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Case Report

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Sarcoidosis, Langerhans Cell histiocytosis, Atrial Septal Defect, and Pectus Excavatum: A Complex Case of Multisystem Disease

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Abstract

We present a rare case of a 28-year-old female with a constellation of multisystem diseases, including sarcoidosis, Langerhans cell histiocytosis, atrial septal defect, and pectus excavatum. The patient presented with dry cough and fatigue of one month. Personal history revealed previous atrial septal defect and pectus excavatum. Laboratory investigations were within normal limits. Dry cough and fatigue that started about a month ago, a negative tuberculin test, and the presence of multiple mediastinal adenopathies on thorax CT revealed a possible diagnosis of sarcoidosis while BAL and TBB results were compatible sarcoidosis and Langerhans cell histiocytosis. This case report outlines the clinical presentation, pathologic mechanisms, diagnostic workup, and therapeutic interventions in a patient with overlapping sarcoidosis, Langerhans cell histiocytosis, and atrial septal defect. We discuss the possible etiological connections and pathophysiological mechanisms involved as well as the implications for clinical management.

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Introduction

Sarcoidosis and Langerhans cell histiocytosis are granulomatous diseases that primarily affect the lungs but also can involve multiple organs displaying a systemic nature. Although sarcoidosis is characterized by non-caseating granulomas, Langerhans cell histiocytosis involves clonal proliferation of Langerhans cells with associated granulomatous inflammation. These diseases are seldom seen together but their coexistence with congenital anomalies like atrial septal defect and pectus excavatum is exceptionally rare. This case aims to explore the potential association between these conditions, to elucidate the common denominator mechanism underlying both diseases, and to highlight the complexities in diagnosis.

Case Presentation

A 28-year-old female was referred to the pulmonary clinic for evaluation of persistent dry cough and fatigue of one month. The patient also reported occasional chest pain and palpitations. The patient had a 24 packages-year smoking history. Personal history revealed frequent respiratory infections during childhood, a diagnosis of atrial septal defect and pectus excavatum. On physical examination, the patient had a visibly sunken chest wall consistent with pectus excavatum and auscultation revealed a fixed splitting of the second heart sound, suggestive of an underlying ASD. Pulmonary examination was significant for bilateral crackles. No skin lesions, lymphadenopathy, or hepatosplenomegaly were noted.

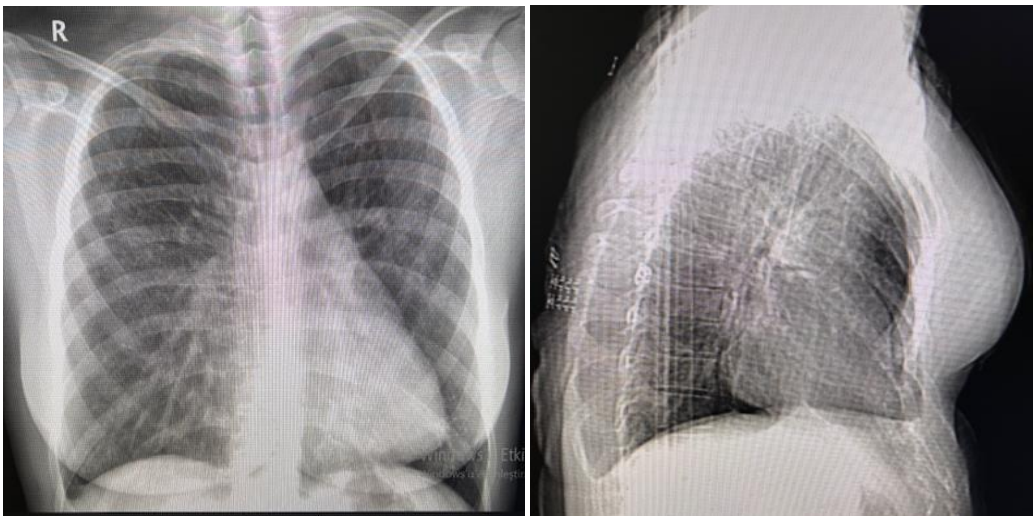

Figure 1: PA and left lateral chest x-ray showing pectus excavatum and scolisosis.

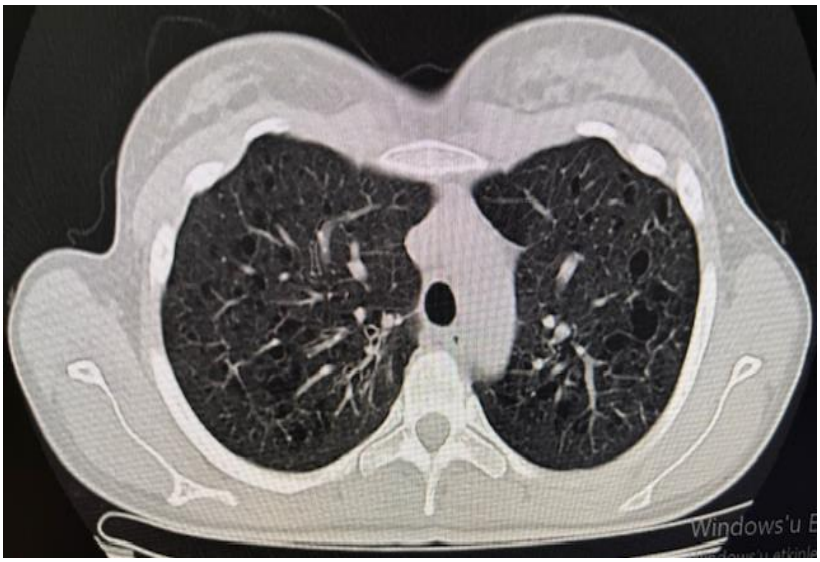

Figure 2: Thorax CT revealing bizarre cysts in the upper lung zones and pectus excavatum.

CBC and serum biochemistry were within normal limits. Serum ACE was 92 IU/L. PA and lateral chest x-ray showed mild scoliosis and pectus excavatum. Tuberculine test was negative. ECG showed incomplete right bundle branch block, consistent with atrial septal defect. Pulmonary function tests revealed a moderate restrictive pattern and a mild reduction in DLCO/VA. Echocardiogram confirmed a secundum-type atrial septal defect with a mild left-to-right shunt. High-resolution computed tomography of the lung revealed a combination of multiple cysts predominantly in the upper lobes with relative sparing of the lung bases suggesting Langerhans cell histiocytosis and enlarged mediastinal lymph nodes. Bronchoalveolar lavage revealed lymphocytosis with an increased CD_4/CD_8 ratio of 4.2 consistent with sarcoidosis. Immunohistochemistry staining of transbronchial biopsy samples showed CD_{1a}-positive Langerhans cells, confirming Langerhans cell histiocytosis and non-caseating granulomatous inflammation compatible with sarcoidosis. The patient was diagnosed with stage 0 sarcoidosis and Langerhans cell histiocytosis with previous coexistence of atrial septal defect and pectus excavatum. Treatment was initiated with 32 mg daily oral prednisolone to address the pulmonary involvement from both sarcoidosis and Langerhans cell histiocytosis. The patient was referred to cardiology for consideration of surgical or percutaneous closure.

Discussion

The coexistence of sarcoidosis, Langerhans cell histiocytosis, atrial septal defect, and pectus excavatum in a single patient is exceedingly rare and its recognition poses a diagnostic and therapeutic challenge. Sarcoidosis and Langerhans cell histiocytosis are distinct granulomatous disorders with overlapping pulmonary manifestations but differing pathophysiology. Both are systemic diseases that primarily affect the lungs that share distinct pathophysiological features. Additional presence of atrial septal defect and pectus excavatum in this patient raises questions about potential genetic or environmental factors that may link these conditions. Pectus excavatum is a congenital deformity that can be associated with underlying cardiopulmonary abnormalities, such as atrial septal defect. In this case, the presence of both atrial septal defect and pectus excavatum may have exacerbated respiratory symptoms. A dry cough and fatigue negative tuberculin test and multiple mediastinal lymphadenopathies made the diagnosis of sarcoidosis highly probable. Smoking history with compatible thorax CT findings have raised a possible suspicion for coexistence Langerhans cell histiocytosis as well. Pathological examination of the samples obtained by bronchoscopic examination confirmed the simultaneous presence of both disorders. The interaction between structural cardiac and pectus excavatum defects and associated lung disease due to sarcoidosis and Langerhans cell histiocytosis adds complexity that serves as a diagnostic challenge.

Coexistent sarcoidosis and Langerhans cell histiocytosis are extremely rare but may occur simultaneously. Both are systemic diseases that primarily affect the lungs that share distinct pathologic features. The underlying mechanisms along with possible common pathways include multiple factors. Immune dysregulation characterized by exaggerated T-helper Th_1 immune responses, granuloma formation involving activated macrophages, CD4+ T-cells, and pro-inflammatory cytokines (e.g., TNF-α, IL-2, IFN-γ) with potential links to infections (e.g., Mycobacterium tuberculosis antigens) or occupational exposures are the underlying pathogenetic mechanisms in sarcoidosis (1-4). Pathogenetic pathways in Langerhans cell histiocytosis include clonal proliferation of Langerhans cells, increased secretion of cytokines like IL-17 and IL-1β that contribute to inflammation and tissue damage, mutations in MAPK pathway associated with BRAF V600E mutations leading to abnormal cell survival and proliferation (5,6,7).

Primary mutual pathways for both disorders involve chronic inflammation and cytokine-driven inflammation. TNF-α is pivotal in both sarcoidosis granuloma stability and LCH-associated tissue injury. Environmentaql factors such as tobacco smoke, organic/inorganic particles, or infectious agents can be shared as triggers for both conditions. Smoking is a known risk factor for pulmonary Langerhans cell histiocytosis. Chronic inflammation can result in fibrotic remodeling of lung parenchyma. Sarcoidosis typically involves upper lobe scarring, while LCH shows mid-to-upper lobe cystic and nodular changes. Shared cytokine networks of IL-6, IL-12, and TNF-α

play roles in sustaining inflammation in both conditions. Overlap in these cytokines may explain coexistence of these disorders. Dysregulated dendritic cell function is central in langerhancs cell histiocytosis, while defective antigen presentation may contribute to sarcoidosis. These processes may interact in overlapping disease states. Epigenetic dysregulation (e.g., histone modifications or DNA methylation changes) affecting immune and inflammatory pathways might be a shared pathogenetic mechanism (1-4,5-10).

The coexistence of sarcoidosis, Langerhans cell histiocytosis, atrial septal defect (11,12), and pectus excavatum (13,14) in a single patient is exceedingly rare, and its recognition poses a diagnostic and a therapeutic challenge. Another landmark of this case is that it is the first case reported in the literature so far. Discussion of the pathogenetic mechanisms along with the diagnostic approaches of four different diseases with similar will also provide an important guide for approaching similar patients.

Conclusions

This case illustrates the challenges of multisystem disease in a patient with sarcoidosis, Langerhans cell histiocytosis, atrial septal defect, and pectus excavatum. Along with similar pathogenetic mechanisms, the presence of identical or overlapping symptoms and imaging manifestations pose a great difficulty for identification of primary disorders along with a differential diagnosis. Our case is an extremely rare and displays an almost impossible clinical profile where four completely different disorders that can cause similar symptoms and imaging findings in the same patient that will probably be the unique patient in the literature.

Author contributions

Cuneyt Tetikkurt contemplated and wrote the case report.
Muammer Bilir prepared the laboratory findings of the patient.
Seza Tetikkurt wrote the pathologic mechanisms of the case.

Conflicts of interest

All authors declare that they do not have any conflicts of interest associated with this case report. Authors confirm that there does not exist any supporting or funding agencies for this case

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