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Venous Thromboembolism and Sarcoidosis: A Case Report

Authors' Contribution:
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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Male, 27
Final Diagnosis: Sarcoidosis
Symptoms: Generalized body pain • productive cough • shortness of breath
Medication: —
Clinical Procedure: —
Specialty: Pulmonology

Objective: Unusual clinical course
Background: Several studies have described an increased incidence of venous thromboembolism in inflammatory conditions such as sarcoidosis.
Case Report: We report a case of a 27-year-old African-American man who developed sarcoidosis with pulmonary involvement after 4 years of unexplained thromboembolism.
Conclusions: This report discusses the relationship between sarcoidosis and venous thromboembolism. Our case raises questions about this relationship. Can sarcoidosis lead to an inflammatory and prothrombotic state prior to the development of other manifestations?

MeSH Keywords: Sarcoidosis • Sarcoidosis, Pulmonary • Venous Thromboembolism • Venous Thrombosis

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Background

Sarcoidosis is a chronic systemic inflammatory disease of unknown cause, which is typically characterized by non-caseating granulomas. This disease may affect multiple organs, including the eyes, skin, lymph nodes, liver, and the lungs. More than 90% of patients with sarcoidosis have intrathoracic involvement [1]. The mortality rate of sarcoidosis is 1–8% and is highest in non-Hispanic blacks, women, and in people over 55 years of age [2].

Several retrospective and observational studies have suggested that patients with sarcoidosis have an increased risk of venous thromboembolic disease [3–6]. Although the mechanism is not entirely clear, it appears that sarcoidosis, like other chronic inflammatory diseases, can lead to a hypercoagulable state [7–10]. Here, we describe the case of a patient with a history of chronic venous thromboembolic disease who presented with extensive pulmonary disease and was diagnosed with sarcoidosis. This case raises interesting questions about this relationship.

Case Report

A 27-year-old African-American man presented to the Emergency Department (ED) with complaints of shortness of breath and cough for 1 month, associated with generalized body aches and night sweats. The cough was productive of blood-streaked sputum and led to chest wall pain. He reported a history of systemic lupus erythematosus (SLE) that was diagnosed 2 years ago. No serologies or medical records regarding this disease were available. He denied prior pulmonary, renal, or skin disease. A chest X-ray taken 17 months ago was reportedly negative, showing clear lung fields. The patient had a history of recurrent deep vein thrombosis (DVT). His first episode of DVT was 4 years ago and he recalled being placed on warfarin with subtherapeutic INRs. Subsequently, he had 2 more episodes of DVT and a pulmonary embolus, after which an inferior vena cava (IVC) filter was placed and rivaroxaban was started. Due to incarceration, he was switched back to warfarin and he subsequently had another DVT and was placed on apixaban 5 mg twice daily.

One month before his current visit, he presented to the ED with shortness of breath and leg pain. He was diagnosed with DVT. Workup for SLE was negative for anti-nuclear antibody (ANA) and anti-double-stranded DNA (anti-dsDNA) testing. The chest X-ray at that time revealed bilateral perihilar opacities. The patient left the hospital against medical advice before receiving treatment.

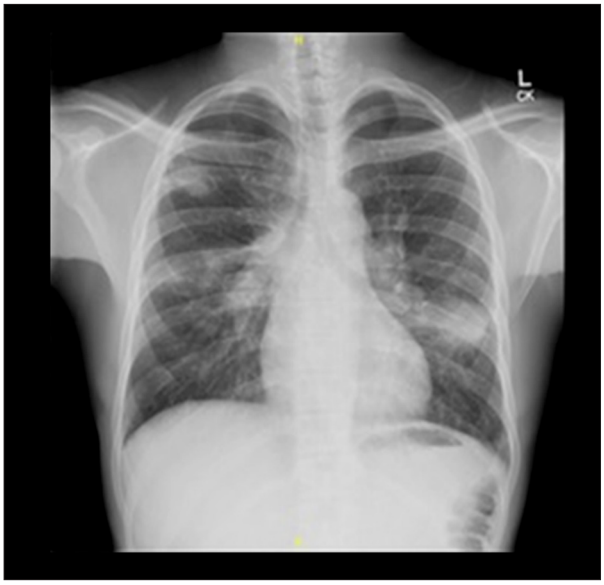

Figure 1. Posteroanterior chest radiograph demonstrating bilateral lung opacities.

Further history included a reported cardiac surgery with repair of a septal defect at age 7, cigarette use of 0.25 packs per day of unknown duration, and use of cocaine and marijuana. His only home medication was 5 mg of apixaban twice daily.

On physical examination, the patient was in no distress and vitals were normal, with a respiratory rate of 18 breaths per minute. No lymphadenopathy was present. The lung exam revealed scattered mild bilateral lower-lobe rales. His abdomen was soft, with distended superficial abdominal veins and no rebound tenderness. His lower limbs had no erythema. Trace pitting edema and pain on palpation of the lower extremities was noted bilaterally.

Chest radiographs exhibited bilateral opacities (Figure 1) that were unchanged from 2 months prior to admission. A computed tomography (CT) scan of the chest showed bilateral dense consolidations involving the right upper lobe, middle lobe, right lower lobe, and left lower lobe. The distribution was predominantly peripheral. Some areas of dense consolidation extended from the hila to the periphery of the lung. Bilateral hilar and mediastinal lymphadenopathy was also present (Figure 2). Laboratory examination revealed a leukocyte count of 3.8 (4.8–10.8 K/uL), hemoglobin of 12.3 (14–18 g/dL), and platelets of 219 (130–400 K/uL). The ANA, antineutrophil cytoplasmic antibodies, anti-dsDNA, and antiphospholipid antibodies were all negative. He tested positive for cocaine and cannabinoids. The lower-limb venous duplex was positive for bilateral DVT. The CT of the abdomen (Figure 3) showed a clotted IVC filter with dilated collateral superficial veins.

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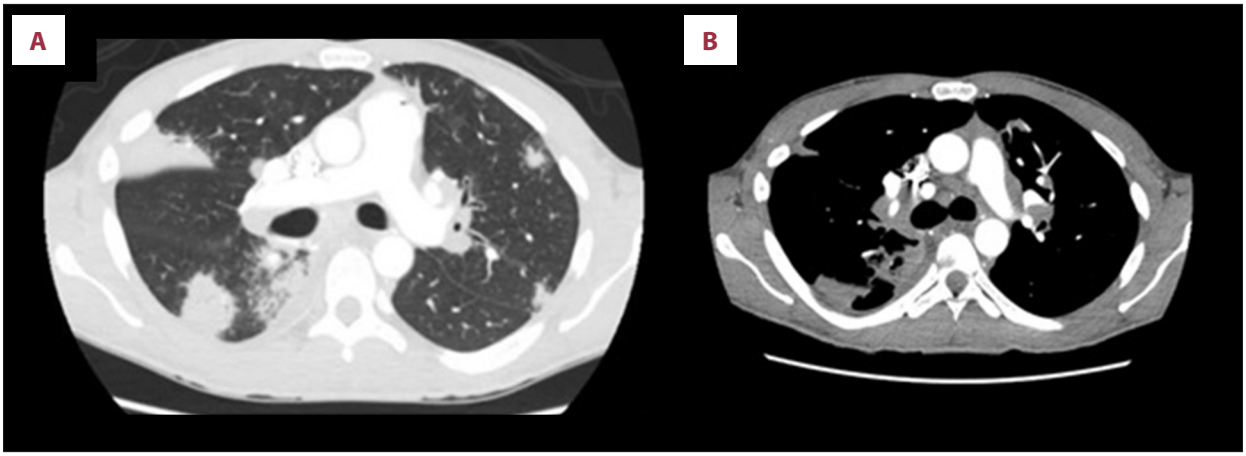

Figure 2. Computed tomography scan of the chest demonstrating (**A**) bilateral areas of dense consolidation with a peripheral distribution and (**B**) bilateral hilar adenopathy.

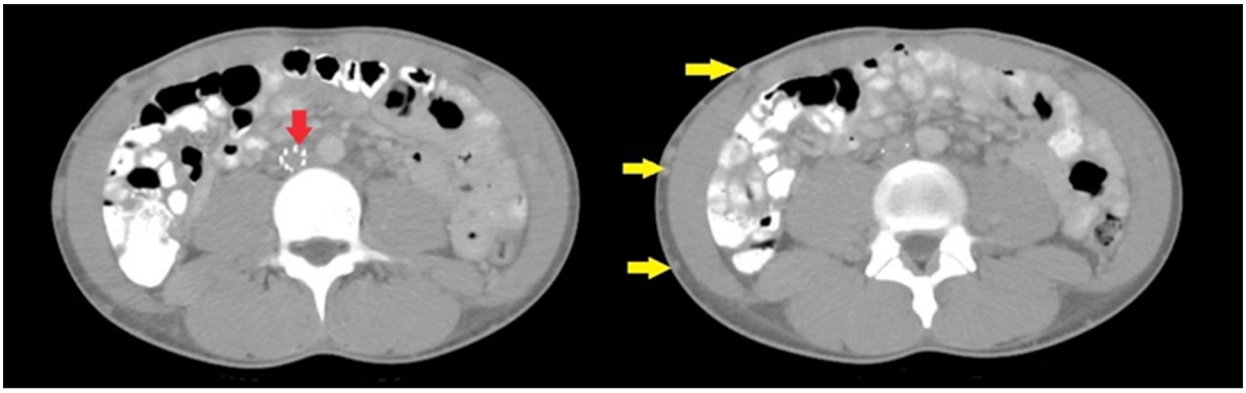

Figure 3. Computed tomography scan of the abdomen showing clotted IVC filter (red arrows) with dilated collateral superficial veins (yellow arrows).

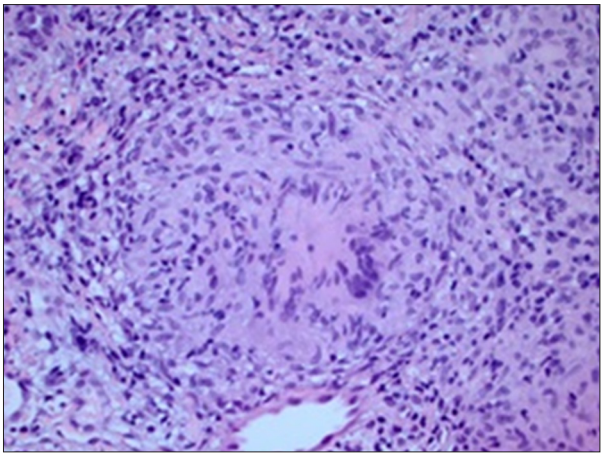

Figure 4. Computed tomography-guided needle biopsy of the left lung tissue showing a well-formed non-caseating granuloma exhibiting epithelioid histiocytes and multinucleated giant cells surrounded by a small rim of lymphocytes.

Hospital course

The primary differential diagnoses on admission for his pulmonary disease centered on sarcoidosis and malignancy. A CT-guided lung biopsy was performed and pathology revealed non-caseating granulomas (Figure 4) consistent with sarcoidosis. Upon further questioning, the patient admitted that he was not fully compliant with his anticoagulation medication. He took 5 mg of apixaban only once every few days because of cost.

The patient was counseled regarding the importance of compliance with anticoagulation medication and efforts were made to provide Xa inhibitor at a price affordable to the patient. He was discharged on rivaroxaban and prednisone at 40 mg daily, after which he was lost to follow-up.

Discussion

Virchow's triad portrays the primary risks of thrombosis formation, which include venous stasis, endothelial injury, and

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hypercoagulability [3]. Chronic inflammation, such as rheumatoid arthritis and vasculitis, has been recognized as a risk factor for VTE [3–5,8]. Inflammation activates endothelial cells, platelets, and leukocytes to form microparticles that induce tissue factor, triggering an increased activation of thrombin and fibrin formation [7,8], which results in a thrombophilic state characterized by abnormalities such as tissue thromboplastin activity, D-dimer levels, and thrombin-activatable fibrinolysis inhibitor. Other abnormalities include decreased plasminogen activator activity and protein C activation [9]. Studies have shown that interleukins, specifically IL-1β, IL-6, and IL-8, play a role in acute and chronic inflammation. These circulating molecules lead to hypercoagulation and hypofibrinolysis by directly causing plasma cells, erythrocytes, and platelets to form fibrin clots [10].

In patients with sarcoidosis, an increased risk of venous thromboembolic disease, which includes pulmonary embolism (PE) and DVT, has been described in several studies. Swigris et al. examined death records from 1988 to 2017 and found that patients with the diagnosis code of sarcoidosis had a greater than 2-fold higher risk of developing PE compared to the general population [4]. The Mayo Clinic conducted a systematic review of observational studies and demonstrated a statistically significant increase in VTE risk in patients with sarcoidosis [5]. Furthermore, a population-based retrospective study from 1976 to 2013 found an increased risk of VTE in patients with sarcoidosis [3]; Yaqoob et al. replicated this study in a larger data set and found that sarcoidosis was associated with an increased risk of VTE [6].

In addition to an inflammatory mechanism, other factors potentially contributing to the development of VTE in sarcoidosis include the presence of disabling disease resulting in immobilization, the use of glucocorticoids, and the presence of additional thrombophilias (antiphospholipid antibodies were detected in 38% of sarcoidosis patients in one study) [11]. It has been suggested that surveillance bias may play a role, as more exams and imaging are done after the diagnosis of sarcoidosis [3].

Our patient had chronic lower-extremity venous thromboembolic disease (worsened by his non-compliance with anticoagulation therapy) and presented with new bilateral pulmonary consolidation leading to a diagnosis of sarcoidosis. Although he had been told he had SLE, serologies were negative and the clinical history was not supportive of this. Unfortunately, the details of the prior evaluations were not available and the patient was lost to follow-up. As mentioned above, several studies support the relationship between sarcoidosis and VTE; however, our patient appears to have developed his VTE prior to the development of sarcoidosis. In a study by Ungprasert et al., the prevalence of VTE prior to the diagnosis of sarcoidosis was not significantly different between patients with sarcoidosis and the non-sarcoidosis cohort [3].

Our patient's presentation raises the possibility that sarcoidosis can cause an inflammatory, hypercoagulable state that predates the presence of clinically evident disease. Alternatively, our patient's coexisting granulomatous lung disease and VTE could be coincidental, or the VTE disease could be secondary to another undefined disease process. There may be an increased incidence of autoimmune disease in sarcoidosis. In a study from Taiwan, 17.6% of sarcoidosis patients were found to have another autoimmune or inflammatory disease [12]. In addition, an epidemiologic study described a significant association between sarcoidosis and other immune-mediated and chronic inflammatory diseases, including SLE and autoimmune chronic hepatitis [13].

Conclusions

We present the case of a patient who developed pulmonary sarcoidosis 4 years after presenting with unexplained recurrent episodes of thromboembolic disease. The relationship between sarcoidosis and VTE has been highlighted in several studies; however, our patient's VTE disease predated his sarcoidosis by several years, raising interesting questions about the relationship between these entities. Could the inflammatory and hypercoagulable state precede the development of clinically evident pulmonary disease? Further investigations are needed to better understand the relationship between sarcoidosis and VTE.

Conflict of interest

None.

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