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# Does miliary sarcoidosis really exist? A case report and review of the literature

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**Abstract. – BACKGROUND: Miliary sarcoidosis is a rare form of sarcoidosis characterized by numerous miliary-like micronodules dispersed throughout the lungs. It has been documented in less than 1% of all sarcoidosis cases. We first described a rare case of miliary sarcoidosis and then conducted a literature review on the subject.**

**CASE PRESENTATION: A 51-year-old male complained about a progressive loss of appetite, significant weight loss, occasional night sweats, and fatigue. After a thorough clinical exploration, a differential diagnosis of miliary lung disease was suspected – miliary tuberculosis, fungal infection, metastatic pulmonary carcinoma, or sarcoidosis. High-resolution chest computed tomography revealed bilateral diffuse micronodules with mediastinal lymphadenopathy. Histopathological analysis of transbronchial bioptic tissue identified non-caseating epithelioid granulomas, while no malignant cells were found. Lung tuberculosis and fungal infections were excluded. The levels of angiotensin-converting enzyme in the blood, as well as serum's and 24-hour urine calcium levels, were elevated. After a multidisciplinary discussion, the diagnosis of miliary pulmonary sarcoidosis was established. The patient was treated with prednisone for a total of 9 months, with full clinical and radiological recovery. Using PubMed, we also conducted a review of the literature on this topic and discovered only a few case reports of patients with miliary sarcoidosis, with just one systematic review accessible. The key findings of studies investigating patients diagnosed with miliary sarcoidosis are tabularly displayed.**

**CONCLUSIONS: Miliary sarcoidosis is an uncommon type of pulmonary sarcoidosis that can mimic several entities that manifest as miliary nodules. Most patients require treatment since it can have a significant impact on lung function.**

*Key Words:*
Miliary sarcoidosis, Diagnosis, Treatment.

## Introduction

Sarcoidosis is a multisystem disorder with an unknown etiology that is characterized by noncaseating granulomas that can affect any organ or tissue and can also involve multiple organs simultaneously. It most frequently affects the lungs and lymph nodes[1]. Miliary sarcoidosis is a rare presentation of sarcoidosis with numerous miliary-like nodules dispersed throughout the lungs. It has been documented in less than 1% of all sarcoidosis cases on chest radiography[2].

Considering this, the purpose of this paper was to describe such a rare case of miliary sarcoidosis. We then conducted a review of the literature on the subject.

## Case Report

A 51-year-old Caucasian male with no prior comorbidities presented with a progressively loss of appetite, significant weight loss, occasional night sweats, and fatigue lasting for two months. The physical examination was unremarkable. A chest X-ray revealed diffuse micronodular opacities throughout the lungs. A high-resolution chest computed tomography (HRCT) showed bilateral dispersed micronodules and mediastinal lymphadenopathy (Figure 1a) with splenomegaly as a secondary finding. The values of serum angiotensin-converting enzyme (ACE), as well as serum



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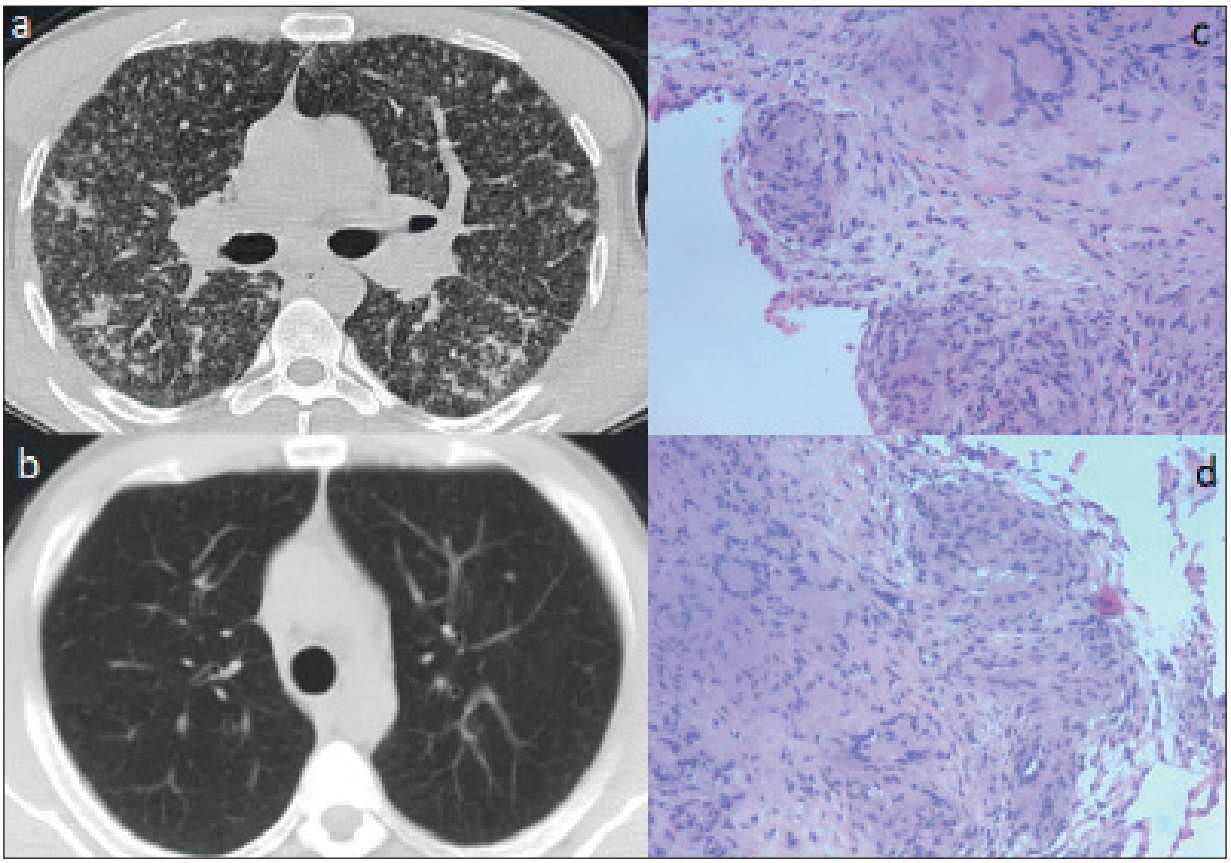


**Figure 1.** High-resolution CT scan shows: (**a**) numerous, bilateral, diffuse micronodules with peribronchial distribution (with fewer confluence in hyperdense masses) and typical "galaxy sign" within the nodular pattern, as well as bilateral mediastinal lymphadenopathy at admission; (**b**) normal CT findings after six months of therapy. Microscopic examination of standard bronchoscopic biopsies: endobronchial (**c**) and transbronchial bioptic material (**d**) showed numerous Langhans giant cells and epithelioid granuloma without necrosis, H&E x 200.

calcium, and 24-hour urine calcium levels were all increased (151 U/L, normal range (NR) 16-85 U/L; 3.2 U/L, NR 2.3-3.0 U/L; 95 U/L, NR 16-85 U/L, respectively). There was no evidence of renal or hepatic impairment or electrolyte imbalance. The QuantiFERON-TB Gold In-Tube assay was negative. Three sputum specimens sent for microscopic detection of acid-fast bacilli for Mycobacterium tuberculosis were negative, while culture later grew negative. Lung function tests revealed a restrictive pattern with a forced vital capacity (FVC) of 68.9% of projected value, a forced expiratory volume in 1 second ($FEV_1$) of 63.0%, $FEV_1$/FVC of 76.9%, and a decreased diffusing capacity of the lung for carbon monoxide (DLCO) of 60.05%. Endoscopic findings during bronchoscopy were unremarkable. Histopathological examination of endobronchial (Figure 1c) and transbronchial lung bioptic samples (Figure 1d) revealed non-caseating epithelioid granulomas, while no neoplastic tissue was found. Real-time reverse-transcriptase polymerase chain reaction (RT-PCR) for typical, atypical or fungal pathogens was not available in our center at the time of making the diagnosis, but special stains for mycobacteria and fungi from bronchoalveolar lavage (BAL) were negative.

A differential diagnosis of miliary tuberculosis, fungal infections, metastatic pulmonary carcinoma, and sarcoidosis was considered. After multidisciplinary discussion, the patient was diagnosed with pulmonary sarcoidosis, and prednisone 40 mg per day (0.5 mg/kg) was initiated with a slow dose taper.

The patient was no longer fatigued and had gained weight after six months of therapy. Serum and urine calcium levels returned to normal, while the chest X-ray, spirometry parameters and DLCO all improved significantly. Repeated HRCT scan revealed normal findings in pulmonary parenchyma

(Figure 1b) and spleen diameter reduction. Three months later, the treatment was discontinued.

After two years of follow-up, a recurrence of the disease occurred in the form of non-miliary sarcoidosis of the lungs and skin, which was confirmed by a skin biopsy. The corticosteroid therapy was re-administered (prednisone 40 mg, gradually tapered to a maintenance dose of 10 mg). Therapy was stopped after 12 months of treatment. For the following five years, the patient has been without any symptoms. He is still under the medical supervision.

## Discussion

Sarcoidosis is diagnosed based on clinical and radiological findings as well as histological evidence of the noncaseous epithelioid cell granulomas. Clinical presentations of lung sarcoidosis are usually nonspecific, with dry cough, dyspnea, and chest pain that can be accompanied by constitutional symptoms[3]. Observation of typical imaging features (bilateral hilar lymphadenopathy, perilymphatic nodules, interlobular septal thickening, and bilateral perihilar opacities) and the presence of noncaseating granulomas in lung biopsy specimen strongly suggest the diagnosis of pulmonary sarcoidosis in the appropriate clinical context[4]. The diagnostic yield is higher when endobronchial and transbronchial biopsies and endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) are combined[5]. Laboratory findings, such as hypercalcemia, hypercalciuria, and elevated ACE levels, may be helpful in making a diagnosis, administering therapy, and following the disease's course[3].

Miliary sarcoidosis is an atypical and rare form of sarcoidosis that was reported in less than 1% of all sarcoidosis patients on chest radiography prior to the use of computed tomography (CT)[6]. The term "miliary" refers to scattered, small, well-defined, 1-3 mm in size nodules on HRCT, with no relation to the pleural surface, small vessels, and interlobular septa[4]. Micronodular lesions may merge into bigger lesions over time, forming macronodules. The main entities that manifest as pulmonary miliary nodules are tuberculosis, fungal infections, pneumoconiosis, and metastatic disease, but over 40 different diseases can be related to this pattern on chest radiography[7]. As a result, careful clinical evaluation is essential when analyzing the pulmonary miliary pattern. Sputum and BAL cytology can identify hematogenous metastases (thyroid, renal, breast), while specimen cultures can reveal tuberculosis or fungal infections (histoplasmosis, coccidioidomycosis). Pneumoconiosis has been associated to a history of beryllium and silica exposure[7]. HRCT can help to narrow the medical diagnosis of miliary lung diseases by dividing miliary patterns into three categories: centrilobular (associated with inflammatory, infectious, or vascular etiologies), perilymphatic (sarcoidosis and lymphangitic carcinomatosis), and random appearance (hematogenous metastases or infections)[8]. The distribution of the nodules associated radiologic findings, and clinical features all lead to an explicit etiologic diagnosis.

Only a few case reports[2,4,6,9,10] of patients with miliary sarcoidosis have been published so far, while only one systematic review[6] is available. In that review, patients with miliary sarcoidosis were mostly older, symptomatic, had a high comorbidity burden, and required treatment at the time of diagnosis. Most patients were given corticosteroids, with a 100% response rate and 14.4% of relapses. Table I summarizes the main findings of studies investigating patients diagnosed with miliary sarcoidosis.

Several aspects should be addressed when treating sarcoidosis, including clinical symptoms, organ involvement, and disease severity. Therapy is not always necessary. Systemic corticosteroids are the mainstay of therapy[5], with immunomodulatory and cytotoxic drugs used in patients who do not respond or cannot tolerate corticosteroids[11]. According to experts, a favorable response to treatment is mostly defined by symptomatic improvement, resolution of radiographic abnormalities, and physiological improvement[12].

## Conclusions

Miliary sarcoidosis is an uncommon manifestation of pulmonary sarcoidosis that can mimic several entities which manifest as pulmonary miliary nodules, such as tuberculosis, fungal infections, pneumoconiosis, and metastatic diseases. In order to establish the accurate diagnosis, it is necessary to use extensive diagnostic methods and include a multidisciplinary team. Miliary sarcoidosis can severely affect lung function; therefore, most patients require corticosteroid therapy, with an excellent response rate and a low risk of relapse.

### Conflict of Interest

The authors declare that they have no conflict of interests.

**Table I.** Findings from several studies that investigated miliary sarcoidosis.

| Study | Study design | No of participants | Gender | Age | Symptoms | Symptoms duration | Radiology findings | Histo-pathology | Treatment/ outcome | Other important findings |
|---|---|---|---|---|---|---|---|---|---|---|
| Rajagopala et al[6] | Systematic review (21 studies analyzed) | 27 | male - 59.2% female - 40.8% | 47.5 ± 13.2 years | Dyspnea and cough (45.4%); Fever (27.3%); Night sweats (11.1%); Weight loss (22.7%) | 8 weeks | Miliary pattern - 65.4%; Mediastinal adenopathy - 50% of all cases | Trans-bronchial biopsy - 85.7% cases | 95.2% treated with steroids, 100% response | Hypercalcemia - 27.3%; Acute kidney injury - 9.1%; Ocular involvement - 13.6%; Bone disease - 4.5%; Sicca syndrome - 4.5%; Pancreatic mass - 4.5% |
| Sugino et al[2] | Case report | 1 | female | 37 years | Dry cough, fatigue, weight loss | 6 months | Bilateral upper lobes miliary opacities | Video-assisted thoraco-scopic lung biopsy | steroids; improvement after 3 months | Elevated levels of ACE and soluble interleukin-2 receptor |
| Khanal et al[4] | Case report | 1 | male | 26 years | Dry cough, malaise, fatigue | 3 days | Scattered infiltrates consistent with a pseudo-miliary pattern | Trans-bronchial biopsy | Methotrexate and prednisone | Not applicable |
| Matsuura et al[9] | Case report | 1 | female | 80 years | Cough | 2 months | Bilateral diffuse micronodular shadows | Trans-bronchial biopsy and bronchial biopsy | No treatment; spontaneous remission after a year | Elevated levels of ACE were observed; Biopsy of pancreatic mass revealed also non-caseating granulomas |
| Joshi et al[10] | Case report | 1 | male | 40 years | Fever, cough, weight loss, nausea, vomiting | 3 months | Bilateral miliary opacities and bilateral lymphadeno-megaly | Skin and liver biopsy | Steroids; improvement after 6 months | Multi-system sarcoidosis (lung, skin, liver, spleen) |

### Informed Consent

An informed consent was obtained from the patient.

### Ethical Consideration

This paper was approved by the written decision of the Board for Medical Sciences of the Ethical Committee, College of Vocational Studies for the Education of Preschool Teachers and Sports Trainers in Subotica, Serbia.

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### Authors' Contributions

SKL conceived the review and acquired data; SKL, JJ, AM and DŽ participated in the process of writing and reviewing of the manuscript; AL and MP gave expert analysis in histopathological features of miliary sarcoidosis, while JĐ wrote expert analysis in radiological features. All authors contributed to the conception and revision of the manuscript and approved its submission.

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