High frequency of endocrine autoimmunity in patients with sarcoidosis

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Autoimmune diseases and sarcoidosis may be related and, especially, the association between sarcoidosis and autoimmune thyroid disease has long been recognized. The frequency and type of endocrine autoimmunity was examined in a series of Swedish patients with sarcoidosis. Of all patients (N = 89) with documented sarcoidosis attending the Department of Pulmonary Medicine between January 1980 and December 1991, 78 patients (44 males and 34 females; median age at the time of the study 48 years, range 22–81 years) were examined at the Department of Endocrinology, Malmö University Hospital, in the present study. Fifteen patients (19.2%) had clinical or serological evidence of endocrine autoimmunity. Two patients had Addison’s disease, both with polyglandular autoimmune (PGA) syndrome type II; evidence of thyroid autoimmunity was found in 13 patients, eight with clinical autoimmune thyroid disease (ATD) (two with Graves’ disease and six with autoimmune thyroiditis), of whom two had PGA syndrome type III, and five with isolated positive thyroid serology; two patients had insulin-dependent diabetes mellitus and one had premature ovarian failure. The frequencies of Addison’s disease, clinical ATD and PGA syndrome type II were significantly higher compared with the frequencies found in the general population. In conclusion, a high frequency of endocrine autoimmunity in patients with sarcoidosis, occurring in about 20% of the cases, was demonstrated. Thyroid autoimmunity and polyglandular autoimmune syndromes occurred most frequently. Complex immunological and genetic mechanisms might explain the association of sarcoidosis and endocrine autoimmune diseases.

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Sarcoidosis, a disease of unknown etiology, is characterized by the presence of non-caseating granulomas that most often are found in lymph nodes, lungs, eyes and skin, but any organ may be involved (1). Patients with pulmonary sarcoidosis appear to have a heightened local cellular immune response, mediated by excess helper T-lymphocyte activity, and a heightened humoral immune response manifested by increased amounts of circulating immunoglobulins, among which are antibodies with reactivity towards multiple antigens, including self-antigens (2). The initiating event for the above aberrant immune response is not known but genetic influences and antigenic insults by viruses, bacteria, mycobacteria and/or autoantigens have been implicated (3). Autoimmune diseases and sarcoidosis may be related (4) and, especially, the association between sarcoidosis and autoimmune thyroid disease has long been recognized (5). Although an autoimmune etiology has been postulated in sarcoidosis (4) and thus an increased prevalence of other autoimmune diseases among patients with sarcoidosis would be expected, a frequency of 3.1% of endocrine autoimmune phenomena was reported in a recent study of Japanese patients with sarcoidosis (6). The aim of the present work was to explore the frequency and type of endocrine autoimmunity in a series of Swedish patients with sarcoidosis.

Materials and methods

Patients

Between January 1980 and December 1991, 89 patients with documented sarcoidosis had attended the Department of Pulmonary Medicine, Malmö University Hospital. Six patients could not be located, one patient was deceased and four patients refused to participate in the present study. Accordingly, the final number of patients was 78 (44 males and 34 females; Table 1), including also patients diagnosed before 1980 (N = 36). All patients were Caucasian except one of Afro-Caribbean origin. During 1992 and after informed consent was obtained, all patient records and all patients (N = 78) were examined at the Department of Endocrinology by one of us (KIP) and blood samples were obtained. All patients with previously diagnosed endocrine disease had attended our Department of Endocrinology earlier and the original endocrine records were traced for confirmation of the diagnoses. The diagnosis of sarcoidosis was based on histological or
clinical, biochemical and radiological evidence (7). Histological diagnosis of sarcoidosis was present in 51 patients (66%).

Controls
The prevalence of Addison's disease in the general population was $5 \times 10^{-3}\%$ when isolated and $2.5 \times 10^{-3}\%$ when associated with polyglandular autoimmune syndrome type II (8). A study of thyroid disease in a community (9) and a Swedish study on the prevalence of insulin-dependent diabetes mellitus provided control data (10).

Definitions
Addison's disease. The confirmation of autoimmune etiology in Addison's disease was based on exclusion of other known causes of adrenal destruction and/or the presence of antibodies to adrenal cortical cells (AA) (11).

Thyroid autoimmunity. In patients with clinical thyroid disease, i.e. hyper- or hypothyroidism and/or goiter, Graves' disease as well as idiopathic myxedema and autoimmune (Hashimoto's) thyroiditis (verified by serological studies and/or fine-needle biopsy) were classified as autoimmune thyroid disease (ATD) (12). Autoimmune thyroid disease was described according to the original diagnosis, e.g. patient with hypothyroidism following treatment for Graves' disease was classified as hyperthyroidism.

Insulin-dependent diabetes mellitus (IDDM). Diabetes mellitus was defined as insulin dependent in patients in need of exogenous insulin to prevent ketoacidosis and to maintain adequate metabolic stability (13). As diabetes mellitus associated with autoimmune disorders may have a rather slow onset, there was no time limit applied for the appearance of insulin requirement (13).

Premature ovarian failure (POF). Premature ovarian failure was defined as menopause (hypergonadotropic hypogonadism) occurring before the age of 35 (14).

Polyglandular autoimmune (PGA) syndromes. Polyglandular autoimmune syndrome type II was defined as idiopathic/autoimmune Addison’s disease co-existing with ATD and/or IDM (15); PGA syndrome type III was defined as ATD co-existing with IDDM and/or pernicious anemia and/or vitiligo/alopecia (15).

Measurements
The following tests were performed on all patients by in-hospital methods: blood hemoglobin, erythrocyte sedimentation rate, serum electrolytes, serum creatinine and fasting blood glucose. Glycated hemoglobin (HbA1c) was measured in all patients by a liquid chromatography assay (16) and serum angiotensin-converting enzyme (ACE) by a fluorimetric assay (reference range 7–30 μmol·min⁻¹·l⁻¹). Serum total T₃ and total T₄ concentrations were determined in all patients by a radioimmunoassay (17) and serum TSH concentrations by an immuno-radioimmunosay with coated tubes (RIA-gnost hTSH; Hoechst, Behring Diagnostica, Marburg, Germany), the detection limit being 0.05 mU/l (reference range 0.4–4.0 mU/l).

Antibody measurements. Adrenal antibodies (AA) were measured in all patients by immunofluorescence using human fetal adrenal tissue (IFL, reference value <1/10). The frequency of adrenal antibodies detected by this IFL in the sera of normal subjects is <0.1% (18). Microsomal thyroid antibodies (MS-ab) and thyroglobulin antibodies (TG-ab) were measured in all patients by a routine hemagglutination procedure (reference values <1/100 and <1/10, respectively). Islet cell antibodies (ICA) were measured in all patients by a two-color immunofluorescence assay using unfixed human pancreatic tissue; detection limit for positive reaction is <3 juvenile diabetes foundation units (JDFU) (courtesy of Associate Professor G Sundkvist, Department of Endocrinology, Malmö University Hospital) (19).

Statistical analysis
Statistical analysis was performed by the exact binomial and the Mann–Whitney test; <0.05 was considered significant. Median values and ranges are given.

The study was approved by the Ethics Committee of the Medical Faculty, University of Lund.

Results
Of 78 patients, 15 (19.2%, eight females and seven males) had clinical or serological evidence of endocrine
autoimmunity (Table 2). The characteristics of this group (group A, N = 15) did not differ significantly compared to the patients without endocrine autoimmunity (group B, N = 63) but males with endocrine autoimmunity were significantly older at the time of the study (median 57 years; range 43–75 (p < 0.014) compared to males without endocrine autoimmunity (median 42 years; range 22–71). Individual characteristics of group A are presented in Table 3 and the type of endocrine autoimmunity is presented in Table 4.

Addison’s disease (Tables 3 and 4)

In two patients, one of each sex, autoimmune Addison’s disease was diagnosed before the study as PGA syndrome type II and the frequency of Addison’s disease was raised (p < 0.001) as compared to the general population (Table 4). In the female, sarcoidosis was diagnosed at age 33 and preceded the endocrine diseases (Graves’ disease at age 38 and Addison’s disease at age 48). In her, Graves’ disease was treated by subtotal bilateral thyroidectomy and histological examination of the thyroid showed no evidence of sarcoidosis. In the male, sarcoidosis was diagnosed simultaneously with Addison’s disease and autoimmune thyroiditis at age 31.

Fine-needle biopsy of the thyroid revealed lymphocytic thyroiditis. Pernicious anemia developed 9 years later and he has been substituted with oral vitamin B12 since.

Thyroid autoimmunity (Tables 3 and 4)

Thirteen patients (16.7%, seven females and six males) had evidence of thyroid autoimmunity, of whom eight (10.2%, six females and two males; Table 2) had clinical ATD. The frequency of overall clinical ATD was higher (p < 0.001) compared to the controls (Table 4). In four patients (three females and one male) clinical ATD was diagnosed before the present study (two with Graves’ disease and two with autoimmune thyroiditis). Sarcoidosis preceded clinical ATD in three cases and in one both diseases occurred simultaneously. In addition, in four euthyroid patients (three females and one male) autoimmune thyroiditis, verified by fine-needle biopsy, was diagnosed during the present study. Polyglandular

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex (M/F)</th>
<th>Age (years)</th>
<th>EAD</th>
<th>TSH (mIU/l)</th>
<th>MS-ab/TG-ab titer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>78</td>
<td>AIT</td>
<td>0.9</td>
<td>400/400</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>53</td>
<td>AIT</td>
<td>1.8</td>
<td>25600/1000</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>53</td>
<td>AIT</td>
<td>0.5</td>
<td>1600/1000</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>56</td>
<td>GD</td>
<td>0.1</td>
<td>&lt;100/1000</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>35</td>
<td>AIT/IDDM</td>
<td>2.2</td>
<td>6400/1600</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>38</td>
<td>GD/Addison</td>
<td>2.1</td>
<td>100/400</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>31</td>
<td>AIT/Addison</td>
<td>0.2</td>
<td>400/1000</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>42</td>
<td>AIT/Vitilgo</td>
<td>3.3</td>
<td>1600/1000</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>33</td>
<td>POF</td>
<td>0.4</td>
<td>&lt;100/1000</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>39</td>
<td>IDDM</td>
<td>2.3</td>
<td>&lt;100/1000</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>57</td>
<td></td>
<td>2.5</td>
<td>&lt;100/20</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>67</td>
<td></td>
<td>1.3</td>
<td>400/1000</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>57</td>
<td></td>
<td>3.3</td>
<td>&lt;400/1000</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>75</td>
<td></td>
<td>0.9</td>
<td>&lt;100/400</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>26</td>
<td></td>
<td>2.1</td>
<td>1600/1000</td>
</tr>
</tbody>
</table>

In 10 patients (nos. 1–10 in the table) there was an associated clinical endocrine autoimmune disease (EAD), whereas in 5 patients (nos 11–15 in the table) positive thyroid autoimmunity was an isolated finding without clinical disease. Age at diagnosis of endocrine autoimmunity is given. The TSH values and antibody titers are values at the time of the study. Patient nos 4–8 were on l-thyroxine therapy. M = male; F = female; MS-ab = microsomal antibodies; TG-ab = thyroglobulin antibodies; AIT = autoimmune thyroiditis; GD = Graves’ disease; IDDM = insulin-dependent diabetes mellitus; Addison = Addison’s disease; POF = premature ovarian failure.
autoimmune syndrome type III was diagnosed in two
patients with ATD. One female, previously described in
detail (20), developed IDDM prior to sarcoidosis, which
in turn preceded autoimmune thyroiditis. The second
patient, a male, was diagnosed during the present
study. In him, sarcoidosis was diagnosed at the age of
31 and was preceded by vitiligo. He had normal thyroid
function but was found to be MS-ab positive and fine-
needle biopsy showed autoimmune thyroiditis.

Serum T₃, T₄ and TSH values were within the reference
range in the remaining 70 patients.

**Insulin-dependent diabetes mellitus (IDDM) (Tables 3
and 4)**

Two patients (one of each sex) had IDDM. In the female,
IDDM was seen as part of PGA syndrome type III and is
described above. In both patients IDDM was diagnosed
before the study, and in the male it followed sarcoidosis.
No additional patients with IDDM were found and the
observed frequency was not significantly higher
(p < 0.052) as compared to Swedish controls (Table
4). The HbA₁c and fasting blood glucose values were
within the reference range in the remaining 76
patients.

**Premature ovarian failure (POF) (Tables 3 and 4)**

One female had been diagnosed with POF at the age of
33 with elevated FSH, LH and low estrogens. No
additional patient with POF was found in this study.

**Antibodies (Table 3)**

In the present study all patients were AA and ICA
negative. Twelve patients (six females and six males)
had positive thyroid serology (three with both MS-ab
and TG-ab, seven only MS-ab and two only TG-ab) and
in five of these (four males and one female) it was an
isolated finding without clinical disease.

**Discussion**

In the present study we found that almost 20% of the
patients with sarcoidosis had clinical and/or serological
evidence of endocrine autoimmunity. This is a rather
high frequency compared with a recent review of 64
Japanese patients with sarcoidosis (6), in which two
patients (3.1%) were found to have clinical and
serological evidence of endocrine autoimmunity with
thyroid antibodies and autoimmune thyroiditis and four
more patients showed evidence of non-organ-specific
autoimmunity. The reason for this discrepancy in
frequencies is not obvious, but one plausible explana-
tion might be ethnically related HLA differences (vide
infra). The frequency of endocrine autoimmune disease
in our patients with sarcoidosis was found to be
significantly higher as compared to the general
population (8–10) and, in addition, 5% of the patients
displayed polyglandular autoimmune syndromes, thus
making the likelihood of a fortuitous association quite
remote.

Macroscopic sarcoid invasion may occur in every
organ, including the endocrine glands, e.g. adrenals,
thyroid gland and pancreas, and might lead to target
organ failure (1, 21) but whether autoantibodies follow
as an epiphenomenon is not known (22). Sarcoidosis
has been reported in association with multiple auto-
immune diseases but in none was the association
indisputably the result of a space-occupying sarcoid
lesion (1, 4, 20, 22–26). Involvement of the adrenal
glands rarely occurs in sarcoidosis (1) and the
association between sarcoidosis and Addison’s disease
is unusual but when it occurs it is likely to be as a result
of autoimmunity (24). The type of association of
Addison’s disease in our study was in accordance with

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Table 4. Endocrine autoimmune entities that occurred in 15 of 78 patients with sarcoidosis.

<table>
<thead>
<tr>
<th>Associated entity</th>
<th>N (%)</th>
<th>F/M</th>
<th>Age at diagnosis of sarcoidosis (years)</th>
<th>Age at diagnosis of clinical AD (years)</th>
<th>Clinical endocrine autoimmune disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addison’s disease</td>
<td>2 (2.6)</td>
<td>1/1</td>
<td>31–33</td>
<td>31–38</td>
<td>2 (2.6)**</td>
</tr>
<tr>
<td>Thyroid AI</td>
<td>13 (16.7)</td>
<td>7/6</td>
<td>33 (20–75)</td>
<td>37 (31–56)²</td>
<td>8 (10.2)**</td>
</tr>
<tr>
<td>IDDM</td>
<td>2 (2.6)</td>
<td>1/1</td>
<td>23–38</td>
<td>18–39</td>
<td>2 (2.6)⁸</td>
</tr>
<tr>
<td>POF</td>
<td>1 (3)</td>
<td>1/1</td>
<td>20</td>
<td>33</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

¹ Medians and ranges are given. Comparisons are made vs the general population (references are given in the table). **p < 0.001 vs controls.
² F/M = female/male; AI = autoimmunity; IDDM = insulin-dependent diabetes mellitus; POF = premature ovarian failure; AD = autoimmune disease.
³ Of four previously diagnosed patients.
⁴ Non-significant vs controls.
⁵ Ref. 8.
⁶ Ref. 9.
⁷ Ref. 10.
a recent report (24) where a high frequency of co-existing PGA syndrome type II was seen when Addison’s disease and sarcoidosis were associated. Diabetes mellitus is not more common in patients with sarcoidosis (1), although necrobiosis lipoidica has been reported in patients with sarcoidosis (27). Sarcoid infiltration of the thyroid gland at necropsy was reported in 1–4.6% (28, 29). However, the relationship between the presence of sarcoid granulomas in the thyroid gland and clinical thyroid disease is not known and a cause–effect relationship has not been established (21, 30). Scadding (30) stated that sarcoidosis rarely, if ever, is the cause of functional derangement of the thyroid, while Karlish and MacGregor (22) reported a prevalence of overt thyroid disease in sarcoidosis in 3.6%, overwhelmingly autoimmune in etiology. In the present study, we report an overall frequency of thyroid autoimmunity of 17% and a 10% frequency of clinical ATD, the latter with a histo-/cytological appearance of the thyroid, pointing to a genuine autoimmune process rather than to a sarcoid dissemination.

Polyglandular autoimmune syndromes occurring together with sarcoidosis have been described in a few cases (22–24). Both of our patients with Addison’s disease had PGA syndrome type II and, in addition, amongst our ATD patients, two had PGA syndrome type III, one with the disease constellation of ATD, IDDM, coeliac disease and sarcoidosis previously described by us in another patient (25). The present patient has been described in detail (20) and we have discussed whether this disease constellation might constitute a new syndrome (20). The relatively high frequency of PGA syndromes in our patients with sarcoidosis might simply reflect the propensity of various autoimmune diseases to occur together (8, 15, 31), but additional factors may contribute (3, 4). Cell-mediated (3, 32) as well as humoral immunity appears deranged in sarcoidosis and in PGA diseases (4, 32). Activated T-helper lymphocytes in the lungs or other sites of active disease in patients with sarcoidosis might stimulate B lymphocytes to produce antibodies (2, 4) with affinity for endocrine cells. Whether endocrine antibodies produced by such a mechanism in sarcoidosis do lead to the associated (poly)glandular deficiencies is not known and in that case sarcoidosis should precede the endocrine autoimmune diseases, which was not always the case in our study. On the other hand, the presence of circulating antibodies that precede for a variable length of time the onset of clinical manifestations is a common event in endocrine autoimmune disease (33). In addition to the formation of antibodies, the presence of circulating immune complexes in sarcoidosis has been documented (34). A defective clearance of such immune complexes and a decreased antigen degradation has been observed in HLA-B8/DR3-positive individuals, both healthy as well as those with dermatitis herpetiformis (35, 36). The HLA-B8/DR3 antigens may be linked to Addison’s disease, ATD, IDDM and PGA syndromes (8), whereas HLA-A1/B8/DR3 appears to be related positively to sarcoidosis in Swedes (37) and other Caucasians (38, 39) but is a very rare antigen in the Japanese (40). This observation, apart from the fact that the prevalence of sarcoidosis is lower in Japan than in Sweden (41), might explain the low frequency of associated endocrine autoimmune diseases reported in the Japanese study (6) as compared to the present work. Hypothetically, an HLA-linked genetic susceptibility in Caucasian patients with sarcoidosis might predispose for the development of autoimmunity and may partly explain the association between sarcoidosis and (poly)glandular failure: HLA studies are in progress in order to determine whether such a predisposition exists in our material.

In conclusion, in the present study we have demonstrated that endocrine autoimmunity is common in patients with sarcoidosis and occurs in about 20% of the cases. Thyroid autoimmunity was the most frequent autoimmune endocrine manifestation. Polyglandular autoimmune syndromes also occurred frequently. Complex immunological and genetic mechanisms might explain the association of sarcoidosis and autoimmune diseases. Further histological and genetic studies are in progress in order to define the significance of these observations.

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References


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