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Necrotizing Sarcoid Granulomatosis with Concurrent Ankylosing Spondylitis: A Case Mimicking Pulmonary Tuberculosis

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Abstract

Histologic tuberculosis eventually turned out to be necrotizing sarcoid granulomatosis, a rare disease. A retired TB ward nurse with recurrent uveitis, a positive TST, pulmonary masses and skeletal pain was diagnosed with clinical tuberculosis (TB) and treated with first line tuberculostatic drugs, but the chest X-ray did not improve after treatment completion. Ensuing reassessment of the pulmonary biopsy resulted in a diagnosis of pulmonary necrotizing sarcoid granulomatosis (NSG) and concurrent ankylosing spondylitis (AS), a very rare combination of inflammatory diseases. Uveitis can be a symptom of TB or AS or NSG, the last being a rare disorder of unknown etiology, mimicking tuberculosis.

Keywords

Case Report, Necrotizing Sarcoid Granulomatosis, Ankylosing Spondylitis, Tuberculosis

1. Introduction

Necrotizing sarcoid granulomatosis (NSG) first described in 1973, is a rare disease primarily affecting the lungs and manifesting as pulmonary vasculitis and granulomatous lesions in the lung [1]. On the chest x-ray, pulmonary masses can be seen with cavitation suggestive of tuberculosis (TB). Hence, in TB endemic areas NSG is frequently misdiagnosed for pulmonary tuberculosis [2] [3] resulting in inappropriate treatment. With 29 new cases per 100,000 population in 2023, Suriname has an intermediate incidence of tuberculosis according to the WHO. In our case presentation, we describe a patient with recurrent uveitis [4], pulmonary

masses, lower back pain and abdominal discomfort who was professionally exposed to tuberculosis patients. A seemingly obvious case of tuberculosis eventually turned out to be NSG mimicking pulmonary tuberculosis with concurrent ankylosing spondylitis (AS), a rare combination of diseases. This rare occurrence of diseases has led us to write a case report after written permission was obtained from the patient.

2. Case Presentation

A female nurse, 58 years of age, who has had excision of a colon polyp and a history of arterial hypertension being treated with captopril, amlodipine and hydrochlorothiazide, consulted the ophthalmologist in May 2020 for nontraumatic redness, photophobia and watery left eye. Slitlamp examination revealed inflammatory cells in the anterior chamber and fine keratic precipitates on the endothelium and some posterior synechiae of the left eye. The vitreous was clear without chorioretinal infiltrates. Typical keratic precipitates, a hallmark of chronic granulomatous disease, were not seen, and the patient was diagnosed with pure iritis. With PredForte and atropine eye drops, the uveitis anterior completely resolved. As systemic and infectious diseases can cause uveitis, she was referred to the internist for evaluation in June 2020. Evaluation by the internal medicine specialist revealed she had worked for 5 years at a TB ward and had long-standing vague abdominal discomfort and low back pain. Her chest x-ray was normal; the ESR was 32 mm/hour, CRP was 25 (normal value < 10), and blood count and differentiation were normal, as well as the liver, kidney, calcium and thyroid laboratory results. Total serum protein and albumin were within normal range, protein electrophoresis was normal, the VDRL test was nonreactive, Toxoplasma IgG was positive and Toxoplasma IgM was negative. Also, no protein was detected in the urine. Because no systemic disease was detected she was not offered specific treatment. As the patient was not BCG vaccinated but had a tuberculin skin test (TST) of 25 mm, considered to be positive and hence indicative for latent tuberculosis infection, she was offered tuberculosis prophylactic treatment which she declined. In April 2021 she had relapse uveitis of the left eye with the same ophthalmological findings and again her eye complaints resolved with the aforementioned eye drops. Because of the abdominal discomfort and low back pain patient remained under the care of the internist for further analysis. A pelvic x-ray made in August 2020 showed bilateral irregular sclerotic and ankylosing lesions of the sacroiliac joint compatible with bilateral sacroiliitis.

In October 2023, the internist referred the patient to the pulmonologist because her chest x-ray showed multiple nodular masses in the right lung (**Figure 1**).

She had no pulmonary complaints, no fever, no night sweats and no weight loss. Her HIV test was negative, and the sputum GeneXpert test was negative for tuberculosis. A chest CT scan of November 2023 showed multiple subpleural contrast-enhanced nodular lesions in the right lung, no enlarged intrathoracic lymph nodes and no rib nor thoracic vertebral column lesions; the overall picture sug-

gestive of tuberculosis (TB) or sarcoidosis (Figure 2).

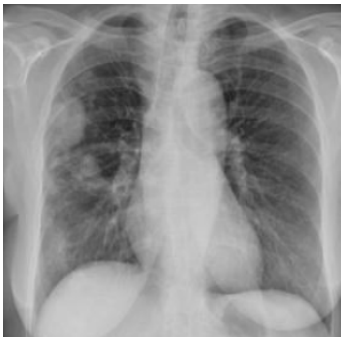

Figure 1. Chest x-ray, October 2023, with multiple nodular masses in the right lung.

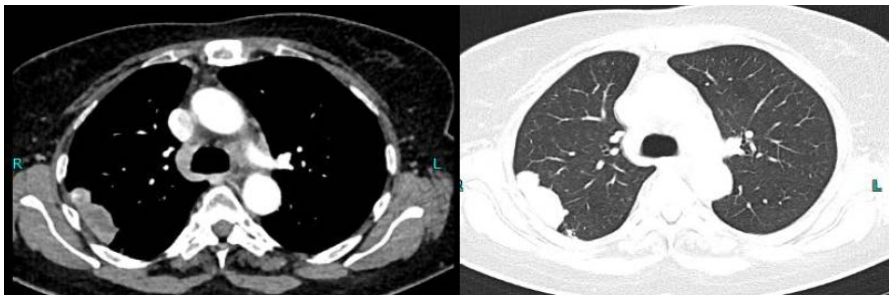

Figure 2. Thoracic CT scan, November 2023, with a nodular mass in the right lung.

Further evaluation with bronchoscopy showed no endobronchial lesion while endobronchial aspirate examination showed no TB by GeneXpert testing. To pursue a histological diagnosis, a CT-guided transthoracic biopsy of a pulmonary lesion was performed, the pathology report of February 2024 showing no cancer cells in haematoxylin & eosin (HE) staining but a granulomatous aspect with 80% tissue necrosis and multiple epithelioid histiocytes at the endpoints of the biopsy, suggesting TB or sarcoidosis (Figure 3).

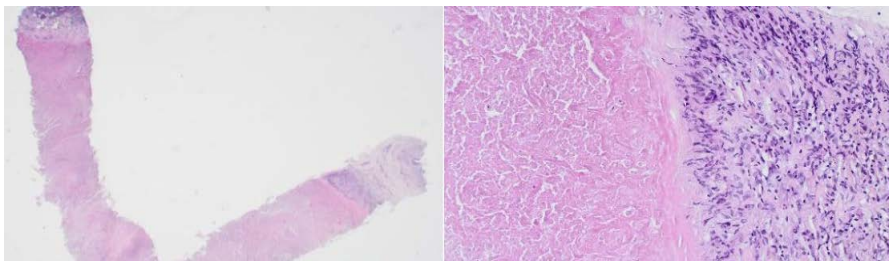

Figure 3. HE staining of the biopsy shows a large area of necrosis on low magnification (left picture ×20), with histiocyte and lymphocyte infiltrates at both ends seen at high magnification (right picture ×200).

Albeit the Ziehl Neelsen stain was negative for acid-fast bacilli, tuberculosis infection was still considered possible and based on her occupational history, the positive TST and the necrotizing granulomas in pulmonary tissue, she was diag-

nosed with clinical TB. In March 2024 she started treatment with first line tuberculostatic drugs and completed the 6 months treatment in September 2024. During TB treatment multiple spatial sputum cultures did not show growth of mycobacteria and a chest x-ray done 2 months after treatment showed no radiological improvement, a phenomenon sometimes seen in suspected pulmonary TB. Even after completion of tuberculosis treatment the pulmonary lesions did not resolve at all on the chest x-ray of September 2024. This finding necessitated reassessment of the pulmonary biopsy specimen in November 2024, subsequently favoring the diagnosis of necrotizing sarcoid granulomatosis (NSG). The meticulous re-examination of the HE-stained biopsy specimen showed faint spore-like structures in the necrotic area, determined to be cryptococcus neoformans or histoplasmosis. Because of the extensive necrosis, histoplasmosis was considered the more likely cause and treatment with itraconazole for 4 weeks was given starting November 2024. When the periodic acid-Schiff (PAS) and Grocott methenamine silver (GMS) staining became available structures were seen indicative of cryptococcus neoformans, and as so treatment was switched to fluconazole in December 2024 (**Figure 4**).

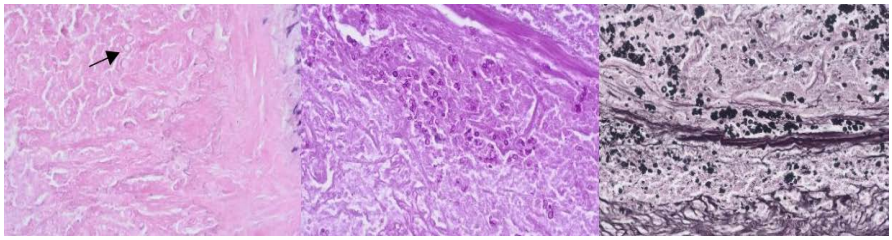

Figure 4. On high magnification (black arrow on the left picture), spherical to oval yeast cells ranging from 3.5 to 10 μm in diameter are seen in the necrotic area. These cells are often surrounded by a thick capsule [HE ×400]. Periodic acid-Schiff staining (middle picture) with the presence of Cryptococcus neoformans [PAS ×200]. Grocott methenamine silver (right picture) also stains positive for Cryptococcus neoformans [GMS ×200].

Despite antifungal treatment there was still no chest X-ray improvement in February 2025 (**Figure 5**), and at follow-up the patient complained about pain and swelling of her right sternoclavicular joint.

Figure 5. Chest X-ray, February 2025: no improvement at all despite treatment for tuberculosis and pulmonary fungal infection.

Revision of the thoracic CT scan which was made in November 2023 revealed the sternoclavicular joint swelling to be already present. This finding and the stiffening of her spine manifesting as neck stiffness and low back pain and the fact that the patient does not meet the radiological criteria for morbus Bechterew, suggest her skeletal pain complaints could be consistent with ankylosing spondylitis (AS). The longstanding abdominal discomfort of the patient was ascribed to irritable bowel syndrome (IBS). Currently no systemic treatment is prescribed but symptomatic treatment for AS and IBS. An overview of the events is shown in Figure 6.

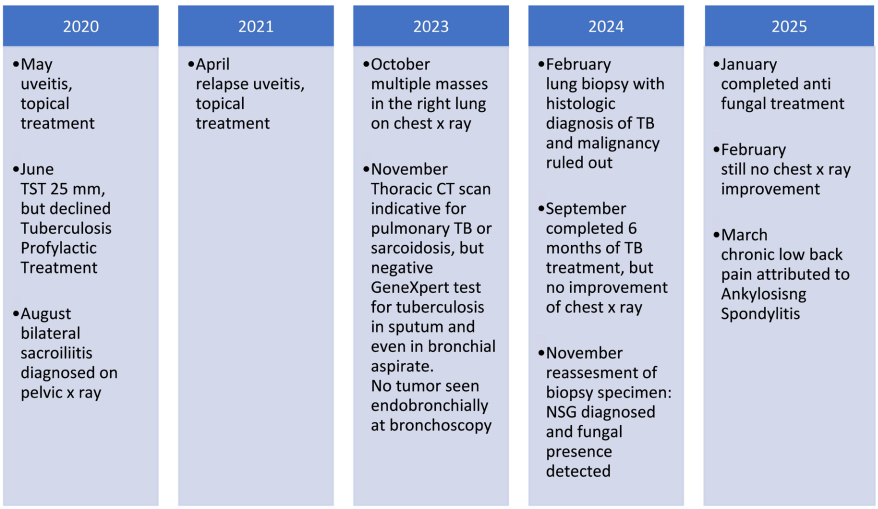

Figure 6. Timeline of events.

3. Discussion

Our patient, with a positive TST, experienced recurrent anterior uveitis [5] without an ophthalmologic cause, giving way to a broad differential diagnosis of infectious and systemic causes [6] [7]. Initial evaluation excluded various infectious agents, but at follow-up multiple nodular masses in the right lung were seen. The ensuing pulmonary workup resulted in a histologic differential diagnosis of TB and sarcoidosis [8] [9], but our patient had no distinct radiologic evidence of sarcoidosis. Unfortunately, we were not able to perform serum angiotensin converting enzyme (ACE) testing, which could have added evidence to the diagnosis of sarcoidosis [10]. Treatment for TB [11] was completed but did not result in improvement of the chest x-ray [12]. The unaltered chest x-ray necessitated reassessment of the pulmonary biopsy with AFB staining being negative for mycobacteria but PAS and GMS stain positive for cryptococcus neoformans, and a revised diagnosis of NSG, which is considered to be a rare form of sarcoidosis or a disease state with unknown etiology [13] [14]. NSG is characterized by well-formed, sarcoid-type epithelioid granulomas with multinucleated giant cells, prominent infarct- or coagulative-like necrosis related to vascular compromise and vasculitis of pulmonary vessels [15]-[18]. Necrotizing sarcoidosis shows sarcoid-type non-

caseating granulomas similar to classic sarcoidosis and may show small necrotic foci while vasculitis is generally absent or minimal [17] [19]. Granulomatous infections show poorly formed granuloma when acute and classic caseating granulomas with epithelioid histiocytes and giant cells in mycobacterial or fungal disease. Invasive fungal or bacterial infections result in a typically suppurative necrotizing vasculitis [18] [20] [21]. The needle biopsy specimen of our patient showed a large area of coagulative necrosis. This necrotic area was rimmed by epithelioid histiocytes but, there were no well-formed sarcoid granuloma present neither were there signs of vasculitis or suppurative inflammation. AFB staining was negative for mycobacteria and PAS and GMS stain were positive for cryptococcus neoformans. The cryptococcal antigen test was positive but treatment with fluconazole did not result in improvement of the lung lesions. Despite treatment for TB and anti-fungal therapy [9] [22] the chest X-ray did not improve with the conclusion that NSG is the most likely diagnosis. The course of events strengthens the diagnosis of NSG and emphasizes its unknown etiology [23]. Although we could not determine the HLA B27 status of our patient, which could support our clinical diagnosis of AS [24], our patient has clinical symptoms and signs, like backpain from the age of 37 years on, sacro-ileitis on the pelvic x-ray and uveitis anterior, to attribute her skeletal complaints to AS according to the ASAS classification criteria [25]. The recurring uveitis can be either an extra pulmonary manifestation of TB [26], an extra-articular manifestation of AS [27] or an accompanying feature of NSG [28]. The positive TST could be false positive [29] or still be a signal of latent tuberculosis infection [11]. Although AS can be associated with Crohn's disease and ulcerative colitis in 5 to 10% of cases [30], the abdominal pain the patient has been experiencing for about 10 years is attributed to irritable bowel syndrome because at colonoscopy there were no signs of inflammatory bowel disease. These findings suggest our patient has 2 conditions based on inflammation: AS and NSG [23] [24]. NSG has a generally benign clinical course and can usually be treated with corticosteroids, although disease recurrence is possible [31] [32].

The concurrent presence in the same patient of the relatively rare disease AS and the even more rare disease NSG [23] [31] [32] made us curious about its concomitant occurrence worldwide. An internet literature search for manuscripts written in English about the simultaneous presence of AS and NSG in the same patient did not result in any published manuscript. As such it seems like the presence of AS and NSG at the same time in our patient is a unique case. Although our case may be the first report in the English language, it has flaws, like not being able to perform the ACE and HLA B27 tests, because these tests could aid in the diagnosis of AS and NSG. Currently our patient has no eye complaints, but in case there is a recurrence of uveitis, local and systemic treatment with steroids will be applied in order to also treat AS and NSG.

4. Conclusion

Sometimes physicians reach a medical diagnosis with an ensuing eureka feeling,

but this case reminds us to be ever alert as clinicians. As our patient seemed to present with an infectious disease, critical evaluation of the case progression resulted in an inflammatory etiology of her symptoms, in this case NSG mimicking tuberculosis.

Conflicts of Interest

We have no conflict of interest to report, nor have we received funding for the preparation of this case report.

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