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REVIEW

Tuberculosis or sarcoidosis: Opposite ends of the same disease spectrum?

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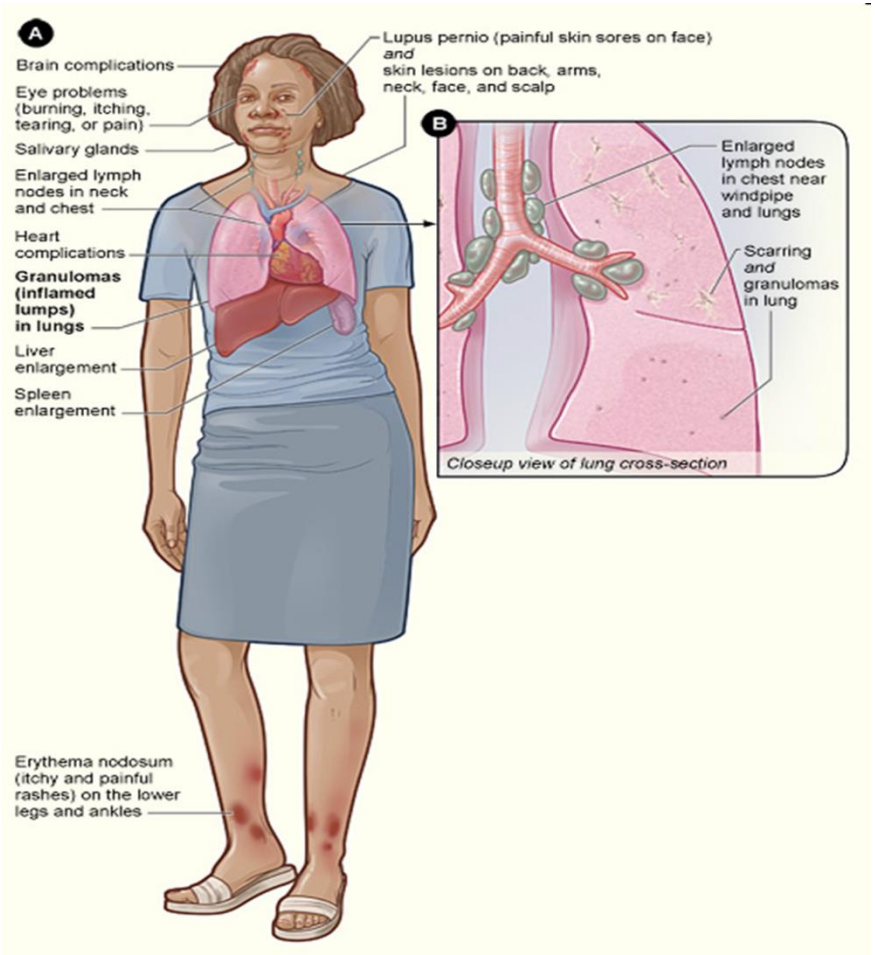
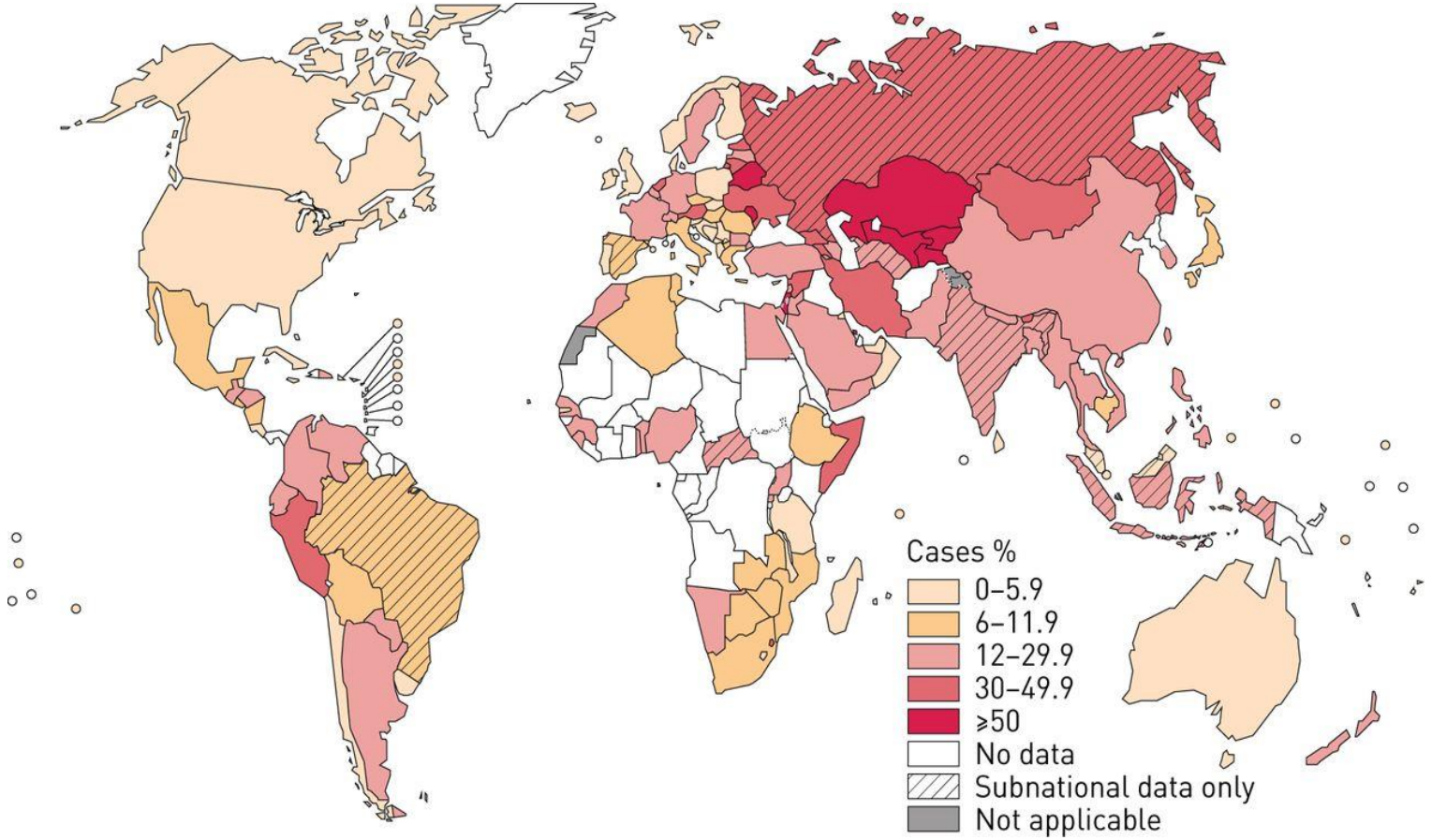
- In our paper, we suggest that tuberculosis and sarcoidosis are two ends of the same spectrum. Given the pathophysiological and clinical link between the two, we also propose a classification system for tuberculosis and sarcoidosis: Sarcoidosis (S); Sarcoid-Tuberculous (ST); Tuberculous Sarcoid (TS) and Tuberculosis (TB).

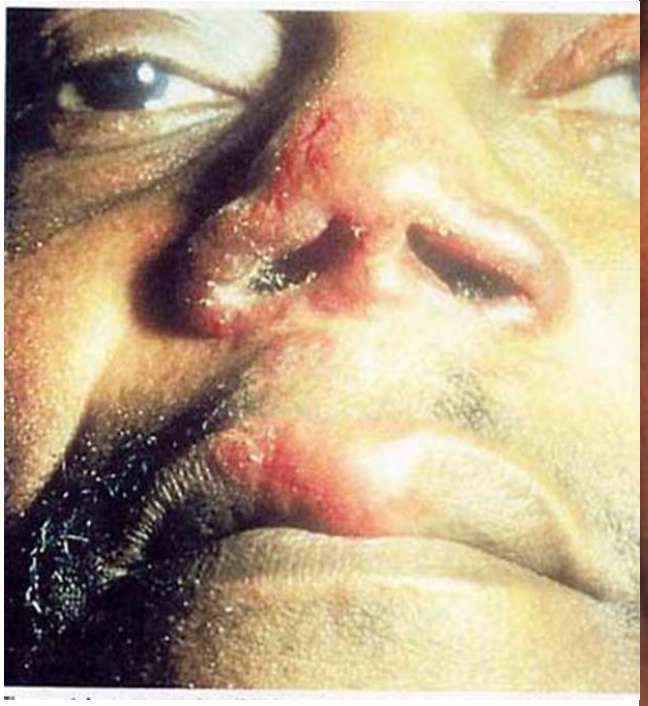
Tuberculosis and sarcoidosis are chronic systemic diseases that have similar pulmonary and extra-pulmonary manifestations.

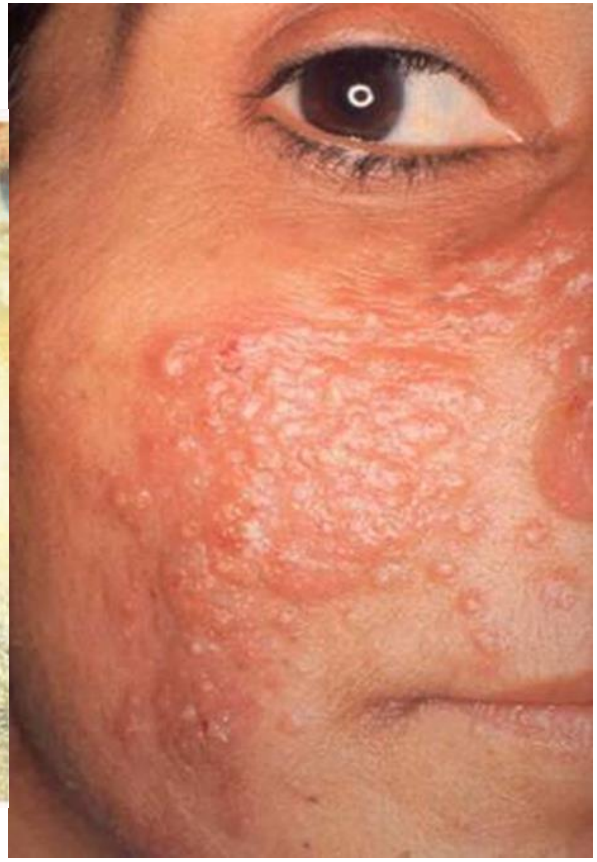


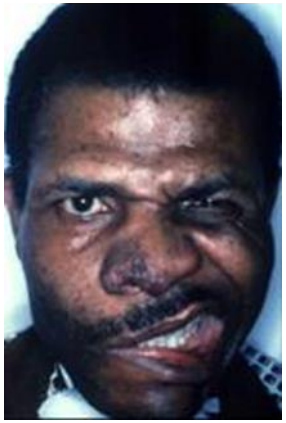
TB, caused by Mycobacterium tuberculosis (MTB) infection, is a global phenomenon affecting approximately one in three people worldwide, with a high mortality of 2 million across the world . TB can manifest as primary or secondary (reactivation or reinfection) disease. Formation of granuloma with characteristic caseous necrosis is the pathologic hallmark of TB.

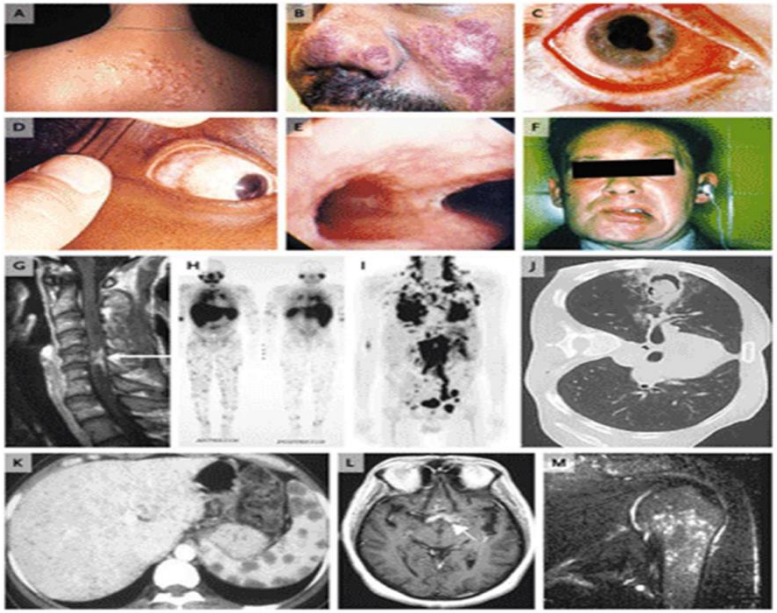


Sarcoidosis has a varied incidence around the world, with highest yearly incidence reported in northern Europe (5–40 cases per 100,000). Its aetiology is unknown and manifests as a multisystem granulomatous inflammation with formation of non-caseating epithelioid granulomas.



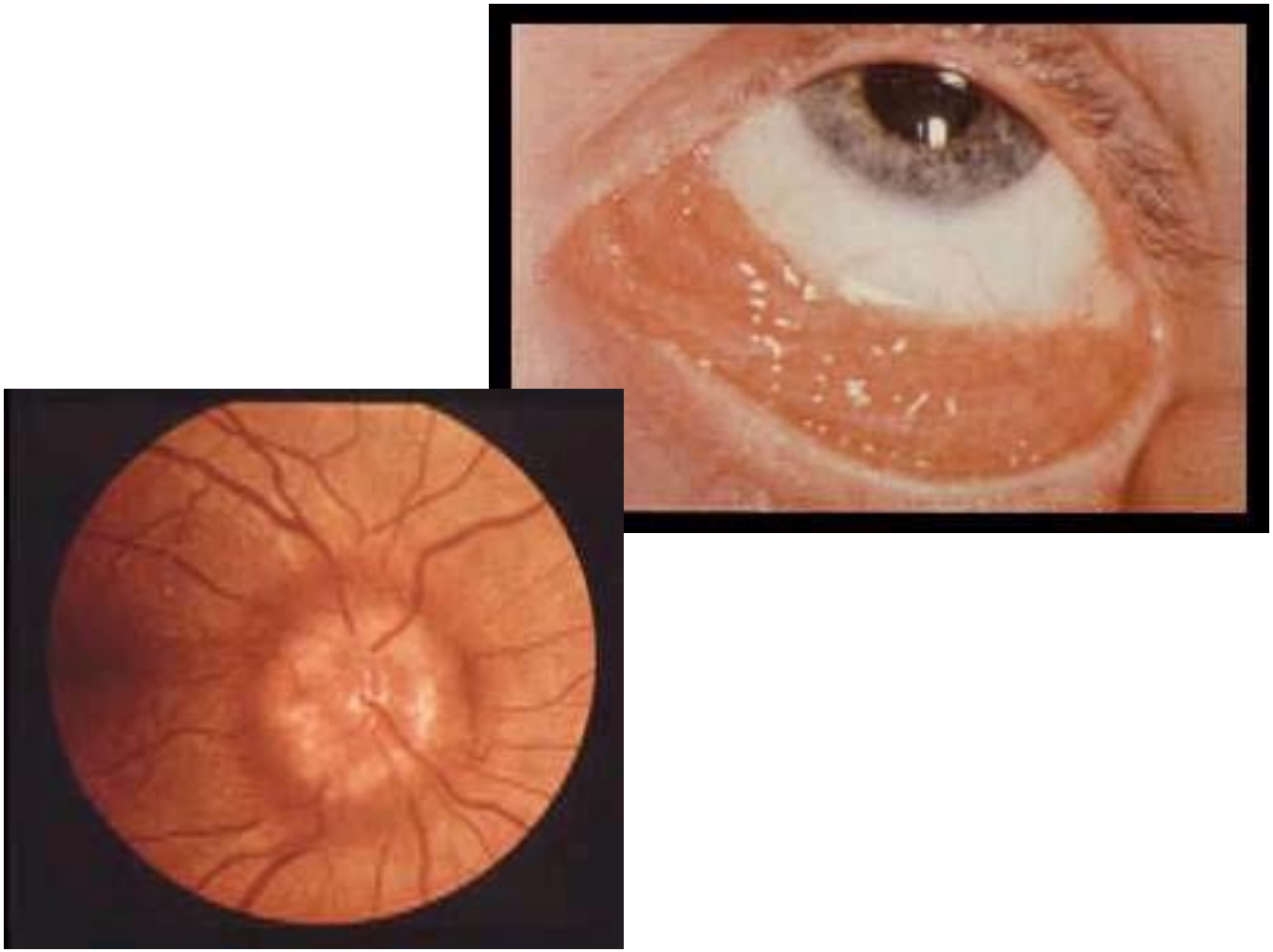




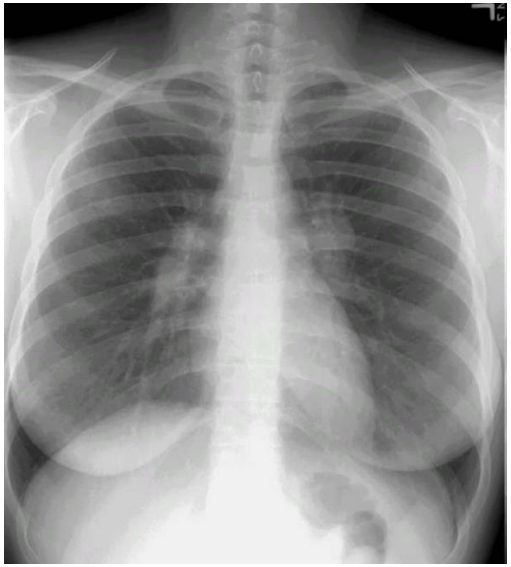


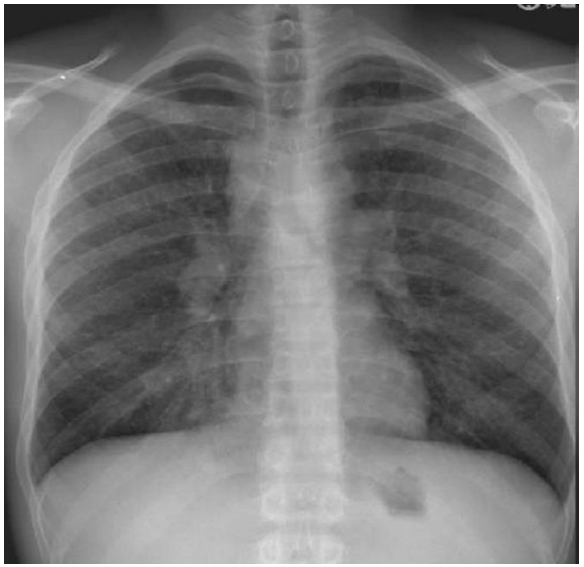
- Often, granulomatous inflammation is associated with infectious diseases like tuberculosis, leprosy and schistosomiasis, and it raises the possibility that sarcoidosis could also be induced by an infectious agent until now not identified. Though the exact agent remains unclear, it can be divided mainly into non-infectious and infectious causes. Non-infective antigens have been speculated due to their epidemiologic association [5]. Infective agents associated with sarcoidosis are many, but Propionibacterium and Mycobacterium [6] and [7] seem to have the strongest associations.

In addition to the pulmonary presentations of both diseases, the extrapulmonary manifestations of TB and sarcoidosis, which includes the ocular presentations, are often much harder to distinguish from one another.



- In addition, the two disease entities share radiological and histological similarities. Moreover, the possibility of mycobacteria being an etiological factor for sarcoidosis, and the limitations in the use of molecular and serological tests to differentiate sarcoidosis from TB, makes the distinction between them, a clinical challenge.
- The aim of this report is to critically evaluate the relationship between TB and sarcoidosis and expand further on the current debate as to whether these two clinical entities are truly unique, or whether they are simply two ends of the same disease spectrum.





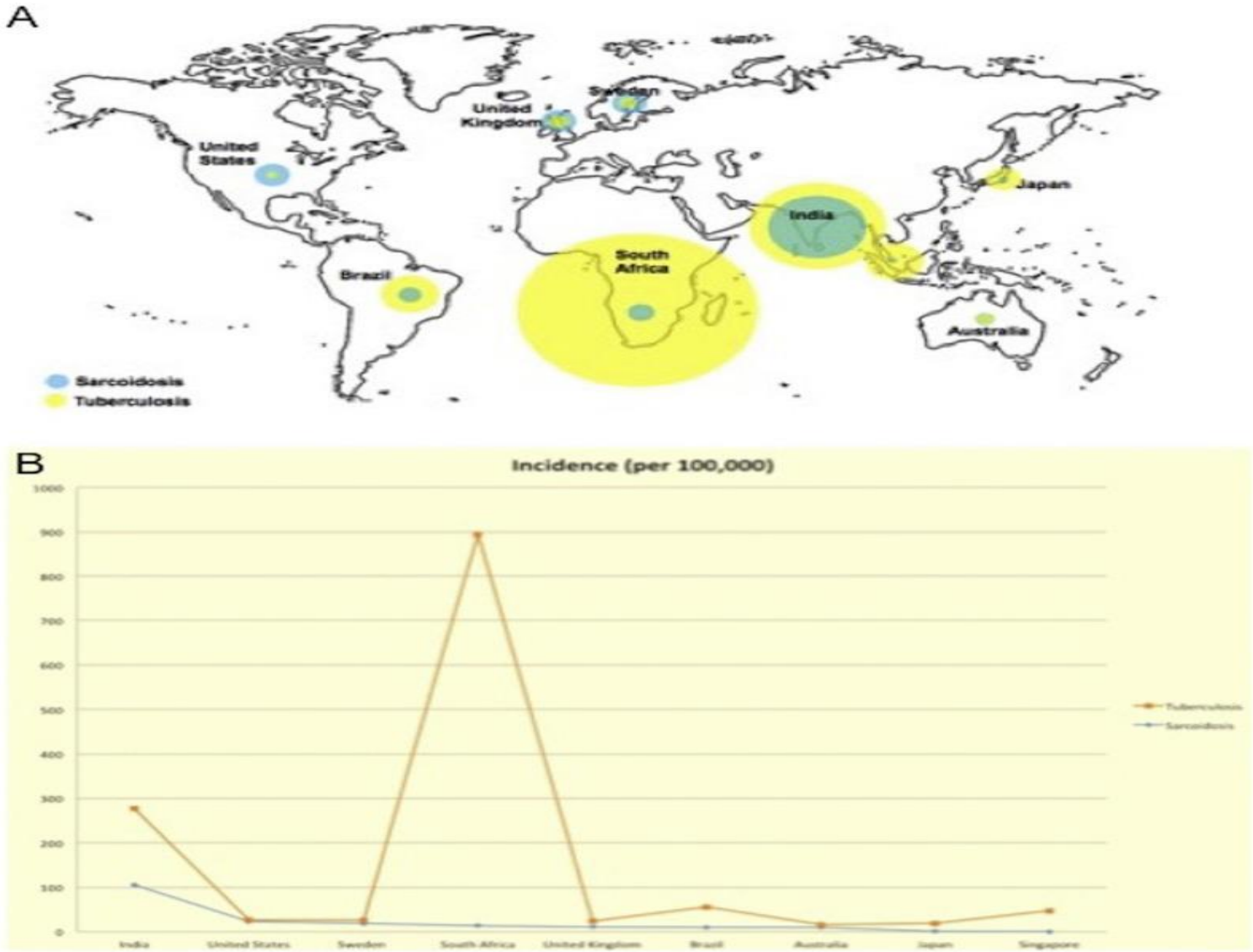
Systemic manifestations

- The majority of patients with TB or sarcoidosis present with non-specific constitutional symptoms – malaise, generalised fatigue, loss of weight and non-specific fever. Classic pulmonary symptoms like exertional dyspnoea, cough and pleuritic chest pain seen in pulmonary TB are similarly seen in patients with sarcoidosis. Patients with Lofgren's syndrome, a type of acute sarcoidosis, may present with fever, bilateral hilar lymphadenopathy and polyarthralgia, which can also be seen as symptoms of TB.
- Clinically, the features are often confused with each other and many cases of TB are misdiagnosed initially as sarcoidosis and vice versa. Moreover, there has been a number of case reports of concomitant TB and sarcoidosis in the same patients.
- Intraocular TB is sometimes referred to as a “great imitator” of many uveitic conditions including sarcoidosis. Any of the seven classical signs, as determined by Papadia et al. during the first International Workshop on Ocular Sarcoidosis (IWOS)

Link between TB and sarcoidosis

- An epidemiological association between TB and sarcoidosis has been found in many studies, where previous contact history with TB [17] and populations with higher prevalence of TB [18] were associated with sarcoidosis. Similarly, there is also a molecular and immunological link between TB and sarcoidosis.

Epidemiologic distribution of sarcoidosis and tuberculosis on world map



Epidemiologic distribution of sarcoidosis and tuberculosis across the world (Incidence; per 100,000)

Table 1
Epidemiologic distribution of sarcoidosis and tuberculosis across the world (Incidence; per 100,000).

	India [18]	United States [2,19]	Sweden [20]	South Africa [21]	United Kingdom [22,23]	Brazil [24]	Australia [25]	Japan [26]	Singapore [27]
Sarcoidosis	61–150	6.1 (10.9 amongst Whites; 35.5 amongst Blacks)	19	3.7 amongst Whites; 23.2 amongst Blacks	20 (1.5 amongst Whites; 19.8 amongst Blacks)	<10	4.4–6.3	1.01	0.56
TB	171	3.3	7.2	880	13	46	6.2	18	47

Molecular

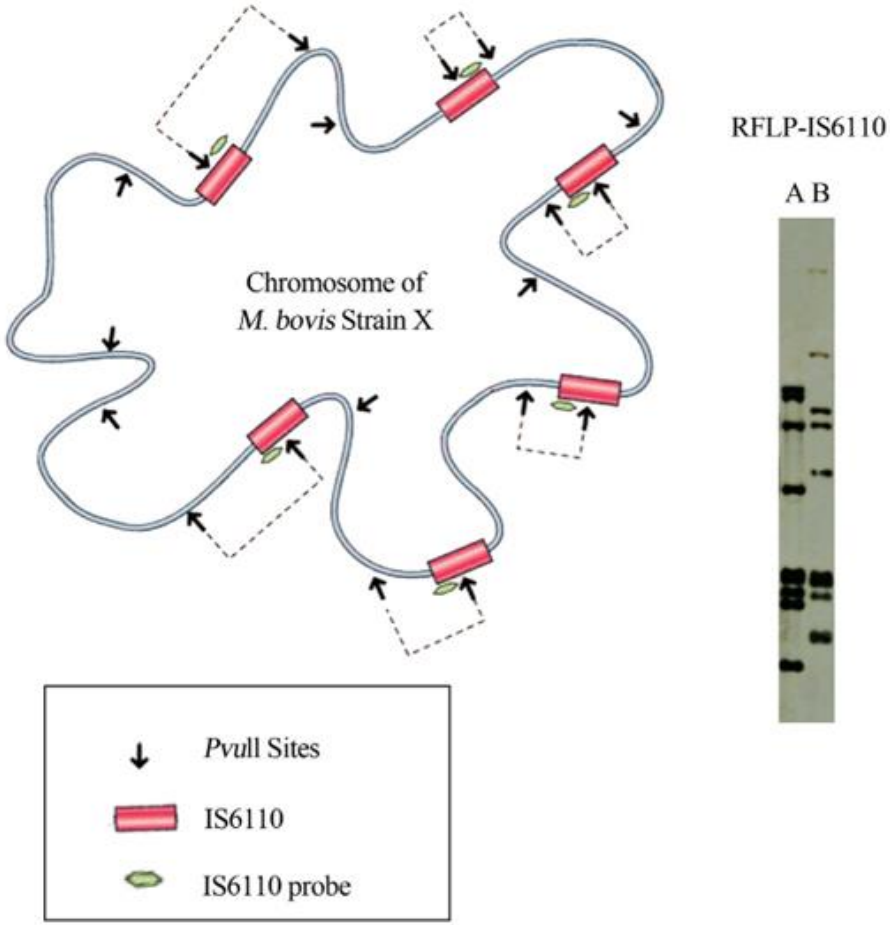
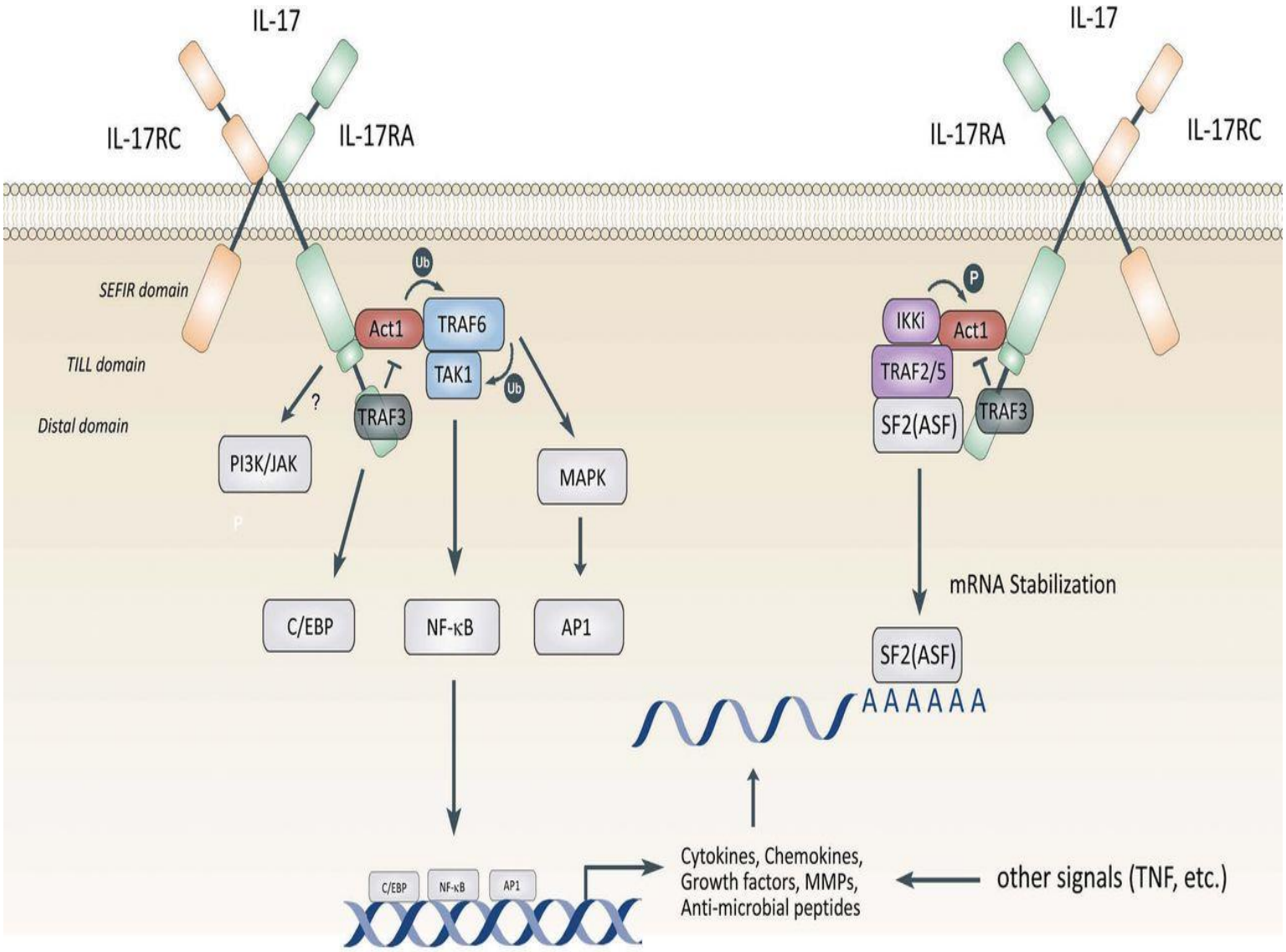


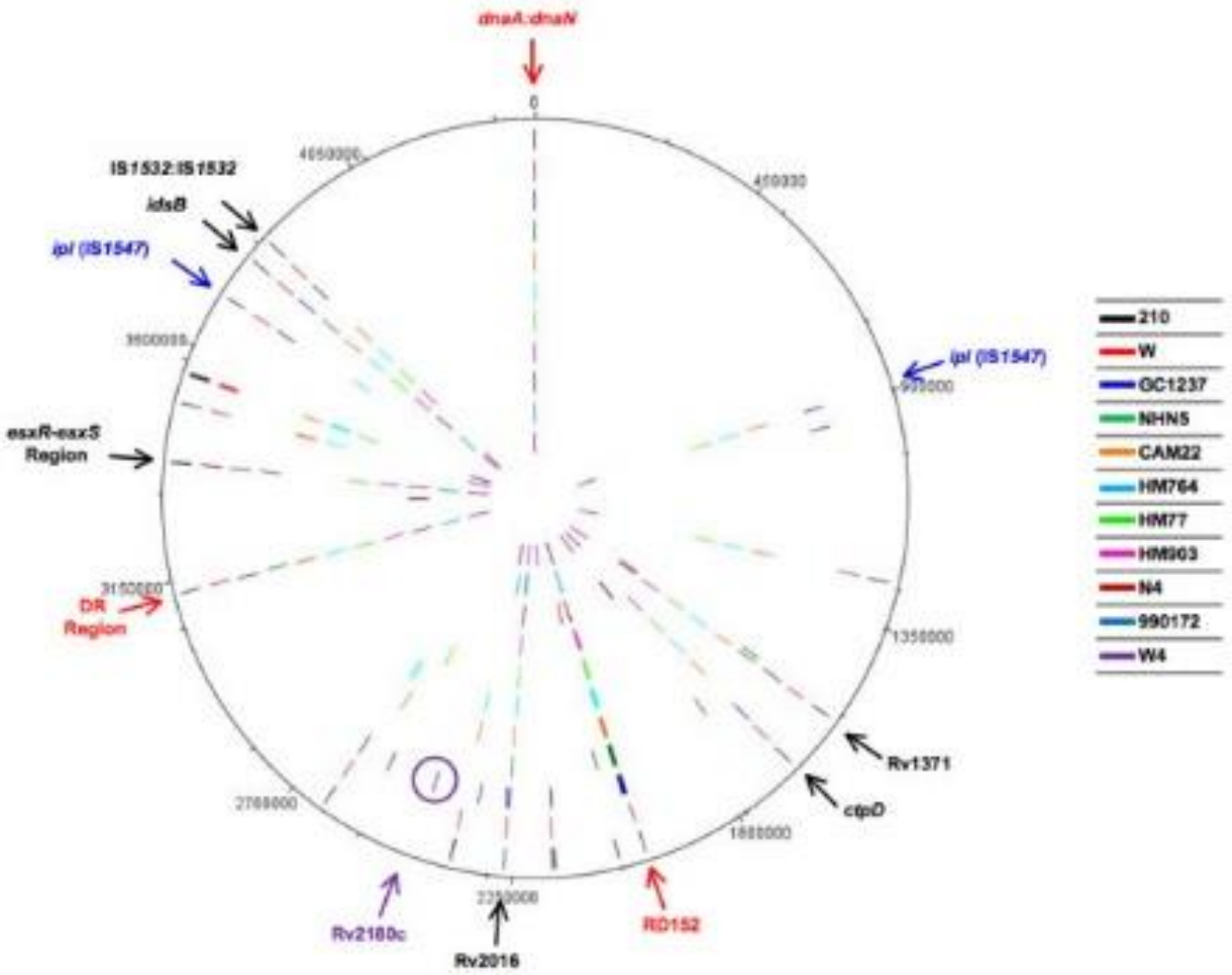
Figure 1 - Representation of the *M. bovis* chromosome with the *IS6110* region (red), *Pvu*II (arrow) restriction sites and the 245 bp (green) *IS6110* probe used for Southern blotting. Different banding patterns result from the number and position of IS6110 copies, as well as polymorphism in the adjacent region where the *Pvu*II site is located. Different strains produce distinct banding patterns as shown in this example with strains A and B.


IL-17
IL-17RC
IL-17RA
SEFIR domain
TILL domain
Distal domain
Ub
Act1
TRAF6
TAK1
Ub
TRAF3
?
PI3K/JAK
MAPK
C/EBP
NF-κB
AP1
C/EBP
NF-κB
AP1
IL-17
IL-17RA
IL-17RC
P
IKKi
Act1
TRAF2/5
SF2(ASF)
TRAF3
mRNA Stabilization
SF2(ASF)
A A A A A A
Cytokines, Chemokines,
Growth factors, MMPs,
Anti-microbial peptides
other signals (TNF, etc.)

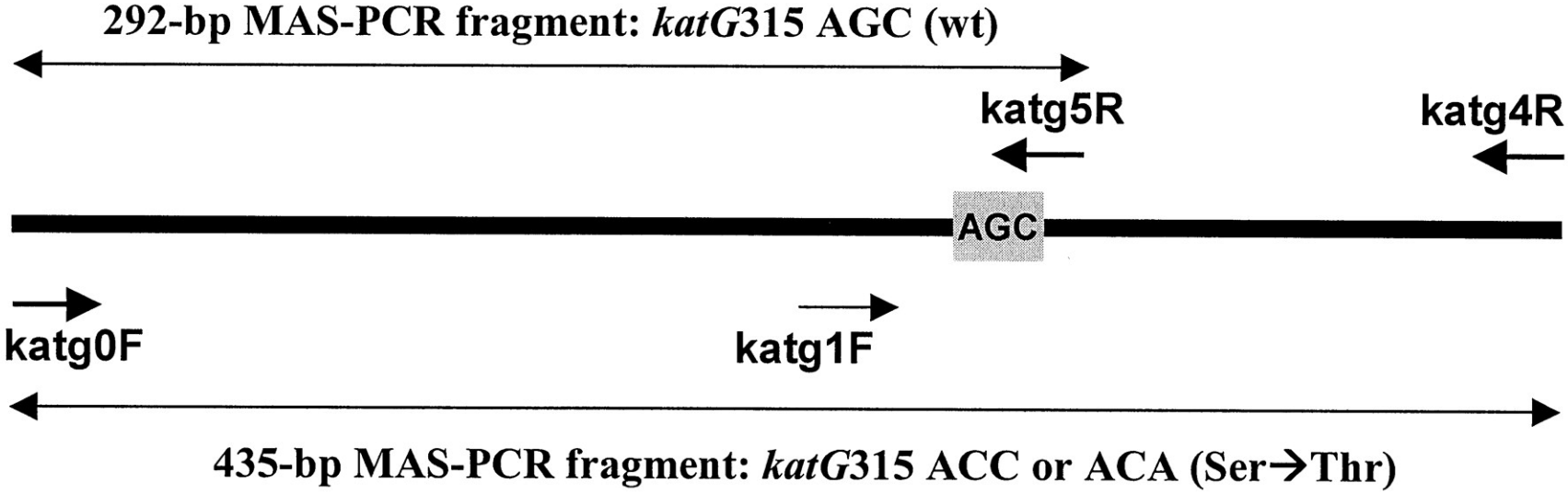
Immunological

- Dubaniewicz and his team have done studies into both humoral and cell-mediated immune responses of sarcoid patients to MTB antigens. Their results showed that mtb-hsp stimulation lead to increased levels of pro-inflammatory cytokines, TNF-alpha, and IL-6 in sera from sarcoidosis and TB patients in comparison with healthy controls. Moreover, sarcoidosis patients demonstrated the lowest levels of IL-4 and the highest levels of IL-10. The close association in immunological response of sarcoidosis and TB patients indicate the possibility of the two diseases arising from similar aetiology.
- They also evaluated the presence of several anti-mtb-hsp antibodies by ELISA in patients with sarcoidosis, TB and normal individuals, and found significantly higher levels of anti-mtb-hsp70 in sarcoid and TB individuals compared to controls. Thus, indicating that this protein in particular may play a potential role in the pathogenesis of sarcoidosis.

Several genes have been identified in the RD1 location of the MTB genome, coding for several specific proteins, such as ESAT-6 and CFP-10.



Another specific mycobacterial protein, mycobacterial catalse-peroxidase (mKatG) reactive, had been previously identified in 55% of sarcoidosis tissues and IgG antibodies to recombinant mKatG was detected in 48% of sarcoidosis individuals compared to 0% of PPD negative controls.



Diagnostic challenges

- A positive culture from the body fluids or tissues is the gold standard for the diagnosis of TB, but may not be possible in particular target organs because of the difficulties of access non-invasively or due to the risks of accessing such compartments - particularly in the setting of extrapulmonary TB.
- In this setting the diagnosis of TB can be supported by a positive tuberculin skin test (TST), interferon gamma release assays (IGRA) (T-SPOT.TB or QuantiFERON gold in tube), radiology, (mainly based on CT scan images) or detection of mycobacterial DNA via PCR of body fluids or tissue .
- On the other hand, a diagnosis of sarcoidosis can be supported by a negative TST or IGRA with elevated serum angiotensin-converting enzyme (ACE), and bilateral hilar lymphadenopathy on chest X-ray/CT . Newer diagnostic methods are still being explored, such as high CD4/CD8 ratios of vitreous T-lymphocytes in sarcoidosis to make an accurate diagnosis of a clinical entity.

Conclusion

- In the meantime, differentiating between the two conditions will continue to be challenging especially in cases where extrapulmonary manifestations like ocular involvement occur with few or no systemic manifestations. Thus, on top of looking at the clinical picture for characteristic symptoms and signs as well as chest x-ray for systemic manifestations, further investigations such as TST and IGRA can be considered for the diagnosis of TB uveitis while serum ACE or lysozyme and liver enzyme tests can be used to aid in the diagnosis of sarcoid uveitis. However, if TB and sarcoidosis are proven to be connected as it has been proposed and a patient develops a disease that falls in between the spectrum, then the subsequent management would not differ.

Thank you