

Peer Review File

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Reviewer A

Wonderful work on the comparison of Sarcoidosis and Pulmonary Tuberculosis expanding from the Clinical presentation, radio imaging, and lab findings, especially in the endemic areas. Very well written and documented. A wonderful read. Congratulations to the whole team.

Reply: We appreciate your feedback on our work. We focus on the diagnosis of sarcoidosis, which is challenging to distinguish from tuberculosis, particularly in endemic regions, and aim to improve the perspectives of clinicians on diagnosis using laboratories, imaging, and advanced molecular techniques.

Reviewer B

This is a timely review of a clinically relevant topic -- how to distinguish between TB and sarcoidosis, i.e. two granulomatous conditions that require completely different treatments. It is a complete treatise of the topic, and should be interesting reading for scientists studying these disorders and clinicians treating patients at risk of either on or both conditions. My only suggestion for further improvement is to make sure to have the manuscript proof-read by a native speaker to correct typos and grammatical errors.

Reply: We appreciate your suggestions regarding the proofreading and grammatical accuracy of our manuscripts. As a co-author, one of our team members is a native English speaker who helps us rectify grammar and typos.

Reviewer C

The review article describes a differential diagnosis method for tuberculosis and sarcoidosis, which can be difficult to distinguish clinically. Sometimes it is difficult to differentiate pulmonary TB and tuberculous lymphadenopathy from pulm sarcoidosis clinically, and it is often misdiagnosed. The review of the literature required to diagnose pulmonary sarcoidosis while excluding tuberculosis is of clinical significance in this regard. The publication of this review paper, however, has many problems.

1. Despite describing diagnosis of pulmonary sarcoidosis in the TB endemic area in the title, the overall content of the thesis contains few data on the endemic TB area. The title does not explain why it refers to an endemic area for TB.

Reply: Due to the difficulty in diagnosing sarcoidosis in tuberculosis-endemic areas, we aim to evaluate the efficacy of laboratory investigation, imaging, and novel molecular techniques in order to assist clinicians in adapting this knowledge to the diagnosis of sarcoidosis, particularly in tuberculosis-endemic areas. However, there are few data on tuberculosis-endemic areas, which is one of our review's limitations, and more research is required to determine the effectiveness of these investigations.

2. Due to the exclusion nature of sarcoidosis diagnosis, non-necrotizing granulomas are excluded through EBUS. The information in this paper appears to indicate the diagnosis of pulmonary tuberculosis than the diagnosis of pulmonary sarcoidosis.

Reply: We appreciate your thoughtful comment. Although the most recognizable pathological feature of tuberculosis is the presence of caseous necrosis in pathological tissue, there is growing evidence that TB can manifest as a non-caseating necrosis, particularly in immunocompromised hosts. On the other hand, sarcoidosis is a non-caseating granuloma.

3. There is a problem with the order of the content of the article. Generally, if it is necessary to distinguish between TB and sarcoidosis in images or tissues, the order of explaining AFB smears, TB cultures, and TB-PCR should be explained first. Also, the order in which the clinical examinations are conducted - imaging, bronchoscopy, and EBUS - should be described first, and the experimental aspects (immunologic study, molecular markers, blood transcriptome) should be described in the second half so that future research directions can be identified.

Reply: Thank you for your great recommendations regarding the content's arrangement. For the convenience of the reader, we intend to organize the review article on diagnostic approaches according to laboratory investigation, invasive diagnostic advancement, and radiographic investigation. However, we agree with your helpful suggestions regarding the experimental aspects, which include immunological study, molecular markers, and blood transcriptome, and have moved them to the second half so that future research directions can be determined.

Changes in the text: we have modified our text as advised (see Page 17, line 470-518)

4. It was difficult to understand the English expression because it was awkward.

Reply: We appreciate your suggestions regarding English expression and grammatical accuracy of our manuscripts. As a co-author, one of our team members is a native English speaker who helps us rectify grammar and typos.

5. Some reference notations contain errors.

Reply: We apologize for any errors that occurred.

As suggested, we have already corrected the reference notation errors.
6. It is also necessary to change the title of Table 2. “Comparisons of clinical characteristics between tuberculosis and sarcoidosis”

Reply: We have modified our text as advised (see Page 27, Table 2)

In addition, hilar lymphadenopathy, cavitation, and military?(miliary distribution) overlap with the imaging findings in Table 5.

Reply: We apologize for any errors that may have occurred. As suggested, we have already corrected the typo. However, the hilar lymphadenopathy characteristic, cavitation, and miliary distribution remain present in Tables 2 and 5.

7. CT images are required for Table 5

Reply: We regret that our review article does not include CT images due to an absence of excellent examples of CT images that can distinguish between two diseases and the fact that our primary objective does not involve image comparison. We only intend to provide a list of interesting CT findings.

Reviewer D

The authors have conducted a narrative review of various examination techniques that can be used to differentiate pulmonary tuberculosis from pulmonary sarcoidosis. However, I think this review article has some serious problems.

1. The methods and results of the narrative review are inadequately described. The review only searched PubMed, but I think searching only one site is inadequate; you should also search other sites such as Web of Science and/or Cochrane. You should also describe how many references you found through these searches, how many of them you excluded, and why you excluded them.

Reply: We appreciate your considerate suggestion. As our search was limited to MEDLINE and PubMed, we will note this as a limitation of our review. The exclusion criteria have already been discussed in Table 1.

Changes in the text: we added some data (see Page 20, line 539-540)

2. I did not understand to whom and what information this review is intended to provide. From the title of the paper, it seems that it is intended for clinicians. If so, there seems to be no need to say much about biomarkers and transcriptomes, which can only be performed in a very limited number of laboratories. On the other hand, if the target is researchers who aim to investigate advanced testing methods, then tuberculin test and radiological examinations may be of little interest. If the emphasis is on testing in TB endemic areas, then the focus should be on the sensitivity and

specificity of tests that can be performed in areas with relatively little medical development, such as African countries. There is little need to describe advanced tests or tests such as MRI and nuclear imaging. I believe that there should be more refining of the purpose of narrative review and the methodology.

Reply: This review article aims to provide clinicians with a summary of data regarding the diagnosis of sarcoidosis in tuberculosis-endemic areas that involves clinical, laboratory, and imaging aspects, and to provide researchers with a summary of data involving molecular and novel methods such as biomarkers and blood transcriptomes for future research directions.

3. If you mention about IGRA, then ELISPOT should also be mentioned. Also, if you are discussing IGRA-positive sarcoidosis patients, you need to consider LTBI. It may be problematic that there is no mention of latent tuberculosis in this manuscript.

Reply: We appreciate your thoughtful recommendation. We provide additional evidence regarding ELISPOT. In our manuscript, we have already discussed latent TB infection in sarcoidosis patients with a positive IGRA.

Changes in the text: we added some data (see Page 8, line 196-198)

4. Bronchoscopy should not be performed in patients who are suspicious of the possibility of tuberculosis. From the point of view of this manuscript, which is to differentiate between sarcoidosis and TB, it should first be mentioned that only a very limited number of patients are indicated for bronchoscopy. In addition, if you discuss TBLC, you should also mention that the risk of bleeding and pneumothorax, its major complications, is extremely high, and its indication should be carefully considered.

Reply: We value your suggestion and concur wholeheartedly with these points, so we've added some information to the manuscript in response to your suggestion.

Changes in the text: we added some data (see Page 12, line 352) and (Page 13; line 381-383)

5. I think it is necessary to summarize how imaging studies are useful in the differentiation between sarcoidosis and tuberculosis.

Reply: We greatly value your suggestion. In Table 5, we have already summarized data on how to distinguish between sarcoidosis and tuberculosis using imaging.

6. It seems strange to me that Africa is not included in the description of TB endemic areas.

Changes in the text: we added some data regarding Africa (see Page 19, line 528-529)

Reviewer E

I read it with great interest, and it helped me to organize my knowledge.
I would like to make a few comments.

1. As the author points out, sarcoidosis itself is relatively rare, and it may indeed be difficult to differentiate it from TB based on pathological findings alone, but the findings of pulmonary TB and sarcoidosis on imaging have been accumulated, and I do not think there is much difficulty in differentiating in clinical practice. A more detailed description of the importance of differentiating between TB and sarcoidosis is needed.

Reply: Regarding sarcoidosis and tuberculosis, we thank you for your interest and appreciate that this review can assist in organizing knowledge. We greatly value your suggestion and have already mentioned the significance of differentiating between these two diseases in our manuscript, which focuses primarily on the selection of an appropriate management strategy that is entirely distinct between the two conditions. We mentioned this point in Background and Objective

2. Are there any reports of cases of TB and sarcoidosis combined?

Reply: There are only a few case reports that describe a patient with both sarcoidosis and tuberculosis. Some case reports suggest that sarcoidosis patients with pulmonary miliary patterns may have underlying risk factors for tuberculosis and advocate for additional research to clarify the relationship.