Sarcoidosis for the Rheumatologist: Advanced and Atypical Cases

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Sarcoidosis is a systemic granulomatous disease of unknown origin that can affect almost any organ. Due to the inflammatory and multisystem nature of the disease, sarcoidosis is relevant to the practice of rheumatology and warrants consideration in the differential diagnosis of a variety of presentations.

CTD/Sarcoidosis Overlap

Connective tissue disease (CTD) may exist concomitantly with sarcoidosis, and therefore clinicians must be vigilant when patients present with new or changing signs and symptoms that may not be entirely attributable to their primary condition. In these scenarios, CTD diagnosis more commonly precedes diagnosis of sarcoidosis, but the reverse order is also well-described.[1] The most common CTD diagnoses concomitant with sarcoidosis are scleroderma, systemic lupus erythematosus, and rheumatoid arthritis. Patients are more likely to be female and have sarcoidosis characterized by skin or pulmonary organ involvement.[1] The possible drivers of this relationship are unknown, but it is hypothesized that in those with CTD preceding sarcoidosis, the underlying CTD may drive granulomatous inflammation leading to sarcoidosis.

Drug-Induced Sarcoidosis

Rheumatologists may also encounter sarcoidosis due to drug reactions. Drug-induced sarcoidosis has been reported to be caused by a variety of medications including interferons, anti-retroviral therapies, immune checkpoint inhibitors, and anti-tumour necrosis factor (TNF) medications, with the immune checkpoint inhibitors and anti-TNF medications being of particular interest recently.[2] Case series or case reports have been published describing sarcoid-like granulomatosis developing in patients prescribed etanercept, adalimumab, and infliximab, among others.[3-5] This association is seemingly counterintuitive due to the well described use of anti-TNF therapy for refractory sarcoidosis.[6] The reactions can affect any organ, resulting in pulmonary, skin, renal, or ocular sarcoidosis. Discontinuation of the offending anti-TNF medication is typically sufficient for resolution of the reaction, although time to remission can vary from 1-12 months.[7] Glucocorticoids may be used to treat patients with significant organ dysfunction or symptoms. Attempts to re-trial a different anti-TNF agent are usually well tolerated, although failed re-trial cases have been reported.[8]

Immune-checkpoint inhibitors (ICI) have been associated with pulmonary and cutaneous sarcoidosis-like reactions.[9] These medications include nivolumab, ipilimumab, and pembrolizumab, with occurrence of drug-induced sarcoidosis reactions ranging from 2-20%.[10] Treatment recommendations vary among clinical practice guidelines, with low quality recommendations to continue ICI in asymptomatic cases, with addition of low dose glucocorticoids if patients are symptomatic. Importantly, all guidelines recommend biopsying concerning lesions, in order to distinguish sarcoidosis from tumour progression.[9]

Advanced Therapies

The sarcoid granuloma is thought to form due to an abnormal cell-mediated immune response of CD4+ T cells. The initial trigger of this reaction is the presentation of an unidentified antigen by antigen-presenting cells, such as macrophages or dendritic cells, to T cells.[11] In refractory cases of sarcoidosis, advanced therapies seek to directly target these pathways.

Infliximab is an antibody targeting TNF-alpha and is generally the preferred third-line agent in refractory patients. Clinical trial data have shown improvements in lung function, quality of life, and 6-minute walk test.[11,12] Patients with ongoing evidence of inflammation or pulmonary disease are more likely to respond favourably.[13] Adalimumab is an antibody that also targets TNF-alpha. There is some evidence for improvements in refractory pulmonary sarcoidosis with adalimumab following infliximab failure.[14] Additionally, it has shown benefit in uveitis, cardiac, or cutaneous sarcoidosis.[15-17] Adalimumab is less immunogenic and carries less risk of severe allergic reactions, but infliximab tends to have a higher response rate.[11]

Other TNF inhibitors are considered less effective than infliximab and adalimumab, specifically golimumab or etanercept. These medications are felt to be ineffective due to their primary action being targeted towards soluble as opposed to membrane-bound TNF.[11] Additionally, etanercept appears to be most strongly associated with the development of paradoxical drug-induced sarcoid-like granulomatosis reactions compared to the other anti-TNF medications.

Interestingly, while sarcoid is a predominantly T-cell-mediated disease, there may be a potential role for B-cell directed therapy such as rituximab in refractory cases. Small case series and one trial have shown mild but non-sustained improvements in forced vital capacity and 6-minute walk test.[18]

Tocilizumab, an IL-6 inhibitor, has demonstrated improvements in symptoms and lung function when used as a fourth-line agent in patients who are refractory to anti-TNF therapy. Patients in this case series had a treatment response despite failure of one or more prior anti-TNF agents, a promising result for a refractory treatment population.[19] Tofacitinib is a janus kinase (JAK) inhibitor, which is an orally available small molecule that acts on numerous pro-inflammatory cytokines involved in sarcoid granuloma formation.[20] Various cytokines associated with sarcoidosis signal through the JAK-STAT pathway. Therefore, JAK inhibitors are exciting therapies that may prove beneficial in sarcoidosis. Tofacitinib has been demonstrated to improve refractory cutaneous and pulmonary sarcoidosis in a small ten patient case series.[21]

Conclusion

In summary, sarcoidosis is a complex disease that may be encountered by the rheumatologist in various clinical scenarios. The diagnosis of drug-induced sarcoidosis or concomitant sarcoidosis with CTD requires keen clinical suspicion and knowledge of these uncommon complications. Treatment options for advanced cases are expanding, providing patients more effective options than have previously existed.

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