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# Single-Site ALK-Positive Histiocytosis With TFG-ALK Fusion: Expanding the Clinical Spectrum of This Rare Entity

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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**Patient:** Male, 50-year-old
**Final Diagnosis:** ALK-positive histiocytosis with TFG–ALK fusion
**Symptoms:** Dsypnea
**Clinical Procedure:** —
**Specialty:** Oncology

**Objective:** Rare disease

**Background:** Anaplastic lymphoma kinase (ALK)-positive histiocytosis is a rare and recently described histiocytic neoplasm characterized by ALK gene rearrangements. Several ALK fusion partners have been reported, particularly in patients with multisystem disease. We report the first case of single-site ALK-positive histiocytosis involving a TFG-ALK fusion, a rearrangement previously linked to disseminated disease.

**Case Report:** A man in his 50s with obesity, obstructive sleep apnea, diabetes mellitus, hypertension, coronary artery disease, and a 40-pack-year smoking history underwent computed tomography for lung cancer screening; the results showed a solitary 1.6-cm left lower lobe pulmonary nodule. Positron emission tomography demonstrated hypermetabolic activity confined to the lesion. He subsequently underwent video-assisted thoracoscopic wedge resection with mediastinal lymphadenectomy. Histopathologic evaluation revealed a well-circumscribed spindle cell neoplasm expressing histiocytic markers CD4, CD68, and CD163, with cytoplasmic ALK positivity. A TFG-ALK gene fusion was detected using Archer FusionPlex Pan Solid Tumor panel testing with anchored multiplex polymerase chain reaction via Illumina NextSeq 500. Immunohistochemical and flow cytometric studies excluded alternative ALK-rearranged neoplasms, including inflammatory myofibroblastic tumor, anaplastic large cell lymphoma, and ALK-positive diffuse large B-cell lymphoma. The patient received no systemic therapy and remains disease-free on radiographic surveillance.

**Conclusions:** To our knowledge, this case represents the first reported instance of single-site ALK-positive histiocytosis with a TFG-ALK fusion. It expands the molecular and clinical spectrum of this rare entity, suggesting that certain ALK fusion partners are associated with localized disease and an indolent clinical course. Recognition of such presentations is essential to avoid unnecessary systemic therapy.

**Keywords:** anaplastic lymphoma kinase • gene fusion • histiocytosis • immunohistochemistry • thoracic surgery
**Full-text PDF:** https://www.amjcaserep.com/abstract/index/idArt/952807

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## Introduction

Anaplastic lymphoma kinase (ALK)-positive histiocytosis is a relatively recently described clonal neoplasm characterized by histiocytes expressing abnormal ALK fusion proteins capable of clonal proliferation and tissue infiltration. The largest published cohort study by Kemps et al included 39 pediatric and adult patients, highlighting the rarity of this disease [1,2]. In that study, KIF5B-ALK was the most commonly reported fusion partner, identified in 27 patients, followed by 5 patients with ALK fluorescence in situ hybridization positivity (ALK-FISH+). Additional ALK fusion partners included CLTC-ALK, TPM3-ALK, EML4-ALK, DCTN1-ALK, and TRK-fused gene (TFG)-ALK. Clinically, ALK-positive histiocytosis demonstrates a broad spectrum of presentations, ranging from isolated single-organ lesions to diffuse multisystem disease [1]. The nervous system, liver, lung, bone, and skin are the most commonly involved organs [1,2]. Among reported ALK rearrangements, TFG-ALK appears to be less frequently identified and has primarily been documented in cases of multisystem disease.

Here, we report a case of single-site ALK-positive histiocytosis harboring a TFG-ALK fusion in a man in his 50s. To our knowledge, this represents the first recorded case of single-site ALK-positive histiocytosis with this specific fusion. The benign clinical course and apparent cure after surgical resection in our patient suggest that not all TFG-ALK rearrangements result in disseminated or aggressive disease.

## Case Report

A man in his 50s with obesity, obstructive sleep apnea, diabetes mellitus, hypertension, coronary artery disease, and a 40-pack-year smoking history was referred to the thoracic surgery clinic after a low-dose computed tomography (CT) scan performed for lung cancer screening revealed a 1.6-cm left lower lobe pulmonary nodule (**Figure 1**). CT-guided biopsy demonstrated a spindle cell neoplasm. A positron emission tomography scan performed before surgical evaluation showed hypermetabolic activity confined to the left lower lobe nodule. Laboratory findings were unremarkable.

The patient underwent video-assisted thoracoscopic surgery with left lower lobe wedge resection and mediastinal lymphadenectomy for diagnostic and curative purposes. Pathologic examination revealed a well-circumscribed lesion composed of uniform spindle cells expressing histiocytic markers CD4, CD68, and CD163 (**Figure 2**), with positive cytoplasmic staining for ALK (CD246). A TFG-ALK gene fusion was detected using the Archer FusionPlex Pan Solid Tumor panel, an anchored multiplex polymerase chain reaction method, on the Illumina NextSeq 500 platform. Immunohistochemistry findings for CD1a, a key marker of Langerhans cell differentiation (**Figure 3**), smooth

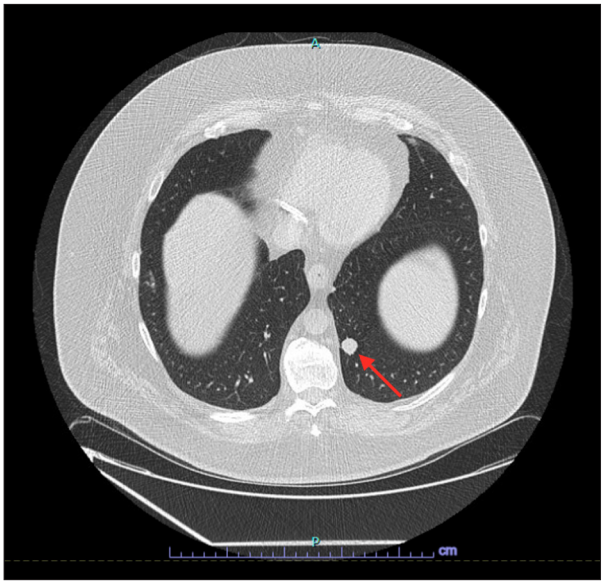


**Figure 1.** Low-dose computed tomography scan demonstrating a 1.6-cm left lower lobe pulmonary nodule (arrow).

muscle actin, and desmin were negative, thereby excluding Langerhans cell histiocytosis, smooth muscle neoplasms, and fibroblastic/myofibroblastic tumors such as inflammatory myofibroblastic tumor (IMT). Tumor cells also showed CD30, CD20, CD43, CD3, CD5, and CD7 negativity according to immunohistochemistry. Additionally, flow cytometry performed on a peripheral blood sample showed no evidence of hematolymphoid neoplasia, making anaplastic large cell lymphoma (ALCL) and ALK-positive diffuse large B-cell lymphoma (DLBCL) unlikely. Based on the combined morphologic and immunohistochemical profile, a diagnosis of single-system ALK-positive histiocytosis with TFG-ALK rearrangement was established.

The patient was referred to malignant hematology for further evaluation. He did not receive systemic therapy and remains under surveillance with non-contrast chest CT scans every 6 months for the first 2 years, followed by annual scans for a minimum of 5 years.

## Discussion

ALK-positive histiocytosis is a rare histiocytic neoplasm. The disease was first reported in 2008 in 3 infants with multisystem disease involving the liver and hematopoietic system [2]. ALK-positive histiocytosis can be categorized into 3 clinical groups: infants with multisystem disease involving the liver and hematopoietic system (group 1A), noninfants with multisystem disease (group 1B), and patients with single-system disease (group 2) [2].

The diagnostic criteria for ALK-positive histiocytosis applied in previously published case reports include: 1) cytoplasmic

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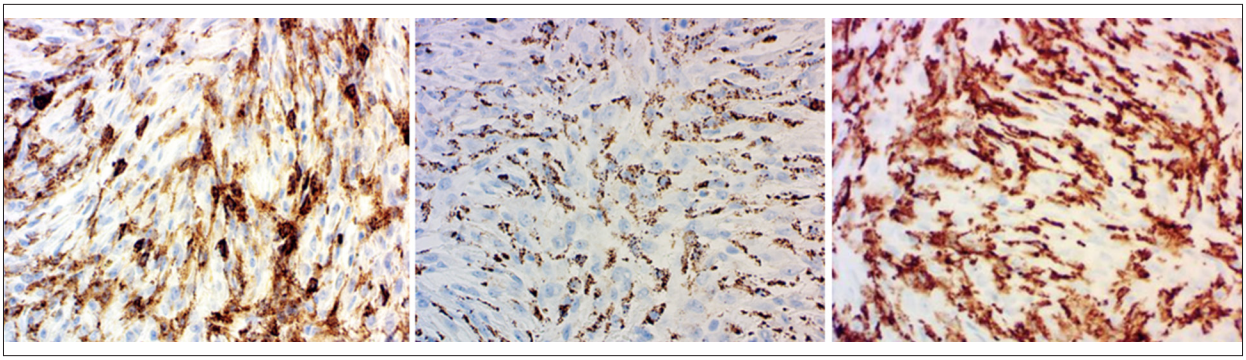

**Figure 2.** Immunohistochemical staining at 400× magnification showing positive expression of CD4, CD68, and CD163 from left to right, confirming histiocytic differentiation.

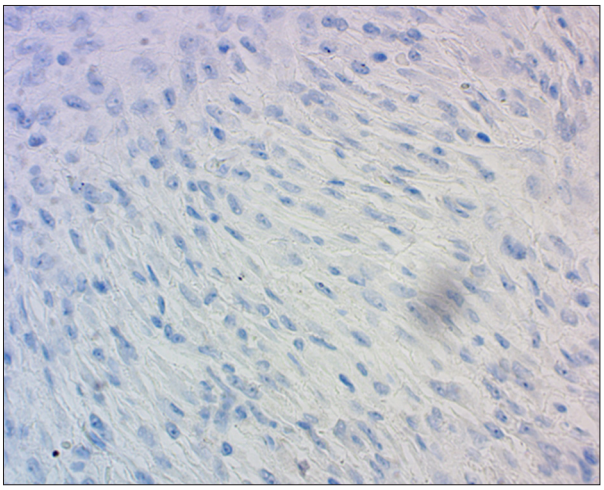

**Figure 3.** Immunohistochemical staining at 400× magnification showing absence of CD1a immunoreactivity, an important marker of Langerhans cell differentiation.

or membranous ALK immunoreactivity and/or molecular confirmation of ALK rearrangement, and 2) confirmation of histiocytic differentiation through lesional cell expression of at least 2 histiocytic markers (CD163, CD68, CD14, or CD4) [2]. These criteria were met in the present case.

Given the rarity of this entity, exclusion of other ALK-rearranged neoplasms (eg, IMT, ALCL, and ALK-positive DLBCL) is essential when establishing the diagnosis. A summary of the key differential diagnoses and distinguishing features is provided in **Table 1**. Smooth muscle actin and desmin are present in a substantial proportion of IMTs; however, both markers were absent in the present case. Additionally, S100 immunoreactivity, which showed patchy positivity in this case (**Figure 4**), has rarely been reported in IMT [3]. Negative expression results concerning T-cell and B-cell markers, as well as CD30, strongly argue against ALCL and DLBCL.

TFG-ALK fusion has been identified in only 2 previously reported cases. The first involved a man in his 20s with multisystem disease affecting the liver, skin, and colorectum; he was treated with corticosteroids and achieved a partial response but subsequently relapsed and died of sepsis [2]. The second case involved a man in his 30s with involvement of the lumbar spine, pelvic bones, proximal femurs, and peritoneum [4]. This patient initially received pegylated interferon-α (PEG-IFN-α) for 2 months with limited response, followed by alectinib therapy with a favorable response, as demonstrated by a reduction in the number of hypermetabolic osteolytic lesions on positron emission tomography imaging. At the time of publication, the patient remained on alectinib therapy [4].

In contrast to these reports, our patient exhibited isolated single-site disease confined to the lung, representing the first documented case of localized ALK-positive histiocytosis harboring a TFG-ALK fusion. Our report is also the first to describe disease resolution after surgical resection. These findings suggest that TFG-ALK rearrangements are associated with a broader clinical spectrum than previously recognized, ranging from disseminated multisystem disease to localized lesions amenable to surgical cure. At present, it remains unclear whether specific ALK fusion partners influence disease distribution, clinical behavior, or prognosis in ALK-positive histiocytosis. Larger case series with molecular characterization will be necessary to determine whether genotype-phenotype correlations exist.

Pulmonary involvement in ALK-positive histiocytosis is rare but recognized. It more commonly presents as multiple pulmonary nodules rather than a solitary lesion. KIF5B-ALK remains the most common fusion identified in both single- and multiple-nodule presentations.

For patients with localized single-system disease, complete surgical resection is often curative [2]. Our patient has remained disease-free since wedge resection. In cases in which resection is not feasible, treatment with ALK inhibitors has shown efficacy. Management of multisystem disease may include surgery, corticosteroids, chemotherapy, intravenous immunoglobulin, and ALK-targeted therapy [2,5].

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**Table 1.** Summary comparison of ALK-positive histiocytosis and key differential diagnoses.

| Disease | Clinical features | Distinguishing histologic features | Immunohistochemistry | Molecular findings |
|---|---|---|---|---|
| **ALK-positive histiocytosis** | Affects adults and children. May present as multisystem or single-system disease. Commonly involves hematopoietic system, liver, nervous system, lungs, skin, and bone | Dense proliferation of plump to large histiocytes in a fascicular growth pattern. Fewer Touton giant cells and foamy histiocytes than in the conditions below [2] | CD4+, CD14+, CD68 +, CD163+, CD1a-, langerin- | ALK gene fusions, most commonly KIF5B-ALK. Other rearrangements include CLTC-ALK, TPM3-ALK, TFG-ALK, EML4-ALK, DCTN1-ALK, and ALK-FISH+ |
| **LCH** | More common in children. Presents with bone lesions, skin rash, pulmonary nodules, and involvement of the bone marrow, liver, spleen, and CNS | Langerhans cells with prominent nuclear grooves/folds in an eosinophil-rich background [6]. Epidermotropism may be present [7] | CD1a+, CD68+, CD207+ (langerin), S100+, CD163- | BRAF V600E mutation is present in more than 50% of cases |
| **RDD** | Typically affects children and young adults. Characterized by massive, painless bilateral cervical lymphadenopathy, lytic bone lesions, and rash [8] | Hypochromatic histiocytes with small nucleoli and abundant pale cytoplasm that may contain engulfed inflammatory cells. Prominent lymphoplasmacytic infiltrate [9] | S100+, CD68+, CD163+, CD1a- | ARAF, MAP2K1, NRAS, and KRAS mutations |
| **Erdheim-Chester disease** | More common in adults. Associated with central diabetes insipidus, restrictive pericarditis, and near-universal sclerotic bone lesions | Abundant foamy histiocytes with more condensed chromatin than lesional cells in LCH and RDD [10]. Frequent Touton giant cells and fibrosis [11] | CD68+, CD163+, facto XIIIa+, fascia+, CD1a-, CD207- [12] | BRAF-V600E or MAPK pathway mutations |
| **Juvenile xanthogranuloma** | Typically occurs in infancy or early childhood. Presents as solitary, well-circumscribed, firm papules or nodules with a yellow-to-orange hue on the head, neck, or upper torso [13]. Systemic involvement is rare [11] | Foamy histiocytes are smaller and form a denser infiltrate, typically within the dermis. Scattered Touton giant cells are present [11] | CD68+, factor XIIIa+, vimentin+, CD4+ [13] | Usually no gene fusion identified |
| **Inflammatory myofibroblastic tumor** | Affects children and young adults. Soft tissue tumor commonly involving the abdominal cavity, retroperitoneum, or lung | Variably cellular lesion composed of spindled myofibroblasts with a prominent mixed inflammatory infiltrate. Myxoid stroma may be present [14,15] | ALK+, SMA+, desmin+, MSA+ | ALK rearrangements |

Abbreviations: ALK, anaplastic lymphoma kinase; ALK-FISH+, ALK fluorescence in situ hybridization positivity; CNS, central nervous system; LCH, Langerhans cell histiocytosis; MAPK, mitogen-activated protein kinase; MSA, muscle-specific actin; RDD, Rosai-Dorfman disease; SMA, smooth muscle actin.

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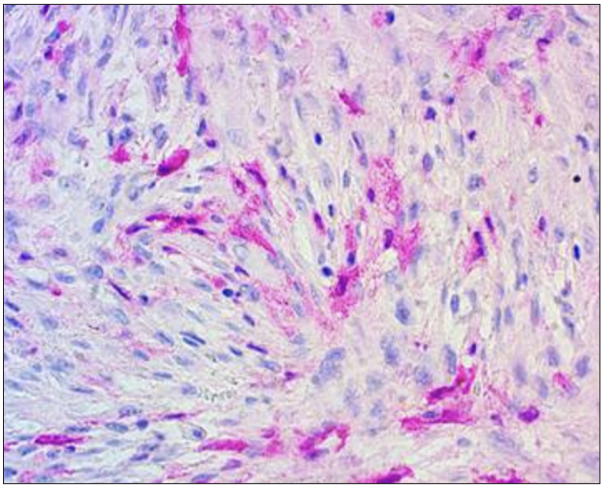

**Figure 4.** Immunohistochemical staining at 400× magnification demonstrating patchy cytoplasmic and nuclear S100 protein expression.

## Conclusions

Although understanding of ALK-positive histiocytosis continues to evolve, its clinicopathologic and molecular spectrum remains incompletely characterized. Recognition of localized forms is crucial to avoid unnecessary systemic therapy. This case underscores that ALK-positive histiocytosis can manifest as single-site disease, even with rare fusion partners such as TFG-ALK, and may follow an indolent clinical course.

### Department and Institution Where Work Was Done

Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, University of Tennessee Medical Center, Knoxville, TN, USA.

### Patient Consent

Consent was obtained from the patient for publication of this case report.

### Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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