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Review Article

Vitiligo Associated With Sarcoidosis: Case Based Review

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Abstract

Sarcoidosis is characterized by non-caseating granulomatous inflammation that predominantly affects the lungs. Cutaneous involvement occurs in 20 to 35 percent of the patients and may emerge as the initial manifestation of the disease. Erythema nodosum and lupus pernio are the specific skin manifestations of cutaneous sarcoidosis. Many different skin lesions including hypopigmentation or hyperpigmentation that mimic other primary skin and systemic diseases may occur in sarcoidosis patients. Cutaneous involvement always poses a diagnostic dilemma in all patients with or without a previous sarcoidosis diagnosis.

In this review, we present two sarcoidosis patients who subsequently developed vitiligo. The main aim is to discuss the underlying pathologic mechanisms of sarcoidosis associated with vitiligo and to define the potential relationship between these two autoimmune disorders. The second target is to specify a diagnostic pathway in sarcoidosis patients associated with skin involvement in the light of the current literature data.

Introduction

Sarcoidosis is a granulomaotus disease of unknown origin that emerges with the existence of non-caseating granulomas primarily in the lungs. Extrapulmonary involvement is quite common in sarcoidosis as none of the organs have immunity against this granulomatous disorder. Cutaneous disease may develop in approximately one third of the patients and skin is second only to the lungs as the most frequently involved organ. Cutaneous manifestations of sarcoidosis are highly variable and may occur as non-caseating sarcoid granulomas or with nonspecific inflammatory reactive skin lesions [1-5]. Cutaneous involvement in all patients, whether or not there is a known diagnosis of sarcoidosis, always present a diagnostic challenge for clinicians. Vitiligo is a chronic autoimmune disorder that causes patches without pigment or color in which some or all of the melanocytes in the affected sites are selectively destroyed. It is characterized by circumscribed depigmented macules and patches. Vitiligo affects 0.5-2% of the world population. The cause of vitiligo is unknown, but it may be related to immune system changes, genetic factors, stress, or sun exposure [6-8]. The diagnostic dilemma for cutaneous involvement in sarcoidosis is strongly associated with the complex underlying mechanisms of sarcoidosis that may uncommonly lead to the development of such skin lesions. A common pathological pathway may have led to sarcoidosis associated vitiligo or vice versa. Another predicament arises as to determine whether these lesions occur due to a primary skin disorder or secondary to sarcoidosis. Coexistence of sarcoidosis and vitiligo is an extremely rare occurence while the underlying mechanisms linking these two conditions are poorly understood. In this review, we present two sarcoidosis associated vitiligo patients to define the underlying pathologic link between the two disorders, clinical manifestations, and the diagnostic pathway for such cases.

Case I

A 45 year-old female presented with a six-month history of progressively worsening dyspnea and a three months history of depigmented skin patches. The patient had thyroidectectomy for papillary thyroid carcinoma. Physical examination revealed erythema nodosum on the lower extremities and multiple depigmented macules on the face, neck, and extremities (Figure 1). Laboratory examination demonstrated mildly elevated CRP (11 mg/L) and ESR (27 mm/h) levels. Chest x-ray and thorax CT revealed normal findings. Pulmonary function tests established a mild restrictive pattern. Ultrasonography of the neck area showed no remarkable findings other than uniform echogenic texture and lack of thyroid tissue due to previous thyroidectomy

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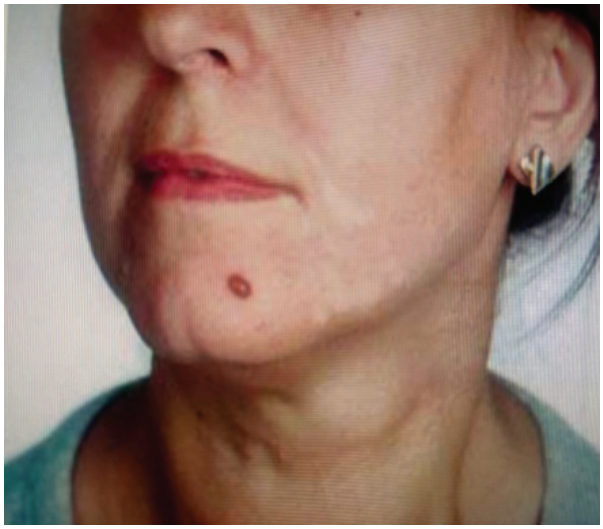

Figure 1. *Vitiligo on the left lower side of the mandible.*

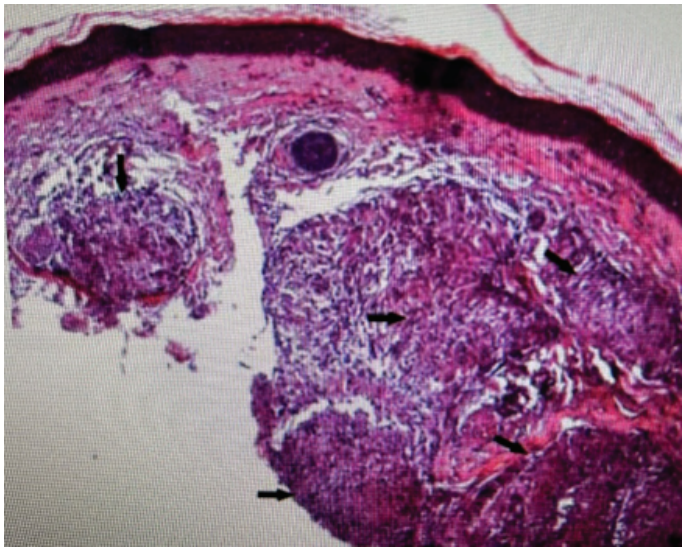

Figure 2. *Subcutaneous non-caseating granulomas (HE stain X100, black arrows).*

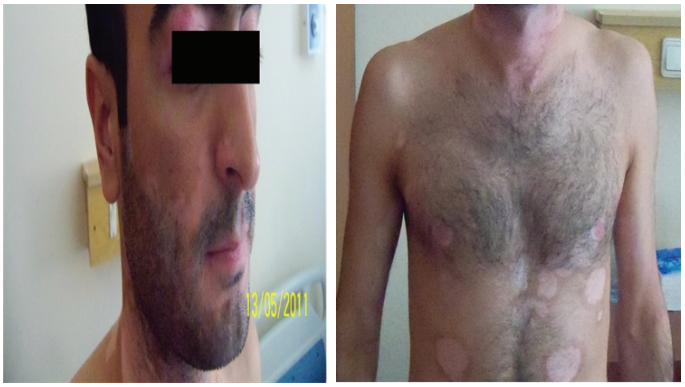

Figure 3. *Vitiligo on the face, anterior thorax, and abdomen.*

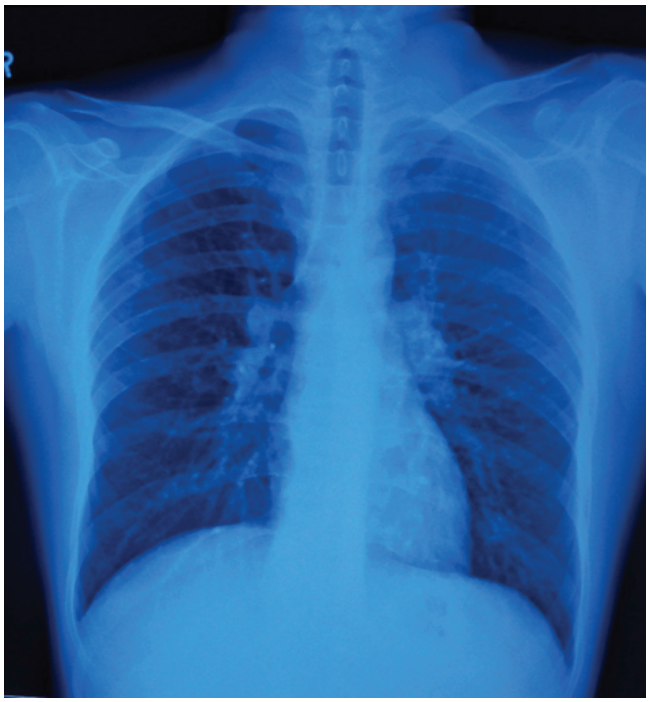

Figure 4. *Chest x-ray showing bilateral hilar lymphadenopathy.*

operation. Skin punch biopsy from the depigmentated areas with staining and immunochemistry of the samples displayed reduced melanin pigmentation in the basal cell layers of the epidermis that confirmed the vitiligo diagnosis. Histopathologic examination of the cutaneous biopsy sample revealed non-caseating granulomas (Figure 2). Smear and culture of the BAL was negative for bacteria, fungus, mycobacterium tuberculosis, and atypical mycobacteria. Histopathologic examination of the transbronchial biopsy specimens revealed non-caseating granulomas while BAL CD_4/CD_8 ratio was 4.8 that were both consistent with a sarcoidosis diagnosis.

Case II

A 27 year old male was admitted for dry cough, fatigue, swelling of the right orbit for three months, recent onset of hypopigmented areas on his face, anterior thorax, and abdomen. Personal and family history did not disclose any chronic disease of concern. Vitiligo was detected on physical examination on the right side of the face, anterior thorax, and abdomen (Figure 3). Laboratory tests were unremarkable except for elevated CRP (18 mg/L), ESR (32 mm/h) levels, and a high WBC count (13.800/μL). Chest X-ray (Figure 4) and thorax CT demonstrated bilateral hilar and mediastinal lymph node enlargement. Smear and culture of the BAL fluid were negative for bacteria, fungus, mycobacterium tuberculosis, and atypical mycobacteria. BAL CD_4/CD_8 ratio was 4.2 and serum ACE level was 84 IU/ml that were compatible with sarcoidosis. Histopathologic examination of the transbronchial samples revealed non-caseating granulomatous inflammation. MRI revealed swelling of the right orbit due to sarcoid granuloma (Figure 5). Punch biopsy from the depigmentated areas and immunochemistry of the samples revealed reduced melanin pigment in the epidermal basal cell layers compatible with vitiligo.

Discussion

Vitiligo is the most frequent cause of skin depigmentation with an estimated incidence ranging from 0.1 to 2% in adults and children. The exact etiology and pathogenesis of vitiligo

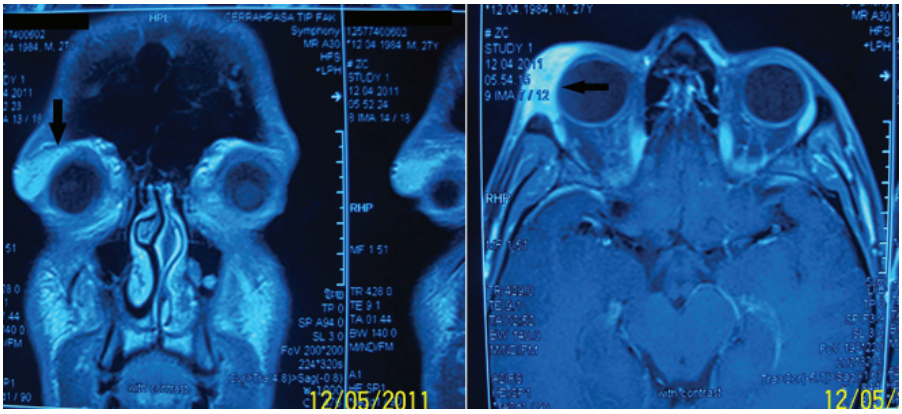

Figure 5. *MRI revealing swelling of the right orbit due to sarcoid granuloma.*

is currently unknown. The onset of vitiligo is commonly attributed to explicit triggering events such as physical injury or illness, sunburn, emotional stress, or pregnancy but there does not exist any data supportive a causitive role for such factors [9-12]. Incidence of comorbid autoimmune diseases is significantly higher in patients with vitiligo and in their first-degree relatives. This finding is strongly associated with an autoimmune phenomena underlying the pathogenesis of vitiligo [10]. Multiple other pathways have been proposed for melanocyte destruction in vitiligo including genetic, neural, biochemical, oxidative stress, viral infection, and, melanocyte detachment mechanisms [13-15]. None of these underlying mechanisms have in themselves revealed sufficient input to explain the development of vitiligo.

Coexistence of sarcoidosis and vitiligo is an extremely rare occurence. The relavence between these two diseases and the precise mechanisms for their association remain unclear. Both conditions are believed to involve dysregulation of the immune system, with an exaggerated immune response leading to tissue damage. It has been proposed that the infiltration of activated T lymphocytes and macrophages in sarcoidosis may trigger an autoimmune response against melanocytes leading to vitiligo. However, further research is needed to elucidate the precise immunological pathways involved as there is insufficient theoretical data to confirm such an association. While still not clearly defined, the most common perspective on the pathogenesis of granuloma formation in sarcoidosis is thought to be mediated mainly by type 1 T-helper (Th_1) cells. Recent studies have also pointed to a potential role for Th_{17} cells, although there still exists conflicting data relevant to an accurate pathogenetic mechanism. Th_1 and Th_{17} may also play a major role in the etiology of some autoimmune cutaneous diseases, such as psoriasis, alopecia areata, and vitiligo [16-23]. These data indicate that this common pathway may contribute to the coexistence of sarcoidosis and vitiligo.

As far as the association of sarcoidosis and vitiligo is concerned there exists only a few cases in the literature. These case reports and studies revealed that in each of these patients sarcoidosis was associated with other autoimmune disorders such as pernicious anemia, thyroiditis, and hepatitis [24-31]. Even though the exact pathogenesis of sarcoidosis still isn't clearly defined, the case reports of the patients and the previous literature data for sarcoidosis associated vitiligo point to possibility of these two disorders have the same underlying mechanism, likely to be mediated by disregulated Th_1 and Th_{17} T-cell response [32,33]. Further studies about the relationship between these two diseases may be able to illuminate the immunopathogenesis behind these diseases and enlighten the exact mechanisms.

Immunologic abnormalities in sarcoidosis comprise increased production of T cell derived cytokines (IL-2, IFN-γ) during the formation of granulomas, an increase in macrophage-derived cytokines (IL-1, IL-6, IL-8, IL-15), tumor necrosis factor α, IFN-γ, and granulocyte-macrophage colony-stimulating factor), chemokines (macrophage inflammatory protein β and IL-16), and fibrogenic cytokines (transforming growth factor β, platelet-derived growth factor, and insulin-like growth factor 1) that may induce tissue destruction along with fibrosis [34]. The coexistence of sarcoidosis and vitiligo occurs rarely while the underlying mechanism is unclear. Both conditions are believed to involve dysregulation of the immune system with an exaggerated immune response leading to tissue damage. It has been proposed that the infiltration of activated T lymphocytes and macrophages in sarcoidosis may trigger an autoimmune response against melanocytes, leading to vitiligo [19-24]. However, further research is needed to elucidate the precise immunological pathways involved.

Although sarcoidosis and vitiligo are different diseases, the basic primary mechanism that plays a role in the emergence of both disorders is an autoimmune disorder that develops through T-lymphocytes. As many distinctive skin lesions may emerge due to cutaneous involvement of sarcoidosis, it is highly likely that sarcoidosis may have triggered the formation of vitiligo. The most likely mechanism for the coexistence of these two disorders seems to be the T cell dysregulation responsible for the pathogenesis of sarcoidosis that may have induced the development of vitiligo in these patients. Occurrence of vitiligo after sarcoidosis in both of our patients makes this theoretical possibility highly probable. Tissue injury in sarcoidosis and meloncyte destruction in vitiligo represent the common underlying pathway. Considering the association of sarcoidosis and vitiligo, it is clear sarcoidosis have induced vitiligo development as the primary disease. Although vitiligo is diagnosed based on inspection of physical examination, an accurate diagnosis requires histopathologic verification. Biopsy samples from the involved sites reveal reduced melanin pigment in the epidermal basal cell. Extensive melanocyte destruction leads to a partial or complete loss of pigment producing melanocytes within the epidermis. Vitiligo can not be solely attributed to a susceptive genetic background. Oxidative

stress triggered by elevated levels of reactive oxygen species accounts for melanocytic molecular and organelle dysfunction. The aberrantly heightened innate immunity, type-1-skewed T helper, and incompetent regulatory T cells tip the balance toward autoreaction, and CD^8 cytotoxic T lymphocytes execute the death of melanocytes due to resident memory T cells. In addition to the well-established apoptosis and necrosis In addition to apoptosis necrosis, oxeiptosis, ferroptosis, and necroptosis are probably employed in melanocyte destruction. Single-nucleotide polymorphisms may emerge as susceptible loci for melanocyte death [35].

In sarcoidosis patients, skin biopsy is required for an accurate definitive diagnosis of cutaneous involvement other than the specific skin lesions like erythema nodosum and lupus pernio. In sarcoidosis patients with systemic disease, the skin is involved in 20-35% of cases [2]. Cutaneous lesions may emerge as the sole manifestation of sarcoidosis in approximately 10% of patients [5]. Among the numerous reported morphologic presentations are papules, micropapules, plaques, subcutaneous nodules, scar sarcoidosis, lupus pernio, erythema nodosum, ulcer and alopecia while multiple other cutaneous lesions although rare are possible with an undetermined incidence. Rare presentations like follicular, verrucous, ichthyosiform, hypomelanotic, and annular lesions have also been described [36]. Psoriasiform lesions have been very rarely reported, as described by Burgoyne et al [37].

It is a known fact that cutaneous sarcoidosis is a great imitator in dermatology. Sarcoidosis skin involvement closely resembles lesions of many primary skin diseases. On the other hand, such skin lesions may emerge as the manifestations of primary skin disorders other than sarcoidosis. Lesions mimick various common dermatologic conditions, causing great a diagnostic and a treatment dilemma. Awareness of these distinctive morphologic presentations of cutaneous sarcoidosis is essential for the early diagnosis and management for this great mimicker. As our cases indicate, the diagnostic pathway in the coexistence of sarcoidosis and vitiligo or other sarcoidosis associated cutaneous lesions can only be achieved by cutaneous punch biopsy. Punch biopsy is the most definitive diagnostic method in the definitive diagnosis of sarcoidosis associated or primary skin lesions accompanying sarcoidosis. Since skin lesions related to sarcoidosis can mimic many primary skin diseases like psoriasis, the most efficient pathway for a definitive diagnosis is punch biopsy.

Conclusions

Sarcoidosis associated vitiligo raises questions about the shared underlying pathogenic mechanisms, possibly involving the dysregulation of immune responses of Th_1 and Th_{17} T-cells. Role of genetic predisposition and environmental triggers for the development of both disorders merits further exploration. It is currently unknown whether sarcoidosis or the vitiligo is the primary is the inciting disease. The clinical course of our patients strongly points out that sarcoidosis may have precipitated the development of vitiligo. From a theoretical point of view, the most likely explanation for the association of these two diseases is the T cell dysregulation responsible for sarcoidosis pathogenesis that induces the development of vitiligo in these patients. Further research is warranted to elucidate the underlying mechanisms linking these autoimmune disorders. Because sarcoidosis is an autoimmune disease, cutaneous involvement closely mimics many primary skin diseases that have a similar autoimmune background, making a clinical distinction impossible. Consequently, whether it is a secondary cutaneous involvement of sarcoidosis or a different primary skin disease accompanying sarcoidosis, a definitive accurate diagnosis passes through puch biopsy without any doubt.

Author contributions

Emre Yanardag designed the case findings.

Cuneyt Tetikkurt wrote the manuscript.

Muammer Bilir analyzed the radiologic manifestations.

Halil Yanardag prepared the laboratory findings of the patients.

Ugur Kimyon defined the patient data.

Conflicts of interest

The authors declare that they do not have not any conflicts of interest to declare associated with this study. We as authors state explicitly that any kind of potential conflicts do not exist.

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