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LETTER TO THE EDITOR

Autoimmunity in sarcoidosis: the tip of the Iceberg

Konstantinos I. Papadopoulos[1] · **Bengt Hallengren**[2,3]

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Abstract
Sarcoidosis is a mysterious condition with an etiology that has to date eluded explanation. Innumerable clinical and serological organ- and non-organ-specific autoimmune associations have been reported. Many of the associated conditions are life-threatening but easily manageable if diagnosed early. Due to the long latency that precedes the clinical onset of autoimmune diseases, it is prudent to ensure a long follow-up and a broad viewing perspective while maintaining a high index of suspicion when viewing the autoimmunity iceberg in sarcoidosis.

Keywords Sarcoidosis · Autoimmunity · Endocrine glands

Main text

We read with interest the study of Shi et al. [1]. We wish to comment that the frequency and diversity of the reported clinical and serological autoimmunity in the present study may be significantly underestimated, especially when the repertoire of possible associations is overlooked.

Sarcoidosis is a mysterious condition with an etiology that has to date eluded explanation. Its association with autoimmunity is long known since over 50 years [2] with several both organ- and non-organ-specific autoimmune associations reported [1, 3, 4]. In our original study in 1996, in a series of Swedish patients (34 females and 44 males) with documented sarcoidosis over 12 years (maximum follow-up 39 years), we reported a high frequency of almost 20% of clinical and serological endocrine autoimmunity alone [3]. Addison's disease in polyglandular autoimmune (PGA) syndrome type II, clinical autoimmune thyroid disease (ATD) (Graves' disease and autoimmune thyroiditis), PGA syndrome type III, insulin-dependent diabetes mellitus and premature ovarian failure were among clinically manifest conditions [3]. 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 [3]. In addition, serological evidence of impending autoimmune endocrine gland involvement was overwhelming [3].

Furthermore, in a later study in the same sarcoidosis cohort, we reported a frequency of over 40% of gastrointestinal immune reactivity with H^+/K^+ ATPase antibodies in 24%, one patient with pernicious anemia and in six patients with elevated serum gastrin levels indicating deranged parietal cell function correlating well with antibody titer. Additionally, associated gluten immune reactivity was encountered in 15%, with overt coeliac disease in one patient [4].

As noted by Shi et al., the most significant weakness of their study is the length of patient follow-up [1]. Wu et al. followed a total of 1237 patients with sarcoidosis (62% females) and 4948 age- and sex-matched control subjects from the National Health Insurance Research Database of Taiwan from 1997 to 2010 and reported an 18% frequency of autoimmune comorbidities, noting that diagnosis of the autoimmune comorbidities strongly associated with sarcoidosis tended to be established after that of sarcoidosis, confirming our previous finding of a significantly higher age in males with autoimmune diseases [3, 5]. Moreover, in concordance with our study (47% males with thyroid autoimmunity), Wu et al. noted gender-specific

✉ Konstantinos I. Papadopoulos
kostas@thaistemlife.co.th

Bengt Hallengren
bengt.hallengren@med.lu.se

[1] THAI StemLife, 566/3 Soi Ramkhamhaeng 39 (Thepleela 1), Prachaouthit Rd., Wangthonglang, Bangkok 10310, Thailand

[2] Department of Endocrinology, Skåne University Hospital, 20502 Malmö, Sweden

[3] Department of Clinical Sciences, Lund University, Lund, Sweden

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associations such as ATD in males, compared to a female preponderance in the study of Shi et al. despite similar geolocation [1, 3, 5]. The long latency that precedes the clinical onset of autoimmune diseases in genetically predisposed individuals is well-known and autoantibodies do remain important serological markers to identify individuals at risk [6]. Moreover, corticosteroids, the mainstay of management in sarcoidosis, with their powerful anti-inflammatory and immunosuppressive effects may quieten a heightened immune reactivity and the ensuing autoimmunity, a phenomenon previously described in a patient with adrenal antibodies and polyglandular autoimmune syndrome type III, sarcoidosis, and celiac disease [7]. It is conceivable that corticosteroid elimination later in the course of sarcoidosis management might re-ignite a latent autoimmune predisposition in genetically susceptible individuals.

Finally, we reported previously significantly higher S-Angiotensin Converting Enzyme (ACE) values and a significant overrepresentation of the ACE D allele/DD genotype in X-ray stage III, theoretically with major granuloma mass in sarcoidosis with associated autoimmune manifestations [8]. The ACE D allele/DD genotype is known to significantly worsen sarcoid disease prognosis, in genetically predisposed individuals, possibly through the higher ACE levels it encodes that subsequently lead to higher angiotensin II (Ang II) levels [8–11]. Ang II-immunomodulatory effects from a functional T-cell renin angiotensin system (RAS) could explain the adverse ACE D allele autoimmunity associations across several ethnicities and autoimmune conditions [9, 12]. Th17 cells under Ang II control demonstrate a potentially pathogenic profile of cytokine expression that could swerve the immune system toward a protracted disease course with aberrant autoantibody expression to account for the polyglandular autoimmunity and immune reactivity observed in sarcoidosis [8, 9]. Ang II's role in autoimmunity in sarcoidosis might be similar to its apparent role in coronavirus disease 2019 associated autoimmunity where pyroptotic inflammatory cell necrosis could lead to autoantigen exposure and stimulate multiple autoantibody production, potentially leading to numerous autoimmune conditions [13, 14].

It is thus prudent to ensure a long follow-up and a broad viewing perspective of the autoimmunity iceberg in sarcoidosis along with maintaining a high index of suspicion for an early diagnosis of life-threatening but treatable autoimmune complications.

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Declarations

Conflict of Interest The authors have no relevant financial or non-financial interests to disclose.

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