Coexistent Sarcoidosis and Alopecia Areata or Vitiligo: A Case Series and Review of the Literature

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Abstract

Importance: Sarcoidosis is a multi-system inflammatory disease that frequently affects the lungs, lymph nodes, eyes and skin. The immunopathogenesis underlying sarcoidosis continues to be an area of active research. The presence of other diseases, such as vitiligo or alopecia, in individuals with sarcoidosis proposes a potential overlap in the immunological and inflammatory pathways of these diseases.

Observations: We present 4 patients with sarcoidosis and coexistent alopecia or vitiligo. Patients 1 and 2 had subcutaneous sarcoidosis and pulmonary sarcoidosis, respectively, and presented with alopecia areata. Patient 3 had a history of alopecia universalis and presented with cutaneous sarcoidosis. Lastly, patient 4 had a history of cutaneous sarcoidosis and presented with vitiligo.

Conclusions and relevance: The presence of prominent Th1 and possible Th17 inflammatory profiles in sarcoidosis, alopecia and vitiligo suggests a possible overlap in the immunological and inflammatory pathways of these diseases. Given the relatively rare combination of these diseases, large scale databases and genetic linkage studies are necessary to further explore the immunopathophysiology underlying these diseases and eventually lead to new therapeutic advances.

Keywords: Sarcoidosis; Alopecia; Vitiligo ; Th1; Th17

Introduction

Sarcoidosis is a rare systemic disease, with a prevalence of 1-40 cases per 100,000 which is characterized by noncaseating granulomatous inflammation, most commonly involving the lungs, intrathoracic lymph nodes, eyes and skin [1]. While the overall pathogenesis of sarcoidosis remains poorly understood, the granulomatous inflammation in sarcoidosis is felt to be a Type 1 helper (Th1) T cell mediated disease, though recent attention has been paid to a potential role for Th17 cells and the innate immune system. Th1 and Th17 are thought to play a central role in the pathogenesis of other cutaneous disorders, such as psoriasis, alopecia areata, and vitiligo [2-5]. Although alopecia areata and vitiligo frequently occur in conjunction with other autoimmune diseases and have a prevalence of 0.1-0.2% and 0.06-2.28%, respectively, the observation of alopecia or vitiligo in patients with sarcoidosis is relatively rare [6,7]. We present a series of 4 patients with sarcoidosis, 2 with coexistent alopecia areata, 1 with coexistent alopecia universalis and 1 with coexistent vitiligo, suggesting a potential overlap in the immunological and inflammatory pathways underlying these diseases. We would expect 0.225 patients (or 0-1 patients) to have sarcoidosis and alopecia, assuming prevalence of alopecia in sarcoidosis patients is the same as the prevalence in the general population. In our 150 sarcoidosis patients, 3 have alopecia, which appears to be more than expected by chance alone.

Report of Cases

Case 1

A 60 year old African American woman with a history of hypothyroidism and subcutaneous sarcoidosis with prior, quiescent pulmonary involvement presented to clinic with a new complaint of sudden onset hair loss of her left scalp which began two months prior. She had a 15-year history of recurrent tender 0.3-2 cm firm subcutaneous nodules on her anterior and posterior calves and thighs. Two biopsies demonstrated subcutaneous noncaseating granulomas and granulomatous panniculitis consistent with subcutaneous sarcoidosis for which she was being treated with hydroxychloroquine sulfate 200 mg once daily and minocycline hydrochloride 100 mg once daily, with near complete resolution (Figure 1A).

Physical examination was notable for a 3 cm round patch of nonscarring complete hair loss on the lateral posterior auricular scalp which had a negative pull test (Figure 1B). Nail pitting and two small 0.5 cm subcutaneous nodules were present on the left calf. She denied a previous personal or family history of hair loss. Laboratory tests were notable for vitamin D 25-OH total of 15 ng/mL and a positive ANA titer of 1:160, and normal tests included complete blood count, thyroid stimulating hormone, vitamin B12, vitamin D 1,25, ferritin, and zinc. Quantiferon gold immunoassay was negative.

Biopsy of the left scalp demonstrated peribulbar lymphocytic inflammation and decreased number of anagen follicles without appreciable scarring, consistent with a diagnosis of alopecia areata. The patient declined intralesional steroids, and treatment with clobetasol
mometasone furoate 0.05% ointment was started with successful hair regrowth within 3 months of treatment (Figure 1C).

Case 2

A 60 year old Caucasian woman with a history of pulmonary sarcoidosis presented with new onset hair loss on her scalp. She was diagnosed with sarcoidosis approximately 15 years prior based on pulmonary symptoms and chest radiography demonstrating bilateral hilar and mediastinal lymphadenopathy, consistent with pulmonary sarcoidosis. Medical history was also notable for recurrent breast cancer requiring lumpectomy, lymphadenectomy, mastectomy and radiation therapy and a recent diagnosis of polycythemia vera requiring routine phlebotomy.

Physical examination was notable for a 1.5 cm × 1.5 cm patch of non-scarring complete hair loss on the left posterior auricular scalp, which had a negative pull test. No other hairless patches or skin findings were appreciated. Laboratory tests were notable for an unremarkable CBC, TSH, vitamin D 25-OH, ESR and ACE as well as a negative ANA (Figure 2).

Triamcinolone acetonide injections were performed, which resulted in central hair regrowth.

Case 3

A Caucasian man in his mid-40s with a 20-year history of alopecia universalis presented with recurrent skin papules localized to areas of scars and tattoos. He was diagnosed with cutaneous sarcoidosis 3 years prior based on biopsy of similar cutaneous lesions. Skin biopsy revealed multiple sarcoidal-type granulomas characterized by relatively well-defined nodular aggregates of epithelioid histiocytes (Figure 3A). The lesions had initially resolved without therapeutic intervention. He presented to us for recurrence of his previously noted lesions.

Physical exam was notable for extensive non-scarring alopecia involving the entire scalp and infiltrated flesh colored papules with mild erythema located on the chin, elbow and along tattoos (Figures 3B and 3C). Laboratory tests were notable for an elevated ACE of 105 U/L and a low vitamin D 25-OH of 27 ng/mL. Normal tests included complete blood count, ESR, complete metabolic panel and thyroid stimulating hormone. Pulmonary evaluation, including chest x-ray and PFTs were normal.

The patient was recently started on hydroxychloroquine.

Case 4

A 60-year-old Caucasian man with a history of cutaneous sarcoidosis, and possible pulmonary involvement based on symptoms, presented with new onset flesh colored papules on the back of his neck.
and depigmentation of his nipples. He was diagnosed with presumed sarcoidosis 10 years prior based on an elevated ACE level in the setting of pulmonary symptoms and joint pain. Physical examination was notable for 4 faint flesh colored papules on the back of his neck and depigmentation of his nipples and areolae (Figure 4A and 4B). Personal and family history was notable for rheumatoid arthritis in his mother; however no histories of skin findings, including depigmentation, were known. Pulmonary evaluation including chest CT and PFTs were unremarkable. Laboratory tests were notable for an ACE level of 109 U/L and normal tests included complete blood count, complete metabolic panel, vitamin D 25, vitamin D 25-OH, TSH, ESR and non-cardiac CRP.

Biopsy of the neck papules demonstrated prominent interfollicular granulomatous inflammation and Wood’s light exam demonstrated enhancement of the depigmented area on the areola. Findings supporting the diagnoses of cutaneous sarcoidosis and vitiligo, respectively (Figures 4C and 4D). The papules on the posterior neck cleared rapidly with twice daily triamcinolone 0.025% cream.

**Discussion**

The 4 patients in our series highlight the coexistence of sarcoidosis with cutaneous autoimmune disorders, specifically vitiligo and alopecia areata, suggesting a possible underlying common genetic and/or immunological mechanism. Sarcoïd granulomas are composed primarily of epithelioid macrophages and CD4-T cells. The pathogenesis of sarcoidosis is not completely understood, however, type 1 helper cells, which secrete interleukin (IL)-2 and interferon (IFN)-gamma, have been shown to be the predominant phenotype of CD4-T cells in sarcoïd granulomas [2,3]. Additionally, recent research demonstrating increased levels of IL-17 messenger RNA in bronchoalveolar lavage fluid and peripheral blood suggest a possible role for the Th-17 immune pathway in the pathogenesis of sarcoidosis possibly through impaired regulatory T cell activity [4]. Alternatively, different sarcoïd subgroups could exist, with variable dependence on the Th1 and Th17 pathways.

Alopecia as a sequela of sarcoïdosis is most commonly secondary to direct sarcoïdosis of the scalp, a rare manifestation of cutaneous sarcoidosis. Among the published cases of sarcoïdosis-induced alopecia, we did not find reference to an association with alopecia areata, alopecia universalis or histological findings suggestive of a lymphocytic process. In our series, alopecia areata was seen in patient 1 (with cutaneous sarcoïdosis and quiescent prior lung involvement), patient 2 (with pulmonary sarcoïdosis) and alopecia universalis was seen in patient 3 (with cutaneous sarcoïdosis).

The coexistence of vitiligo and sarcoidosis, as seen in patient 4, has been rarely reported as well. Five previous reports exist in the literature; these reports include one case with subcutaneous nodules, pernicious anemia, autoimmune thyroiditis, and vitiligo, a second case with scar sarcoidosis, autoimmune thyroiditis, autoimmune hepatitis, and vitiligo, a third case with recurrent scar sarcoidosis followed by vitiligo, a fourth case with co-existent vitiligo and sarcoidosis with circulating autoantibodies and a fifth case of vitiligo vulgaris with strict localization of cutaneous sarcoidosis to lesions of vitiligo [5].

Studies demonstrate that vitiligo lesions exhibit predominantly a Th1 and Th17 cytokine profile [8]. Similarly, in alopecia areata, autoimmune inflammation primarily involves Th1 cytokines, with recent reports demonstrating involvement of the Th17 arm of the immune system [9]. Sarcoïdosis has long been thought of as predominantly a Th1-type immune response, though recent evidence has suggested a role for the Th17 pathway in some patients. These similar inflammatory patterns provide support that a common immunological pathway may contribute to the coexistence of sarcoidosis with vitiligo and/or alopecia areata in some patients. Alopecia areata, vitiligo, and sarcoidosis all have an increased risk of developing thyroid autoimmune disease, also thought to be a primarily Th1-mediated process [10-12]. Furthermore, Fischer et al. identified chromosome 11q13.1 as a novel risk locus influencing susceptibility to sarcoidosis in Europeans. This locus was previously reported to be associated with alopecia areata (in addition to Crohn disease, psoriasis, and leprosy), suggesting a common genetic pathway for immune dysregulation [13]. Diseases such as systemic lupus erythematosus have been reported in association with both sarcoidosis and alopecia areata further highlighting the potential role of immune dysregulation as a common thread tying these diseases together [14,15].

Skin lesions in alopecia areata and vitiligo have elevated levels of IFN-γ and IFN-γ-induced chemokines, which are required for disease pathogenesis in animal models. In addition, CD8+ T cells appear to play a prominent role in each disease, consistent with a Th1-mediated immunopathogenesis [16,17]. Reports of co-incident alopecia areata and vitiligo in patients suggest that they occur more commonly than simply by chance, implying similar disease mechanisms and predisposing factors. In addition, overlapping lesional patterns of each disease at a specific anatomic site within a patient provide a natural experiment that offers even stronger evidence of similar mechanisms, as lesional patterns are potentially limitless, such that perfect overlap is unlikely to occur by chance [18]. The patients in our case series did not have lesional overlap of alopecia and vitiligo with sarcoidosis; however they were co-incident at different sites, potentially providing evidence of overlapping disease susceptibility.

Although the exact etiology of sarcoidosis remains unknown, our patients’ relatively rare combination of alopecia areata or vitiligo in the setting of sarcoïdosis underscores the possibility that aberrant immune responses mediated by Th1 and/or Th17 may be responsible. In the future, large scale databases and genetic linkage studies will...
be needed to further explore whether patients with sarcoidosis have immunological or genetic features increasing their likelihood for autoimmune disorders which are less frequently reported, such as alopecia areata and vitiligo. Further investigation may provide valuable insight into the immune-pathophysiology behind these diseases and ultimately aid in new therapeutic advances.

Author Contributions

Dr(s) Misha Rosenbach and Laura Melnick had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Rosenbach, Melnick, Wanat. Acquisition, analysis, and interpretation of data: Rosenbach, Melnick, Wanat. Drafting of the manuscript: Rosenbach, Melnick and Wanat. Critical revision of the manuscript for important intellectual content: Rosenbach, Wanat, Harris, Cotsarelis, Novoa. Statistical analysis: N/A. Obtained funding: N/A. Administrative, technical, or material support: N/A. Study supervision: Rosenbach.

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