BRIEF ARTICLES

Sarcoidosis Developing During Secukinumab Therapy: Case Report

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\begin{abstract}
\textbf{Introduction:} Sarcoidosis is a systemic granulomatous inflammatory disease with an unknown etiology and complex pathogenesis. Existing literature supports the relationship of new-onset sarcoidosis with the use of a several biologic agents. Since the skin is the second most commonly involved organ in sarcoidosis and often precedes systemic involvement, dermatologists must be able to recognize its non-specific clinical presentation.

\textbf{Case Report:} We present a 45 year old female with psoriatic arthritis who developed biopsy proven cutaneous sarcoidal granulomas with pulmonary involvement shortly after initiating secukinumab for treatment of psoriatic arthritis. Despite discontinuation of secukinumab, the sarcoidosis has persisted.

\textbf{Discussion:} This is the first case report of secukinumab or any IL-17 inhibitor related sarcoidosis that we are aware of in the literature. Dermatologists should be aware of this as a possible side effect of secukinumab use. As the research on the role of IL-17 in the pathogenesis of sarcoidosis continues to develop, the implications of this side effect of IL-17 inhibition may have important future implications.
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\section{INTRODUCTION}

Sarcoidosis is a systemic granulomatous disease and skin is the most common organ affected after the lungs.\textsuperscript{1} Sarcoidosis is a diagnosis of exclusion, supported by clinical, radiologic, and histologic findings consistent with the disease.\textsuperscript{2} Non-caseating epitheloid granulomas without a known cause warrants consideration of sarcoidosis in the differential diagnosis.\textsuperscript{1} Cutaneous sarcoidosis has been associated with several chemotherapeutic medications, biologic agents, and injection sites.\textsuperscript{3} Among the many possible associations, there have been no reported associations with IL-17 inhibitors in the literature at this time.

Recent studies have made advances in defining the role of IL-17 in sarcoidosis.\textsuperscript{2,4} IL-17 is involved in numerous other autoimmune processes, including ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis.\textsuperscript{2} Though some studies have suggested that IL-17 inhibition may be a mechanism of treatment for sarcoidosis,
other studies have demonstrated that IL-17 has a protective effect from the development of sarcoidosis.

CASE REPORT

A 45 year old female was referred to our dermatology office by her rheumatologist who was treating her for psoriatic arthritis with secukinumab. Around the same time secukinumab was initiated, she developed firm, tender, cord-like and linear subdermal nodules involving mainly the upper extremities and right ankle. Medical history revealed she had a history of IV drug use and hepatitis C, completely treated with ledipasvir/sofosbuvir.

Excisional biopsy of the left forearm was performed to the depth of the subcutaneous tissue and the specimen was sent to pathology for diagnostic purposes. The initial differential diagnosis included interstitial granulomatous dermatitis of the forearms, deep granuloma annulare, sarcoidosis, and calcinosis cutis. The histopathologic report revealed a diagnosis of superficial and deep non-caseating granulomatous inflammation consistent with sarcoidosis (Figure 1, Figure 2).

When the patient returned for follow up in 14 days to discuss the pathology report, we counseled her on her diagnosis of sarcoidosis and she decided to discontinue secukinumab treatment, with her last dose being 12 days prior. She reported partial improvement in the bilateral antecubital fossa, but the cutaneous manifestations persisted. Chest x-ray revealed mild bilateral hilar prominence reflecting lymphadenopathy and a mild diffuse bilateral interstitial prominence suggestive of sarcoidosis, viral process, or reactive airway disease.

FIGURE 1: Low-power magnification displays non-caseating granulomatous inflammation

FIGURE 2: High-power magnification displays superficial and deep dermal and subcutaneous granulomatous inflammation comprised of epithelioid histiocytes and giant cells in tight-formed granulomas
Sarcoidosis is an inflammatory disease characterized by non-caseating granulomas with mononuclear cell infiltration and localized injury. The skin may be the initial site involved in 30% of patients. Cutaneous sarcoidosis has a variable presentation, and specific morphologies of some cutaneous lesions have prognostic significance. The complex pathogenesis of sarcoidosis is highlighted by the many biologic drugs implicated with causing this disease.

Sarcoidosis is associated with the use of: ipilimumab, pembrolizumab, vemurafenib, TNF-α inhibitors, interferon, ustekinumab, and anakinra. The relationship of sarcoidosis with TNF-α inhibitors is a dichotomous one, as TNF-α inhibitors both cause and treat sarcoidosis. Some of these studies have suggested monitoring new agents such as IL-17 and IL-23 inhibitors for similar paradoxical adverse events. To date, there are no previously reported cases of sarcoidosis in the PubMed database related to the initiation of secukinumab.

Secukinumab is a fully human, monoclonal antibody to IL-17A. The use of secukinumab leads to a decrease in IL-17A levels, dermal inflammatory infiltrate, and epidermal thickening. Secukinumab is approved by the Food and Drug Administration (FDA) for use in moderate to severe plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis. Common side effects are nasopharyngitis, upper respiratory infection, headache, and diarrhea.

IL-17 levels are elevated in the tissues, serum, and bronchoalveolar lavage (BAL) samples of patients affected with sarcoidosis. Evidence for the involvement of IL-17A in the pathogenesis of sarcoidosis includes: (1) increased circulating IL-17A+ memory T cells, (2) increased IL-17A producing cells (IL-17A/IFN-γ and IL-17A/IL-4 cells) in BAL samples, (3) increased T cells producing IL-17A in the lungs of sarcoidosis patients, and (4) differential distribution of IL-17A producing T cells in local granulomas. Thus, some authors suggest IL-17 inhibition may be a treatment for sarcoidosis. IL-17 producing cells are present in the periphery of granulomas localized in the peri-lymphocytic region as well as inside granulomas. IL-17 is required to clear primary infections and establish effective memory cell responses. Granulomatous inflammation occurs when macrophages are unable to eradicate an antigen. Historical knowledge about the complexity of immune-mediated diseases such as sarcoidosis demonstrates why it could be possible to induce sarcoidosis with IL-17 inhibition.

Sarcoidosis has been described as an immune paradox because peripheral anergy occurs in the setting of enhanced inflammation at disease sites. IL-17 expressed in sarcoidosis has both a pro-inflammatory role and protective role in the development of sarcoidosis. Sarcoidosis patients have a subset of T cells that are able to produce IL-17 and IFN-γ simultaneously, known as IL-17/IFN-γ T cells. These hybrid Th1/Th17 cells may be more pathogenic than conventional Th17 cells. Furthermore, the majority of Th17 cells can produce IFN-γ. Given these data, IL-17 inhibition by secukinumab could lead to an imbalance of IL-17 production that would favor granulomatous IF-γ production. Furthermore, the plasticity of T cell populations has been demonstrated in animal studies, as Th17 cells can take on a Th1 phenotype.
In patients suffering from sarcoidosis, increased levels of IL-17 found in the BAL fluid is correlated with a better disease prognosis. Cautious optimism regarding systemic suppression of IL-17 is encouraged, as the complexity of the immunologic system can reveal unintended consequences from cytokine suppression. There is a tenuous balance between cytokine signaling processes in immune-mediated diseases such as psoriasis. TNF-α, IFN, and IL-23/Th17 axis cytokines are linked together in such a way that targeting one of these cytokines can cause immunologic consequences on the other two. With the advent of this case report, biologic drug-induced sarcoidosis has been demonstrated by targeting each of these same 3 cytokines.

**CONCLUSION**

Continuing studies demonstrating the mechanisms of sarcoidosis pathogenesis are needed. IL-17 is increasingly recognized as playing a fundamental role in the pathogenesis of sarcoidosis. While studies have demonstrated increased IL-17 levels in patients with sarcoidosis, we report a paradoxical case where an IL-17 inhibitor was related to the onset of sarcoidosis. While there is much more that can be said about the relationship of IL-17 and sarcoidosis, this report will fortify future exploration regarding the dichotomous relationship of IL-17 with sarcoidosis.

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