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WHEN ERDHEIM-CHESTER DISEASE REACHES THE PECTORAL MUSCLE

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ABSTRACT

Erdheim-Chester disease (ECD) is a rare histiocytic disorder. The underlying etiology has not yet been fully elucidated. Recent technological and molecular advances have identified aberrant activation of the MAPK/ERK signalling pathway as a central driver of disease, leading to its reclassification as a neoplastic entity rather than solely a multisystem fibroinflammatory condition. These insights have significantly advanced the understanding of disease pathogenesis and are fundamental to the development and implementation of targeted therapeutic strategies.

We describe a case of KRAS-mutant ECD with pleural, pericardial, diaphragmatic, and pectoral muscle involvement in a patient with a prior hematologic history. The disease was refractory to corticosteroid therapy, prompting escalation to second-line treatment with a MEK inhibitor.

KEYWORDS

Erdheim-Chester disease, muscle involvement, KRAS mutation, MEK inhibitor

LEARNING POINTS

- This case underscores the clinical heterogeneity of Erdheim–Chester disease. The disease can affect virtually any organ system, although skeletal muscle involvement remains exceedingly rare.
- The present case highlights the critical role of comprehensive whole-body imaging and the acquisition of multiple tissue biopsies from different affected sites to establish an early and definitive diagnosis.
- Molecular profiling is essential to identify alterations in the MAPK/ERK signalling pathway, as this enables the use of targeted therapies that are associated with substantial improvements in clinical outcomes and overall survival.

INTRODUCTION

Erdheim-Chester disease (ECD) is a rare histiocytic disorder, marked by infiltration of organs with CD68+/CD1a- histiocytes[1]. It was first described in 1930 by William Chester and Jakob Erdheim as a 'lipoid granulomatosis' and classified as a neoplasm by the World Health Organization in 2016[2-3].

Currently, there are an estimated 1500 cases reported

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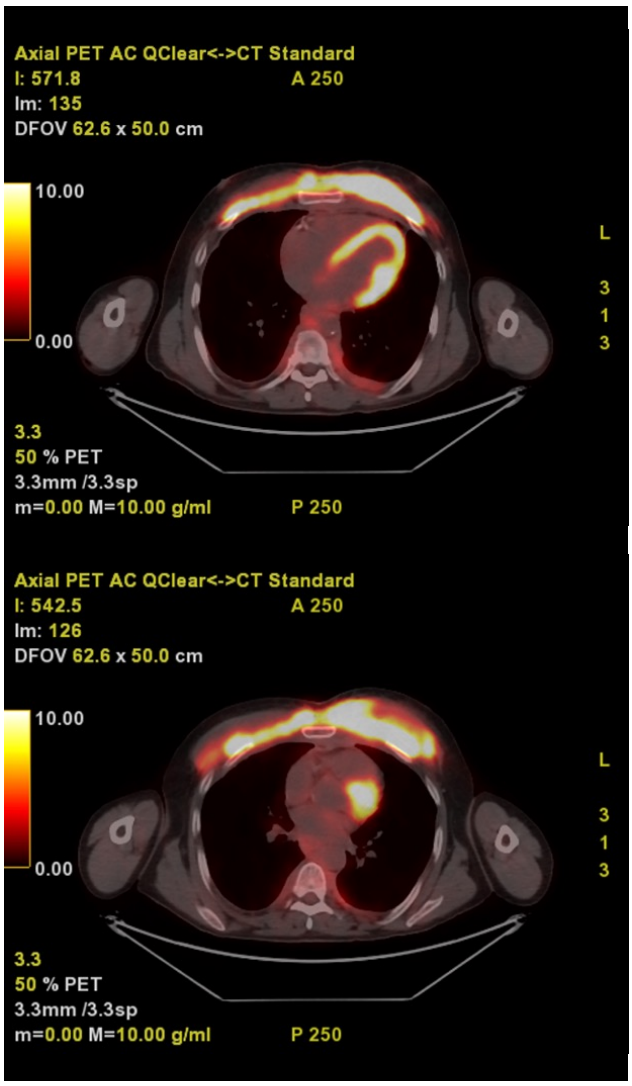


Figure 1. Positron emission tomography/computed tomography scan shows extensive pectoral muscle involvement.

worldwide in the medical literature[5]. The underlying aetiology of ECD is still not fully known. Since 2012, progress in molecular techniques has led to the discovery that the disease is driven by an aberrant activation of MAPK/ERK signalling pathway. These activating mutations include BRAFV600E, MAP2K1, KRAS, NRAS, PIK3CA, ARAF, RAS, PIK3CA, and translocations in BRAF, ALK, and NTRK1[4].

ECD is a multisystemic disease with a wide clinical spectrum ranging from asymptomatic, incidental findings to severe, life-threatening organ dysfunction. Long bone osteosclerosis is the most common presentation, but cardiac, pleural, retroperitoneal, central nervous system, and soft tissue involvement are also described[1].

The condition most often presents at a mean age of 51.7 years and is diagnosed at an average age of 56.4 years, with a marked male predominance (male-to-female ratio 3:1)[4]. This delay highlights the challenges of making an accurate diagnosis of this rare condition.

Lesion biopsies with histological analysis and immunohistochemical (IHC) staining are mandatory for ECD diagnosis, as well as to rule out differential diagnoses. Histological findings commonly include fibro-inflammatory infiltrates containing foamy (lipid-containing) histiocytes, accompanied by Touton giant cells. IHC characteristics of ECD histiocytes are CD68+, CD163+, factor XIIIa+, CD1a-, CD207- and rarely positive S100 (only 20%). Whole-body imaging is recommended as a tool to guide biopsy targets and to assess disease burden with subsequent risk assessment of end-organ failure[5-6].

We present a case of a KRAS-mutant ECD with pleural, pericardial, diaphragmatic, and pectoral muscle involvement in a patient with a hematologic history.

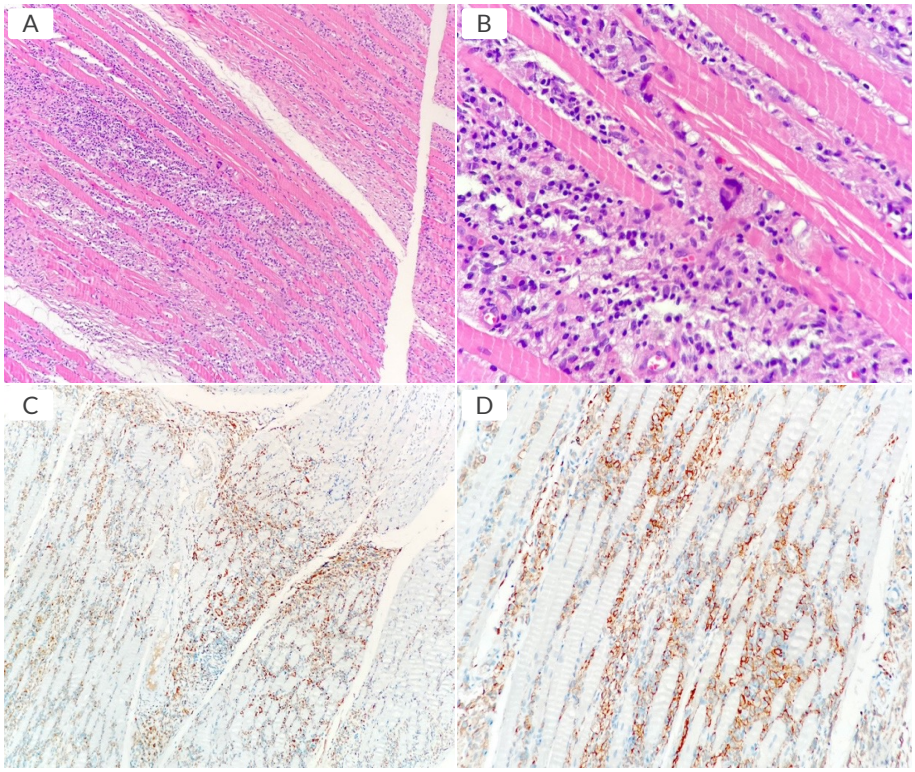


Figure 2. Bilateral pectoral muscle biopsy results. A) Foamy cytoplasm–containing histiocytes, multinucleated giant cells, lymphocytes, and plasma cells between striated muscle fibres (H&E ×100); B) Foamy cytoplasm–containing histiocytes, multinucleated giant cells, lymphocytes, and plasma cells between striated muscle fibres (H&E ×100); C) Bilateral pectoral muscle biopsy results. CD68 immunohistochemical staining (×100); D) CD163 immunohistochemical staining (×200).

Marker	Result	Marker	Result
CD20	+	LCA	+
CD3	+	EMA	+
BCL2	+	CD79a	+
BCL6	+	**CD68**	**+**
Ki67	+	**CD163**	**+**
CD30	-	**CD1a-**	**-**
Mum1	+	Langerine	-
PAX5	+	**S100**	**-**
CD4	+	CD138	+
CD8	+	**BRAFV600E**	**-**

Table 1. Result of immunohistochemical staining of pectoral muscle biopsy left and right.

CASE DESCRIPTION

A 44-year-old male was admitted due to progressive shortness of breath (New York Hear Association functional class III), night sweats, and unintentional weight loss of 10 kg in the past 1.5 months. There was no fever, no haemoptysis, and no chest pain. Clinical examination revealed bibasilar reduced breathing sounds, a normal saturation in rest, and no signs of cardiac decompensation.

The patient had a history of immune thrombocytopenic purpura (ITP), diagnosed 20 years earlier and followed without the need for medication. He had ceased smoking 2 months before presentation, with a limited smoking history of approximately one pack per month in social settings. He was employed in the recycling industry.

Investigation with computed tomography (CT)-scan showed bilateral pleural and pericardial effusion (8mm), and widespread lymphadenopathy in the mediastinum. Subsequent positron emission tomography (PET)-CT scan revealed generalized lymphadenopathy (cervical, supra- and infraclavicular, axillary, mediastinal, and abdominal). Microbiological evaluation, including bronchoscopy, was negative.Extensive histopathological assessment was subsequently performed, including biopsy of the left supraclavicular lymph node, pleural tissue, and pericardium. In the setting of clinical deterioration, progressive respiratory distress, and increasing oxygen requirements, systemic corticosteroid therapy (1 mg/kg/day, maximum 64 mg/day) in combination with colchicine was initiated. This intervention was associated with a rapid and favourable clinical response.

Histopathological examination of all biopsy specimens demonstrated fibrinoid necrosis, mature histiocytic infiltration, and fibrosis, findings consistent with ECD. Further molecular analysis identified a KRAS mutation, supporting the initiation of second-line therapy with a MEK inhibitor if the disease should be corticosteroid-refractory.

On follow-up, complete radiological remission was achieved

Manifestation (%)	Cohen-Aubart et al	Estrada-Veras et al
Long bone osteosclerosis	80	95
Vascular involvement	64	-
Retroperitoneal involvement	58	65
Cardiac involvement	53	-
Coated aorta	46	62
Right atrium pseudo-tumor	41	37
CNS involvement	37	38
Lung involvement	35	52
Skin involvement	33	25
Pericardial involvement	31	8
Diabetes insipidus	28	47
Coronary infiltration	27	-
Xanthelasma	27	33
Retro-orbital involvement	22	27
Cerebellar involvement	17	-

Table 2. ECD organ involvement in Pitié-Salpêtrière (n=165) and NIH (n=60) cohorts].
Abbreviations: ECD, Erdheim -Chester disease; CNS, central nervous system.

Author	Manifestation	Histopathology	Treatment
Tan et al.[9]	59-year-old woman: Osteosclerosis of both tibia Soft tissue involvement of the left breast Pericardial involvement Retroperitoneal involvement Involvement of both rectus abdominis muscle and subcutaneous tissues Enlarged kidney's	Biopsy of pericardium, left breast and subcutaneous tissues of abdominal wall	Cyclophosphamide, vincristine and prednisone; progression after five cycles. Epirubicin was associated with stabilization of the disease.
Yamamoto T et al.[8]	66-year-old male: Osteosclerosis of both tibia, distal femora and humeri Involvement of right quadriceps femoris muscle	Biopsy of right femur and quadriceps femoris muscle	Prednisolone 10mg/day with stabilization of the disease.
Ambrosini V et al.[10]	Unspecified patient: Osteosclerosis of right femur and left humerus with surrounding muscle involvement Diabetes insipidus Hypergonadotropic hypogonadism Pericardial mass and myocardial septal infiltration Bilateral interstitial lung disease	Unspecified *Only FDG PET/CT	Unspecified
Golagha M et al.[11]			
Case 1	39-year-old male: Osteosclerosis of the bilateral femurs, tibiae and radii Pituitary involvement with diabetes insipidus Achilles tendon and left abductor hallucis muscle involvement	Distal femur biopsy	3 million units of alfa-interferon, 3x/week
Case 2	41-year-old male: Osteosclerosis of the left knee and elbow Peri-orbital masses Right atrial mass Involvement of left external obturator muscle, left pectineus muscle and right quadratus femoris muscle	Sinus and proximal left femur bone biopsy	3 million units of alfa-interferon, unspecified frequency

Table 3. Summary of manifestations, histopathology and treatment of ECD-cases reported with muscle involvement.
Abbreviations: ECD, Erdheim-Chester disease; FDG, fluorodeoxyglucose; PET-CT, positron emission tomography-computed tomography.

after 12 months of corticosteroid therapy. Corticosteroids were tapered and discontinued after a total treatment duration of 27 months. Following cessation, the patient remained in remission for 19 months, when he developed progressive swelling of the left anterior chest wall and shortness of breath.

PET-CT imaging *(Fig. 1)* revealed a 25 cm conglomerated infiltrative mass in the pectoral muscles (SUVmax 19.8), left supraclavicular lymph node involvement (SUVmax 22), bilateral pleural fibrotic thickening (SUVmax 6.2), and anterior diaphragmatic thickening (SUVmax 7). These findings were consistent with multisystemic inflammatory involvement. Bilateral pectoral muscle biopsy demonstrated lymphoplasmacytic infiltration, foamy histiocytes, and fibrosis, confirming ECD *(Fig. 2, Table 1)*. Consequently, off-label approval was obtained for MEK inhibitor therapy (trametinib), and treatment was initiated. At 4-month follow-up, there was near-complete remission of pectoral muscle swelling and resolution of dyspnoea. A mild anaemia was observed, with no additional adverse effects reported. The patient will remain under regular clinical follow-up.

DISCUSSION

ECD is characterized by multisystemic inflammation with infiltration of histocytes that causes progressive organ damage, which can become life-threatening without intervention or treatment.

Manifestations

All organs can virtually be affected by ECD. The most frequent manifestation is long bone osteosclerosis, followed by cardiovascular and retroperitoneal involvement, as demonstrated by two cohort studies *(Table 2)*. Our patient had pleural, pericardial, diaphragmatic, and pectoral muscle involvement. A review of the literature identified only 4 previously published cases of ECD with muscle involvement *(Table 3)*[8-11]. A key strength of the present case is the confirmation of ECD across multiple tissue biopsies, including pericardial, pleural, lymph node, and pectoral muscle specimens. Among the previously reported cases, muscle biopsy confirmation was performed in only 1 of the 4.

Treatment and survival

The outcome is dependent on the extent and location of the disease. Before 2004, approximately 60% of patients died

within three years of diagnosis[7]. Recent advances have identified activating mutations in the MAPK/ERK signalling pathway as a key pathogenic mechanism in ECD, leading to improved disease characterization and the implementation of targeted therapies. As a result, ECD has become a treatable, chronic condition with significantly improved survival outcomes.

In a retrospective study conducted by the French National Referral Center for Histiocytosis at Pitié-Salpêtrière Hospital in Paris between April 2012 and December 2019, Cohen-Aubart et al. evaluated the efficacy of targeted therapies in 117 patients with severe and refractory ECD, including 28 patients with mixed histiocytosis. Of these patients, 86 (74%) were treated with the BRAF inhibitor vemurafenib and 42 (36%) with the MEK inhibitor cobimetinib, with some patients receiving combination therapy. As of December 2019, the median survival for patients receiving targeted therapies had not been reached, while those who did not receive targeted therapies had a median survival of 133 months (HR 0.64, 95% CI 0.42–0.99; p = 0.04), indicating a significant survival advantage associated with targeted treatment strategies[7].

Another retrospective study conducted by the University of Texas followed 26 patients with progressive non-Langerhans cell histiocytosis (ECD and/or RDD), who were treated with trametinib. At a median follow-up of 23 months, treatment effects were durable, with a median time-to-treatment failure of 37 months, whereas the median progression-free and overall survival were not reached (at 3 years, 90.1% of patients were alive)[12].

The authors confirmed previously reported results with cobimetinib, suggesting that MEK inhibitors can induce sustained clinical responses with an acceptable safety profile[13]. Although dose reductions due to treatment-related toxicities, such as acneiform rash, were required in the majority of patients, therapeutic efficacy was generally maintained at lower doses, allowing continuation of therapy[14].

Nevertheless, the optimal duration of MEK inhibitor treatment and the risk of disease recurrence or progression following treatment discontinuation remain uncertain.

CONCLUSION

This case describes KRAS-mutant ECD with pleural, pericardial, diaphragmatic, and pectoral muscle involvement in a patient with a prior hematologic history. Identification of a KRAS mutation supports the clonal, neoplastic nature of the disease and underscores the role of targeted therapies, such as MEK inhibitors, which are currently employed in corticosteroid-refractory ECD and have been associated with significant improvements in survival.

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