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Challenges in diagnosing sarcoidosis in tuberculosis endemic regions: clinical scenario in India

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Abstract. Sarcoidosis is a chronic, systemic disease of unknown etiology that affects multiple organs. The disease was considered rare in developing countries like India. More recently sarcoidosis is being increasingly diagnosed in countries where tuberculosis continues to be endemic. There is a general perception among physicians that the prevalence of sarcoidosis has increased over the last two decades in countries like India. This may be true but could also be related to better awareness of the condition, availability of improved diagnostic facilities and the increased ability of physicians to differentiate it from tuberculosis. In India, diagnosis of tuberculosis is entertained first in patients who may have sarcoidosis and thus, it is very likely for sarcoidosis to be misdiagnosed as tuberculosis, owing to the high prevalence of tuberculosis and clinicoradiological resemblance to the disease. This editorial highlights the challenges in diagnosing tuberculosis in countries where tuberculosis still continues to be endemic. *(Sarcoidosis Vasc Diffuse Lung Dis 2016; 33: 381-384)*

Key words: sarcoidosis, tuberculosis, clinical scenario, India

Sarcoidosis is a chronic, systemic disease of unknown etiology that affects multiple organs (1). It was not until the late 1890s that sarcoidosis surfaced in the medical community. In recent years, a greater understanding of the condition has led to its characterization as a multisystem disorder with several phenotypes causing a type of granulomatous interstitial lung disease (2,3). Sarcoidosis is prevalent globally and affects all age groups and ethnicities (4). The actual incidence of sarcoidosis in India is unknown and the available data may be an underestimate due to lack of reliable epidemiological information from the subcontinent. Some estimates suggest that sarcoidosis constituted 10-12 cases per 1000 new registrations of respiratory patients annually at a respiratory unit in Kolkata and 61.2 per 100,000 new cases seen at the Vallabhbhai Patel Chest Institute, Delhi (5). Data from other studies indicate a wide variation in the prevalence rate of sarcoidosis ranging from 0.03 to 640 per 100,000 individuals (6). There is a general perception among physicians that the prevalence of sarcoidosis has increased over the last two decades. This may be true but could also be related to better awareness of the condition, availability of improved diagnostic facilities and the increased ability of physicians to differentiate it from tuberculosis.

In most patients, sarcoidosis predominantly affects the lungs (95%), followed by skin (15.9%), non-

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thoracic lymph nodes (15.2%), eyes (11.8%) and liver (11.5%) (7). The condition resolves within 3 years in most patients but in 10%-30% of patients, it might develop into a chronic disease requiring long-term treatment (4). The mortality rate in sarcoidosis is estimated to be about 1%-5% (8). There is also paucity of data regarding extrapulmonary manifestations of sarcoidosis, including cardiac and neurosarcoidosis, although such manifestations have been reported from India (9). The clinical presentation of sarcoidosis among Indians is significantly different from people of European and African/African-American origin, with the disease having a later onset and a male preponderance. Similarly, there is low prevalence of acute presentation in the form of "Löfgren's syndrome" and "Heerfordt's syndrome" in people of Indian origin (5).

Early diagnosis is vital to prevent irreversible damage to the lungs, particularly in treatment-responsive ILD such as sarcoidosis; however, currently, there is no "gold standard" diagnostic test for sarcoidosis (5,10). Diagnosis of sarcoidosis is generally done based on the evidence of compatible clinical and/or radiological pictures, along with histopathological confirmation of noncaseating granulomas in tissue biopsy specimens. Furthermore, other diseases that manifest similar clinical or histopathological appearances need to be excluded before confirming sarcoidosis (5).

In India, diagnosis of tuberculosis is entertained first in patients who may have sarcoidosis and thus, it is very likely for sarcoidosis to be misdiagnosed as tuberculosis, owing to the high prevalence of tuberculosis and clinicoradiological resemblance to the disease (1,10). Constitutional symptoms of fever, malaise, weight loss, and fatigue can be observed in both, tuberculosis and sarcoidosis. Additionally, respiratory symptoms are common to both conditions. Similar ocular manifestations such as dry eye and bilateral lacrimal gland enlargements can be seen in both sarcoidosis and tuberculosis. In the Indian context, the presence of serpiginous-like choroiditis is more likely to be associated with tuberculosis than with sarcoidosis (1). Differentiating sarcoidosis from tuberculosis in countries with a high burden of the latter, therefore, requires a high index of clinical suspicion of both diseases, clinical acumen, and a detailed evaluation that should include a thorough evaluation of clinical, radiologic, and laboratory findings. With the exception of LÖfgren's syndrome, sarcoidosis is always a diagnosis of exclusion of infection (especially mycobacterial and fungal infection). In endemic areas of these infections such as India, the burden of excluding is very high given the very incidence and prevalence of tuberculosis. Quantitative polymerase chain reaction (PCR) is considered to be a useful modality to differentiate sarcoidosis from tuberculosis. However, it has not received widespread encouragement in India because it may also detect latent tuberculosis. The role of quantitative PCR in distinguishing between latent and active tuberculosis needs further investigation before it can be considered as a viable tool to differentiate tuberculosis from sarcoidosis in patients of Indian origin living in India (11). In India, Genxpert which uses PCR technology is becoming more popular for sputum samples and other tissue samples for the diagnosis of tuberculosis. In a given clinical setting, a positive result by Genxpert strongly favors a diagnosis of tuberculosis over sarcoidosis.

Some useful indicators for differentiating these two conditions are depicted in Table 1 (5,12-14). The Tuberculin test may be of value, though interferon-γ release assays (IGRAs) may not be reliable in countries with a high tuberculosis burden (10). The role of serum markers of disease activity, such as angiotensin converting enzyme (ACE) levels in differentiating sarcoidosis from TB remains controversial in India. Increased levels of these serum markers have also been observed in tuberculosis and other granulomatous diseases, though less frequently, and therefore these may not serve as reliable markers (5,15).

Li *et al.* developed four types of comprehensive scoring systems (clinical-radiographic; clinical- radiographic-radionuclide; clinical-radiographic-pathological and clinico-radiographic-radionuclide-pathological) to differentiate sarcoidosis from sputum negative tuberculosis effectively. The investigators established that any of these scoring systems to be an effective tool for differential diagnosis based on the availability of clinical-radiographical/histopathological data. Application of these types of scoring systems may ease the decision making process and help in differentiating sarcoidosis from atypical tuberculosis (16).

Although the diagnosis of sarcoidosis in countries with high TB burden such as India pose a considerable challenge, there are other unmet needs in the subcontinent such as the lack of guidelines, low

Table 1. Indicators for differentiating sarcoidosis form tuberculosis in high tuberculosis prevalence countries (5,12-14)

Indicator	Sarcoidosis	Tuberculosis
	Similarities	
Constitutional symptoms	Asymptomatic or with mild fever, anorexia and loss of weight, particularly with advanced radiological abnormalities	More symptomatic and ill
Respiratory symptoms (Cough)	Common (Mainly dry cough, hemoptysis is rare)	Common with expectoration and/or hemoptysis
Calcified hilar nodes	Seen (discrete, bilateral, symmetrical)	Seen (central necrosis and asymmetric conglomerate lymph nodes)
Presence of fibrosis (in the apical regions)	Seen (cavitation is rare)	Seen
Miliary distribution of lesions	Also seen	Seen
Cutaneous anergy to tuberculin	May be seen	May be seen
Splenomegaly	May be seen	May be seen
	Differentiating Features	
Intrathoracic lymph node involvement	Typically symmetrical bi-hilar and paratracheal, smooth, discrete, and solid looking nodes	Asymmetrical, large, may be conglomerate, usually with central areas of hypodensity
Extrathoracic lymph node involvement	Seen in about 10% patients only	Cervical and axillary lymph node involvement is common
HRCT scan of lungs (In case of diffuse involvement)	Micro and macro-nodules which have characteristic distribution in peribronchovascular region, subpleural interstitium and interlobular septa	Micro-nodules, randomly distributed with tree-in-bud appearance
Tuberculin test	Nearly always negative	Nearly always positive
Increased SACE levels	Common	Less common
Sputum positive for M. tuberculosis on smear or culture	False-positive acid fast bacilli or rarely coexisting TB with sarcoidosis. Patient should never receive glucocorticoids alone	Confirmatory for TB
Biopsy of involved site	Noncaseating, compact granulomas, sparse lymphocytic cuffing around granuloma ("naked," with inclusion bodies at times)	Caseating necrosis, ill formed granuloma with intense inflammatory reaction and may be positive for acid fast bacilli
No response to antitubercular therapy	Very common; however, spontaneous resolution in sarcoidosis is known	Very rare, only in case of primary multidrug resistance
Clinicoradiological response to steroids	Usual	No response or may worsen

HRCT: high-resolution computerized tomography; SACE: serum angiotensin converting enzyme; TB: tuberculosis.
These indicators are only based on common clinical observations with unknown sensitivity and specificity for most of them.

awareness and knowledge gaps in physicians (5). Also, there is very little data on the prevalence of sarcoidosis in extra pulmonary sites like the heart and the central nervous system from India. Additionally, there is paucity of literature on the pattern, determinants, distribution and response to treatment of ILD in India (17). Over the last decade, significant strides have been made in understanding this enigmatic disease. However, further research should focus on identifying specific causes, the genetic nature, and populations at risk for sarcoidosis and to delineate this condition from tuberculosis. Therefore, there is an urgent need to set new standards and formulate consensus recommendations for the diagnosis, treatment and follow-up of sarcoidosis from an Indian perspective.

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