ORIGINAL ARTICLE

Prevalence of thyroid autoantibodies in a large series of sarcoidosis patients: Implications for autoimmune thyroid disease screening

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ABSTRACT.

Background and aim: Sarcoidosis is a potentially multisystem granulomatous disease frequently associated with autoimmunity. Previous cohort studies have reported an elevated risk of developing autoimmune thyroid disease (AITD) in sarcoidosis patients. Aim of the study was to assess the prevalence of thyroid autoimmunity in a large, biopsy-proven sarcoidosis cohort and compare it to established general population rates, thereby highlighting the clinical significance of screening.

Methods: To explore the prevalence of AITD, we examined a cross-sectional cohort of 668 patients with biopsy-proven sarcoidosis. Serum Thyroperoxidase Antibodies (TPOAb) and Thyroglobulin Antibodies (TgAb) were quantified using standard electrochemiluminescence immunoassays (ECLIA). The prevalence of positive thyroid autoantibodies was compared to previously published regional healthy control rates (11.4%, n=1,108) using a two-sample Z-test for comparing two proportions.

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Results: The overall prevalence of positive thyroid autoantibodies (TPOAb and/or TgAb) in the sarcoidosis cohort (n=668) was found to be 27.4% (95% CI: 21.7%–28.3%). This rate was significantly higher compared to the pooled historical control group prevalence of 11.4% ($p < 0.001$).
Conclusion: The prevalence of positive thyroid autoantibodies in patients with sarcoidosis is significantly elevated compared to the healthy population. This finding underscores the strong autoimmune linkage between sarcoidosis and AITD and supports the recommendation for systematic screening for thyroid autoimmunity in patients diagnosed with sarcoidosis.

Key words: sarcoidosis, autoimmune thyroid disease, thyroid autoantibodies, hashimoto's thyroiditis, hypothyroidism, screening

Introduction

Sarcoidosis is a systemic disease of unknown etiology characterized by the formation of non-caseating epithelioid cell granulomas (1), predominantly affecting the lungs but capable of involving almost any organ. It is an immune-mediated inflammatory disorder that occurs primarily in genetically predisposed individuals exposed to specific antigens. The potential influence of epidemiological factors — including geolocation and ethnicity — on sarcoidosis phenotype is substantial (2). The incidence and clinical presentation of sarcoidosis show marked variability across different geographical regions and ethnic groups. The inflammatory milieu and immune dysregulation inherent to sarcoidosis often lead to the clustering and co-occurrence of other immune-mediated inflammatory diseases (IMIDs) (3,4). Autoimmune thyroid disease (AITD), which includes Hashimoto's thyroiditis (HT) and Graves' disease, represents one of the most frequent IMID associations in patients with sarcoidosis (5,6). Hashimoto's thyroiditis, the most common AITD, is characterized by the presence of thyroid autoantibodies, primarily anti-thyroid peroxidase (TPOAb) and/or anti-thyroglobulin (TgAb) (7). A growing body of literature supports this association. A large systematic review summarizing the co-occurrence of sarcoidosis and IMIDs confirmed AITD among the conditions showing the strongest clustering with sarcoidosis (3,8). Epidemiological studies have shown varying results regarding specific risk factors, potentially influenced by geo-ethnic differences and methodological approaches (2). For example, a recent nationwide case-control study in Taiwan reported an association between sarcoidosis and autoimmune thyroiditis predominantly linked to male patients (9). This contrasts with the generalized understanding of AITD, which is known for its strong female predominance globally (7,10). Such observations emphasize the critical role of geographical and population studies in characterizing these complex relationships. Given the heterogeneity of these findings, obtaining reliable prevalence data from large, well-characterized regional cohorts remains essential for informing clinical practice and identifying high-risk patients. This prospective, cross-sectional study aimed to assess the prevalence of positive thyroid autoantibodies in a large, biopsy-proven sarcoidosis cohort and compare this prevalence to established healthy control rates to confirm the strength of this autoimmune linkage and define the local need for systematic AITD screening.

Methods

Study design and patient selection

This study was a retrospective cross-sectional investigation. The analysis was conducted on a series of 68 patients with biopsy-proven sarcoidosis. For this large patient series, serum thyroid autoantibodies were measured.

Measurement of thyroid autoantibodies

Serum TPOAb and TgAb were determined by using conventional commercially available immunoassays depending on the cutoff values defined by the manufacturer. More in detail, electrochemiluminescence immunoassays (ECLIA) by Roche Diagnostics (Elecsys Anti-TPO assay, normal levels <34 IU/mL & Elecsys Anti-Tg, normal levels < 115 IU/mL; Basel, Switzerland) were used to define seropositivity.

Statistical analysis

Descriptive statistics comprised frequencies and percentages, which were calculated to summarize the overall prevalence of positive thyroid autoantibodies within the cohort with sarcoidosis, along with 95% Confidence Intervals (95% CI). Comparative Analysis (Z-Test against Historical Controls) was done to assess whether the prevalence of positive thyroid autoantibodies in our series (n=668) was significantly greater than expected rates in healthy populations; more in detail a two-sample Z-test for comparing two proportions was conducted (11,12). Although reliance on historical controls requires cautious interpretation because of possible biases relating to differences in patient characteristics, outcome measurements, and disease processes, using regional data provides context when contemporary controls are not available (11). For the primary comparison, we used aggregate thyroid antibody positivity data from studies of healthy control populations conducted in Greece (13-15). This pooled historical control group (n=1,108) had an overall thyroid antibody positivity rate of 11.4%. Secondary comparisons used a generalized control rate of 20%, similar to the rates reported in middle-aged healthy women in the US (16) or the 23.7% of a large Croatian series (17), versus a hypothetical large control group (n=1,000). For all tests, the level of statistical significance was $p<0.05$.

Results

Subjects' characteristics and autoantibody prevalence

The study included 668 patients (254 men, 414 women) with a mean age of 52.87 ± 11.71 years. The overall combined antibody status prevalence was 27.4% (Table 1), whereas TPOAb positivity was 19.0%. Women showed a higher rate of combined antibody positivity, 30.6%, compared to men, 22.4% (Table 1).

In subjects with sarcoidosis, the seropositivity rate was 27.4%, significantly higher than the 11.4% rate in Greek historical control populations (n=1,108) (Table 2).

The two-sample Z-test comparing our sample with Greek controls resulted in a Z-value of 9.6 ($p<0.0001$); the result is statistically significant and thus the null hypothesis of equal proportions should be rejected (12). The difference remained highly statistically significant even compared to a conservative high estimate for the general population prevalence of 20% (Z-value of 4.2, $p < 0.0001$).

Discussion

The robust finding of a significantly higher prevalence of thyroid autoantibodies in our large, biopsy-proven sarcoidosis cohort reinforces the existence of a strong pathophysiological link between sarcoidosis and autoimmune thyroid disease (AITD) (5,6, 18-22). This association aligns with numerous previous

Table 1. Thyroid Autoantibody Positivity in Subjects with Sarcoidosis

	Frequency (n)	Prevalence (%), 95% Confidence Interval
Any TPOAb and/or TgAb (AnyTPOTg)	183	27.4%, 23.6%-31.6%
Anti-TPO positive	124	19.0%, 15.4%-22.1%
Men positive (AnyTPOTg)	57	22.4%, 17.0%-29.1%
Women positive (AnyTPOTg)	126	30.6%, 25.3%-36.2%

Table 2. Comparison of Thyroid Autoantibody Prevalence: Sarcoidosis vs. Historical Controls.

Subjects	n	AnyTPOTg (+)	Odds Ratio (95% Confidence Interval)
Subjects with Sarcoidosis (this study)	668	27.4%	Sarcoidosis Vs A: 2.409, 1.961-2.958, Sarcoidosis vs B: 1.369, 1.149-1.631
Pooled Greek Historical Controls (A)	1,108	11.4%	
Hypothetical General Population (B)	1000	20.0%	

findings reporting increased frequencies of AITD in sarcoidosis patients across different populations and supports the concept that sarcoidosis is an immune-mediated inflammatory disorder (IMID) prone to disease clustering (1,3,4). However, the interpretation of this finding must be approached forensically, considering potential complexities: the precise pathogenic relationship between sarcoidosis and AITD, and the inherent limitations of diagnosing true primary autoimmunity solely through seropositivity in a systemic inflammatory setting.

Differentiating primary autoimmunity from secondary phenomena

Sarcoidosis, a prototypical immune-mediated inflammatory disease (IMID), is marked by broad immune dysregulation driven predominantly by exaggerated T-helper cell activity—particularly Th1 and Th17.1 polarization—und er the influence of cytokines such as interferon-γ (IFN-γ) (1). Within this heightened inflammatory milieu, the detection of thyroid autoantibodies (seropositivity) may arise through two mechanistically distinct pathways, each with important diagnostic and prognostic implications for clinicians. The first mechanism reflects true coexistence of primary autoimmune thyroid disease (AITD). In this scenario, the patient harbors bona fide Hashimoto's thyroiditis or Graves' disease, rooted in overlapping genetic susceptibility loci shared between sarcoidosis and other autoimmune disorders (3,4). The well-described association between thyroid autoantibody positivity and the subsequent development of overt hypothyroidism in such patients further supports an underlying primary autoimmune process (23). The second mechanism represents a secondary phenomenon, driven by granulomatous inflammation or para-inflammatory immune activation. Direct thyroid involvement by sarcoidosis can manifest as granulomatous thyroiditis, a process that may yield detectable autoantibodies despite the absence of classic autoimmune pathophysiology (22). More broadly, systemic inflammation in sarcoidosis promotes chronic immune activation, which is known to induce de novo autoantibody formation—typically at low titers—without indicating established autoimmune disease (24). Contemporary evidence from severe and critical COVID-19 provides a compelling analogy: the emergence of neutralizing anti–IFN-γ autoantibodies in such patients illustrates how intense inflammatory stress can generate secondary, para-inflammatory autoantibodies (24,25). In this study, we employed commercial assays with clearly defined cut-off values (TPOAb <34 IU/mL and TgAb <115 IU/mL), thereby ensuring analytic standardization (26). Nevertheless, the cross-sectional nature of our design limits our ability to discriminate between high-titer, functionally pathogenic autoantibodies consistent with primary AITD and low-titer antibodies arising as epiphenomena of systemic inflammation. To address this limitation, future prospective investigations should correlate autoantibody levels with validated markers of sarcoidosis activity and with discrete clinical phenotypes—particularly distinctions among D86.0/D86.2 and D86.8 subtypes, the latter increasingly recognized in older adults (27). Such work will be essential to clarify the clinical significance of low-titer or secondary autoantibody production in sarcoidosis.

Geo-epidemiological and phenotypic implications

The observed association between sarcoidosis and AITD may also exhibit variations based on ethnicity and geography (2). The nationwide Taiwanese study (9) reported an association between sarcoidosis and autoimmune thyroiditis predominantly linked to male

patients (9). This is notably counterintuitive to the generally observed strong female-linked epidemiology of Hashimoto's thyroiditis (HT) observed globally, where prevalence in adult females is approximately four times higher than in males (10,7). Understanding such phenotypic differences requires future large-scale, international collaborative efforts to integrate genotypic data, environmental exposures, and standardized clinical outcomes (2).

Clinical recommendation

Despite the ongoing etiological debate surrounding primary vs. secondary autoimmunity, the prevalence rate observed in our cohort vastly exceeds the population prevalence of 11.4%, confirming that sarcoidosis patients represent a high-risk group. The strong link to subsequent hypothyroidism necessitates clinical action. Therefore, the immediate clinical implication remains clear: systematic serological screening for TPOAb and TgAb upon diagnosis of sarcoidosis is warranted to facilitate early identification and therapeutic intervention for patients at risk of developing overt thyroid dysfunction (28).

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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