SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2020; 37 (3); e2020005 DOI: 10.36141/svdld.v37i3.9926

Latent tuberculosis infection associates with cardiac involvement in patients with sarcoidosis

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Abstract. *Background:* Sarcoidosis is a systemic disease characterized by formation of non-caseating granulomas. About 5% of patients have symptoms of cardiac sarcoidosis. Identification of cardiac involvement is important since it is a major cause of death. Mycobacterial antigens have been linked to sarcoidosis pathogenesis. Previous findings suggest that a latent tuberculosis infection (LTBI) might associate with development of cardiac involvement in patients with sarcoidosis. The aim of the present study was to further evaluate these findings in another cohort of cardiac sarcoidosis patients. *Methods:* Interferon release assays (IGRAs) or tuberculin skin tests (TST) were analysed in a cohort of cardiac sarcoidosis patients (n=103) and compared to non-cardiac sarcoidosis patients (n=153). *Results:* In the cohort of patients with cardiac sarcoidosis, 7 could be diagnosed with a LTBI (6.8%) compared to only one of the non-cardiac patients (0.7%), p = 0.008. *Conclusions:* To conclude, we were able to show an association between a LTBI and cardiac involvement in patients with sarcoidosis. Future research is however required to unravel the mechanism involved in this association. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (3): e2020005)*

Key words: sarcoidosis, cardiac sarcoidosis, mycobacteria, tuberculosis

List of abbreviations
CI: Confidence interval
CMR: Cardiac resonance imaging
CS: Cardiac sarcoidosis
FDG-PET: Fluorodeoxyglucose positron emission tomography
HRS: Heart Rhythm Society
IGRA: Interferon gamma release assay
LTBI: Latent tuberculosis infection
MEC-U: Medical research Ethics Committees United
MTB: *Mycobacterium tuberculosis*
Non-CS: Non-cardiac sarcoidosis
OR: Odds ratio
P. acnes: *Propionibacterium acnes*
RA: Rheumatoid arthritis
TST: Tuberculin skin test

Received: 28 May 2020
Accepted after revision: 14 September 2020
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Introduction

Sarcoidosis is a systemic disease characterized by the formation of noncaseating granulomas. Although intrathoracic lymph nodes and the lungs are the most common affected organs, any organ can be involved in this disease (1). About 5% of sarcoidosis patients have symptoms of cardiac sarcoidosis (CS), although the prevalence of CS is 20-30% in autopsy and imaging studies (2). Identification of cardiac involvement is important since it is a major cause of death in sarcoidosis patients (3,4).

The aetiology of sarcoidosis is not clear do date. However, several antigens have been related to sarcoidosis, including inorganic agents (5,6), auto-antigens (7) and bacteria (8). The two most extensive studied bacteria in relation to sarcoidosis pathogenesis are *Propionibacterium acnes* (*P. acnes*) (9) and Mycobacteria (10). Studies regarding *P. acnes* and mycobacteria in relation to sarcoidosis mainly focussed on cellular immune responses to antigens of *P. acnes* and mycobacteria (11,12) as well as detecting DNA or antigens in biopsy material of sarcoidosis patients and controls (13,14). Trigger related phenotypes, however, have not been described previously. In recent work from our group (15) sarcoidosis patients were tested for an immunological response towards several antigens related to sarcoidosis pathogenesis. In a total cohort of 201 patients with sarcoidosis, a latent tuberculosis infection (LTBI) was found in 5 patients (2.5%). Interestingly, when defining trigger-related phenotypes it was found that three of these LTBI patients had cardiac involvement of their sarcoidosis. The aim of the present study was to further evaluate these unexpected results. We used another cohort of CS patients to investigate whether a LTBI associates with cardiac involvement in sarcoidosis.

Methods

Study subjects

A cohort of CS patients registered in our hospital was retrospectively studied and included as CS group (approved by the local institutional review board (Z.19.004) of the St Antonius Hospital. Due to the use of clinical data, the need for informed consent was waived). A diagnosis of CS was made after advanced imaging with cardiac resonance imaging (CMR) and fluorodeoxyglucose positron emission tomography (FDG-PET). The likelihood of CS was assessed in a multidisciplinary team consisting of a pulmonologist, cardiologist, radiologist, nuclear specialist and nurse, predominantly based on the diagnostic criteria from the Heart Rhythm Society (HRS) consensus statement (16). Definite and probable CS were the gold standard for the diagnosis of CS.

Biopsy proven sarcoidosis patients or Löfgren syndrome patients without cardiac involvement, seen for the first time at the ILD outpatient clinic of the St Antonius hospital (Nieuwegein, The Netherlands) from May 1st 2016 till December 2017, were also retrospectively studied and included in the non-cardiac sarcoidosis (non-CS) group (approved by the Medical research Ethics Committees United (MEC-U) (R14.023), all these patients signed informed consent). The diagnosis of sarcoidosis had been established according to the criteria of the American Thoracic Society/European Respiratory Society (17).

Diagnosis of LTBI

Following the diagnostic criteria for sarcoidosis to exclude other causes of granulomatous disease, an Interferon Gamma Release Assay (IGRA) or tuberculin skin test (TST is performed in all sarcoidosis patients in the St. Antonius Hospital. Medical records of patients were searched for data of IGRAs (TB ELISpot or QuantiFERON tests). When data of those tests were not available, medical records were searched for results of tuberculin skin tests (TST). If IGRAs or TSTs were not performed in our hospital, available data of referring hospitals were retrieved. If data of IGRAs or TSTs were not available, patients were excluded from the study. Results of IGRAs or TSTs were compared between the CS group and the non-CS group. A diagnosis of LTBI was made when a cellular immune response against antigens of *Mycobacterium tuberculosis* (MTB) was present without bacterial, radiological or clinical signs of an active tuberculosis infection according to the current guidelines (18,19).

Statistics

Data were analysed using IBM SPSS statistics version 24. An unpaired T-test was used to compare numerical data between the non-CS and CS group. Non-parametric tests were used for non-normally distributed data (Mann-Whitney U test). Categorical data were compared using the Chi-squared test. If expected cell frequencies were below 5, Fisher's exact test was used for categorical data up to two categories. Odds ratios were calculated using a binary logistic regression model.

Results

Retrospective data of IGRAs or TSTs was available from 153 non-CS patients and 103 CS patients, which were included in the study (table 1). Establishment of the diagnosis of cardiac sarcoidosis is shown in supplementary table1. The CS group was significantly older at time of the IGRA or TST and consisted of more men. No difference in ethnicity was observed between the two study groups and also the percentage of patients that originated from another country than the Netherlands did not significantly differ between the non-CS and CS group either (3.9% vs 7.8%, p = 0.189, supplementary table 2).

In total, 7 CS patients were diagnosed with LTBI (6.8%) compared to only one patient of the non-CS group (0.7%), p = 0.008 (figure 1). When looking at the two different assays, in the CS group 6 of 96 patients had a positive IGRA (6.3%) compared to 1 of 149 patients of the non-CS group (0.7%) (p = 0.016). A positive TST was found in 1 of 7 CS patients (14.3%) and in none of the 4 non-CS patients (p = 1.000). An increased OR of 11.08 (CI: 1.34; 91.49) was observed for CS and a LTBI and an increased odds ratio (OR) of 9.87 (CI: 1.17; 83.29) was observed for a positive IGRA and CS. Furthermore, when these ORs were adjusted for age, also significant increased ORs of respectively 10.17 (CI: 1.23; 84.50) and 9.06 (CI: 1.06; 77.13) were observed.

Besides cardiac involvement, we also compared other involved organs between the 8 sarcoidosis patients with a LTBI and the other sarcoidosis patients. Prevalence of other involved organs was not different

Table 2. Organ involvement of LTBI and no LTBI sarcoidosis patients

Involved organ:	No LTBI (n=248)	LTBI (n=8)	P-value*
Heart (%)	96 (38.7)	7 (87.5)	0.008
Lymph nodes (%)	237 (96.3)	8 (100)	1.000
Lungs (%)	185 (74.6)	7 (87.5)	0.684
Nervous system (%)	36 (14.5)	0 (0.0)	0.605
Skin (%)	32 (12.9)	0 (0.0)	0.601
Eyes (%)	30 (12.1)	1 (12.5)	1.000
Bone (%)	16 (6.5)	0 (0.0)	1.000
Liver (%)	13 (5.2)	1 (12.5)	0.366
Spleen (%)	18 (7.3)	0 (0.0)	1.000

Table 1. Demographics of study patients

	Non-CS (n=153)	CS (n=103)	P-value *
IGRA / TST	149 /4	96 / 7	0.124
Age (mean ± SD)	47.23±12.64	51.39±10.87	0.005
Sex (male / female)	80 / 73	77 / 26	<0.001
Ethnicity (white / non-white)	135 / 18	92 / 11	0.788
Organ involvement:			
Lymph nodes (%)	146 (96.1)	99 (97.1)	0.744
Lungs (%)	114 (74.5)	78 (75.7)	0.825
Nervous system (%)	28 (18.3)	8 (7.8)	0.017
Skin (%)	28 (18.3)	4 (3.9)	0.001
Eyes (%)	23 (15.0)	8 (7.8)	0.081
Bone (%)	8 (5.2)	8 (7.8)	0.411
Liver (%)	7 (4.6)	7 (6.8)	0.443
Spleen (%)	5 (3.3)	13 (12.6)	0.004

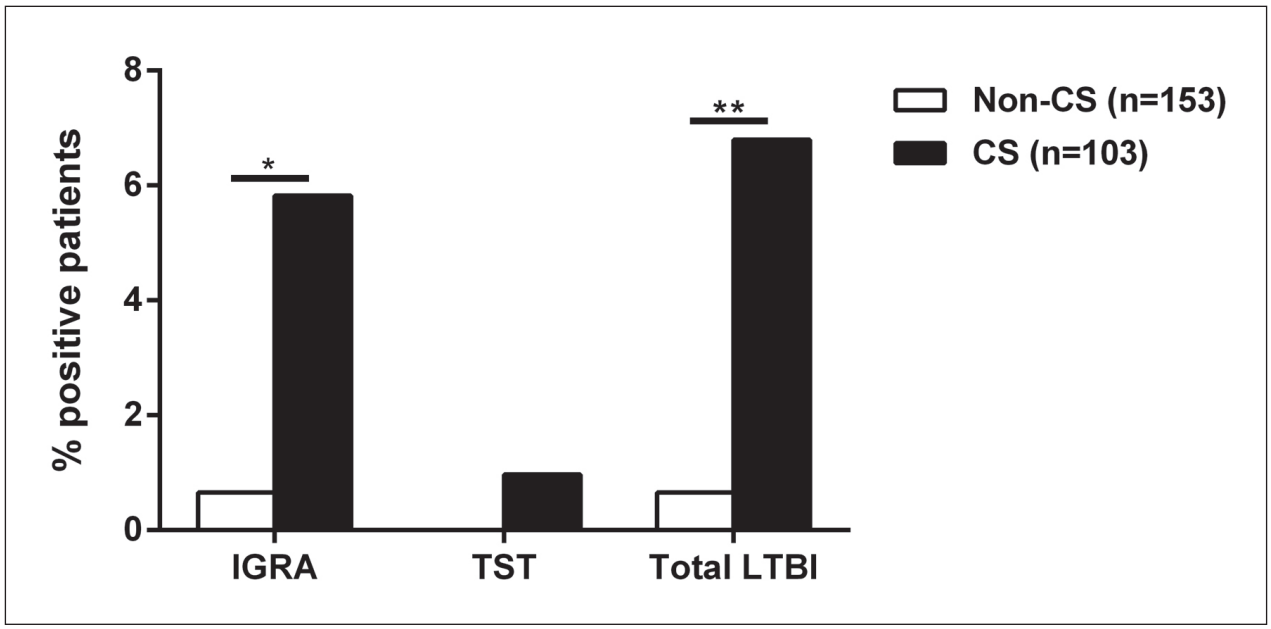

Fig. 1. Percentage of patients with a positive IGRA or TST, to determine a latent tuberculosis infection
Significant more CS patients had a positive IGRA test compared to the non-CS group (6 versus 1, respectively) (P = 0.016). In total, significant more CS patients were diagnosed with a LTBI compared to non-CS patients (7 versus 1, respectively) (P = 0.008).
IGRA included a QuantiFERON test or TB elispot.
Non-CS: Non-cardiac sarcoidosis, CS: Cardiac sarcoidosis, IGRA: Interferon gamma release assay, TST: tuberculin skin test, LTBI: latent tuberculosis infection.

between the patients with a LTBI and the remaining patients (table 2).

Discussion

In this study we were able to show that a latent tuberculosis infection is associated with cardiac involvement in patients already diagnosed with sarcoidosis, which is in line with our initial observation (15).

Although the finding that 6.8% of patients with CS were diagnosed with a LTBI seems low, this is an interesting observation since the Netherlands is a very low tuberculosis incidence country with a tuberculosis incidence of about 5 per 100.000 and a LTBI incidence of about 8 per 100.000 (20).

In previous papers, a possible link between LTBI and sarcoidosis has already been suggested (21). However, to the best of our knowledge, this is the first study to relate LTBI specifically to CS. It is known from literature that myocardial involvement in tuberculosis exists, but this is rare and has been occasionally described in case reports (22). Luk *et al*. a described a case of CS who underwent heart transplantation, developing recurrent CS in the graft following a mycobacteria tuberculosis infection (23). Since data of IGRAs or TSTs before heart transplantation were not presented, it is unclear whether this patient was suffering from a reactivation of a LTBI already present before heart transplantation, or a newly acquired tuberculosis infection. In a recent study in mice it was demonstrated that after intranasal infection, *Mycobacterium avium* was able to disseminate into cardiac tissue (24). Interestingly, infection with *Mycobacterium avium* was able to induce intracardial inflammatory gene expression and induce intracardiac tissue fibrosis. Although quite speculative, if other species of mycobacteria are also capable of inducing such damage to cardiac tissue, this could perhaps trigger a local granulomatous reaction in the heart we define as cardiac sarcoidosis. A possible explanation for our findings, may be molecular mimicry. Molecular mimicry has been described in T cell specific autoimmune diseases including multiple sclerosis and rheumatoid arthritis (RA) but also my-

ocarditis (25,26). Chodisetti *et al.* identified several T cell epitopes that are similar to peptides of mycobacterial antigens. Those epitopes may act as molecular mimics and result in an autoimmune response during an infection with *M. tuberculosis* (27). Cross-reactive antibodies with heart tissue were observed in rheumatic carditis patients (28). Further studies should clarify whether such cross reactive antibodies or shared epitopes are also present for mycobacteria and cardiac tissue.

If the association between LTBI and CS can be confirmed in further studies, this could be of interest for clinical management. For instance, it could be relevant to screen sarcoidosis patients with a LTBI for CS, even though symptoms may not be present (yet). Identification of cardiac involvement seems important since it is a major cause of death. Furthermore, in current clinical practice, if a patient is diagnosed with a LTBI they can either choose follow-up without medication or start LTBI treatment using Isoniazid/Rifampicin (29). One could speculate whether it would be beneficial for this group to start LTBI treatment instead of a wait-and-see policy directly after the diagnosis of LTBI is made.

A limitation of this retrospective study design is that the diagnosis of a LTBI was based on a positive result of different assay types (TST or IGRA). So, not all study patients had the same assay performed, although an IGRA was performed in over 95% of cases and results remained statistical significant when only LTBIs diagnosed by an IGRA were taken into account. A study regarding RA patients showed that results of IGRA tests did not correlate with use of corticosteroids, making these assays useful in RA patients (30), and likewise in sarcoidosis patients (31). Where results of IGRA are not affected by previous BCG vaccination, the TST is. However, no evidence for a previous BCG vaccination was found for the patient with a LTBI based on a positive TST. Moreover, there are several methods to search for an *Mycobacterium tuberculosis* (MTB) infection, which all have a different sensitivity and specificity. For instance, Masoud *et al.* showed that purified protein derivative antigens of MTB were present in tissue cells of 3 out of 10 sarcoidosis patients even when MTB DNA could not be detected (14). Based on our retrospective study design, we were not able to examine different methods to search for a MTB infection such as detection of mycobacterial antigens in tissue of patients. It would however be interesting to examine in future studies whether mycobacterial antigens are present in myocardial tissue of cardiac sarcoidosis patients diagnosed with a LTBI.

Another study limitation was that the non-CS and CS group were not similar regarding sex and age. Although tuberculosis is more common in the Netherlands among people with a higher age (32), the OR was still significantly increased after adjustment for age, suggesting that this difference between the groups have not induced a bias in our results. Although patients in the non-CS group did not have symptoms associated with CS, we cannot completely exclude the possibility that there might be some asymptomatic CS patients in this group, since a PET or MRI was not performed for the complete non-CS group.

To conclude, our data suggest that a latent tuberculosis infection associates with cardiac involvement in patients with sarcoidosis. Future research is required to unravel pathways involved in the association between a latent tuberculosis infection and cardiac involvement in sarcoidosis.

Funding: This study is part of the TopZorg Lung grant funded by ZonMw (nr 842002001).

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APPENDIX

Table 1 Establishment of the diagnosis of cardiac sarcoidosis

Total CS	103	
1.Histological diagnosis from myocardial tissue	3	
2a + 2b	**Histological diagnosis of extra-cardiac sarcoidosis (n=78)**	**Consensus diagnosis extra-cardiac sarcoidosis based on expert opinion (n=21)**
Steroid+/- immunosuppressant responsive cardiomyopathy or heart block	1	3
Unexplained reduced LVEF (<40%)	11	2
Unexplained sustained (spontaneous or induced) VT	9	4
Mobitz type II 2nd degree heart block or 3rd degree heart block	11	9
Patchy uptake on dedicated cardiac PET (in a pattern consistent with CS)	63	16
Late Gadolinium Enhancement on CMR (in a pattern consistent with CS)	67	15

The likelihood of cardiac sarcoidosis (CS) was assessed in a multidisciplinary team consisting of a pulmonologist, cardiologist, radiologist, nuclear specialist and nurse, predominantly based on the diagnostic criteria from the Heart Rhythm Society (HRS) consensus statement (17). Definite and probable CS were the gold standard for the diagnosis of CS

Table 2 Country of origin of study patients

Country of origin	Non-CS (n=153)	CS (n=103)
The Netherlands	146 (96.1)	95 (92.2)
Morocco	0	3 (2.9)
Curacao	0	2 (1.9)
Sri Lanka	2 (1.3)	0
Suriname	1 (0.7)	1 (1.0)
Colombia	1 (0.7)	0
Germany	0	1 (1.0)
Grenada	1 (0.7)	0
India	1 (0.7)	0
Syria	0	1 (1.0)
Unknown	1 (0.7)	0

The percentages of patients who originated from another country than the Netherlands did not significantly differ between the CS and non-CS group (p = 0.189).