Review Article

Diagnosis of pulmonary sarcoidosis in tuberculosis endemic area—a narrative review

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Background and Objective: Pulmonary sarcoidosis and tuberculosis (TB) are the most frequent tissue-confirmed granulomatous diseases. Due to its unknown etiology, pulmonary sarcoidosis is diagnosed by ruling out other granulomatous diseases and necessitating clinical, radiological, and pathological evidence. There are many factors that contribute to the diagnostic dilemma between these two diseases. Even though some aspects of both diseases, such as their pathological evidence and abnormal X-ray findings, are quite similar, the treatment options for each are entirely different. The standard treatment for sarcoidosis is immunosuppressive agents such as glucocorticoids, which can exacerbate TB. Consequently, the overlap between clinical and radiological features constitutes a significant challenge for many physicians in selecting the optimal treatment for each patient. Therefore, the exclusion of pulmonary TB is a mandatory step for the diagnosis of pulmonary sarcoidosis. This article reviews and summarizes basic science and clinical research on distinguishing these two disorders.

Methods: A systematic search of the MEDLINE and PubMed databases focusing on studies published within the last 35 years was conducted. The last search date is February 4, 2023. The authors used the following combinations of terms: tuberculosis, sarcoidosis, diagnosis, bronchoscopy, biomarkers, and radiography. All studies were reviewed, and 69 references from 1990 to 2023 were found to be relevant.

Key Content and Findings: Innovative laboratory tests are essential for distinguishing between pulmonary sarcoidosis and TB. The Xpert MTB/RIF assay diagnoses TB with 98% sensitivity and 89% specificity. Loop-mediated isothermal amplification (LAMP) and simultaneous amplification and testing method for *Mycobacterium tuberculosis* rRNA (SAT-TB) are also highly sensitive and specific for TB diagnosis. Several novel tests, such as the difference of immune complexes for the ESAT-6/SFP-10 antigen in vitro with dynamic light scattering (DLS), lung tissue-based molecular markers, and the blood transcriptome, are promising for differentiating TB from sarcoidosis.

Conclusions: Recent advancements in laboratory investigations, non-invasive procedures, and invasive procedures play an important role in the diagnosis of sarcoidosis in TB-endemic areas. However, further study is needed to evaluate the diagnostic performance of all tests in terms of their competency in distinguishing between TB and sarcoidosis.

Keywords: Sarcoidosis; tuberculosis (TB); diagnosis

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Introduction

Background

Sarcoidosis is a chronic granulomatous disease of unknown etiology. Criteria for the diagnosis of sarcoidosis have recently been established by the American Thoracic Society (ATS) in 2020, although some criteria remain poorly standardized. The diagnosis consists of three aspects including clinical presentation, non-necrotizing granulomatous inflammation in tissue samples, and exclusion of other causes of granulomatous diseases (1). The global epidemiological data of sarcoidosis is different among ethnicity and geographical location and there are many registries in the world which report different prevalence of this disease (2,3). It is known that sarcoidosis is more prevalent among Scandinavian, Northern Europeans and African Americans, whereas it is rare in Asians (4). The recent nationwide register-based Swedish study estimated a prevalence of 0.16% and an incidence of 11.5 per 100,000 per year which is almost identical to the recent cohort study from the Mayo Clinic using data from northern European ancestry with an incidence rate of 11 per 100,000 per year (5,6). The Nurses' Health Study II (NHSII), a prospective cohort of sarcoidosis among U.S. women with the majority of Caucasian female population, reported a prevalence of 0.10% and a similar incidence of 11 per 100,000 per year (7). The Optum health insurance medical claims database in the USA also reported an incidence rate ranging from 7.6 to 8.8 per 100,000 per year and revealed that African Americans had a higher prevalence and incidence compared with Asians, Caucasians, and Hispanics (8). In Asia, there was a population-based and nationwide database called the Taiwan National Health Insurance Research Database (NHIRD) which reported an overall sarcoidosis prevalence of 0.03% (9). In Thailand, the epidemiological data on sarcoidosis is still unknown. A single-center retrospective cohort study from Thailand showed the high prevalence of uveitis and the marked female predominance among sarcoidosis patients but has not reported any data on the overall prevalence or incidence of sarcoidosis in Thailand (10).

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis* (MTB) infection. According to World Health Organization (WHO), TB has been considered as a world-health problem with an estimated 9.9 million people suffered from TB in 2020 which is equal to 127 cases per 100,000 population according to the 2021 Global Tuberculosis Report. Although the most well-known pathological hallmark of TB is evidence of caseous necrosis in pathological tissue, there is some growing evidence showing that TB can be present as a non-caseating necrosis especially in the immunocompromised host (11,12). In contrast, sarcoidosis is considered as a non-caseating granuloma. Therefore, the gold standard for diagnosis of TB is a positive culture from body fluids or tissues. Moreover, there are other choices for TB diagnosis which produce various sensitivity and specificity such as a positive tuberculin skin test (TST), interferon gamma release assays (IGRAs), and other molecular techniques.

Rationale and knowledge gap

The overlapping between sarcoidosis and TB has been reported in many aspects. In histological aspect, both diseases show granulomatous inflammation. In clinical aspect, they also have common clinical presentations including constitutional symptoms such as fatigue and weight loss, respiratory symptoms such as dyspnea, and bilateral hilar lymphadenopathy which is the most common finding of sarcoidosis in both asymptomatic and symptomatic patients (13,14). Also, imaging studies and histological findings could not distinguish between TB and sarcoidosis in some cases. Moreover, it has been speculated that approximately 15–20% of the patients might be misdiagnosed between TB and sarcoidosis based on immunological tests (15).

Objective

There are many ongoing studies that aim to distinguish between these two diseases in many aspects. In this article, we aim to review and summarize available studies that emphasize how to differentiate between pulmonary sarcoidosis and pulmonary TB from basic science studies to clinical studies. We present this article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-

Table 1 The search strategy summary

Items	Specification
Date of search	February 4th, 2023
Databases and other sources searched	MEDLINE, PubMed
Search terms used	"tuberculosis [AND/OR] sarcoidosis [AND] diagnosis", "tuberculosis [AND/OR] sarcoidosis [AND] radiography", "tuberculosis [AND/OR] sarcoidosis [AND] biomarkers", "tuberculosis [AND/OR] sarcoidosis [AND] bronchoscopy"
Timeframe	January 1st, 1990–February 4th, 2023
Inclusion and exclusion criteria	Inclusion criteria: prospective cohort studies, retrospective cohort studies, case control studies, case reports, reviews, systematic reviews, metanalyses, and clinical practice guidelines, English language
	Exclusion criteria: abstracts, books, documents
Selection process	The first author conducted the initial literature selection and review, with suggestions for additional feedback from corresponding authors

192/rc).

Methods

A systematic search of the MEDLINE and PubMed databases focusing on studies published within the last 35 years was conducted. The date of the last search is February 4, 2023. The following combinations of terms were utilized by the authors: tuberculosis, sarcoidosis, diagnosis, bronchoscopy, biomarkers, and radiography. All studies were reviewed, and 69 references from 1990 to 2023 fell within the scope of our interest. A search strategy summary can be seen in *Table 1*.

Clinical-radiological and histological spectrum among sarcoidosis and TB

Sarcoidosis has various clinical presentations which range from asymptomatic to severe symptoms. One of the most common presentations is isolated mediastinal and bilateral hilar lymphadenopathy (1). Approximately 25% of patients with sarcoidosis progress to chronic disease (2). Lungs and intrathoracic lymph nodes are the two most common organs affected. Common symptoms include dyspnea, cough, and chest tightness. In addition to pulmonary involvement, there are many other extrapulmonary organs including skin, eyes, joints, liver, nervous system, kidneys, heart, and gastrointestinal tract. Among the extrapulmonary involvement, skin is the most common extrathoracic manifestation occurred one-third of cases and followed by ocular involvement ranging from 12% to 76% based on race, with some Japanese studies reporting as high as 80% (16,17). Uveitis is the most common ocular involvement ranging from 10% to 25% of all patients (18). The multi-organ manifestation of sarcoidosis is an important feature of the disease and can prove helpful in the diagnosis (19). Recently, the Sarcoidosis Diagnostic Score (SDS) which consists of both clinical domain and the presence of granuloma on biopsy has been developed in multicontinental study to differentiate sarcoidosis from alternative diagnoses, including MTB with excellent performance (19).

TB shares many clinical manifestations with sarcoidosis. Constitutional and respiratory symptoms can present in both diseases. Hilar lymphadenopathy is also a presentation of both diseases with some different characteristics of lymph nodes (*Table 2*) (20). While both diseases can affect many organs, the spectrum of diseases is various and different as described in *Table 2* (18,21,22).

Diagnostic approach

Laboratory investigation

Lymph node sampling

The characteristics of lymphadenopathy in sarcoidosis are discrete, bilateral, and symmetrical with rarely show central hypodensity which is common in TB (20).

TST

The positivity of TST has been well-known described

Table 2 Comparisons of clinical characteristics between tuberculosis and sarcoidosis

Clinical characteristics	Tuberculosis	Sarcoidosis
Pulmonary symptoms	+	+
Extrapulmonary symptoms		
Skin	Vary (inflammatory papules, verrucous plaques, suppurative nodules, chronic ulcers)	Papules, plaques and subcutaneous nodules, lupus pernio
Eyes	Ocular TB	Uveitis
Joints	TB spondylitis; TB arthritis (monoarthritis, hip and knee joints); TB tenosynovitis; TB osteomyelitis	Inflammatory arthritis (5–15%) (oligoarthritis, large joint, ankle joint); enthesitis (5–8%)
Liver	Solid-organ TB	Hepatic sarcoidosis (5–30%)
Nervous system	TB leptomeningitis, tuberculoma, TB radiculomyelitis	Cranial neuropathy (CNII, VII, VIII) (facial palsy, optic neuritis, hearing loss, peripheral vertigo)
Kidneys	Genitourinary TB	Granulomatous interstitial nephritis
Heart		Cardiac sarcoidosis (1–23%)
Gastrointestinal tract	Intestinal TB (most common—ileocecal); peritoneal TB; solid-organ TB (common—liver, spleen)	GI sarcoidosis (rare, less than 1%)
Constitutional symptom	+	+
Hemoptysis	+, fibrocavitary TB	–
Hilar lymphadenopathy	+	+
Characteristics of lymphadenopathy	Asymmetrical, central necrosis	Discrete, bilateral, symmetrical, rarely central hypodensity
Cavitation	+	Rare
Miliary distribution	++	+

++, very common; +, common; –, less common. TB, tuberculosis; CN, cranial nerve; GI, gastrointestinal.

when an induration is ≥10 mm for Bacillus Calmette-Guerin (BCG)-unvaccinated and hemodialysis patients and induration ≥15 mm for BCG-vaccinated controls (23).

Though, the sensitivity of TST is diminished in TB prevalent area (20), the negativity of TST can help in distinguishing sarcoidosis from TB with negative predictive value of 86% (95% CI: 72–94%), except of immunocompromised patients (24,25). In immunocompetence, it has been known that patients with hemodialysis were at increased risk of latent TB reactivation, TST has been reported that its competency in diagnosis of latent TB reactivation was diminished when compared with QuantiFERON-TB-Gold in Tube assay (QFG-IT). The sensitivity, specificity, positive predictive value, and negative predictive value of QFG-IT and TST for reactivation of TB were 100% and 25%, 62% and 67%, 10% and 3%, 100% and 95%, respectively (26).

IGRAs

IGRAs are new-generation assays that measure in-vitro T-cell responses to *M*TB-specific antigens (27). QFG-IT, one of the IGRAs, has been recognized for its superiority of competency compared with TST in both detecting TB and latent TB infection in hemodialysis patients (26). In sarcoidosis, IGRAs have been claimed their competency in the diagnosis of latent TB infection among sarcoidosis patients, but their ability in the diagnosis of sarcoidosis has not been reported yet.

QFG-IT

QFG-IT is one of the IGRAs which has been claimed its superiority in detection of *M*TB over conventional TST. However, the positivity of QFG-IT occurs in both latent TB infection and sarcoidosis with some evidence claiming that IGRAs could identify latent TB infection in sarcoidosis patients both in high-prevalence and low-prevalence of

TB areas (24,28). Recently, a prospective cohort study from the United Kingdom has been reported that the new-generation QuantiFERON (QuantiFERON-TB Gold Plus; QFT-Plus) which added the second TB antigen to stimulate a CD8 T-call response in addition to CD4 in previous version had a comparable performance with commercial QFG-IT with 80% of sensitivity for detection, 5.7% of positive predictive value, and 99.4% of negative predictive value (29).

The ELISPOT TB test

The ELISPOT TB test is one of the IGRAs. When compared to QFG-IT, QFG-IT is easier to perform and has less inter-assessor variability (30).

Considering competency between TST and IGRAs

According to WHO systematic review, both TST and IGRAs have low positive predictive value in high-burden areas but both of them have high negative predictive value in all settings (31). A recent study reported no significant differences in negative predictive value between IGRAs and TST with 99.4% negative predictive value for QFG-IT, 99.5% for T-SPOT.TB, 99.6% for TST-5, 99.6% for TST-10, and 99.5% for TST-15 (32). In terms of competency in distinguishing between pulmonary sarcoidosis and pulmonary TB, TST and IGRAs are almost equal in negative predictive value.

Molecular techniques

Multi-targeted polymerase chain reaction (PCR) for MTB

PCR is one of the nucleic acid amplification tests (NAATs) which has been claimed its ability in rapid detection of MTB within hours, whereas the turnaround time of mycobacterial cultures, the gold standard, required 2 to 6 weeks duration. In recent years, real-time polymerase chain reaction (RT-PCR) has been developed and claimed its superiority in speed, automation, sensitivity, and specificity above conventional PCR methods with good diagnostic performance for MTB (33).

The accuracy of in-house polymerase chain reaction (hPCR) has been reported in a recent systematic review and meta-analysis with a total of 97% area under the curve (AUC) indicating that it was useful in the rapid detection of TB and the negative result guaranteed the certainty of ruling out active TB (34).

In terms of scanty positive acid-fast-bacillus (AFB) sputum smears, RT-PCR performance to detect MTB is still challenging because of low bacillary loads. A 5-year retrospective study from Thailand which is one of the endemic areas of TB reported that the sensitivity, specificity, positive predictive value, and negative predictive value of RT-PCR were 62.5%, 98.1%, 96.2%, and 77.3%, respectively. As a result, a negative RT-PCR could not exclude TB (35). Also, a study from Korea, another country in an endemic area of TB, reported the result including the sensitivity, specificity, and accuracy of RT-PCR from sputum were 44%, 99%, 86%, and 65%, 97%, and 87% from bronchoscopic samples, respectively. In conclusion, the overall respiratory specimens had 59% of sensitivity, 98% of specificity, and 89% of accuracy which were almost similar number to a study from Thailand (36). Moreover, a study in Shanghai reported that MTB genome quantification by RT-PCR provides a good performance in distinguishing between sarcoidosis and TB with highly significant ($P<0.001$) accuracy using receiver operating characteristic (ROC) curve analysis. Also, the MTB genome copies number of 1.14×10^3 copies per mL is a preferred value to differentiate between sarcoidosis and MTB (37).

In 2010, WHO launched the Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) which was a new automated cartridge-based NAAT that could simultaneously detect Mycobacterium TB complex and rifampicin resistance within 2 hours (38). In 2014, The Cochrane Review on the diagnostic accuracy of Xpert MTB/RIF for TB detection and rifampicin resistance detection in adults revealed that Xpert MTB/RIF had 89% detection rate of TB cases with high specificity (99%) when used as an initial test instead of smear microscopy, 67% detection rate with high specificity (99%) when used as an add-on following smear microscopy, 98% of sensitivity for smear-positive and culture-positive TB, and could increase detection rate by 23% in comparison with smear microscopy (39). Furthermore, there was a systematic review reported that the pooled sensitivity and specificity of Xpert MTB/RIF were 89% and 98%, respectively (40).

Considering the extrapulmonary aspect of TB involvement, multi-targeted PCR has been used for the detection of TB in various issues. There was a study showing that IS6110, MPB64, and protein b were specific for presumed tubercular uveitis with 100% of specificity, 77.77% of sensitivity, 100% of positive predictive value, and 88.88% of negative predictive value (41). Another study found that overexpression of IL-17RC on CD8 T-cells detected by PCR in peripheral blood was associated with ocular sarcoidosis (4).

Table 3 Diagnostic performance of tuberculosis

Method	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
TST	25	67	3	99.5–99.6
IGRAs				
QFG-IT	100	62	10	99.4
QFT-Plus	80	–	5.7	99.4
RT-PCR	62.5	98.1	96.2	77.3
LAMP	93	94		
SAT-TB	96	88		
Xpert MTB/RIF	89	98		

PPV, positive predictive value; NPV, negative predictive value; TST, tuberculin skin test; IGRAs, interferon-gamma release assays; QFG-IT, QuantiFERON-TB-Gold in Tube assay; QFT-Plus, QuantiFERON-TB Gold Plus; RT-PCR, real-time polymerase chain reaction; LAMP, loop-mediated isothermal amplification; SAT-TB, simultaneous amplification and testing method for *Mycobacterium tuberculosis* rRNA.

Simultaneous amplification and testing method for Mycobacterium tuberculosis rRNA (SAT-TB)

While PCR is one of the effective ways to distinguish between these two diseases, it cannot distinguish active TB from sarcoidosis with inactive TB which contains a dead MTB-DNA (42). SAT-TB which used the endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) specimens has been developed to distinguish sputum-negative TB from sarcoidosis with a statistical significance and has been reported that it can identify active TB as accurately as conventional methods (42). There was a systematic review that reported that the pooled sensitivity and specificity of SAT-TB were 96% and 88%, respectively (40). Moreover, this method could decrease the false-positive rate compared with the PCR method (42).

Loop-mediated isothermal amplification (LAMP)

LAMP was one of the nucleic amplification tests which requires no specialized nucleic acid amplification equipment. LAMP was suitable for developing countries because of its low-cost and high accuracy. There was a systematic review that reported that the pooled sensitivity and specificity of LAMP were 93% and 94%, respectively (40).

Test competency among three of the NAATs

Considering the sensitivity to detect MTB, the SAT-TB had the highest pooled sensitivity (96%), followed by LAMP (93%) and Xpert MTB/RIF (89%). In contrast, the Xpert MTB/RIF had the highest pooled specificity (98%), followed by LAMP (94%) and SAT-TB (88%). Regarding the AUC for summary receiver operating characteristic (sROC) curves, LAMP, SAT-TB, and Xpert MTB/RIF had 0.9812, 0.9147, and 0.9897 of AUC respectively, which means that all methods are highly accurate for the diagnosis of pulmonary TB (40).

In *Table 3*, the overall diagnostic performance of each laboratory technique is compared.

Procedural invasive diagnostic advancement

Bronchoscopy has been considered a standard specimen in the diagnosis of diffuse parenchymal lung diseases including sarcoidosis. This procedure can provide many diagnostic specimens including endoscopic ultrasonography such as EBUS-TBNA, and endoscopic ultrasound-guided fine needle aspiration (EUS-FNA). Transbronchial lung biopsy (TBLB) is another choice for the diagnosis of sarcoidosis (43). Bronchoalveolar lavage (BAL) and bronchial washings can be examined for infections such as MTB as well as cytologic examination for malignancy. However, bronchoscopy is indicated for a very small number of patients.

EBUS-TBNA

Nowadays, the EBUS-TBNA is widely used to perform mediastinal lymph node biopsy or aspiration for specimen collection which is used for the detection of MTB by RT-PCR which is an effective method to differentiate TB from sarcoidosis (42). The competency of differentiation between these two diseases using RT-PCR is valuable with a cut of value at 1.14×10^3 copies/mL which provides 96.8%

Table 4 Diagnostic performance for diagnosis of sarcoidosis

Variables	Diagnostic yield
EBUS-TBNA	79% diagnostic yield, 84% sensitivity
TBLB	37–90% diagnostic yield

EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; TBLB, transbronchial lung biopsy.

sensitivity and 98.1% specificity (37). EBUS-TBNA is recommended because of its high-yield efficacy compared to TBLB plus endobronchial biopsy (44). It has been reported that EBUS-TBNA had a significantly greater diagnostic yield to detect granuloma in sarcoidosis with an 85–94% detection rate compared with TBLB which had only a 31–37% detection rate especially in stage I/II pulmonary sarcoidosis (44). The diagnostic value of EBUS-TBNA drops significantly in patients with no evidence of adenopathy on chest imaging. A systematic review and meta-analysis revealed an excellent diagnostic performance of EBUS-TBNA in sarcoidosis with a pooled diagnostic yield of 79% and 84% sensitivity (45). Considering the role of EBUS-TBNA in the diagnosis of TB, there was a study on adolescents showing that EBUS-TBNA had a 66.7% diagnostic yield (46). Also, a meta-analysis revealed pooled sensitivity and specificity of 80% and 100%, respectively for diagnosis of intrathoracic TB using EBUS-TBNA (47).

TBLB

TBLB was commonly used for diagnosis of sarcoidosis with 40% to 90% diagnostic yield depending on the burden of lung parenchyma and could increase diagnostic yield by approximately 20% with endobronchial biopsy supplementation (18). The earlier American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders (ATS/ERS/WASOG) statement on sarcoidosis considered TBLB a first choice for tissue sampling diagnosis with 37–90% diagnostic yield (48). Considering the role of TBLB in the diagnosis of TB, Chan *et al.* reported the highest sensitivity of TBLB (77% of sensitivity) when using radial probe endobronchial ultrasound guidance, whereas other studies also reported the sensitivity range of 16–77% for the diagnosis of TB by using TBLB alone (49,50). Transbronchial lung cryobiopsy (TBLC) which retrieves lung tissue by freezing probe via bronchoscopy is considered to provide better diagnostic yield than TBLB in interstitial lung diseases including sarcoidosis as described in recent studies (51,52). However, the risk of hemorrhage and pneumothorax, the main complications of TBLC, is extremely high, and its indication should be carefully considered.

Bronchoalveolar lavage fluid (BALF) CD4/CD8 ratio

Non-caseating granulomas in sarcoidosis was believed that it developed from the accumulation of CD4 T lymphocytes in affected tissues from T-helper-1 hyperimmune response (53). Many studies had shown that the elevation of CD4/CD8 ratio in BALF may supplement the results of other tests for diagnosis of sarcoidosis (54). However, the role of the BALF CD4/CD8 ratio alone is still controversial in the diagnostic performance of sarcoidosis. The sensitivity and specificity of BALF CD4/CD8 ratio were various among studies because of the difference in cut-off value among studies which fell between 2 and 4. A meta-analysis was performed and revealed low pooled sensitivity of 70% and specificity of 83% (55). Fewer studies have evaluated BAL in MTB. BAL lymphocytosis with an increased CD4/CD8 ratio can be seen in TB. A meta-analysis reported that the CD4/CD8 ratio in BALF was increased in TB, whereas the ratio was reduced in peripheral blood for TB patient (56).

The diagnostic efficacy of invasive diagnostic procedures for sarcoidosis is compared in *Table 4*.

Radiographic investigation

Conventional chest X-ray

The chest X-ray is an initial modality of sarcoidosis and TB diagnosis. The finding of bilateral hilar lymphadenopathy has been described as characteristic of sarcoidosis. Symmetrical hilar adenopathy is common with sarcoidosis and rare with MTB except in human immunodeficiency virus (HIV)-infected individuals. In contrast, unilateral hilar/paratracheal lymphadenopathy has been considered as a highly suggestive of TB. Moreover, consolidation/air-space involvement with ipsilateral lymphadenopathy, thick-walled cavities, empyema, military nodules are also considered as highly suggestive of TB (57).

However, there are some overlapping features among these two diseases including mediastinal and/or hilar lymphadenopathy, parenchymal nodules, and fibrosis. Therefore, other radiographic modalities play an important role in distinguishing these two diseases.

Comparing the chest X-rays findings of sarcoidosis and TB is depicted in *Table 5*.

Table 5 Radiographic findings of tuberculosis and sarcoidosis

Variables	Tuberculosis	Sarcoidosis
Chest X-rays		
Lymphadenopathy	Unilateral hilar/paratracheal lymphadenopathy	Bilateral hilar lymphadenopathy
Other findings	Thick-walled cavity, empyema, miliary nodules, consolidation with ipsilateral lymphadenopathy	
Computed tomography		
Micronodules	Centrilobular (tree-in-bud), bilateral, upper, right middle lobe, lingula, superior segment of lower lobe	Perilymphatic, bilateral, upper, right middle, lingular lobe
Consolidation	Consolidation with ipsilateral lymph node enlargement	Peribronchovascular, bilateral, upper, and middle lobe
LN enlargement	Peripheral rim enhancing mediastinal LN	Bilateral hilar, right paratracheal LN
Other signs	Miliary nodules, thick-walled cavity, empyema with split pleura sign	Galaxy sign, sarcoid cluster sign

LN, lymph node.

Computed tomography (CT)

Contrast-enhanced CT (CECT) has proved useful in detection of intranodal necrosis and mapping of lymph nodal stations which can provide benefits in differentiation between TB and sarcoidosis. Considering CT characteristics of sarcoidosis, the peri-lymphatic distribution of micronodules in bilateral upper, right middle, and lingular lobe is considered a highly suggestive finding and the most common pattern of parenchymal involvement of active sarcoidosis together with bilateral peri-bronchovascular ill-defined consolidation in upper and middle lobes, multiple bilateral coalescent interstitial nodules, enlarged bilateral hilar and right paratracheal nodes. In contrast, centrilobular nodules (especially tree-in-bud) in bilateral upper lobe, right middle lobe, lingula, and superior segment of lower lobe are considered as a highly suggestive finding of active TB together with consolidation with ipsilateral lymph node enlargement, military nodules, thick-walled cavity, peripheral-rim enhancing mediastinal lymph nodes and effusion, empyema with split pleura sign (57).

Considering the pattern of calcification of lymph nodes, the egg-shell pattern of calcification has been found in approximately 5% in sarcoidosis while this pattern has not been found in TB (57).

There are many radiographic signs including "galaxy sign" and "sarcoid cluster sign" which have been described in parenchymal opacities in sarcoidosis. To illustrate, "galaxy sign" is the appearance of nodules and patchy consolidation with multiple satellite nodules at the periphery and "sarcoid cluster" denoted multiple clusters of micronodules in peri-lymphatic distribution especially in subpleural region of upper and middle lung zone. However, these signs could be found in TB with lymphatic dissemination (57).

Table 5 illustrates the comparison of CT findings in sarcoidosis and TB.

Magnetic resonance imaging (MRI)

Necrosis is one of the MRI features which can distinguish between TB and sarcoidosis with multiple paradigms including signal detection on T2 weighted (T2W) sequence, diffusion characteristics, and enhancement pattern (57). One study found MRI findings had a good correlation with CT in gross parenchymal opacification and reticulation in sarcoidosis (58). In TB, many studies have reported that MRI had comparable competency with CT in the identification of morphological changes and had superiority in tissue characterization (59).

Nuclear imaging

Gallium-67 scanning

Gallium-67 could detect in areas of increased blood flow such as inflammatory causes. "Lambda" sign which is the showing of bilateral paratracheal and hilar uptake is a characteristic pattern in sarcoidosis (60). "Panda sign" which is an uptake in parotid and lacrimal glands is another pattern of uptake in sarcoidosis but it can also show in other causes such as lymphoma (61). Some study shows that it is highly specific for sarcoidosis when showing both panda and lambda sign (60). Unfortunately, the intensity of activity of the Gallium-67 uptake is rapidly suppressed by

glucocorticoids, which block the uptake of gallium through the transferrin receptor. Therefore, the scan has limited value in patients on prednisone or similar treatments.

Positron emission tomography (PET)

F-18 fluorodeoxyglucose (FDG) PET/CT scan demonstrates tracer uptake in areas of sarcoidosis with active inflammation and shows increased uptake in active TB (57). A retrospective study reported that F-18-FDG PET/CT had 78% correction in demonstration of biopsy-proven sarcoidosis locations with 100% sensitivity for sino-nasal and thoracic sarcoidosis (62). In comparison to Gallium-67 scanning, the PET/CT scan had superior sensitivity and specificity. The limitations of PET/CT scan include the relatively low sensitivity to small lesions and the intense activity normally seen in the brain. The current technology limits the ability to detect neurologic diseases. Also, increased activity can be seen with any active inflammatory process, such as MTB.

Experimental aspects and laboratory investigation for future research direction

Immunological study

The difference of immune complexes for the ESAT-6/SFP-10 antigen *in vitro* with dynamic light scattering (DLS) has been proposed as a method for distinguishing between pulmonary sarcoidosis and TB with 94.3% sensitivity and 87.5% specificity and 92.2% diagnostic significance (15). To illustrate, ESAT-6/SFP-10 was the specific immune complex formation of TB which had been significantly difference in detection rate among three groups of TB, sarcoidosis, and control group with 100% detection rate, 10.7% detection rate, and 11.1% detection rate, respectively (15). Moreover, measuring of specific immune complexes after adding "healthy tissue lung extract" antigens revealed a significant difference in detection rate among three groups of patients with 100% detection rate of immune complexes in sarcoidosis group, 4% of detection rate in TB group, and 0% detection rate in control group (15). This observation needs to be confirmed by larger studies. However, the current investigation of the efficacy of antimicrobial therapy, which is a concomitant levofloxacin, ethambutol, azithromycin, and rifabutin (CLEAR) regimen, shows that a significant decline in ESAT-6 provides no physiological benefit in forced vital capacity (FVC) and 6-minute walk distance in sarcoidosis patients (63). As in previous studies, sarcoidosis has been thought that it was mediated by Th1 lymphocyte while a recent study also showed that IL-17A mediated by Th17 cells play a role in sarcoidosis both induction of sarcoidosis and maintenance of disease (64).

Lung tissue-based molecular markers

To elucidate specific lung molecular signatures of TB and sarcoidosis, A modular approach based on weighted gene co-expression network analysis (WGCNA) has been applied to divide transcriptional profiles into 27 modules and show the correlation of modules 4, 21 and 26 with TB and sarcoidosis (65).

According to gene ontology enrichment analysis, the modular signature of TB (module 4) exhibited an over-representation of genes related to extracellular matrix (ECM) organization, whereas the modular signature of sarcoidosis (module 26) exhibited an over-representation of genes related to cell proliferation and oxidation-reduction process (65).

Matrix mettaloproteases-8 (MMP8), a neutrophil collagenase, has been identified as a TB specific ECM protease that aggregated in the necrotizing part. It is postulated that MMP8 is potentially a specific ECM protease for TB which shows over-represented genes involved in ECM organization-related transcriptional signature (65).

Considering the lung sarcoidosis modular signature, it has been shown that there was an over-representation of many genes involved in the arachidonic acid (AA) pathway and there were 6-gene markers among AA metabolism-related genes that could be used to differentiate sarcoidosis from TB including *PLA2G6*, *PLA2G7*, *AKR1C1*, *AKR1C3*, *LTA4H*, and *PTGER4* (65).

Blood transcriptome

Blood transcriptome analysis is one of the noninvasive methods used for the exploration in sarcoidosis's inflammatory pathway. Gene expression in blood transcriptional profile of sarcoidosis is shown a significant similarity with active pulmonary TB with only 4 of 25 modules divergent (66). To illustrate, both TB and sarcoidosis are shown over-abundance of interferon (IFN) signaling with IFN-inducible neutrophil-driven signature together with their immune response pathways (67). However, some studies found some differences between these two diseases which indicate that there are some downregulated genes in sarcoidosis but not in TB (66) and there are 144 differentially expressed transcripts which are over-abundant only in TB such as IFN-inducible transcripts (67). Using machine-learning algorithms, it has been postulated that there were many divergent genes downregulated in sarcoidosis but not in TB including

guanylate-binding protein 6 (*GBP6*), Septin4 (*SEPT4*), translocase of inner mitochondrial membrane 10 (*TIMM10*), and Noggin (*NOG*) (66).

Different approach toward diagnosis of pulmonary sarcoidosis in TB endemic area

In India, PCR for MTB is considered as one of the most useful methods to distinguish these two diseases, but it has still not widespread used because it still detects latent TB infection (68). While IGRAs are considered as an unreliable method in India, TST may be a valuable method. In conclusion, the diagnosis of sarcoidosis in India is still a challenging topic and lack of consensus guidelines so the approach toward the diagnosis of sarcoidosis is often an empiric approach which firstly entertains the diagnosis of TB in patients who may have sarcoidosis (68).

In China, The SAT-TB with EBUS-TBNA method has been considered as a currently sensitive and specific method for distinguishing between sarcoidosis and sputum-negative TB (42).

In South Africa, a TBLB and histological confirmation from the skin and mediastinal lymph nodes are crucial for distinguishing sarcoidosis from TB (69).

Limitations

Despite the fact that the purpose of this narrative review is to provide a comprehensive, objective analysis of the current diagnostic efficacy of sarcoidosis in TB-endemic areas, there are some limitations. First, this review aims to summarize the diagnostic efficacy of both diseases, which ranged from laboratory to invasive procedures. However, it was discovered that there are few studies that directly compare the diagnostic efficacy of each method to differentiate between sarcoidosis and TB, indicating the need for more focused research. Second, this review focuses on the diagnosis of pulmonary sarcoidosis only in TB-endemic regions, and certain laboratory or advanced techniques are only available in some regions. Thirdly, our search was limited to MEDLINE and PubMed, so the future trajectory of review articles on this topic should incorporate Web of Science and/or Cochrane.

Conclusions

To date, diagnosis of pulmonary sarcoidosis requires the exclusion of other granulomatous diseases. In TB endemic areas, the exclusion of pulmonary TB which is one of the granulomatous diseases is a mandatory step in the diagnosis of sarcoidosis because of their difference in management of choices. Since both diseases share the same clinical presentation and radiological findings, the novel laboratory tests play an important role in the distinguishment steps among both diseases. Xpert MTB/RIF assay provides high sensitivity and specificity for diagnosis of TB with 89% and 98%, respectively. LAMP and SAT-TB also have high sensitivity and specificity for diagnosis of TB. Moreover, there are many novel tests including the difference of immune complexes for the ESAT-6/SFP-10 antigen *in vitro* with DLS, the lung tissue-based molecular markers, and blood transcriptome are the promising test in the distinguishment between TB and sarcoidosis. However, further study is needed to evaluate the diagnostic performance of all tests in terms of competency in distinguishing between TB and sarcoidosis.

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Footnote

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