Cutaneous Sarcoidosis: A Review and Approach to Treatment

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Keywords: Cutaneous sarcoidosis, papular sarcoidosis, violaceous papules, dermatology, rheumatology

INTRODUCTION

Sarcoidosis is a multisystem, granulomatous, inflammatory condition. There are numerous clinical manifestations of cutaneous sarcoidosis, the most common being papular sarcoidosis, which presents as red-brown or violaceous papules on the face, trunk, or extremities. Cutaneous lesions of sarcoidosis can present similarly to other conditions such as psoriasis, lichen planus, nummular eczema, granuloma annulare, and cutaneous T-cell lymphoma. It is important that an accurate diagnosis is made when patients present with cutaneous lesions as sarcoidosis can affect multiple organ systems. A patient diagnosed with sarcoidosis will typically require comprehensive care with dermatology, rheumatology, pulmonology, and other specialties as needed. Clinicians often face difficulty determining the best and most effective treatment for cutaneous sarcoidosis while keeping side effects in mind. In this article, the author presents a clinical vignette of a patient with cutaneous sarcoidosis then reviews the disease process, diagnostic work up, and treatment/management.

Table 1. Differential Diagnosis for Cutaneous Sarcoidosis

<table>
<thead>
<tr>
<th>Psoriasis</th>
<th>Atopic Dermatitis</th>
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<tr>
<td>Lichen planus</td>
<td>Cutaneous T Cell lymphoma</td>
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<tr>
<td>Discoid lupus erythematosus</td>
<td>Morphea</td>
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<tr>
<td>Granuloma annulare</td>
<td>Vasculitis</td>
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<tr>
<td>Necrobiosis lipoidica</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Xanthelasma</td>
<td>Erythema Nodosum</td>
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There are numerous cutaneous presentation morphologies for sarcoidosis, with the most common being papular lesions, which are brown to red or violaceous papules on the trunk and extremities. Nodal lesions can sometimes accompany papular lesions, which consist of 1-2cm tender, granulomatous subcutaneous nodules. Plaque sarcoidosis consists of flesh-colored to erythematous oval-shaped, indurated plaques to extremities/trunk. Plaque sarcoidosis can be misdiagnosed as psoriasis, lichen planus, granuloma annulare, CTCL, and annular syphilis. Also, there are numerous less common morphologies such as morpheaform, verrucous, and erythrodermic. In addition to the classic presentation, clinicians should consider sarcoidosis in special locations such as scars, tattoos, alopecia sites, genitalia, and nails. Sarcoidosis has been noted in areas of hypertrophic scars from previous procedures or medical conditions.

CASE PRESENTATION

A 53-year-old black woman with a past medical history of type 2 diabetes mellitus (T2DM) presented to the dermatol-
ogy clinic complaining of oval, erythematous plaques with slight scaling to bilateral shoulders and erythematous, violaceous subcutaneous tender nodules to the scalp for two months. She denied any discharge or bleeding from nodules on the scalp; but reported pain measuring 5 out of 10 on the pain scale. She denied alleviating or aggravating factors. The patient reported being treated for "eczema" with a topical corticosteroid cream from an urgent care center with no relief. All other pertinent reviews of systems were negative.

The patient reported that her T2DM was well-controlled with metformin, and she denied use of any other oral medications. The patient's past surgical history included cholecystectomy. She did report allergies to penicillin, latex, and blue dye.

The patient presented to the dermatology clinic after receiving a referral from her primary care provider. At the dermatology clinic, a thorough history and physical was performed and two skin biopsies were taken from the scalp and shoulder. Biopsy results indicated sarcoidal reaction—foreign body type. In cases like this one where the sarcoidosis is a clinical possibility and underlying systemic sarcoidosis cannot be excluded, the provider should consider correlation with radiographic studies of the chest. After reviewing the pathology report, a chest x-ray was ordered for the patient. Chest x-ray indicated bilateral hilar and mediastinal adenopathy, nonspecific small pleural based nodule or minimal focal pleural thickening in the right lower lung zone. Further blood work was ordered, and the patient was advised to follow up with pulmonology and rheumatology in conjunction with receiving care from dermatology for cutaneous lesions. The clinical course of the patient is outlined in Table 2.

**TREATMENT**

Treatment for cutaneous sarcoidosis is based on the extent of the disease process, symptoms, and impact on life quality. Treatment selection must consider the side effect profile and consider disease severity and rate of progression. Treatment protocols are summarized in Table 3.

*Mild, localized disease.* Topical corticosteroids will be considered first-line therapy for localized cutaneous involvement. If trunk or extremities are involved, a high potency topical steroid such as halobetasol or clobetasol can be considered under occlusive dressing. If there is only facial involvement, consider a lower potency topical corticosteroid such as hydrocortisone 2.5% or triamcinolone 0.025%. Additionally, intraleSIONal corticosteroid (triamcinolone acetonide injectable suspension) therapy can be considered for localized cutaneous involvement. Side effects include skin atrophy, hypopigmentation, telangiectasia, and striae. Topical calcineurin inhibitors can be used as a corticosteroid-sparing agent. A twice-daily application of topical tacrolimus 0.1% would be a great option to use either to the face or localized skin lesions in conjunction with topical steroid use. Side effects of topical calcineurin inhibitors include a burning sensation with the application of the topical.

Topical retinoids, such as tretinoin 0.1%, can also be considered in conjunction with topical steroids or nonsteroidal options. A pea-sized amount mixed with moisturizer is applied at bedtime to affected areas due to drying side effects.

Non-topical treatment options include photo-dynamic therapy, laser therapy, and ultraviolet A (UVA) phototherapy. For localized cutaneous involvement, the stepwise consideration of laser and light therapy should be as follows: Pulsed dye laser (PDL) → Fractionated carbon dioxide (CO2) laser → Intense pulsed light therapy (IPL) → YAG or Q-switched ruby laser. If patients present with diffuse cutaneous involvement, UVA phototherapy & Photodynamic therapy (PDT). Side effects of PDT to keep in mind are post-inflammatory hyperpigmentation/erythema or burning at treatment site, desquamation, and headaches. The treatment side effects of UVA phototherapy include only a few reports of erythema and burning. Treatment with lasers can lead to significant improvement in cutaneous lesions, however, patients can expect mild erythema and mild swelling post-procedure with the YAG laser and Q-switched ruby laser.

**Mild to moderate disease.** Oral tetracyclines such as doxycycline or minocycline can be considered in the treatment of mild to moderate disease. Despite being antibiotics; their anti-inflammatory properties allow for the inhibition of the inflammatory cascade that prevents the formation of the

### Table 2. Clinical course for patient

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<tr>
<th>Dermatology</th>
<th>Rheumatology</th>
<th>Pulmonology</th>
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<tr>
<td>Oral doxycycline 100mg twice daily for 30 days</td>
<td>Blood work ordered: CBC with Diff/Platelet, CMP, SED rate, C-reactive protein, ACE levels, ANA titers, C3/C4, UA, rheuma-toid factor, CCP, HLA B27.</td>
<td>Pulmonary function testing was ordered</td>
</tr>
<tr>
<td>Topical clobetasol 0.05% ointment was started twice daily for two weeks to the affected areas on the scalp and shoulders, then weekends only.</td>
<td>Oral Methotrexate 2.5mg, 4 tablets orally once a week for 90 day and folic acid 1mg tablet orally once</td>
<td>CBC: complete blood count</td>
</tr>
<tr>
<td>Topical tacrolimus 0.1% was to be used twice daily after the two initial weeks of using topical clobetasol</td>
<td></td>
<td>CMP: complete metabolic panel ACE: angiotensin converting enzyme ANA: antinuclear antibody</td>
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<tr>
<td></td>
<td></td>
<td>UA: Urinalysis</td>
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<tr>
<td></td>
<td></td>
<td>CCP: cyclic citrullinated peptide</td>
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<td></td>
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<td>HLA: human leukocyte antigen</td>
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granulomas. Dosing of the tetracyclines should be 100mg twice daily (BID) x 1-6 months, then decrease to daily (QD), and then discontinue. The main side effects are increased risk of photosensitivity and risk of sunburn, hearing changes, severe headaches, and vision changes. Minocycline has been associated with lupus-like syndrome. No blood work is required; however, due to the potential for tooth and bone abnormalities, these medications should not be used in women of childbearing age who are not protected against pregnancy.

Antimalarials such as hydroxychloroquine and chloroquine can be used in the treatment of moderate severity cutaneous sarcoidosis. Hydroxychloroquine has a lower side effect profile and therefore is usually the first choice. To minimize adverse reactions and side effects, the therapeuti
c doses should not exceed 5mg/kg per day for hydroxychloroquine and 2.5mg/kg per day for chloroquine. Unlike chloroquine, if a patient is maintained with hydroxychloroquine with doses <6.5mg/kg/day, the risk of experiencing the side effect of retinopathy is significantly decreased. The preferred dosing of hydroxychloroquine is 200 to 400 mg per day. The preferred dosing for chloroquine is 250mg per day. Patients require ophthalmologic evaluation at baseline and throughout the treatment due to ocular toxicity's side effect profile. Symptomatic side effects include GI upset, dizziness, ataxia, photosensitivity, tinnitus, and weight loss. Some adverse reactions to monitor the patient for include hepatic toxicity, myopathy, thrombocytopenia, leukopenia, retinopathy, and arrhythmias. ECG and CBC should be considered in patients on prolonged therapy duration with antimalarials.

Moderate-to-severe disease. Oral corticosteroid therapy is a first-line treatment option for diffuse, worsening, or disfiguring cutaneous sarcoidosis involvement. There are no exact guidelines on the dosing of oral corticosteroids; however, it can start with 0.5-1mg/kg per day and then titrate down. The taper will depend on extent of skin disease as well as if there is lung involvement for the patient. There are no definitive taper guidelines through literature. While tapering the patient off oral corticosteroids, they should be started on topical and oral therapy with fewer side effects to maintain remission. Long-term side effects include weight gain, insomnia, osteoporosis, mood changes, psychosis, diabetes, iatrogenic Cushing syndrome, increased risk of infection, hypertension, glaucoma. For prolonged therapy, G1 prophylaxis, calcium and vitamin D supplementation or bisphosphonates can be started. Oral methotrexate is often used in patients with severe disease and as a steroid-sparing agent therapeutic option. Methotrexate can be dosed from 7.5-25mg/week and can be tapered and adjunctively treated with topical and oral therapy with fewer side effects. Methotrexate requires baseline and
frequent blood work monitoring of CBC and LFTs. Side effects to keep in mind include nausea, GI upset, rashes, loss of appetite, pale stools, dark urine, hair loss, and oral ulcers. Adverse reactions include leukopenia, hepatotoxicity, pneumonitis, and pulmonary fibrosis. Patients need to be started on folic acid supplementation while taking methotrexate to prevent a folate acid deficiency. Patients should also discontinue methotrexate at least three months in advance before planning a pregnancy.

Severe disease and "refractory to all other options." TNF-alpha inhibitors such as Infliximab and adalimumab can be used for severe disease states. Infliximab is a chimeric monoclonal antibody directed against TNF-alpha considered in patients with extensive cutaneous involvement. A proposed dosing schedule consists of intravenous administration of 3-10mg/kg/dose at 0, 2, and 5 weeks, then 5mg/kg every 8 to 10 weeks. Adverse reactions to be aware of are infusion therapy-related reactions (fevers, chills, rashes, GI upset), increased risk of and reactivation of infections.

Adalimumab is an anti-TNF monoclonal antibody that can be considered for refractory cutaneous sarcoidosis. Suggested dosing for cutaneous sarcoidosis can be 80 to 160 mg at week 0, 40 mg at week 1, and then 40mg once every week or every other week can be used by to maintain cutaneous sarcoidosis. Side effects to be aware of are increased risk of infection, skin rashes, headaches, GI upset, worsening of CNS disease, and reactivation of tuberculosis. Blood work monitoring for TNF-alpha inhibitors would include QuantiFERON gold, CBC with differential, CMP, Hepatitis B and C panel, HIV, ANA with titer and yearly tuberculosis testing.

Thalidomide is both a TNF-alpha inhibitor and interferon-gamma inhibitor and should only be considered in refractory patients due to the high side effect profile. Adverse reactions include neuropathy, neutropenia, sedation, venous thrombosis, and teratogenicity. Starting dose of thalidomide includes 100-200 mg per day and can be decreased to 50-100mg per day for maintenance.

CONCLUSION

Cutaneous sarcoidosis is challenging to treat as there are limited studies regarding immunosuppressive treatment options. However, for patients who experience a refractory manifestation of the disease state, have failed topical therapy, and have worsening symptoms, alternative treatment options need to be explored in the stepwise fashion discussed in this review. It is essential to keep in mind the various side effects of the oral therapy available, contraindications, and interactions with medications. Inflammation that is a result of the formation of granulomas can take months to respond to therapy and, therefore, treatment options should be trialed for at least three months before concluding treatment failure.

DISCLOSURES

The author has disclosed no potential conflicts of interest, financial or otherwise, relating to the content of this article.
REFERENCES


