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A Case Report

Subclinical Pulmonary Cavitary Lesion and Ulcerating Leg Lesion: A Rare Case Report of Sarcoidosis

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Abstract:

Sarcoidosis is a granulomatous inflammatory disorder that affects multiple organs, and lung being the most commonly affected organ. Typically, pulmonary sarcoidosis manifests radiologically as bilateral hilar and mediastinal lymphadenopathy, reticulonodular opacities, consolidation, pleural effusion, but may also present as a cavitary lesion. We hereby report an incidental finding of asymptomatic pulmonary cavitary sarcoidosis in a female patient who was referred for the evaluation of leg ulcer before her elective cholecystectomy. This case reports that an ulcerating leg lesion may be over-looked by the physicians for an underlying infection in the absence of any systemic features, and enlightens the importance of ruling out inflammatory and/or autoimmune disorder(s) before administering antibiotics and antifungals for treating skin lesion.

Keywords: Female, Cavitation, Ulcer, Non-caseating granuloma, Sarcoidosis, Prednisolone

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Introduction

Sarcoidosis is a multisystem granulomatous disorder that typically affects young adults between the ages of 20 and 60 [1]. It commonly affects females more frequently than men [2]. In about half of the cases, it is usually asymptomatic. In remaining cases, it either presents with respiratory symptoms, skin changes, joint problems, or eye involvement; wherein nearly 90% of patients have pulmonary involvement [3,4]. Studies have shown that pulmonary involvement is characterized by bilateral hilar adenopathy, pulmonary reticular opacities, pulmonary effusion, consolidation, and rarely as cavitation [5,6]. In addition, abnormal laboratory findings includes leukopenia, hypercalciuria, hypercalcemia, and elevated erythrocyte sedimentation

rate (ESR), C-reactive protein (CRP), and ACE levels [7]. Here, we present the case of pulmonary cavitary sarcoidosis in a young female patient referred to us for management of left leg ulcer before her elective cholecystectomy. In the absence of systemic symptoms and history significant for prolong use of antibiotics for left leg lesion, further workup for suspected autoimmune disorder, vasculitis, and infective etiology were ordered. Her chest X-ray (CXR) showed bilateral hilar and mediastinal lymphadenopathy and a cavitary lesion in the upper lobe of left lung. Her blood workup showed anemia and elevated erythrocyte sedimentation rate (ESR). With broad differentials in mind, the diagnosis of pulmonary sarcoidosis was made after excluding malignancy and infection, roentgen evidences of bilateral hilar lymphadenopathy, and histopathological findings of non-caseating granuloma on skin biopsy. Other less common causes of pulmonary cavitary lesions such as bronchiectasis, rheumatologic diseases (eg, Wegener granulomatosis), autoimmune diseases (rheumatoid arthritis, primary amyloidosis), bronchiolitis obliterans organizing pneumonia, trauma and pulmonary embolism were also excluded by serological tests and imagings. As reported here, the incidental finding of pulmonary cavitary lesion in the absence of typical pulmonary symptoms depicts highly variable clinico-radiological manifestation of pulmonary sarcoidosis, and skin ulcer as one of the manifestation of sarcoidosis.

Case Presentation

A 40-year-old female patient with a medical history significant for hypertension, type 1 diabetes mellitus, obesity, childhood asthma, and hyperuricemia was referred to us for medical clearance, prior to her scheduled elective cholecystectomy. Upon a thorough evaluation, patient reported a painful skin ulcer on left leg since five months of duration. Review of all systems was negative. Her vitals were significant for temperature of 96^{o}F, heart rate of 96 beats per minute, respiratory rate of 20 breaths per minute, blood pressure of 160/90 mmHg, SaO_2 of 94% on room air, and body mass index of 31 kg/m^2. Physical examination was significant for pallor conjunctiva, and non-pruritic, erythematous and tendered ulcerating lesion on left leg above medial malleolus. Rest of examination was unremarkable. Suspected for an underlying infectious and/or autoimmune disease, the patient was admitted to medical ward for further evaluation.

Prior to admission, this patient developed a small erythematous skin lesion on left leg, that progressively increased in size over the duration of five months. She was seen by multiple health care providers in peripheral clinics, where upon she was prescribed topical and oral medications. Over the course of five months, she applied topical fusidic acid thrice daily and topical clotrimazole 1% twice daily for duration of three weeks, took oral cephradine 500 mg twice daily for the duration of two weeks and oral doxycycline 100 mg twice daily for the duration of ten days. Despite five months of multiple treatment regimen, her skin lesion didn't improve. Out of frustration, she didn't seek further treatments until she developed epigastric pain and was diagnosed with cholelithiasis.

On admission, her laboratory findings were significant for low hemoglobin of 9 g/dL with normocytic and normochromic anemia, normal white blood cell count of 9.5 x 10^3/µL (reference range: 5 – 11 x 10^3/ µL), lymphocytes of 55%, normal CRP of 0.3 mg/dL (reference range: 0 – 1 mg/dL), and high ESR of 110 mm/hr (reference range: <30 mm/hr). CXR was significant for bilateral hilar enlargement and a cavitary lung lesion in the left upper lobe. The serial sputum samples for nucleic acid amplification test (Gene-Xpert) was negative for Mycobacterium Tuberculosis. Computed tomography (CT) scan of chest was significant for bilateral hilar and mediastinal lymphadenopathy, and a cavitary lesion in the left lung. Her other diagnostic investigations were significant for normal D-dimer, normal serum calcium levels, normal urinary calcium, normal rheumatoid factor levels, normal angiotensin-converting enzyme (ACE) levels, normal total IgE levels, normal urinalysis, negative anti-nuclear antibody (ANA) levels, negative sputum for fungus (KOH) smear, negative bio-fire film array for respiratory panel, negative acid-fast bacilli cultures, negative fungal cultures, and negative blood cultures. Her severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) polymerase chain reaction (PCR) was negative. Findings on Hepatitis A, B, and C serology and a rapid plasma regain test were within normal limits. Her hemoglobin A1c was 7.1%. Her electrocardiogram was normal. Ultrasound Doppler for left leg vein and artery were normal. The decision for bronchoscopy and bronchoalveolar lavage was made, however, patient refused for bronchoscopic interventions; hence, skin lesion was biopsied. The results were significant for non-necrotizing granulomatous inflammation, suggesting our final diagnosis of sarcoidosis.

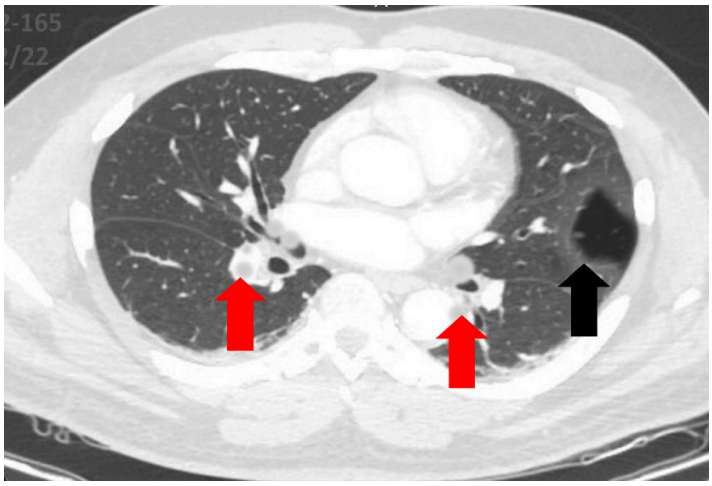

Figure 1: Mediastinal and bilateral lymphadenopathy with left upper lobe cavitation (before prednisolone treatment).

Black arrow: cavitary lesion. Red arrow: hilar lymphadenopathy.

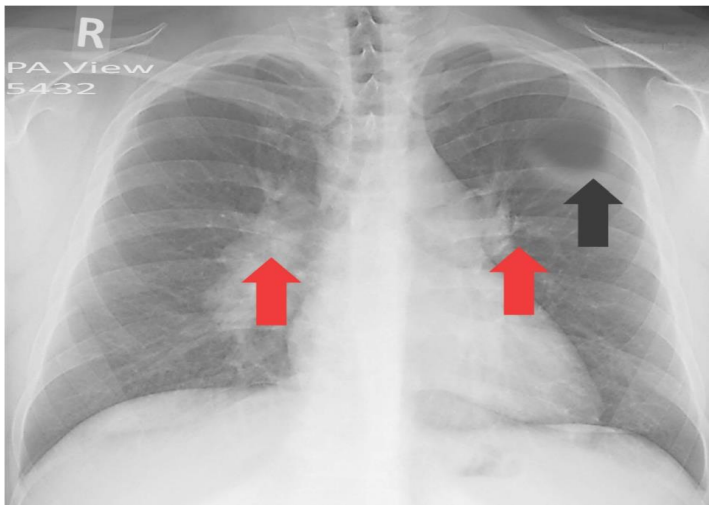

Figure 2: Chest X-ray demonstrating mediastinal and bilateral hilar lymphadenopathy with cavitary lesion in left upper lobe.

Black arrow: cavitary lesion. Red arrow: hilar lymphadenopathy.

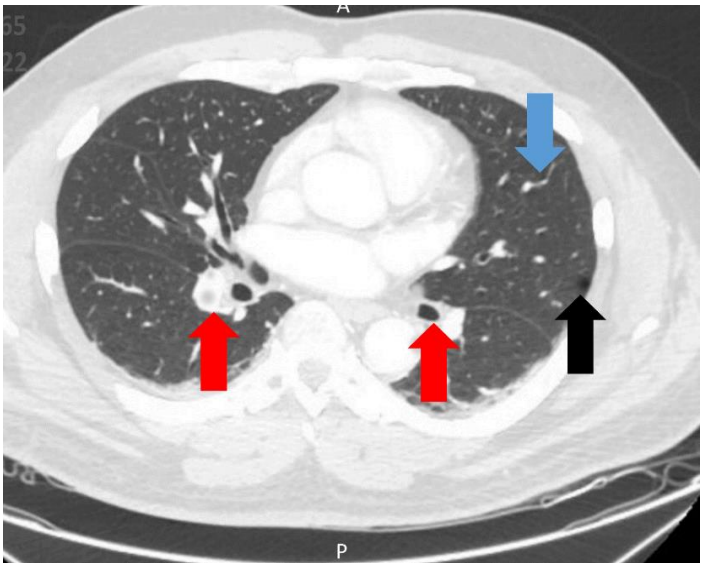

Figure 3: Mediastinal and bilateral lymphadenopathy with decrease cavitation in left upper lobe (after prednisolone treatment).

Black arrow: cavitary lesion. Red arrow: hilar lymphadenopathy. Blue arrow: lobular septae.

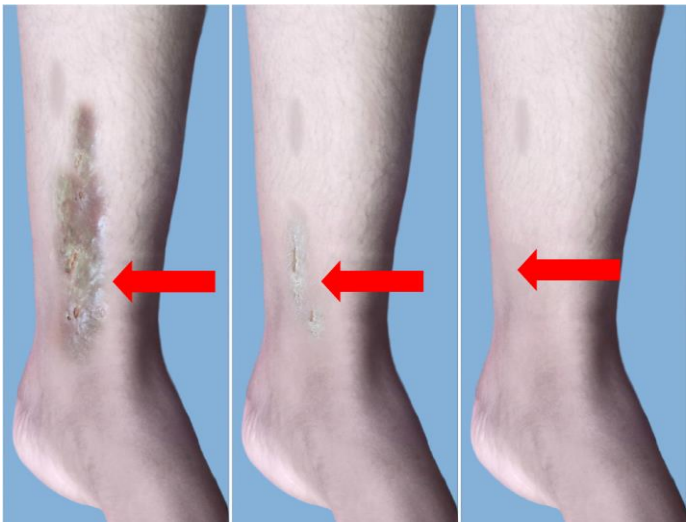

Figure 4: Left leg skin ulceration before treatment with prednisolone and after treatment with prednisolone (left to right).

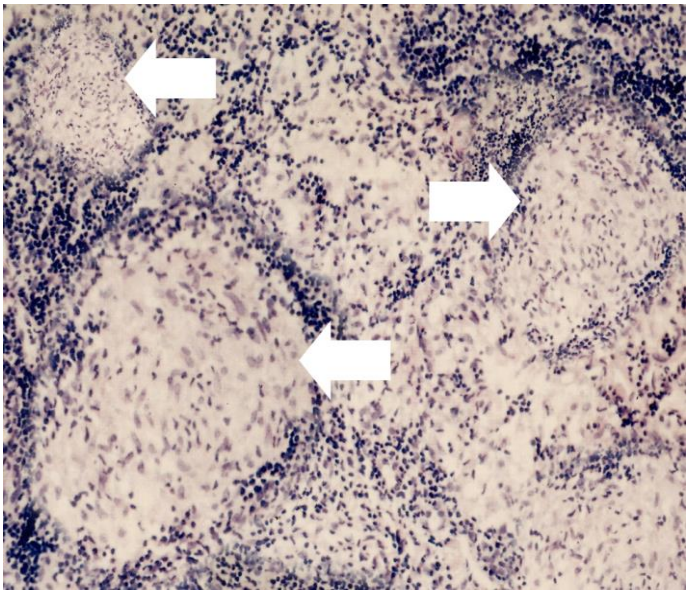

Figure 5: Histopathology of left leg ulceration – showing multiple non-caseous granulomas

White arrows: Non-caseous granulomas

During hospitalization, this patient was started on oral prednisolone 20 mg two times daily. Her home medications including insulin 70/30 twenty three units twice daily, perindopril 4 mg twice daily, and allopurinol 100 mg once daily were continued. Of note, ESR persistently remained elevated till fifth day of hospitalization, however, it declined subsequently over next five days in hospital. Multidisciplinary approach was made regarding decision for her scheduled surgery, and it was deferred till the resolution of pulmonary lesion on

imaging and healing of left leg ulcer. Patient was discharged from hospital on the day tenth after admission. Upon discharge, ulcer care with chlorhexidine, and oral prednisolone 20 mg twice daily and diclofenac sodium 75 mg PRN were added to the regimen, and perindopril was changed to amlodipine/valsartan 5/80 mg once daily due to her uncontrolled blood pressure.

Upon regular follow-ups till nine months, her skin lesion on left leg resolved and pain relieved. She still had no pulmonary symptoms during multiple follow-ups. No prednisolone related gastric symptoms were reported by this patient. Laboratory value of hemoglobin improved and ESR returned to baseline. Repeat ACE levels were significant for 45 nanomoles per milliliter per minute (reference range: <40 nanomoles per milliliter per minute). Repeat CT chest was significant for decrease in size of hilar and mediastinal lymph nodes, and reduce size of cavitary lung lesion in the left lobe.

Discussion

In 1914, Schaumann first described the term sarcoidosis (also known as Besnier-Boeck-Schaumann disease) [8]. It is a rare, immune-mediated inflammatory disease characterized by non-caseating epitheloid cell granulomas predominantly in persons aged 20-50 years. Among multiple factors, ethnicity significantly influences sarcoidosis, with highest incidence of 40 cases per 100,000 African Americans, and females being the most commonly affected gender. The Hispanics and Asians have half the rate of incidence when compared to black African Americans. In Asia, the highest prevalence is reported in India, while Middle East countries have similar figures to Mediterranean countries, and East Asian countries have the lowest worldwide incidence and prevalence rates. The worldwide prevalence of sarcoidosis is 50 to 60 per 100,000 population [4,9]. The exact pathogenesis and etiology of sarcoidosis remains unknown despite multiple investigations [10].

Sarcoidosis is a multisystem disorder that clinically manifests based on the severity of the disease and the involvement of organs. It predominantly affects lungs, but with a myriad of possible extra-pulmonary manifestations in many organ systems, most commonly the lymphatic, integumentary, ophthalmic and gastrointestinal systems [11]. When the disease affects the lungs known as pulmonary sarcoidosis, it commonly presents with cough, dyspnea, fatigue, chest pain, weight loss, fever, and malaise [12]. Cough and dyspnea have been reported as the most prominent symptom of cavitary pulmonary sarcoidosis, however, our patient was uniquely asymptomatic despite significant pulmonological radiographic findings.

In 1935, Salvesen first described cavitation as a probable finding in patients with pulmonary sarcoidosis [13]. When airspace cavitations are seen in sarcoidosis, it is called pulmonary cavitary sarcoid. Cavitary lesion is uncommon manifestation of pulmonary sarcoidosis with an estimated prevalence of 2.2% [14]. Multiple theories have been reported to explain the occurrence of cavitation in sarcoidosis. These includes bullae formation, intercurrent infections with bacterial or fungal agents, extrusion of necrotic hyaline material from conglomerate areas of fibrosis, and development of cystic bronchiectasis. Release of tumor necrosis factor-α from macrophages and lymphocytes in active granulomatous lesions incites cellular damage and necrosis, resulting in cavitation. De novo cavitation due to sarcoidosis, results from ischemic necrosis of conglomerate granulomatous lesions [14,15]. It has been proposed that patients with pulmonary cavitary sarcoidosis usually have concomitant comorbidities, and usually occur in active and severe sarcoidosis. Though this patient's comorbidities might have contributed in the disease process, her presentation was unusual in terms of severity.

In pulmonary sarcoidosis, the high-resolution computed tomography (HRCT) scan is more sensitive and correlates with histologic and pulmonary function test abnormalities more closely than the plain CXR [16]. The radiological findings in pulmonary sarcoidosis can be classified by typical and atypical characteristics. The typical findings include symmetric hilar and mediastinal lymphadenopathy, bronchovascular nodular opacities, and bronchiectasis. The atypical findings include unilateral lymphadenopathy, ground-glass opacities, interlobar septal thickening and linear opacities, pleural effusions, cavitation, and airspace consolidation and opacities [6,17]. Our patient's CT showed some of the typical sarcoidosis findings such as perihilar and mediastinal lymphadenopathy, as well as atypical findings such as lung cavitation in her left upper lobe.

Because sarcoidosis can affect all organ systems, extrapulmonary manifestations include visual changes, skin lesions, enlarged lymph nodes, weight gain, joint pain, muscle weakness, peripheral neuropathy, facial nerve palsy, abdominal pain, palpitations, and syncope [18]. Cutaneous involvement is seen in approximately 25% of patients with sarcoidosis, and is often an early and only finding, as reported in this patient. Cutaneous sarcoidosis includes wide spectrum of lesions including specific lesions such as papules, nodules, plaques, and infiltrated scars. Erythema nodosum is the most common

non-specific cutaneous lesion of sarcoidosis. Moreover, the cutaneous lesions are also divided as specific and non-specific based on histolopathological features. Specific skin lesions contain noncaseating (sarcoidal) granulomas, while all other histolopathological findings on cutaneous lesions are classified as nonspecific [19]. Our patient's skin biopsy was significant for noncaseating granuloma suggestive of specific skin lesion, with ulcerating skin lesion suggestive of specific skin lesion.

Laboratory evaluation of sarcoidosis often reveals leukopenia with lymphopenia, hypercalcemia, hypercalciuria, elevated serum alkaline phosphatase, hypergammaglobulinemia, an elevated ESR and CRP. Serological evaluation in patients with sarcoidosis often includes markers such as serum ACE, adenosine deaminase, serum amyloid A, soluble interleukin-2 receptor, and D-dimer. Serum ACE levels are elevated in many patients with untreated sarcoidosis (~75%) but have relatively poor specificity and sensitivity [20]. Of note, ACE inhibitors lower the serum ACE level, so patients should be tested when off these medications. ACE levels sometimes correlate with active pulmonary disease and normalize with successful therapy but in only a minority of patients [21]. The only laboratory values in this patient were low hemoglobin and elevated ESR levels. Among the serological markers, ACE levels were found to be mildly elevated in this patient upon discontinuation of her anti-hypertensive perindopril. The other common sarcoidosis markers were not found in our patient.

In this case, our patient had typical and atypical radiological features of pulmonary sarcoidosis in absence of pulmonary symptoms, and blood tests were significant for negative blood cultures, thus, giving us a new insight for highly unpredictable clinico-radiological presentation of pulmonary cavitary sarcoidosis. Furthermore, the ulcerating lesion on left leg reflects the atypical manifestation of sarcoidosis, and can easily be misdiagnosed by the physicians in the absence of typical features of fever, warmth skin, discharge from wound, and laboratory findings of leukocytosis and elevated acute phase reactants such as CRP. This patient's skin lesions didn't improve despite using topical and oral multiple antibiotics and topical antifungals. The oral prednisolone 40 mg once daily resulted in the significant improvement of skin lesion in six months as shown in figure 4B. However, the radiological manifestation of cavitary lesion improved after nine months of treatment with prednisolone. From this patient findings, we suggests the role of prednisolone for the management of pulmonary cavitary sarcoidosis as well as skin lesions related to sarcoidosis.

As of diagnosis, there is no definitive test for patients with sarcoidosis. Therefore, the diagnosis consists of compatible clinical and radiographic manifestations, exclusion of other diseases that may present similarly, and histopathologic detection of noncaseating granulomas [22,23]. In this case, our patient met these three elements that must be present in sarcoidosis to make a definite diagnosis.

Conclusion

Pulmonary cavitary sarcoidosis is relatively a rare presentation of pulmonary sarcoidosis, and usually manifests as an active sarcoidosis. Our case was a unique presentation of asymptomatic pulmonary cavitary sarcoidosis in a patient who just had ulcerative skin lesion in the absence of other features of sarcoidosis. In cases such as ours, it is essential to remember that an ulcerating skin lesions may be overlooked by physicians as simple skin lesion and be improperly treated by antibiotics and antifungals. Furthermore, the thorough systemic evaluation should always be performed in skin lesions, as extrapulmonary findings of sarcoidosis may precede the most common involved pulmonary system. In the context of absent literature on the pulmonary cavitary sarcoidosis and its association with ulcerative skin lesions, we emphasize the need for more extensive research on the diversity of this multi-system disorder.

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