Clinical Infection in Practice 20 (2023) 100244

Contents lists available at ScienceDirect

Clinical Infection in Practice

journal homepage: www.sciencedirect.com/journal/clinical-infection-in-practice

Case Reports and Series

An unexpected diagnosis of disseminated sarcoidosis in a patient investigated for drug-resistant tuberculosis: A case report

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ARTICLE INFO

Keywords:
Sarcoidosis
Tuberculosis
Drug-resistant tuberculosis

ABSTRACT

Background: Sarcoidosis can mimic both pulmonary and extrapulmonary tuberculosis (TB). Past TB infection or exposure can lead to diagnostic overshadowing. We present a case of a patient exposed to drug-resistant TB presenting with a multisystem inflammatory syndrome ultimately diagnosed as disseminated sarcoidosis.
Case Report: A 55-year-old Congolese male with type 2 diabetes presented to clinic with a one-month history of cough. There were no fevers, night sweats or weight loss and a chest radiograph showed bilateral miliary changes. Five years previously his daughters had both been treated for isoniazid and ethambutol resistant TB and he had received preventive therapy with rifampicin and isoniazid. Computed tomography scanning showed diffuse bilateral tiny nodules in the lungs, enlarged mediastinal, hilar and abdominal lymph nodes and splenomegaly. He subsequently developed headache and complex partial seizures. Lumbar puncture and magnetic resonance imaging of the brain were normal. Early diagnostics on induced sputum were inconclusive. One sputum sample detected *Mycobacterium tuberculosis* DNA, but not to a reportable amplification level and this result was deemed invalid on further testing. Endobronchial ultrasound and mediastinal lymph node biopsy showed histology typical of sarcoidosis with poorly defined, non-caseating granulomas and foci of dystrophic calcification. Tissue staining for mycobacteria and fungi were negative. A serum ACE level was markedly elevated at 264 U/L. The patient was diagnosed with a flare of disseminated sarcoidosis and the illness remitted without immunosuppression.
Conclusion: In patients with a suspected diagnosis of pulmonary or extrapulmonary TB without microbiological confirmation, consider sarcoidosis in the differential diagnosis and consider tissue sampling to support histological differentiation. Molecular tests are increasingly used to diagnose TB and establish TB resistance profiles, but expert knowledge and specialist input regarding the technological pitfalls of molecular tests is essential to guide correct interpretation.

Case

A 55-year-old Congolese male with insulin-dependent type 2 diabetes was referred to a pulmonology clinic with a one-month history of non-productive cough and chest pain. He was clinically well and did not report fever, weight loss or night sweats and had been resident in the UK for over ten years. Five years previously he was seen in tuberculosis (TB) clinic as part of contact tracing when his co-resident daughter was treated for smear-positive pulmonary TB with phenotypic resistance to isoniazid and ethambutol. Screening for TB at this time revealed no symptoms of active disease, a normal chest radiograph and he was unable to produce sputum. His Mantoux test was suggestive of TB exposure with an 8 mm response, interferon gamma release assay (IGRA) testing was not performed and he received 3-months of rifampicin/isoniazid 600/300 mg once daily TB preventive therapy at this time with excellent compliance.

To investigate the current presentation with cough, a chest radiograph was performed and reported as possible miliary TB (Fig. 1). He

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https://doi.org/10.1016/j.clinpr.2023.100244
Received 17 April 2023; Received in revised form 15 September 2023; Accepted 17 October 2023
Available online 23 October 2023

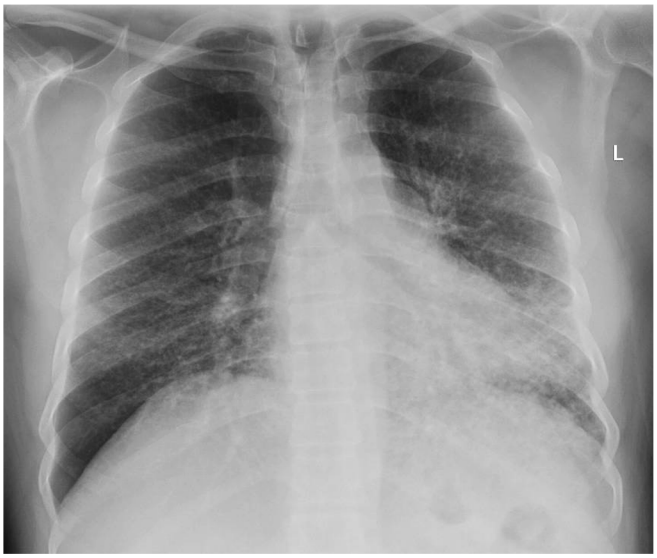

Fig. 1. Chest X-ray showing bilateral miliary opacities with left lower zone consolidation.

received a 7-day course of oral doxycycline to treat lower respiratory tract infection and further tests for TB were pursued. Routine blood tests were normal apart from alkaline phosphatase 292 IU/L (normal 30–150 IU/L) and erythrocyte sedimentation rate 120 mm/hr (normal, <7mm/hr). HIV, syphilis, hepatitis B and C, and autoimmune panels were negative. Three sputa were negative for acid fast bacilli (AFB) and *Mycobacterium tuberculosis* (MTB) polymerase chain reaction (PCR). As active TB was suspected, IGRA testing was not conducted. A computed tomography (CT) scan of the chest and abdomen with contrast showed diffuse lung nodules bilaterally and ground-glass changes in the left lower lobe. Enlarged mediastinal, hilar and abdominal nodes were seen with splenomegaly (15 cm) and no ascites.

While awaiting pulmonology clinic review, he was admitted to the infectious diseases unit with a 2-week history of headache and confusion without meningism, rash or fever. Lumbar puncture had normal opening pressure, protein, glucose and cell counts. Cerebrospinal fluid (CSF) was negative for varicella zoster, herpes simplex, enterovirus and parechovirus PCR as well as AFB, bacterial and mycobacterial culture.

During admission he had multiple vacant episodes with left arm twitching and pain, and impaired awareness lasting 1–2 min, consistent with focal seizures. These were witnessed by senior clinicians and felt to be genuine seizures. Magnetic resonance imaging (MRI) of the brain and electroencephalogram were normal. MRI cervical spine showed osteophytes at C5-7 with compression of left C7 nerve. He was reviewed by neurologists and commenced on levetiracetam and gabapentin, which achieved seizure and pain control.

Five induced sputum samples collected during admission were smear negative for AFB. Direct PCR testing was performed on two samples. Preliminary results on one assay detected MTB DNA, but not to a reportable amplification level, rendering the result invalid.

A diagnosis of pulmonary and extrapulmonary TB with possible drug resistance was considered based on: chest radiograph and CT results, neurological findings (despite normal CSF), previous epidemiological exposure and TB preventive therapy with rifampicin/isoniazid. After discussion in a regional TB multidisciplinary team meeting (MDT), a drug-resistant-TB (DR-TB) treatment regimen of bedaquiline, levofloxacin, linezolid, clofazimine, prothionamide, pyrazinamide and ethambutol was constructed with a presumption of central nervous system (CNS) disease with potential rifampicin, isoniazid and ethambutol resistance. He remained clinically stable, the regimen was not commenced, and tissue sampling was pursued.

Endobronchial ultrasound biopsy of intrathoracic lymph nodes on day 22 of admission showed occasional, poorly defined, non-caseating granulomata, strongly suggestive of sarcoidosis (Fig. 2). There was no evidence of mycobacterial infection histologically or microbiologically and fungal cultures were negative. A serum angiotensin-converting-enzyme (ACE) level was elevated (264 U/L; normal, 8–52 U/L), though CSF ACE testing was not performed. AFB were not seen in the lymph node biopsy.

On day 27 of admission, he had clinically improved without any immunomodulatory or anti-tuberculous treatment. He was discharged home with respiratory follow-up and the likely diagnosis of a flare of previously undiagnosed disseminated sarcoidosis. Neurosarcoidosis was considered unlikely due to normal CSF and MRI results and his seizures remained controlled by levetiracetam. Mycobacterial culture of CSF, sputa, and lymph node samples were all negative at 6 weeks. On review in outpatient respiratory clinic at 1, 3 and 6 months after discharge he remained asymptomatic, chest radiograph appearances were markedly improved and did not require any immunomodulatory treatment.

Discussion

TB and sarcoidosis have similar clinical features but some distinguishing radiological and histological features (Table 1). Radiologically, TB commonly causes pulmonary cavitation, though this is rare in sarcoidosis. Thoracic adenopathy in sarcoidosis tends to be bilateral and symmetrical, whereas in TB unilateral or asymmetric adenopathy predominates (Bhalla et al., 2017). Histologically, granuloma formation is typical in both conditions, with caseation typical in TB but not in sarcoidosis (Rosen, 2007). However, non-caseating granulomata have been found in patients with microbiologically-diagnosed TB and sarcoid-associated granulomata may exhibit necrosis in rare instances (Gupta et al., 2012). Raised serum calcium and ACE are non-discriminatory as they can be raised in both sarcoidosis and TB, as well as other granulomatous diseases (Kwon et al., 2007).

Epidemiologically, there is some evidence to suggest an association between TB and sarcoidosis. In a matched cohort study, sarcoidosis has been found to be more common in people with previous TB infection or

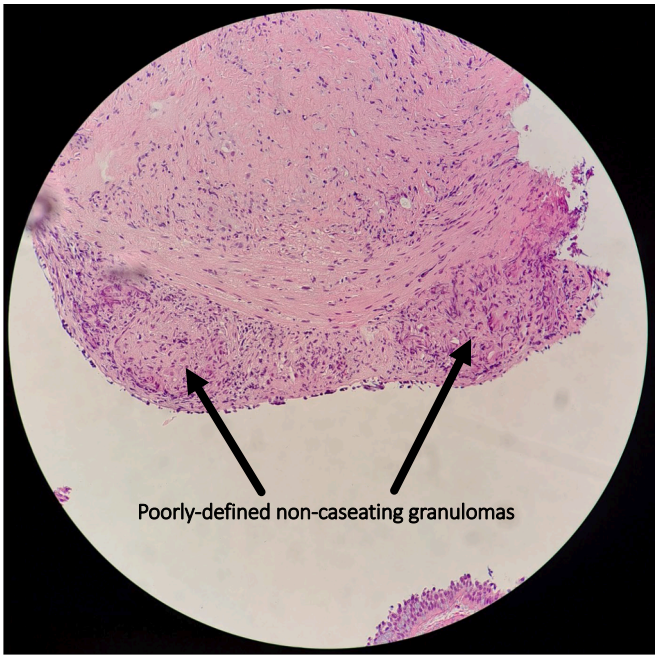

Fig. 2. Mediastinal lymph node histology: Poorly-defined, non-caseating granulomas within the fibrous tissue. Foci of dystrophic calcification including in 'burnt out' granulomas. Staining, PCR and culture negative for mycobacteria and fungi. Features strongly suggest of sarcoidosis.

Table 1
Key histological, biochemical, and radiological features of TB and sarcoidosis.

Key Differentiating Features(Bhalla et al., 2017; Gupta et al., 2012)	Tuberculosis	Sarcoidosis
Histology	Caseating granulomas Lymphocytes dense necrotising granulomas	Non-caseating granulomas Lymphocyte poor non-necrotising "naked" granulomas
Biochemistry	Hypercalcaemia uncommon Hypercalciuria uncommon	Hypercalcaemia common Hypercalciuria common
Radiology	Pulmonary cavitation common Unilateral thoracic lymphadenopathy more common and tends to be asymmetric when bilateral	Pulmonary cavitation rare Bilateral symmetrical thoracic lymphadenopathy

disease (Wang et al., 2019). There are plausible biological reasons why TB exposure – rather than simple misdiagnosis – may predispose to sarcoidosis. Mycobacterial DNA has been isolated in sarcoidosis biopsy samples and is hypothesized to be a potential inciting agent for an aberrant immune response (Fang et al., 2016; Drake et al., 2007). Conversely, immunosuppressive therapy for sarcoidosis may increase vulnerability to infections including TB. There have also been rare case reports of concurrent tuberculosis and sarcoidosis requiring treatment with both antitubercular and immunosuppressive treatments (Carbonelli et al., 2017; Pedroso et al., 2020).

Without a more reliable molecular or immunological marker to diagnosis sarcoidosis, distinguishing between these conditions remains reliant on clinical judgement and histological and microbiological investigations (Carbonelli et al., 2017). Even amongst people at high risk of TB who present with compatible pulmonary and/or systemic symptoms, in the absence of microbiological diagnosis, sarcoidosis should be considered in the differential diagnosis.

Although this patient had classical radiological features of pulmonary sarcoidosis, the clinical presentation with seizures is not typical. Neurosarcoidosis is seen in approximately 5 % of cases of sarcoidosis and shares common clinical features with CNS TB including headache, cranial nerve palsy, seizures and spinal cord lesions. The most common presenting feature of neurosarcoidosis is cranial nerve palsy which can be secondary to nerve granuloma, raised intracranial pressure or aseptic meningitis. MRI imaging of the brain or spine are usually abnormal. CSF usually has raised protein, white cell counts, ACE and oligoclonal bands (Gupta et al., 2012). On specialist review, it was felt the patient did not have neurosarcoidosis as radiological and CSF findings were not typical and the aetiology of the seizures remains unclear.

This patient fulfilled the National Institute for Health and Care Excellence (NICE) recommended criteria for rapid diagnostic nucleic acid amplification testing. One sputum sample was tested using the HAIN Lifesciences fluorotype MTB Ver1.0 assay which identified MTB complex but not to a reportable level suggesting there was not enough DNA in the amplification reaction. A second sample was tested using the HAIN Lifesciences Genotype MTBDRplus line probe assay which demonstrated reverse hybridisation of the MTB probe but no hybridisation of the wild-type isoniazid or rifampicin probes. In both these instances the results are invalid. The underlying reason for these specific results is unclear but highlights the complexity of molecular diagnostics. It may have been that there was cross reactivity with other substances in the samples or presence of *Mycobacterium tuberculosis* DNA relating to his past exposure. Additionally, as discussed above, isolation of mycobacterial DNA in sarcoid lesions is well described (Kwon et al., 2007).

Both PCR results were reported as invalid, but the low-level amplification in the first test and reverse hybridisation in the second were discussed in the regional TB MDT. It is possible that the discussion could have impacted on the decision to treat. As diagnostics become ever more complex, it is vital that biomedical scientists and laboratory-interfacing clinicians maintain a thorough understanding of these technologies, including the advantages and disadvantages, to aid clinical interpretation of the test.

When a diagnosis of TB was suspected, the clinical team considered the patient's epidemiological risk including that: his most recent TB exposure had been from his daughter who had been treated for isoniazid and ethambutol resistant pulmonary TB; he had received preventive TB therapy with rifampicin and isoniazid; and had not travelled to a high TB incidence setting since that time. The clinical team had concerns that, rather than latent TB infection, he may have had subclinical or undiagnosed TB disease at the time of preventive treatment and that preventive therapy might have induced rifampicin resistance in addition to possible isoniazid and ethambutol resistance.

Where DR-TB is suspected it is prudent, when possible, to await initial molecular tests for rifampicin (RpoB) and isoniazid (KatG and InhA) resistance mutations before starting treatment. Further culture and phenotypic sensitivities over the coming weeks may allow the regimen to be tailored further or inform any modifications needed to mitigate adverse drug reactions. Starting therapy too early may reduce the yield of subsequent microbiological tests, especially TB culture, and using empirical DR-TB regimens in the absence of a resistance profile is suboptimal management.

Given the complexity of this case, the regional TB MDT selected an empirical standby regimen to be used in circumstances of clinical deterioration or confirmed TB diagnosis. The regimen was constructed with three goals in mind: covering the potential resistance profile (assuming isoniazid and ethambutol resistance from daughter and possible acquired rifampicin resistance), ensuring CNS penetration and avoiding the exacerbation of seizures. In line of current WHO guidance for the treatment of MDR-TB (WHO). 3 group A drugs were included (bedaquiline, levofloxacin, linezolid). Clofazimine was chosen as the only group B drug because cycloserine can potentiate seizures. For the class C drugs, prothionamide and pyrazinamide were chosen for reliable CNS penetration and ethambutol was kept despite the potential resistance due to its potency and generally favourable side effect profile. The duration of treatment was also considered and a standard 12–18 month regimen was perceived to be safer than a shortened 9-month regimen in view of potential isoniazid and ethambutol resistance.

This case illustrates how sarcoidosis can mimic TB and highlights the importance of obtaining a clear microbiological or tissue diagnosis where possible. It also reminds us of the complexity of the advancing field of molecular diagnostics and the need for expert interpretation of results. Besides sharing clinical features, these two diseases may be more linked than previously thought, with some evidence suggesting TB infection is associated with the development of sarcoidosis. Further research is needed to understand the complex relationship between these diseases and how they might be better differentiated in clinical practice.

Ethical statement

Funding information: Funding for publication was received through United Kingdom Research & Innovation grants held by Dr Tom Wingfield including from: the Medical Research Council, Department for International Development, and Wellcome Trust, UK (Joint Global Health Trials, MR/V004832/1); the Medical Research Foundation, UK (MRF-131–0006-RG-KHOS-C0942); and the Medical Research Council (Public Health Intervention Development "PHIND" award, MR/Y503216/1).

Declaration of Competing Interests statement: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Consent for publication: Written consent was obtained from the patient for publication of this case report.

CRediT authorship contribution statement

Alastair Yeoh: Writing – original draft, Data curation, Conceptualization. **Charlotte Brookfield:** . **Stephen Aston:** . **Dennis Wat:** Writing – review & editing, Conceptualization. **Tom Wingfield:** Writing – review & editing, Conceptualization, Supervision.

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Acknowledgements

Tom Wingfield is supported by United Kingdom Research & Innovation grants including the Medical Research Council, Department for International Development, and Wellcome Trust, UK (Joint Global Health Trials, MR/V004832/1); the Medical Research Foundation, UK (MRF-131-0006-RG-KHOS-C0942); and the Medical Research Council (Public Health Intervention Development "PHIND" award, MR/Y503216/1). For the purpose of open access, the author has applied a CC BY public copyright licence (where permitted by UKRI, 'Open Government Licence' or 'CC BY-ND public copyright licence may be stated instead) to any Author Accepted Manuscript version arising.

References

Bhalla, A.S., Das, A., Naranje, P., Goyal, A., Guleria, R., Khilnani, G.C., 2017. Dilemma of diagnosing thoracic sarcoidosis in tuberculosis endemic regions: An imaging-based approach. Part 1. Indian Journal of Radiology and Imaging. 27 (4), 369–379.

Carbonelli, C., Giuffreda, E., Palmiotti, A., Loizzi, D., Lococo, F., Carpagnano, E., et al., 2017. Coexistent Sarcoidosis and Tuberculosis: A Case Report. Respiration [Internet]. 93 (4), 296–300.

Drake, W.P., Dhason, M.S., Nadaf, M., Shepherd, B.E., Vadivelu, S., Hajizadeh, R., et al., 2007. Cellular recognition of Mycobacterium tuberculosis ESAT-6 and KatG peptides in systemic sarcoidosis. Infect. Immun. 75 (1), 527–530.

Fang, C., Huang, H., Xu, Z., 2016. Immunological evidence for the role of mycobacteria in sarcoidosis: A meta-analysis. PLoS One1 11 (8).

Gupta, D., Agarwal, R., Aggarwal, A.N., Jindal, S.K., 2012. Sarcoidosis and tuberculosis: The same disease with different manifestations or similar manifestations of different disorders. Curr. Opin. Pulm. Med. 18, 506–516.

Kwon, C.I., Park, P.W., Kang, H., Il, K.G., Cha, S.T., Kim, K.S., et al., 2007. The usefulness of angiotensin converting enzyme in the differential diagnosis of Crohn's disease and intestinal tuberculosis. Korean J. Intern. Med. 22 (1), 1–7.

Pedroso, A., Ferreira, I., Chikura, T. 2020. Tuberculosis and Sarcoidosis Overlap: A Clinical Challenge From Diagnosis to Treatment. Cureus.

Rosen, Y., 2007. Pathology of sarcoidosis. Semin. Respir. Crit. Care Med. 28 (1), 36–52.

Wang, S.H., Chung, C.H., Huang, T.W., Tsai, W.C., Peng, C.K., Huang, K.L., et al., 2019. Bidirectional association between tuberculosis and sarcoidosis. Respirology 24 (5), 467–474.

World Health Organization. WHO consolidated guidelines on drug-resistant tuberculosis treatment. 99 p.