.[4] However, any organ or system potentially may be affected. This breadth of involvement makes identifying a classic ECD presentation challenging, as the clinical picture varies greatly depending on the systems involved and the extent of disease.[2] While central nervous system involvement is less common, it – along with involvement of the heart and lung – is associated with a worse prognosis.[5]

Our patient's presentation was unique: while she was ultimately found to have extensive ECD that had spread to involve her lungs, pleura, pericardium, lymph nodes, bone, and soft tissue, her presenting complaints were persistent leukocytosis on routine labs and diarrhea. It was only while undergoing workup that she was found to have pleural and pericardial effusions, along with perinephric soft tissue masses, which eventually led to the biopsies that confirmed the diagnosis. While her presentation was not suggestive of ECD, her leukocytosis was concerning for an underlying neoplastic process; thus, considering ED as part of the differential diagnosis is crucial in such nonspecific cases, especially as this condition is so infrequently encountered that no conclusive diagnostic paradigm short of tissue biopsy and imaging of bony lesions have been identified.

Treatment options vary; however, all patients with ECD – barring those with asymptomatic or single-organ involvement – will require systemic therapy.[4] Somatic activating mutations in proto-oncogene B-rapidly accelerated fibrosarcoma (*BRAF*)-V600, along with mitogen-activated protein kinase (MAPK), have been associated with ECD; BRAF mutations also have been identified in Langerhans-cell histiocytosis, suggesting the possibility of a common origin or process between the two diseases.[6] Vemurafenib, a selective inhibitor of BRAF kinase, has been utilized as a targeted therapy for patients who test positive for the *BRAF-V600* mutation. Although it continues to be studied in this population, it has been shown to achieve dramatic, robust responses in involved organ systems and, as in other systemic diseases such as sarcoidosis, PET scans may be used to monitor disease progression and treatment response.[4,7,8] Other therapeutic options include MEK (mitogen-activated extracellular signal-regulated kinase) inhibitors and mTOR (mammalian target of rapamycin) inhibitors; however, unlike in some studies of vemurafenib, neither has been shown to achieve reversal of severe or even life-threatening illness.[4] In some cases, combination therapies have been used with promising results, although further study is needed.[9,10] Conventional therapies encompass IFN-α, cytotoxic chemotherapeutics, interleukins and TNF-α antagonists, and corticosteroids.[11-14] From literature review, recommended treatment approaches for patients with systemic *BRAF*-V600 mutation ECD is typically with BRAF inhibitors for targeted treatment; those without the mutation often benefit from MEK-inhibitor therapy.[8] Interferons are typically beneficial for patients without access to targeted therapies, although these agents have been shown to confer an increased risk of relapse and, therefore, necessitate longer treatment durations; intolerable side effects have been shown to develop in up to 50% of patients treated with interferon as well.[8,15,16] Corticosteroids are not an effective monotherapy, although they may be used adjunctively to improve acute symptoms. They also have not been shown to confer a survival benefit. Unless in the case of single-organ disease or tumors causing significant symptoms, surgical resection is generally of little benefit given that ECD frequently has multisystem involvement. Similarly, radiation therapy is most useful when utilized for palliation of significant disease burden, not with curative intent.[8,17]

Our patient was *BRAF*-V600 positive and treated with a combination of vemurafenib and systemic corticosteroids. Vemurafenib was selected for its significant benefits as a targeted treatment against her specific disease mutation. Although her presenting complaint of diarrhea belied her significant systemic

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disease burden, she was started on adjunctive prednisone in hope of optimizing her response to therapy.

CONCLUSIONS

The lack of an identified classic presentation of ECD likely underlies the underrecognition and underreporting of this condition. By presenting this case, we hope to contribute to the growing body of literature on ECD a case of a patient whose long illness course was not immediately concerning for ECD, yet who had extensive involvement of multiple organ systems. Much as in our patient's case, many who are ultimately diagnosed with ECD experience a prolonged period of illness, during which time they are often seen by multiple clinicians and specialists, which may contribute to the delay in diagnosis often seen in ECD cases.[8] While ECD is not a pathologic diagnosis, due to the variability of presentation, no validated diagnostic framework yet exists.[8] As more cases are identified and reported, we hope that a deeper understanding of the disease process and its many manifestations may enable the diagnosis and treatment of patients prior to the development of severe sequelae.

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