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ADOPTING AN ORPHAN DISEASE: MANAGING SARCOIDOSIS IN THE ERA OF BIOLOGIC MEDICATIONS

Introduction

Sarcoidosis is a granulomatous immune-mediated inflammatory disorder. It remains a challenging disease to diagnose and treat because it has multiple cutaneous presentations, it can affect any organ system, and it is a diagnosis that can only be made when other granulomatous conditions, including infections, have been ruled out. However, making a diagnosis of sarcoidosis and providing effective treatment can be life-saving.

An increased understanding of this complex condition has led to new treatment options, including the innovative off-label application of biologic medications and small-molecule inhibitors (SMIs). This article will review key clinical aspects of cutaneous sarcoidosis, provide a quick refresher on necessary investigations for the busy dermatologist, and review the evidence for use of biologic medications and SMIs in the treatment of cutaneous sarcoidosis.

Etiology and pathophysiology:

Sarcoidosis is hypothesized to occur when an environmental exposure triggers an exuberant pro-inflammatory response in a genetically predisposed individual. Th1 cytokines are upregulated, Th2 cytokines are downregulated and regulatory T-cells are decreased, leading to granuloma formation and a persistently dysregulated inflammatory response[1]. Tumour Necrosis Factor alpha (TNF-α) is a Th1 cytokine that has been identified as pivotal in the development and maintenance of infectious granulomas[2]. In sarcoidosis,

TNF-α is a critical mediator of the inflammatory response, along with Interferon-gamma and the intracellular signal transducers and activators of transcription (STAT)1 [3–5]. An enhanced knowledge of what drives sarcoidal granuloma formation provides molecular targets for diagnostic purposes, monitoring disease progression, and ultimately, for treatment.

Clinical Variants:
Cutaneous sarcoidosis is notorious for its variety of morphologic presentations; hence it has been called a "great imitator". The classic presentation of sarcoidosis on the skin is red-brown papules or plaques with an "apple jelly" appearance on diascopy (Figure 1). But other common presentations include lupus pernio, subcutaneous or "Darier-Roussy" nodules, tattoo and scar sarcoidosis[6]. Recall, that although uncommon, cutaneous sarcoidosis can also display psoriasiform, annular, hypopigmented, or ulcerative morphology.

Work-up:
Certain clinical variants, such as lupus pernio and subcutaneous nodular sarcoidosis, are typically associated with systemic sarcoidosis[6], but a diagnosis of cutaneous sarcoidosis warrant a complete systemic work-up[7]. The goal of bloodwork is to evaluate systemic involvement, to anticipate management and for disease monitoring. Investigations should include CBC, liver function, renal function, thyroid stimulating hormone (TSH), calcium and vitamin D levels, and urinalysis[7]. Angiotensin-converting enzyme (ACE) which is produced by macrophages and other constituents of the granuloma, was originally thought to be positively correlated with a diagnosis of

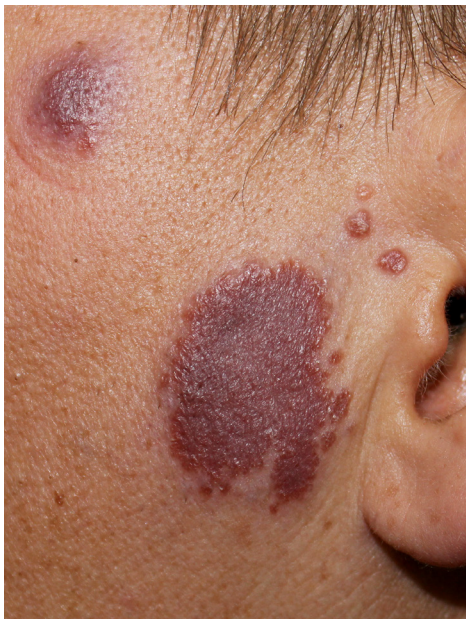

Figure 1. A case of cutaneous sarcoidosis in a young man.

sarcoidosis[8], however, recent data suggest it has low sensitivity and specificity as a diagnostic marker[9]. In a high-volume practice, I rely on my electronic medical records – using macros and pre-populated bloodwork requisitions – to streamline this. Additionally, I ask the patient's primary care provider to organize an electrocardiogram (ECG), echocardiogram, chest X-ray, pulmonary function tests, and ophthalmic exam for the patient locally. Finally, since sarcoidosis is truly a multi-system disease, referrals to, and coordinated management with, multiple specialties is often required.

Approach to Treatment:
Treatment of cutaneous sarcoidosis follows a similar treatment ladder to other inflammatory skin diseases – topical therapies, intralesional injections, classic oral systemic treatments, biologics, and SMIs. Systemic treatment is usually considered when patients have failed topical and intralesional treatments or when their cutaneous disease is widespread or disfiguring[6]. Further, treatment is warranted if patients have certain systemic manifestations of sarcoidosis such as hypercalcemia, progressive pulmonary involvement, symptomatic cardiac involvement, ocular disease, or central nervous system involvement.

Classic systemic treatments:
Oral corticosteroids have been used to effectively treat sarcoidosis since the 1950's with early studies showing objective and subjective improvement to varying degrees in all patients treated (N=13)[10]. However, treatment of chronic disease with corticosteroids in the long-term can result in significant morbidity, and therefore having effective steroid-sparing treatment options is very important. In a small study of cutaneous sarcoidosis, 93% of patients showed subjective improvement and 86% showed objective improvement (N=14)[11]. Methotrexate appears to reach a maximal effect for cutaneous sarcoidosis at 6 months of treatment[12]. Numerous studies have examined antimalarial drugs, including chloroquine[13,14] and hydroxychloroquine[15], in the treatment of sarcoidosis. Hydroxychloroquine is effective for cutaneous sarcoidosis but not for pulmonary involvement as demonstrated in a cohort of 17 patients diagnosed with cutaneous sarcoidal granulomas and treated with hydroxychloroquine (2 to 3 mg/kg/day) in an open clinical trial[15]. Tetracycline antibiotics, including minocycline[16,17] and doxycycline[18], may also be effective in the treatment of cutaneous sarcoidosis. A prospective study showed improvement in 83% of patients (N=12) treated with minocycline at 200 mg/d, for a median duration of 12 months[17] and a retrospective study showed improvement in 74% of patients (N=27)[16] treated with minocycline with 6 (22%) having

complete remission;[14] (52%) having partial remission; and 7 (26%) having had no remission. Other agents, including allopurinol[19,20], leflunomide[21], mycophenolate mofetil[22,23], pentoxifylline[24], and thalidomide[25–29], have varying levels of evidence to support their use in sarcoidosis.

Novel systemic treatments – Biologic agents:

Since TNF-α is thought to be a key upstream mediator of granuloma formation, it follows that inhibition of TNF-α should be an effective therapeutic target for sarcoidosis[5,30]. Infliximab has the most data supporting its use in sarcoidosis with randomized control trials showing benefit in pulmonary[31,32], extrapulmonary[33] and cutaneous disease[34]. Infliximab treatment of twelve patients versus placebo showed a significant change between baseline and week 24 in desquamation ($p<0.005$) and induration ($p<0.01$) of cutaneous sarcoidosis, but no difference in erythema or area of involvement[34].

The data for adalimumab also support its use in pulmonary[35] and cutaneous sarcoidosis[36]. A randomized placebo-controlled trial of 12 weeks, followed by open-label treatment for an additional 12 weeks, followed by 8 weeks of no treatment, showed improvement in several measures of cutaneous disease, including dermatology life quality index (DLQI) ($P = .0034$), in the adalimumab treatment arm (N=10) compared to placebo (N=6) at 24 weeks; with some loss of response after 8 weeks of treatment withdrawl[36].

Lastly, golimumab may be another treatment option for cutaneous sarcoidosis in the TNF-α inhibitor class, with a trend towards improvement in the physician global assessment (PGA) score at 28-weeks compared to placebo with a nonsignificant numerically greater Skin Physician Global Assessment response observed following golimumab treatment (53%) when compared with the placebo group (30%)[37]. The same study found no significant differences in pulmonary sarcoidosis outcome with golimumab treatment and found no significant differences in pulmonary or cutaneous sarcoidosis outcomes with ustekinumab[37].

Etanercept does not have the same efficacy as other TNF-α antagonists in treating sarcoidosis. While case reports have shown improvement of cutaneous sarcoidosis with etanercept treatment[38,39], overall, the evidence is mixed and etanercept treatment of other diseases has been seen to paradoxically induce sarcoidosis[5].

The other biologic agent which has been proposed as treatment of sarcoidosis is rituximab. Again, the evidence is mixed, with limited benefit seen in a prospective early-phase trial in ten patients with refractory pulmonary sarcoidosis[40].

Novel systemic treatments – Small Molecule Inhibitors:

Small molecule inhibitors are oral medications that inhibit an intracellular signaling process and regulate downstream gene expression. There has been enormous interest in this therapeutic area for inflammatory diseases with a recent surge in drug development, especially in the janus kinase (JAK) inhibitor class of medications.

Janus kinase inhibitors modulate the JAK/STAT signaling pathway, inhibiting STAT phosphorylation thereby regulating downstream pro-inflammatory cytokine production. Tofacitinib (a JAK 1/3 inhibitor approved for use in adult patients diagnosed with rheumatoid arthritis, psoriatic arthritis or ulcerative colitis) has been used to effectively treat a case of recalcitrant multiorgan sarcoidosis[41] and three cases of recalcitrant cutaneous sarcoidosis[42]. Use of ruxolitinib (a JAK 1/2 inhibitor), for on-label treatment of polycythemia vera rubra, demonstrated resolution of concomitant cutaneous sarcoidosis in a single case report[43]. Mechanistically, this makes sense since STAT1 appears to be a key mediator in the sarcoidosis pathway and therefore JAK inhibition warrants further investigation for sarcoidosis treatment.

As mentioned above, pentoxifylline, which is a phosphodiesterase (PDE) inhibitor and has weak anti-TNF-α activity, has been shown to be an effective treatment for sarcoidosis. Apremilast (a PDE4 inhibitor approved for use in moderate-to-severe psoriasis and psoriatic arthritis) has been examined as a treatment for cutaneous

DRUG CLASS	THERAPEUTIC AGENT
ORAL CORTICOSTEROIDS	VARIED
DMARD/IMMUNOMODULATORY AGENTS	METHOTREXATE; LEFLUNOMIDE; THALIDOMIDE
ANTI-MALARIAL	CHLOROQUINE; HYDROXYCHLOROQUINE
TETRACYCLINE ANTIBIOTICS	MINOCYCLINE; DOXYCYCLINE
XANTHINE OXIDASE INHIBITOR	ALLOPURINOL
IMMUNOSUPPRESSIVE AGENT	MYCOPHENOLATE MOFETIL
TNFα INHIBITOR	GOLIMUMAB; INFLIXIMAB; ADALIMUMAB
JANUS KINASE INHIBITORS	TOFACITINIB; RUXOLITINIB
PHOSPHODIESTERASE INHIBITOR	APREMILAST; PENTOXIFYLLINE

Table 1. Potential treatment options for sarcoidosis

sarcoidosis. Fifteen patients were treated with Apremilast 20 mg PO bid for 12 weeks and showed a significant improvement in induration of the index lesion compared to baseline ($p<0.02$); however no improvement was noted in erythema, desquamation or area of involvement[44].

Discussion and Conclusion

Cutaneous disease is one of the most common findings of sarcoidosis, and therefore dermatologists are often charged with making the diagnosis, directing systemic work-up and initiating treatment of this immune-mediated inflammatory disease. With many dermatologic diseases being relatively rare, with our comfort level understanding the immunology behind more common dermatologic conditions, and with so many of our treatments being "off-label", dermatologists are uniquely positioned to leverage immunological principles and novel therapies in the treatment of sarcoidosis.

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