

# Erdheim-Chester Disease

## A Case Study and Literature Review

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*Diagnosis and treatment of patients who present with respiratory compromise are challenging. What happens when these patients do not respond to your intervention, and their condition declines rapidly? Having a variety of differential diagnoses is key. An addition to your differential list can include a rare disorder of non-Langerhans cells histiocytosis also known as Erdheim-Chester disease. This disease often presents as an interstitial lung disease that fails many different treatment modalities. A full understanding of how this disease process works is still being investigated. Provided are a literature review and case study for better understanding of this disease.*

*Keywords: Erdheim-Chester disease, Histiocytosis, Idiopathic pulmonary fibrosis*

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Erdheim and William Chester first discovered Erdheim-Chester disease in 1930. It is a disease process with only 250 reported cases.<sup>1</sup> It typically affects middle-aged and elderly men.<sup>2</sup> It is a progressive disease with multisystem involvement. Mortality is 57% typically from respiratory distress, and because of its rarity and wide spectrum of clinical manifestations, it is difficult to diagnose and treat. According to literature, pulmonary involvement has the worst prognosis because 35% of patients with a diagnosis of Erdheim-Chester disease have pulmonary involvement.<sup>3</sup> Diagnosis of Erdheim-Chester is confirmed by histopathology (non-Langerhans histiocytosis) and radiological studies of the long bones.<sup>4</sup> Oftentimes, Erdheim-Chester disease is misdiagnosed as interstitial lung disease or other pulmonary disorders. When evaluating patients with possible idiopathic pulmonary fibrosis, Erdheim-Chester should be one of your differential diagnoses.

### ■ CASE SCENARIO

A 34-year-old woman with a medical history of hypertension, type 2 diabetes mellitus, hyperlipidemia, and ob-

structive sleep apnea noticed increasing dyspnea on exertion and orthopnea, which has progressively worsened over the past 3 years. She also experienced a 30-lb weight gain. She was initially seen by a cardiologist for signs and symptoms of congestive heart failure (CHF). A transthoracic echocardiogram was done that showed normal findings. She was treated for fluid overload and was administered diuretics. Recently, she was hospitalized for a ruptured ectopic pregnancy that was complicated by acute kidney injury, hemolytic anemia requiring steroids, left perinephritic abscess, and recurrent pancreatitis status post pancreatoduodenostomy and splenectomy. She was discharged on a 6-week steroid taper for the hemolytic anemia and required home oxygen. She stated that her breathing was the best it has ever been while she was on the steroids; however, once the steroids were completed, her breathing worsened. One month later, she presented to the emergency department with severe dyspnea and bilateral lower-extremity edema. Her arterial blood gas revealed a hypoxic respiratory acidosis, and chest x-ray revealed bilateral infiltrates. She was admitted to the medical

**TABLE 1** Initial Laboratory Values

Laboratory Test	Patient's Laboratory Values	Reference Range
Sodium, mEq/L	139	135-145
Potassium, mEq/L	4.1	3.5-5.0
Carbon dioxide, mEq/L	32	22-30
Chloride, mEq/L	97	98-106
Blood urea nitrogen, mg/DL	37	10-20
Creatinine, mg/DL	2.6	0.7-1.4
Anion gap, mEq/L	10	10-15
White blood cells, / $\mu$ L	15.1	5000-10 000
Hemoglobin, $\mu$ L	15.1	12-16
Hematocrit, %	40.5	37-47
Platelets, / $\mu$ L	631 000	140 000-400 000
International normalized ratio	1	1
Activated partial thromboplastin time, s	27.4	20-35
pH	7.1	7.35-7.45
Pco <sub>2</sub>	107	35-45
Po <sub>2</sub>	64	80-100
Base excess, mEq/L	4	-3 to 3
Bicarbonate, mEq/L	36	22-26

Abbreviations: Pco<sub>2</sub>, partial pressure of arterial carbon dioxide; pH, hydrogen ion concentration; Po<sub>2</sub>, partial pressure of arterial oxygen.

intensive care unit (MICU), where she was intubated for respiratory failure and hypoxia. Her laboratory and radiographic findings on admission are shown in Table 1.

Her chest x-ray showed bilateral edema and/or infiltrates with layering right greater than left pleural effusions, whereas her chest computed tomography (CT) scan of the pulmonary system revealed smooth but diffuse bilateral interlobular septal thickening and bilateral trace pleural effusions. Cardiovascular system showed multi-chambered cardiomegaly with a hyperdense septum and no pericardial effusion.

During her stay in the MICU, she had acute kidney injury with 80% right renal artery stenosis, in addition to her left perinephritic abscess and multilobe pneumonia. After an appropriate course of antibiotic treatment for the multilobe pneumonia without ventilation improvement, a pulmonary artery catheter was placed to differentiate cardiogenic versus pulmonary etiology for appropriate volume status management. Pulmonary artery wedge pressures were normal, and a lung biopsy was conducted at this time. Results from the lung biopsy were positive for

S-100 protein, suggestive of Erdheim-Chester disease. The disease was then confirmed by long-bone x-rays, which showed diffuse sclerosis throughout the metaphyses and diaphyses in the long bones of the lower extremities. The patient was unable to wean from mechanical ventilation after 16 days. At this time, she was started on pulse dose steroids and was extubated 2 days later. Her hospital course was again complicated by multiple readmissions to the MICU requiring 2 intubations and mechanical ventilation for respiratory failure. After multiple steroid adjustments, she stated that her lungs felt "fuller and can now breathe easier." She also developed leukocytosis from a suspected central line infection, and once her infection clears, she will be administered interferon  $\alpha$  and cyclosporins for suggested management of Erdheim-Chester disease.

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## ■ PATHOGENESIS

With current information provided, Erdheim-Chester disease is known to be a rare non-Langerhans cell histiocytosis with progressive multisystem involvement.<sup>1</sup> Non-Langerhans cell histiocytosis refers to a group of conditions called histiocytosis that are caused by an overgrowth of cells called histiocytes. Histiocytes can be divided into 2 groups based on their characteristics. The first group is a monocyte-macrophage group that includes monocytes, macrophages, and Kupffer cells.<sup>5</sup> The second group is the Langerhans cell-derived group and is the histiocytic cell type that is responsible for Langerhans cell histiocytosis. Non-Langerhans cell histiocytosis is split into 2 groups, classes IIa and IIb. Class IIa involves dermal dendritic cells and includes dermatofibroma, xanthogranuloma, reticulocytosis, and Erdheim-Chester disease. Class IIb involves cells other than Langerhans cells and dermal dendrocytes. This class includes hereditary and acquired diseases such as familial hemophagocytic lymphohistiocytosis, familial sea-blue histiocytosis, and hereditary progressive mucinous histiocytosis.<sup>6</sup> The etiology of this disease process is still unknown. The disease has been described as a rare focal or systemic infiltrative disorder resulting from xanthogranulomatous infiltration of multiple tissue and organs.<sup>2</sup> In most of the cases, the bone involvement is constant and includes symmetric osteosclerosis of the diaphyses and metaphyses of the long bones, especially of the lower extremities.<sup>5</sup> The differentiation between Erdheim-Chester disease and

Langerhans cell histiocytosis is in its histopathology. Erdheim-Chester differs in its age distribution and immunochemical and radiological characteristics.<sup>7</sup>

**CLINICAL PRESENTATION**

There are several clinical manifestations of Erdheim-Chester disease, which makes it difficult to diagnose and treat (Table 2). Extraskelatal manifestations may affect the lungs, pericardium, aorta, retroperitoneum, skin, and ocular orbits. The most common manifestations include skeletal, neurological, orbital, retroperitoneal, and respiratory.

**Skeletal**

Knee pain and leg pain are the most common symptoms because the disease affects mainly the lower extremities.<sup>7,8</sup> The findings on plain long-bone x-rays show osteosclerosis of the diaphyses and metaphyses with sparing of the epiphyses.<sup>7</sup> Also on bone scintigraphy is bilateral symmetric uptake of bone seeking radiopharmaceutical within the metadiaphyses of the skeleton.<sup>7</sup> The patient in the case study never complained of pain.

**Neurological**

The most common neurological manifestations are diabetes insipidus and ataxia of gait. These symptoms arise from lesions found on magnetic resonance imaging, which are typically seen on the cerebellum and pons. Magnetic resonance imaging findings are often confused with multiple sclerosis by showing a demyelinating process.<sup>7</sup>

**Orbital**

Orbital involvement in Erdheim-Chester disease usually involves middle-aged and elderly patients, rarely children. The classic signs of orbital involvement are bilateral xanthelasma and proptosis.<sup>9</sup> The variety of orbital manifestations includes infiltration of the fat and optic sheath to large retrobulbar intraconal masses.<sup>7</sup> These symptoms are usually verified with CT contrast of the head and face to reveal the intraconal masses.<sup>9</sup>

**TABLE 2 Erdheim-Chester Disease**

Erdheim-Chester Disease Medical Treatment Options
Prednisolone
Interferon $\alpha$
Bisphosphonates
Combination of prednisolone and clodronate
Chemotherapeutics with steroids
Combination of cladribine and prednisolone

**Retroperitoneal**

Retroperitoneal involvement is from the infiltration of fat and surrounding structures by histiocytes.<sup>7</sup> It may occur in isolation of a single organ or present as a widespread disease with multiple organ involvement. Histiocytic infiltrates may impair retroperitoneal organs including the kidney, pancreas, or adrenal gland. Also, perivascular infiltrates may cause some stenosis of renal arteries as well as some biliary obstruction from pancreatic head involvement. In some cases, renal involvement is included by the direct invasion of the renal sinus or by distal ureter obstruction.<sup>10</sup> One study done by Haroche and colleagues<sup>11</sup> studied 22 patients with Erdheim-Chester disease and suggested that a possible cause of morphological changes in adrenal size and infiltration could be related from Erdheim-Chester disease.<sup>11</sup>

**Pulmonary**

The most common presentation with pulmonary involvement is progressive dyspnea as the case scenario patient presented.<sup>7</sup> Approximately 20% of patients present with pulmonary involvement, which has a poor prognosis.<sup>12</sup> A review of literature by Allen and colleagues had pulmonary involvement.<sup>13</sup> Eighteen of those patients had an overall survival rate of 66%. Eleven of those patients died of their diseases, 3-16 years of life span from time of diagnosis.<sup>13</sup> Patients with pulmonary involvement present with signs and symptoms of interstitial lung disease, mostly cough and shortness of breath.<sup>14</sup> Patients with cardiac involvement in addition to the primary pulmonary involvement have a worse prognostic outcome. Pulmonary cases were reviewed by Veyssier-Belot and colleagues,<sup>4</sup> which showed that many of the patients' manifestations included nonspecific symptoms such as dyspnea and cough, which may be from underlying pulmonary, cardiac, or renal disease.<sup>14</sup> Pulmonary function tests in patients with Erdheim-Chester typically indicate moderate restrictive ventilatory defects with normal or reduced carbon monoxide diffusion capacity.<sup>3</sup>

**DIAGNOSTIC TESTING**

Erdheim-Chester disease is typically confirmed by radiology and histology findings. Radiography is used to identify pleural and bone changes that are common to the white cell-mediated group of diseases that are categorized as histiocytoses.<sup>15</sup> This group of diseases is pathologically identified by an infiltrate of lipid-laden foamy macrophages, which are the histiocytes or chronic inflammatory cells that lead to fibrosis.<sup>16</sup> Histology can further characterize the foamy macrophages, distinguishing them from Langerhans cells by using special staining techniques; positive results on staining for negative S-100 protein and CD1a indicate Erdheim-Chester disease.<sup>15</sup> Although

there is neither sensitivity nor specificity reported for either radiological or histological tests, experts commonly cite specific findings from these diagnostic tests in establishing the diagnosis.<sup>5,7,16,17</sup>

## Radiology

Radiographic findings help differentiate between Erdheim-Chester and Langerhans cell histiocytosis. In the case of diagnosing lung involvement, plain chest films often show pleural thickening and pleural effusions in Erdheim-Chester disease. Computed tomography of the chest predominately shows smooth interlobular septal and visceral pleural thickening predominately in the upper lobes of the lungs. In regard to diagnosis of other body system involvement, CT findings are associated with histopathologic changes and cellular aggregation and fibrosis.<sup>3</sup> The criterion-standard diagnostic test used to confirm Erdheim-Chester disease is long-bone x-ray. These x-rays show diffuse sclerosis throughout the metaphyses and diaphyses of the long bones of the upper and lower extremities. Trabecular coarsening and cortical thickening produce osteosclerosis, and this finding is diagnostic of Erdheim-Chester disease.<sup>3</sup>

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## Histology

A tissue biopsy can also diagnose Erdheim-Chester disease in addition to a positive long-bone x-ray. Bone or retro-orbital tissue has been the most beneficial area on which to perform a biopsy in the confirmation of Erdheim-Chester. The lesions that are biopsied generally consist of lipid-storing CD68-positive and S-100- and CD1a-negative, as well as non-Langerhans cell histiocytes, either localized to the bone or involving multiple organ systems in the body.<sup>17</sup> In the case of lung involvement, obtaining a transbronchial or open lung biopsy of the affected tissue will often confirm non-Langerhans cell histiocytic infiltrates.<sup>3</sup> The absence of Birbeck granule or the presence of immunostaining negative for S-100 protein is often found. S-100 cells are derived from the neural cells, which include Langerhans cells, schwann cells, glial cells, and melanocytes. The function of S-100 cells, which are proteins that regulate protein phosphorylation, transcription factors, calcium homeostasis, enzyme activities, and cell growth are linked in the inflammatory response.<sup>18</sup> Several of the

S-100 proteins are used for tumor markers. In the case of Erdheim-Chester disease, the presence of Langerhans cells allows for differential between Langerhans cells and non-Langerhans cell histiocytosis.<sup>19</sup> CD68 is a transmembrane glycoprotein of unknown function highly expressed by human monocytes and tissue macrophages. CD1a is a group of glycoproteins, which are often expressed as immature thymocytes, Langerhans cells, and dendritic cells. When S-100 and CD1a are negative, the histology confirms Erdheim-Chester disease mostly related to the negative test for Langerhans cells.<sup>20</sup>

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis for Erdheim-Chester disease is broad due to multisystem involvement and rarity of the disease. The age of the patient should be considered as Erdheim-Chester disease is rarely diagnosed in children.<sup>3</sup> The primary differential diagnosis should include Langerhans cell histiocytosis. Both Erdheim-Chester disease and Langerhans cell histiocytosis manifest with cellular infiltration of the bone, diabetes insipidus, and interstitial lung disease<sup>3</sup> (Table 2). To differentiate between the two, bone and pulmonary radiographs are used. In Erdheim-Chester disease, long-bone x-rays will show long-bone osteosclerosis, whereas with Langerhans cell histiocytosis skeletal osteolytic lesions are observed. In regard to the pulmonary radiology, Erdheim-Chester will often reveal infiltrates to the perilymphangitic and subpleural lung tissue. In Langerhans cell histiocytosis, tissues surrounding the bronchi are usually involved.<sup>3</sup>

According to the case study provided, the patient's differential diagnosis included CHF exacerbation, interstitial pulmonary fibrosis, and adult respiratory disease syndrome (ARDS). These diagnoses were explored related to her course of progression. She initially presented with increasing shortness of breath and a 30-lb unexplained weight gain. She had invasive hemodynamic monitoring as well as an echocardiogram to rule out CHF. Her pulmonary status was very difficult to differentiate. From an ARDS standpoint, she had bilateral pulmonary effusions, PaO<sub>2</sub>/FiO<sub>2</sub> ratio less than 200, and noncardiogenic pulmonary edema. Her oxygen requirements and positive end-expiratory pressure improved once a stress dose steroid was initiated for possible idiopathic pulmonary fibrosis. Idiopathic pulmonary fibrosis is evaluated by daily chest x-rays. Because treatment was not improving her symptoms from a pulmonary standpoint, it was decided to do an open lung biopsy to rule out any other possible treatable diseases.

## DIAGNOSIS OF LUNG INVOLVEMENT

Pertaining to the case study provided, it was difficult to arrive at the diagnosis. The differential diagnoses included were CHF exacerbation, idiopathic pulmonary fibrosis,

and ARDS. After several days of requiring mechanical ventilation and failure to wean off of mechanical ventilation, a decision was made to take an open lung biopsy of a mass noticed on the chest x-ray. After investigation of the mass and identification of a negative S-100 protein was identified from the lung tissue biopsy, long-bone x-rays confirmed Erdheim-Chester disease with noticeable diffuse sclerosis throughout the metaphyses and diaphyses of the lower extremities. At this time, hematology and rheumatology consultations were made for treatment and management of Erdheim-Chester disease.

**TREATMENT**

Treatment is on an individual basis (Table 3). There have been no randomized controlled trials in the literature. Unfortunately, 60% of patients with a diagnosis of Erdheim-Chester expire within 32 months of presentation.<sup>14</sup> A standardized treatment regimen of Erdheim-Chester has not been implicated because the history of this rare disease is not well known. Treatment options have included surgical resection of lipid mass, corticosteroid therapy, cytotoxic agents, stem cell transplantation, radiation, and interferon.<sup>3,14</sup> Corticosteroids are the first line of treatment used to control symptoms but are not indicated for long-term management because of their potential for serious adverse effects of long-term use.<sup>5</sup> There are studies investigating different treatment options. One study investigated the use of interferon  $\alpha$  on 3 patients with diabetes insipidus and vision impairments. The interferon  $\alpha$  had a long-lasting response that improved outcomes for 3 to 4.5 years.<sup>1</sup> The use of bisphosphonate has been studied with bone involvement for Erdheim-Chester disease. This line of drug choice is suggested to work well because of its antimacrophage activity.<sup>21</sup> Authors of a study noted that the use of combination therapy of oral prednisone and intravenous clodronate over 5 years decreased the turnover of bone markers in their patients.<sup>21</sup> Because of the rarity of pulmonary involvement, treatment is not well established. It is suggested in literature that the use of

combination therapy including prednisolone and a chemotherapeutic agent is successful in a few cases.

*There are other studies investigating different treatment options.*

A study done by Bourke and colleagues<sup>15</sup> reviewed a patient who received combination therapy that included cyclophosphamide and prednisolone. The patient originally received prednisolone alone, and when taken off of the medication, the patient's condition declined rapidly. Once the patient was restarted on prednisolone and the cyclophosphamide was initiated simultaneously, the patient showed improvements in symptoms, function, and radiological findings and slowed rate of progression.<sup>15,22</sup> Another potential treatment option studied is cladribine, a purine analog that is toxic to monocytes.<sup>22</sup> A study done in 1999 investigated the use of this drug on a patient with orbital and pericardial involvement.<sup>22</sup> This patient also received steroids over a period, and when the dose was tapered off, his symptoms worsened. After restarting the prednisolone and initiating cladribine, the patient showed increasing monocyte production and a significant improvement in symptoms. The long-term effects of the treatment are not well known, but this patient had a good quality of life for 2 years after treatment was discontinued.<sup>22</sup>

**SUMMARY**

When assessing a patient who has decreasing pulmonary function that does not improve with treatment, critical-care nurses should be aware of the possibility of this rare disease. There are several different treatment options available for Erdheim-Chester disease, all of which do not have enough evidence to support definitive treatment. More research is needed in this area. It is important to treat the patient based on presenting symptoms and system involvement. Steroids are the suggested initial treatment for symptom management and slow the rate of progression but are not recommended for long-term use. Combination therapy of steroids and a chemotherapeutic agent seems to be the most successful treatment pertaining to longer life expectancy and symptom management at this time.

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**TABLE 3 Treatment Options**

Erdheim-Chester Disease	Versus	Langerhans Cell Histiocytosis
Long-bone osteosclerosis	Long bone x-rays	Skeletal osteolytic lesions
Infiltrates to the perilymphangitic and subpleural lung tissue	Pulmonary radiology	Bronchial tissue abnormality
Non-Langerhans cells	Histology	Langerhans cells

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