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Refractory sarcoidosis presenting as chylothorax: a case report

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Abstract

Sarcoidosis is a systemic granulomatous autoinflammatory disease that primarily affects lymphoid organs, the skin, and the lungs. While recurrent pleural effusion is documented in sarcoidosis, chylothorax is exceedingly rare.

We present a male patient in his seventies who presented to the emergency department with long-standing fatigue, a ten-kilogram weight loss over six months, new-onset snoring, and nasal congestion. Evaluations, including respiratory function tests and chest computed tomography, revealed findings consistent with sarcoidosis, such as hilar lymphadenopathy, reduced carbon monoxide diffusion, and elevated serum angiotensin-converting enzyme levels, along with pleural effusion. Analysis of the pleural fluid showed it to be exudative, with high triglycerides level. We concluded that chylothorax resulted from extensive lymph node involvement.

During two years of follow-up, combinations of methylprednisolone and other immunosuppressants were ineffective, leading to disease progression. Infliximab was then initiated, resulting in a dramatic clinical response and improvement in Positron Emission Tomography/Computerized Tomography (PET/CT) imaging.

Key words: chylothorax, sarcoidosis, PET/CT, anti-TNF.

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Introduction

Sarcoidosis is a systemic granulomatous autoinflammatory disease of unknown etiology, characterized by a diverse range of clinical manifestations, primarily affecting the lungs and lymph nodes.[1] Pleural effusion may occur in approximately 1% of cases during the course of sarcoidosis.[2] Chylothorax is much rarer in the context of sarcoidosis, with documented cases reported primarily as case reports in the literature.[3] While some patients experience spontaneous remission, lung fibrosis resulting from active disease is irreversible; thus, treatment should be administered to those with active disease. Glucocorticosteroids represent the first-line treatment, achieving complete remission in most patients. Methotrexate serves as another first-line therapeutic alternative. For patients who do not respond to or cannot tolerate glucocorticosteroid therapy, second-line treatments such as leflunomide, azathioprine, mycophenolate mofetil, and hydroxychloroquine are considered.[4]

Refractory sarcoidosis is not well-defined within the medical literature. Tumor necrosis factor-alpha inhibitors (e.g., infliximab, adalimumab) are third-line treatments whose efficacy has been established through randomized controlled studies.[5] Additionally, Fluorodeoxyglucose-Positron Emission Tomography /Computerized Tomography (FDG-PET/CT) is highly useful in the diagnosis and monitoring of sarcoidosis, with its utilization increasing in recent years.[6] In this report, we aim to highlight a rare case of refractory sarcoidosis presenting with chylothorax, which responded favorably to third-line treatment with infliximab.

Case Report

A male patient in his seventies presented with long-standing fatigue, involuntary weight loss, new-onset snoring, and nasal congestion. He did not report shortness of breath, dry cough, fever, or night sweats. A neck ultrasonography, performed a few months prior due to vertigo and presyncope, revealed conglomerate bilateral cervical lymphadenomegaly and atherosclerotic plaque in the right carotid artery, for which a stent was placed.

The patient had no known diseases or allergies other than newly diagnosed peripheral artery disease. A former smoker with a 50-pack-year history, he did not consume alcohol, and there was no significant family history of connective tissue disease, sarcoidosis, or malignancy.

On physical examination, enlarged, painless, mobile lymph nodes were noted in the cervical, axillary, and inguinal regions. No significant findings were observed in other system examinations, including the respiratory system. Initial laboratory tests indicated normocytic anemia, elevated acute phase reactants, and erythrocyte sedimentation rate. Complete urine analysis and liver and kidney function tests were within normal limits.

With a preliminary diagnosis of lymphoproliferative disease, the patient underwent Contrast-Enhanced Computerized Tomography (CECT) of the neck, thorax, and abdomen, revealing widespread lymphadenopathy (cervical, axillary, mediastinal, intra-abdominal, pelvic) measuring 2-3 cm, hepatosplenomegaly,

minimal pleural effusion, a nasal polypoid lesion, and micronodular densities in the lower lung parenchyma. Pathology results from an excisional biopsy of the right cervical lymph nodes and the nasal polyp reported non-necrotizing granulomatous inflammation.

Considering these findings, differential diagnoses included granulomatous polyangiitis, sarcoidosis, or tuberculosis. Additional tests, including FDG-PET/CT, Antinuclear Antibodies (ANA), serum Angiotensin-Converting Enzyme (ACE) level, Perinuclear Antineutrophil Cytoplasmic Antibodies (p-ANCA), Cytoplasmic Antineutrophil Cytoplasmic Antibodies (c-ANCA), Interferon-γ Release Assay (IGRA) for tuberculosis, Pulmonary Function Tests (PFT), and diffusing capacity of the lungs for carbon monoxide (DLCO), were ordered. The PET/CT scan indicated the involvement of all lymphatic stations, with Maximum Standardized Uptake Value (SUV max) ranging from 2 to 6, and more significantly in the mediastinal lymph nodes (SUV max: 6) (Figure 1). All laboratory tests were negative except for serum ACE level being 2-3 times the upper limit. PFT revealed decreased diffusion capacity (DLCO: 61%) and a mild obstructive pattern.

Based on these findings, sarcoidosis was suspected, and the patient, with mild pulmonary involvement at that time, was monitored. Three months later, the patient reported exertional dyspnea and dry cough. Physical examination revealed rales and decreased breath sounds in the lung bases. Thoracic CT demonstrated micronodules clustering in the peribronchovascular area, ground-glass opacities in the lower lobes, and bilateral pleural effusion measuring 4 cm at its deepest point. The pleural fluid sample was exudative, with high triglyceride levels, suggesting chylothorax likely due to extensive lymph node involvement. Methylprednisolone treatment was initiated.

After three months, due to inadequate response to methylprednisolone and ongoing exertional dyspnea, Methotrexate (MTX) was added. However, the patient's condition did not improve, and subsequent evaluations revealed DLCO at 52%. An incisional biopsy from the hilar lymph node confirmed non-necrotizing granulomatous inflammation, leading to the diagnosis of refractory sarcoidosis. Methotrexate was discontinued, and treatment was adjusted to methylprednisolone and Azathioprine (AZA), resulting in decreased complaints and improved exercise capacity. The patient maintained remission for approximately one year, and serum ACE levels remained between two and three times the upper limit. As his symptoms worsened and moderate thrombocytopenia developed, azathioprine was discontinued, and Mycophenolate Mofetil (MMF) was initiated; however, this was also stopped due to diarrhea and worsening thrombocytopenia. A bone marrow biopsy revealed non-necrotizing granuloma consistent with sarcoidosis. During this time, the patient was hospitalized three times for massive chylothorax. Following the ineffectiveness of second-line treatments, infliximab was started as a third-line therapy. By the fourth month of infliximab treatment, the patient exhibited significant improvement, and FDG-PET/CT showed complete regression of previously increased FDG uptake in lymph nodes and the spleen (Figure 1). Unfortunately, the patient subsequently developed COVID-19 pneumonia, presenting with fever, cough, and acute shortness of breath, necessitating hospitalization. His condition deteriorated into sepsis during follow-up, leading to intensive care admission. The patient passed away due to sepsis approximately five months after the initiation of infliximab treatment.

Discussion

Chylothorax is defined as a chylous pleural effusion characterized by the presence of triglycerides greater than 110 mg/dL or chylomicrons in the pleural fluid. A milky appearance is observed in 22-44% of patients with chylothorax.[6] In our case, the triglyceride level in the pleural fluid sample was measured at 224 mg/dL; however, a milky appearance was absent. Possible mechanisms leading to chylothorax in sarcoidosis include compression of the

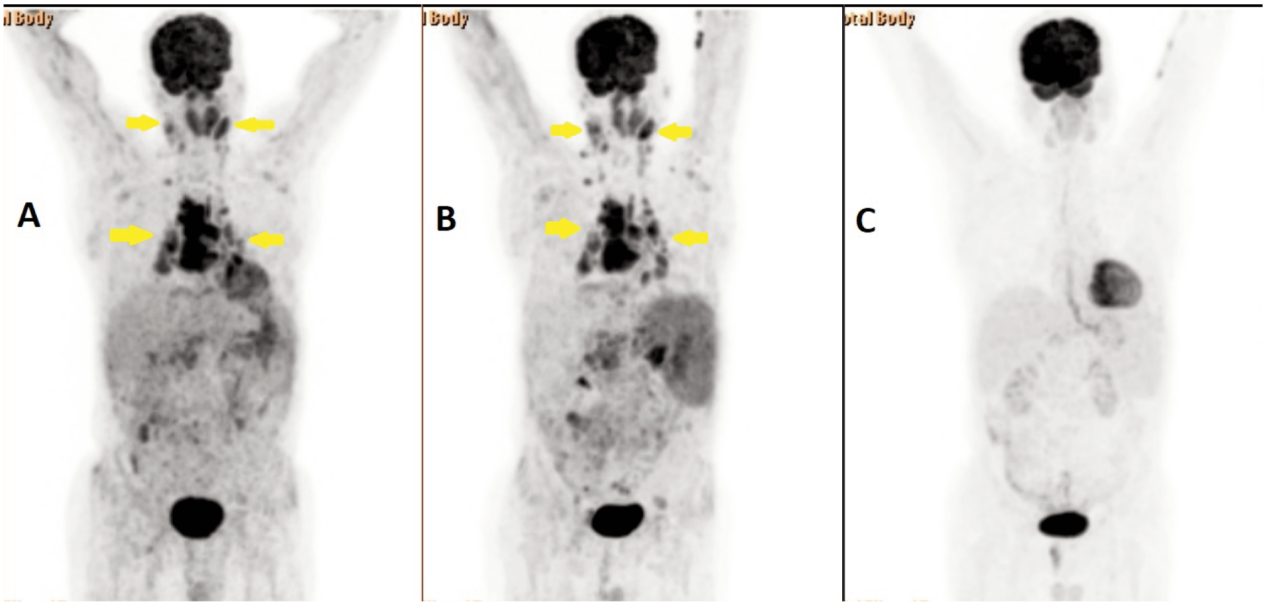

Figure 1. Positron Emission Tomography/Computerized Tomography (PET/CT) scans at baseline (**A**, extensive thoracic and cervical lymph node involvement of sarcoidosis), 6 months (**B**, no response), and 18 months (**C**, no lymph node involvement/complete radiological response); the yellow arrows indicate thoracic lymph node involvements.

thoracic duct, granulomatous pleural inflammation, lymphangiectasia, or thoracic lymphadenopathy.[3] In our patient, the first detected finding consistent with sarcoidosis was lymphadenopathy, with severe lymphatic involvement evident in both initial and subsequent PET/CT scans. We attributed the chylothorax to this severe thoracic lymphadenopathy. Bikash Bhattarai *et al.*[7] reported a case of a female patient in her fifties who developed chylothorax secondary to sarcoidosis, emphasizing that the prognosis for patients with chylothorax is worse than for those without. The prognosis in our case deteriorated rapidly. At the time of sarcoidosis diagnosis, the patient's symptoms were mild; however, three months later, he presented with severe exertional dyspnea, cough, and fatigue. The patient did not respond to methylprednisolone alone or to other immunosuppressive agents until infliximab treatment was initiated, showing improvement only with the combination of azathioprine and methylprednisolone. Additionally, he required hospitalization three times due to massive chylothorax. Aysel Sünnetçioğlu *et al.*[8] reported a case of chylothorax due to sarcoidosis without significant pleural effusion, identifying pleural involvement using FDG-PET/CT. The application of PET scanning in the diagnosis and follow-up of connective tissue disorders has increased in recent years.[9] In our case, PET/CT scans were instrumental in guiding clinical decision-making and monitoring treatment. Biopsies were performed on the cervical lymph node, nasal polypoid lesion, mediastinal lymph node, and bone marrow, with pathological examinations confirming sarcoidosis in each specimen. Although the patient's sarcoidosis was advanced, he exhibited significant clinical and imaging responses to infliximab treatment over approximately three months. Unfortunately, we could not assess the long-term outcomes of infliximab therapy, as the patient ultimately succumbed to sepsis.

Conclusions

The clinical course of sarcoidosis is highly variable; it can progress rapidly and severely, as observed in our case. Chylothorax is a rare complication of sarcoidosis, more likely to occur in patients with significant thoracic lymph node involvement. While this represents a single case, it suggests that anti-Tumor Necrosis Factor (TNF) agents, such as infliximab, may be effective in treating refractory sarcoidosis.

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