Systematic Review

Primary cavitary sarcoidosis: A case report, systematic review, and proposal of new diagnostic criteria

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ABSTRACT

Primary cavitary sarcoidosis (PCS) is a rare form of pulmonary sarcoidosis. In this report, we present a case of a 47-year-old male patient with PCS who was initially treated as pulmonary tuberculosis. We also systematically review the literature on PCS and propose a new classification for this entity.

KEY WORDS: Cavity, computed tomography, interstitial lung disease, sarcoidosis, tuberculosis

INTRODUCTION

Pulmonary sarcoidosis most commonly presents with symmetric hilar and mediastinal adenopathy.[¹] Other radiologic manifestations include peribronchovascular nodules, nonresolving consolidation, and fibrocystic lesions.[²] Bullous lesions, cysts, cavities, and traction bronchiectasis are commonly encountered in chronic pulmonary sarcoidosis. However, cavititation as the presenting manifestation of pulmonary sarcoidosis, termed as primary cavitary sarcoidosis (PCS), is extremely rare.[³] Herein, we report a case of PCS and systematically review the literature for this rare form of pulmonary sarcoidosis.

CASE REPORT

A 47-year-old man presented with complaints of cough and progressive breathlessness of 2 months' duration. There was fever, malaise, anorexia, and weight loss. Auscultation revealed crackles in the right mammary region. Rest of the physical examination was unremarkable. Complete blood count, fasting plasma glucose, liver and renal function tests were all within normal limits. Chest radiograph showed bilateral hilar enlargement and nonhomogenous opacities in the mid and lower zones of both lungs along with cavititation in the right middle zone. Sputum examination for acid-fast bacilli performed on 3 consecutive days was negative. The patient received empiric antituberculosis treatment with isoniazid, rifampicin, ethambutol, and pyrazinamide for a period of 2 months, followed by isoniazid and rifampicin for 4 months. Despite good compliance with treatment, cough and dyspnea worsened over the course of treatment. Chest radiograph after 6 months of therapy showed bilateral hilar adenopathy, reticulonodular opacities in both upper zones, bilateral perihilar consolidation, and a cavity in the right middle lobe [Figure 1A]. The patient was referred to us with a suspicion of drug-resistant tuberculosis.

Computed tomography (CT) of the chest showed enlarged intrathoracic lymph nodes with bilateral perihilar consolidation and cavitition in both the lower lobes [Figure 1B]. There were extensive peribronchovascular nodules and subpleural nodules. Tuberculin skin test performed with 5 tuberculin units

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was negative and serum angiotensin-converting enzyme levels were 110 U/L (normal 8–65 U/L). Spirometry showed moderate restrictive defect (forced vital capacity [FVC], 50% predicted). Diffusion capacity for carbon monoxide was decreased (2.74 mmol/min/kPa; 32% predicted). Flexible bronchoscopy revealed widespread fine nodularity in the entire bronchial tree. Transbronchial lung biopsy and endobronchial biopsy showed compact noncaseating epitheloid granulomas; stain for acid-fast bacilli or fungi revealed no organisms. Bronchoalveolar lavage fluid was negative for fungus, *Mycobacterium tuberculosis* (culture and nucleic acid amplification assay) and malignant cells. A diagnosis of PCS was made.

The patient was treated with oral glucocorticoids for 9 months. There was improvement in dyspnea and exercise capacity. CT performed 1 year after stopping treatment showed clearing of perihilar consolidation and peribronchovascular nodules. Furthermore, there was resolution of the cavity on the left side; however, a thin-walled cavity persisted in the right lower lobe [Figure 1C]. There was improvement in lung function (FVC, 65% predicted) and diffusion capacity (68% predicted). The patient remains stable on follow-up without any relapse or complication.

**DISCUSSION**

Cavitation in sarcoidosis is uncommon. In a study involving 1254 patients from 10 centers, cavitary lesions were reported in only 3 (1.3%) of the 235 patients. In another study involving 200 patients, cavities were reported in only 3 (1.3%) of the 235 patients. Prevalence, however, a thin-walled cavity persisted for months to years [Table 1]. The patients (n = 16) had symptoms of chronic cough and dyspnea; only three patients were asymptomatic and were diagnosed by abnormal chest radiographs. PCS has a good prognosis and majority of the patients improve with treatment. Of the 25 patients, 12 (48%) had complete resolution with treatment while in 11 (44%) thin walled cavities persisted for months to years [Table 1]. The followup information was not available in two cases. Our patient had excellent clinical and radiological response with glucocorticoids. A few complications have been reported in patients with PCS including hemoptysis in three patients, pneumothorax in two cases, aspergilloma in one case, and bronchopneumonia leading to respiratory failure and death in one case. A systematic review of the PubMed database using the free text terms: Sarcoidosis AND cavit* yielded 311 references of which 17 citations [25 cases, Table 1] were that of PCS. The cases have been reported from across the globe including areas with high tuberculosis prevalence [further exemplified by the index case. The patients with PCS are usually young (mean age, 32.4 [range, 12–63] years), show no gender predilection (M:F; 14:11) and can be asymptomatic. As in the index case, cavities can be detected at the time of diagnosis or may develop weeks to months later, either spontaneously or during therapy. The cavities are generally small, round and thin walled. However, it is not uncommon to find cavities of varying shape with thick irregular walls. Generally single, occasionally they may be multiple. Majority of the patients (n = 16) had symptoms of chronic cough and dyspnea; only three patients were asymptomatic and were diagnosed by abnormal chest radiographs. PCS has a good prognosis and majority of the patients improve with treatment. Of the 25 patients, 12 (48%) had complete resolution with treatment while in 11 (44%) thin walled cavities persisted for months to years [Table 1]. The followup information was not available in two cases. Our patient had excellent clinical and radiological response with glucocorticoids. A few complications have been reported in patients with PCS including hemoptysis in three patients, pneumothorax in two cases, aspergilloma in one case, and bronchopneumonia leading to respiratory failure and death in one case.
Table 1: Primary cavitary sarcoidosis cases (n=25) reported in literature

| Author                        | Age | Sex | Race  | Symptoms                        | Cavity number and location | Cavity size | Hilar/mediastinal lymph nodes | Course and complications                                                                                     | Radiologic status after treatment |
|-------------------------------|-----|-----|-------|---------------------------------|----------------------------|-------------|-------------------------------|----------------------------------------------------------------------------------------------------------------|---------------------------------|
| Harden and Barthakur[^12^]    | 30  | Female | AA    | NA                              | RUL                        | 4-5         | No                            | Pneumothorax, underwent pleurectomy. Developed chronic dyspnea                                                | NA                              |
| Hamilton et al[^13^]          | 30  | Male  | AA    | NA                              | LUL                        | 3 cm        | Yes                           | Hemothysis, stable after surgery                                                                               | NA                              |
| Bistrong et al.[^14^]         | 20  | Male  | C     | Asymptomatic                    | LUL                        | <3 cm       | No                            | Asymptomatic                                                                                                  | NA                              |
| Schiffner and Sharma[^13^b]   | 31  | Female | AA    | Chronic cough and weight loss   | Bilateral RUL, LUL         | 4 cm×8 cm   | No                            | Left pneumothorax drained with chest tube chest radiograph revealed bilateral cavities and perihilar consolidation. Died due to bronchopneumonia and progressive respiratory failure. Autopsy had thick-walled fibrotic cavities lined with granulomas in both lungs. | NA                              |
| Tellis and Putnam[^13^a]      | 21  | Male  | C     | Chronic cough                   | Bilateral lung nodules with cavity LUL, Bilateral RUL and left mid lung filed | NA          | No                            | Surgical lung biopsy confirmed sarcoidosis No treatment given Marked improvement with steroids                  | Partial resolution of lesions at 6 months on CXR Thin-walled cavity persisted after treatment on CXR Lesion remained unchanged at 6 months on CXR Cavitation seen at 7 weeks in RMZ nodular lesion on CXR Chest radiographs showed minimal scarring after 1 year Lung lesions regressed with treatment |
| Rohatgi and Schwalb[^13^b]    | 21  | Male  | AA    | Asymptomatic                    | Bilateral RUL, LUL         | NA          | Yes                           | No treatment was given                                                                                         | No treatment was given          |
|                               | 26  | Male  | AA    | Cough                           | Bilateral RUL and LLL      | R 5 cm      | Yes                           | No treatment was given                                                                                         | No treatment was given          |
|                               | 25  | Female | AA    | Dyspnea                         | Bilateral nodular lesions without cavity LUL, Bilateral lung cavity RUL and lingula | NA          | Yes                           | Treatment with steroids improved                                                                               | Treatment with steroids improved |
| Dauber et al.[^17^c]          | 24  | Female | NA    | Cough and weight loss with anorexia | Bilateral lung cavity RUL and lingula, thin-walled cavity at the periphery of right lower lobe | NA          | Yes                           | No improvement with ATT, improved with steroids Also, had skin nodules and left frontal lobe mass lesions which regressed with oral steroids | No improvement with ATT, improved with steroids Also, had skin nodules and left frontal lobe mass lesions which regressed with oral steroids |
| Morikawa et al.[^19^c]        | 12  | Female | Asian | Dyspnea progressively increased to respiratory failure | Thin-walled cavity at the periphery of right lower lobe mass lesions | NA          | Yes                           | Improved without any treatment                                                                                   | Improved without any treatment |
| Canessa et al.[^19^b]         | 25  | Male  | C     | Asymptomatic                    | Single cavity RMZ          | 1.5 cm      | Yes                           | Developed RUL thick-walled cavity after 6 years of irregular follow-up and three course of oral steroids. Left pneumothorax requiring needle aspiration | Cavity resolved without treatment |
| Mihaescu and Veres[^20^b]     | 27  | Male  | NA    | Cough                           | Bilateral cavity on HRCT   | 3 cm        | NA                            | Improved without any treatment                                                                                   | Improved without any treatment |
| Ichikawa et al.[^21^b]        | 27  | Male  | NA    | Asymptomatic                    | Multiple cavitary lesions in both lungs | NA          | Yes                           | Developed multiple cavities at 2 years of follow-up                                                                 | Improved without any treatment |
| Ozseker et al.[^22^b]         | 43  | Female | NA    | Cough dyspnea and fever         | Cavity RUL on HRCT         | NA          | Yes                           | Improved with steroid treatment                                                                                   | Improved with steroid treatment |
|                               | 33  | Female | NA    | Cough and malaise               | Bilateral cavity on HRCT   | RUL 3 cm LUL 6 cm | Yes                           | Resolution with steroid treatment                                                                                   | Resolution with steroid treatment |

Contd...
Table 1: Contd...

| Author          | Age | Sex | Race | Symptoms              | Cavity number and location          | Cavity size                        | Hilar/mediastinal lymph nodes | Course and complications       | Radiologic status after treatment |
|-----------------|-----|-----|------|-----------------------|-------------------------------------|------------------------------------|-------------------------------|---------------------------------|----------------------------------|
| Sandhu et al.[23b] | 44  | Male | Asian | Fever, cough and cough | Two cavities RLL apical and basal segments | RLL (apical) 7 cm x 6 cm x 5 cm and RLL (basal) 4 cm x 3 cm | Yes                           | Improved with treatment          | Spontaneous improvement with resolution of cavity |
| Hours et al.[11b] | 28  | Male | NA   | Dry cough and dyspnea  | Two cavities                        | 1.1 cm largest                     | NA                           | Improved with treatment          | CT chest complete resolution of cavity |
|                 | 54  | Female | NA  | Dry cough and dyspnea  | Four cavities                       | 1.1 cm largest                     | NA                           | Worsened with treatment          | HRCT chest worsening of cavity |
|                 | 39  | Male | NA   | Dyspnea                | Seventeen cavities                  | 6 cm largest                       | NA                           | Worsened with treatment          | HRCT chest worsening of cavities |
|                 | 33  | Female | NA  | Dry cough and dyspnea  | Five cavities                       | 2 cm largest                       | NA                           | Worsened with treatment          | HRCT chest worsening of cavities |
| Panjabi et al.[24b] | 48  | Male | NA   | Dry cough and dyspnea  | 2                                    | 1.5 cm largest                     | NA                           | Improved with treatment          | HRCT chest complete resolution of cavity |
|                 | 35  | Male | NA   | Dry cough and dyspnea  | Two cavities                        | 2 cm largest                       | NA                           | Improved with treatment          | HRCT chest showed aspergilloma  |
| Okada et al.[25b] | 34  | Male | NA   | Cough                  | RUL and LUL multiloculated cavities | NA                                | NA                           | Became asymptomatic without treatment | HRCT chest complete resolution of cavity |
| Yap et al.[26b]  | 37  | Female | NA  | Dry cough              | Single cavity RUL                   | NA                                | NA                           | Treated with glucocorticoids      | HRCT chest resolution of cavity |
| Index case      | 47  | Male | Asian | Fever, cough, dyspnea  | RLL and LUL cavities                | RLL 6 cm x 5 cm x 4 cm and LUL 3 cm x 2 cm | Yes                           | Improved with treatment          | HRCT resolution of the cavity in LLL, RLL thin-walled cavity persisted at 1 year |

*Definite PCS; *Probable PCS; *Possible PCS (see Table 2 for details). AA: African American, C: Caucasian, RUL: Right upper lobe, RLL: Right lower lobe, LUL: Left upper lobe, LLL: Left lower lobe, NA: Information not available, CXR: Chest radiograph, HRCT: High-resolution computerized tomography of the chest, RMZ: Right middle zone, ATT: Antituberculous treatment, PCS: Primary cavitary sarcoidosis

Table 2: Classification of primary cavitary sarcoidosis

**Diagnostic criteria**

**Common features**

- Presenting manifestation with cavity or development of cavity within two years of disease onset
- Imaging showing single or multiple cavities without any evidence of surrounding fibrosis as evidenced by lack of architectural distortion, traction bronchiectasis and parenchymal bands on computed tomography. Presence of interlobular septal thickening, peribronchovascular and subpleural nodules point towards the presence of sarcoidosis
- Clinicoradiological response to glucocorticoids

**Definite**

1. 2, 3 plus surgical lung biopsy demonstrating non-necrotizing granulomas in the wall of the cavity without the presence of any microorganism

**Probable**

1. 2, 3 plus bronchoscopic lung biopsy showing non-necrotizing granulomas without the presence of any microorganism; bronchoalveolar lavage (BAL) negative

**Possible**

1. 2, 3 plus demonstration of non-necrotizing granuloma from any site other than lung without the presence of any microorganism

The pathology of PCS is characterized by noncaseating granulomas with minimal fibrosis in the cavity walls in contrast to dense fibrous tissue with few hyalinized granulomas seen in bullae and cystic bronchiectasis due to chronic sarcoidosis. In the present case, there were classical findings of active sarcoidosis without any granulomatous angiitis or ischemic necrosis in bronchoscopic lung biopsy. Based on the clinical and biopsy findings, we propose a new classification for PCS [Table 2]. In sarcoidosis, the initial two years following diagnosis are considered to be “acute stage”, and cavitation developing beyond this period is likely to be secondary to chronic fibrocystic sarcoidosis. Hence, we have used two years as the cutoff for diagnosing PCS. According to our classification, nodular sarcoidosis with cavitation or sarcoidosis with NSG pattern and cavities would all be classified under PCS as the occurrence of granulomatous angiitis is not specific for NSG but could also be encountered in classical sarcoidosis.[9]

The index case had bilateral cavities in the right and left lower lobes and the cavity in the right lower lobe was larger at 6 cm x 5 cm x 4 cm size. Lung biopsy revealed noncaseating granulomas without any granulomatous angiitis or ischemic necrosis. Tests for the presence of mycobacteria and fungi were negative. The patient responded to corticosteroid treatment. Thus, a diagnosis of probable PCS was tenable. To our knowledge,
there has been a single case of PCS reported from India, while PCS does not find mention in several case series from India.[1,27,28] It is likely that the overwhelming presence of tuberculosis in India “drowns” the occasional cavitary sarcoidosis in primary care.[1] The index case was treated as sputum-negative pulmonary tuberculosis for 6 months before being referred as a case of suspected drug-resistant tuberculosis. The differentiation of sarcoidosis from tuberculosis poses great challenge to physicians, radiologists and pathologists, especially in countries with high prevalence of tuberculosis.[29] Most patients presenting with prolonged cough, cavitary lesions on chest radiograph, and negative sputum smear for acid-fast bacilli are diagnosed as “sputum smear-negative” pulmonary tuberculosis in high tuberculosis burden countries and are empirically treated with antituberculous treatment.[30] There are several features that can help in differentiating between cavitary lesions of sarcoidosis and tuberculosis [Table 3]. Recently, the advent of rapid cartridge-based nucleic acid amplification test such as XpertMTB/RIF has greatly helped in distinguishing pulmonary tuberculosis from pulmonary sarcoidosis.[31]

**CONCLUSION**

Active sarcoidosis can rarely present with cavitary in the lungs. This diagnosis must be considered in patients with compatible clinicoradiological presentation when microbiological investigations for bacteria, mycobacteria, and fungi are negative.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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