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CASE REPORT

A Case Series of Refractory Cutaneous Sarcoidosis Successfully Treated with Infliximab

Papapit Tuchinda · Matthew Bremmer · Anthony A. Gaspari

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ABSTRACT

Introduction: Sarcoidosis is a systemic granulomatous disease of unknown cause. The management of sarcoidosis remains problematic. Systemic and topical corticosteroids are the mainstay of therapy but may cause unacceptable side effects. Biologic therapies, such as infliximab, have recently been proposed as another treatment option for cutaneous sarcoidosis.

Case Report: The authors describe three patients who were diagnosed with cutaneous sarcoidosis with systemic involvement. All of the patients were refractory to conventional therapies but responded to infliximab therapy.

Conclusion: Infliximab is an alternative medication for refractory sarcoidosis that has a relatively benign side-effect profile. However, definite indications, dosage, interval, and duration of treatment for cutaneous sarcoidosis are not firmly established.

Keywords: Biologic; Cutaneous; Infliximab; Sarcoidosis; Therapy; Treatment; Tumor necrosis factor inhibitor

INTRODUCTION

Sarcoidosis is a multisystemic granulomatous disease of unknown origin. Cutaneous manifestations occur in approximately one quarter of sarcoid patients, and these lesions may present at the onset of the disease or following other systemic involvement [1]. The management of sarcoidosis remains a significant therapeutic challenge. Systemic and topical corticosteroids are popularly used treatment methods in cutaneous sarcoidosis but are a poor long-term management strategy given the range of side effects. Treatment with

P. Tuchinda · M. Bremmer · A. A. Gaspari (✉)
Department of Dermatology, University of Maryland School of Medicine, 419 W. Redwood Street, Suite 240, Baltimore, MD 21201, USA
e-mail: agasp001@umaryland.edu

P. Tuchinda
Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

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biologic agents has recently been proposed as another treatment option for cutaneous sarcoidosis [2–5]. In the past decade, a number of case series has shown that infliximab is an effective and well-tolerated management strategy for this condition [3–26]. The authors report three cases of cutaneous sarcoidosis that were refractory to standard therapy but responded to infliximab treatment. The authors also review the literature concerning the treatment of sarcoidosis with infliximab.

CASE REPORT

Case 1

A 43-year-old African American man with a history of pulmonary sarcoidosis was seen in the authors' clinic in December 2007 because of a 4-month history of lesions on the patient's cheeks and legs. The patient was treated with increasing doses of prednisone, hydroxychloroquine, and intralesional corticosteroids without improvement. As a result of a combination of lack of efficacy and intolerable side effects of these medications, the patient was switched to infliximab 5 mg/kg intravenously on weeks 0, 2, and 6, and then every 8 weeks in November 2008. After three infusions, the patient showed significant improvement of skin lesions, and prednisone was tapered back to 2.5 mg every other day. However, after 6 months of infusions, the patient began to experience some flaring of cutaneous lesions. Methotrexate 7.5 mg weekly was added in May 2009 in addition to infliximab in an effort to improve further the patient's cutaneous lesions. In addition, infliximab was increased to 5 mg/kg every 7 weeks, and shortly thereafter was increased again to 7.5 mg/kg every 7 weeks in November 2009 for flares near the time of infusion. The patient's cutaneous sarcoidosis was stable on this dose of methotrexate and infliximab for 9 months. In June 2011, the dosage again had to be increased to 10 mg/kg every 5 weeks due to flaring of lesions before infusions, which was able to control the disease better (Table 1).

Case 2

A 53-year-old African American woman with a history of pulmonary sarcoidosis for 15 years was referred to the authors' clinic on April 2002 for management of 5 years of cutaneous sarcoidosis lesions. The patient's cutaneous lesions were primarily involving the nasal ala and bilateral cheeks in a distribution consistent with lupus pernio. The patient was treated with oral prednisone, hydroxychloroquine, methotrexate, minocycline, topical tacrolimus, and topical imiquimod at various points and only showed moderate improvement with systemic steroids. The patient was started on mycophenolate mofetil 500 mg twice a day in December 2003, increasing to as high as 4 g/day. However, the patient continued to experience refractory lesions at this dose (Fig. 1), with multiple erythematous to violaceous papules and plaques on the patient's right cheek, tip of the nose, and corner of the mouth. Infliximab 7.5 mg/kg was started in May 2004 at weeks 0, 2, and 6, and then every 8 weeks, and the dosage of mycophenolate mofetil was decreased to 1 g twice a day and prednisone 10 mg/day. Five months after initiating infliximab, the patient's skin lesions showed moderate flattening without any adverse side effects. Mycophenolate mofetil was slowly tapered in October 2007 and was stopped in May 2008. Prednisone was tapered over the course of 6 weeks and ended in November 2011.

Table 1 Patient demographic data

	Case 1	Case 2	Case 3
Demographics	43-year-old African American man	53-year-old African American woman	48-year-old African American woman
Other organ involvement	Pulmonary	Pulmonary and eye	Pulmonary and eye
Cutaneous features at diagnosis	Nodular lesions on face, eyelids, and earlobes	Multiple erythematous to violaceous papules on eyelids, right cheek, tip of nose, and corner of mouth	Multiple erythematous annular plaques around eyes, nose, perioral area, neck, arm, back and knees
Histopathology	From right cheek: granulomatous inflammatory infiltrate (lymphocytes, histiocytes, and giant cells)	From right cheek: non-necrotizing granulomas (epithelioid cells and multinucleated giant cells)	N/A
Previous treatment before initiating infliximab	Prednisone Hydroxychloroquine Intralesional corticosteroids	Prednisone Hydroxychloroquine Methotrexate Minocycline Topical tacrolimus Topical imiquimod Mycophenolate mofetil	Prednisone Hydroxychloroquine Methotrexate Pulse methyl prednisone Thalidomide Topical corticosteroids
Therapeutic side effects or complications	A significant amount of weight gain Hypertension New onset diabetes A spontaneous hairline left 5th metatarsal fracture	Hypertension Diabetes Right hip avascular necrosis	Corticosteroids-induced gastrointestinal upset, fatigue Hydroxychloroquine-induced diarrhea and abdominal pain Methotrexate-induced leucopenia and abnormal liver function tests Thalidomide-induced peripheral neuropathy
Duration of disease before infliximab therapy	2 years	18 years	8 years
Treatments used at the time of infliximab initiation	Hydroxychloroquine (200 mg twice a day) Intralesional corticosteroids	Mycophenolate mofetil (4 g/day) Prednisone (15 mg/day)	Prednisone (40 mg/day) Thalidomide (100 mg/day)

Table 1 continued

	Case 1	Case 2	Case 3
Infliximab dose, duration	5 mg/kg on weeks 0, 2, and 6, then every 8 weeks 6 months later: add methotrexate 7.5 mg weekly after tapering prednisone 6 months later increased infliximab to 5 mg/kg and 7.5 mg/kg every 7 weeks 9 months later increased infliximab to 10 mg/kg every 5 weeks	7.5 mg/kg on weeks 0, 2, and 6, then every 8 weeks	7.5 mg/kg on weeks 0, 2, and 6, then every 8 weeks 4 years later tapered to 5 mg/kg every 16 weeks 3 years later taken off infliximab
Time to achieve clinical response	3 years	5 months	4 years
Treatments at the time of last follow-up	Infliximab (10 mg/kg every 5 weeks) Methotrexate (7.5 mg weekly) Prednisone (2.5 mg/day every other day)	Infliximab (7.5 mg/kg every 8 weeks)	Discontinued infliximab
Follow-up	Still gradually increase new lesions	Improvement after mycophenolate mofetil and prednisone discontinuation	No new lesions

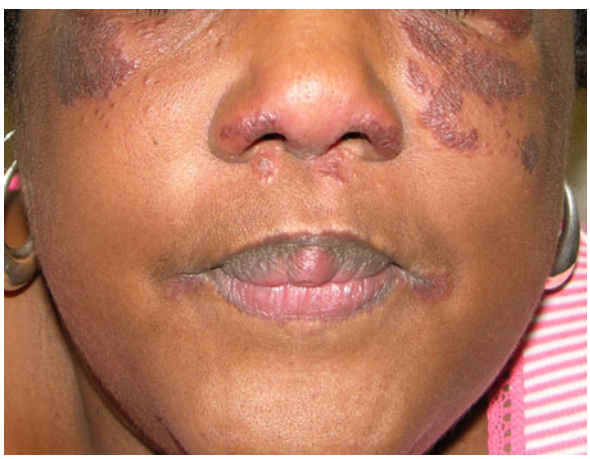

Fig. 1 The clinical manifestations of case 2 before initiating infliximab

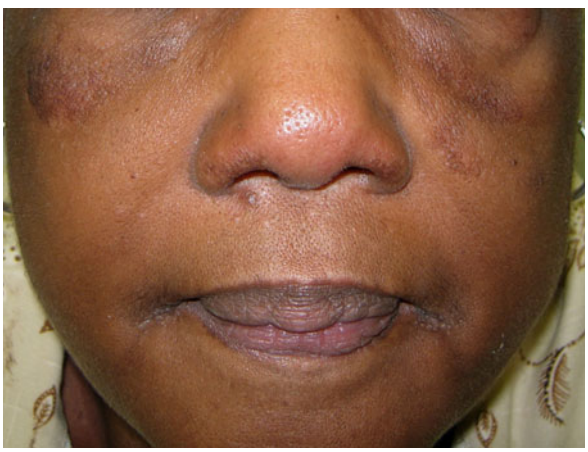

Fig. 2 Case 2 after missing two doses of infliximab and experienced a flare of the cutaneous disease

The patient's lesions have since maintained improvement with infliximab 7.5 mg/kg every 8 weeks (Fig. 2; Table 1).

Case 3

A 48-year-old African American woman was first seen in the authors' clinic in 2001 for management of cutaneous sarcoidosis lesions. The patient was diagnosed with cutaneous sarcoidosis by biopsy of the preauricular area in 1996. The patient was originally treated with hydroxychloroquine and prednisone, but these medications were discontinued due to side effects. The patient was subsequently started on methotrexate 15 mg/week and minocycline 100 mg twice a day. Methotrexate was increased to 22.5 mg/week, prednisone was increased to 40 mg/day, and hydroxychloroquine 250 mg/day was initiated. Because of side effects from prednisone and methotrexate, these medications were discontinued. The patient was then lost to follow-up for approximately 2 years. In May 2004, the patient's lesions flared, and thalidomide 100 mg/day was initiated with prednisone 20 mg/day and topical corticosteroids. As a result of peripheral neuropathy, thalidomide was discontinued after 2 months of treatment. Infliximab 7.5 mg/kg at weeks 0, 2, and 6, and every 8 weeks thereafter was started in August 2004. Figure 3 shows the lesions on the patient's upper extremities were significantly flattened compared with initial presentation.

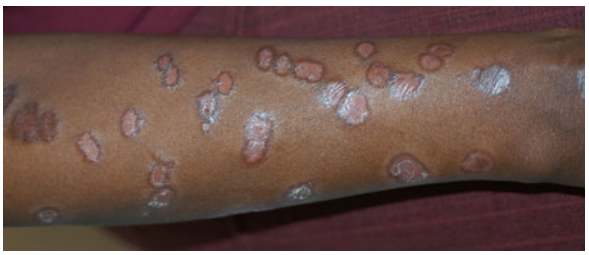

Fig. 3 The clinical manifestation of case 3, 2 years after initiating infliximab

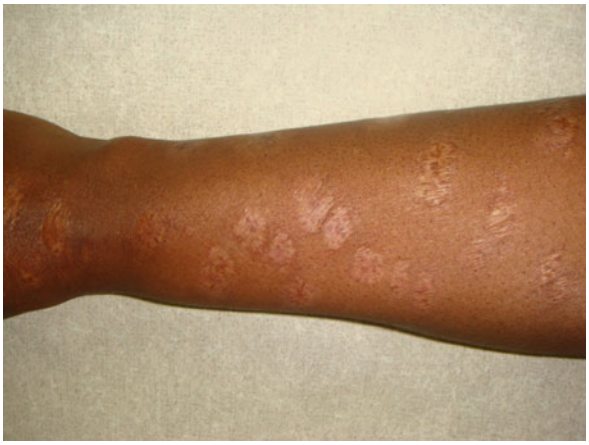

Fig. 4 The clinical manifestations of case 3, 6 years after initiating infliximab

The patient's lesions slowly improved with no new lesions manifesting; Fig. 4 shows the lesions on the patient's upper extremities are dramatically flattened compared with initial presentation. Infliximab was tapered in October 2008 to 5 mg/kg every 12 weeks and was discontinued in November 2011. The patient has currently not developed any new lesions (Table 1).

DISCUSSION

Sarcoidosis is a multisystemic non-caseating granulomatous disease of unknown origin that is driven by T-helper type 1 immune responses [27]. Cutaneous manifestations occur in 25–35% of cases and may present at the onset of the disease process [28–31]. Diagnosis is usually made by clinical suspicion in conjunction with biopsy and the exclusion of other conditions [32]. The clinical history and prognosis of sarcoidosis is variable. In cutaneous sarcoidosis, there are no definite guidelines for systemic therapy, but progressive, widespread, and disfiguring lesions should certainly be treated [33].

Systemic and topical corticosteroids remain the mainstay of treatment for various manifestations of sarcoidosis, including cutaneous sarcoidosis [33]. Unfortunately, the long-term side effects make corticosteroids a less than ideal long-term treatment option, and some patients remain refractory to this management strategy.

Tumor necrotic factor (TNF)-alpha is an important proinflammatory cytokine involved in the pathogenesis of sarcoidosis. Macrophages of sarcoidosis patients have been implicated as major releasers of TNF-alpha in sarcoidosis [34, 35]. Higher serum TNF-alpha levels have been shown not only in patients with slow onset sarcoidosis compared with acute onset, but levels have been shown to fluctuate in correlation with disease activity [36–38]. In addition, increased levels of TNF-alpha have been correlated with a greater risk of disease progression, relapse, and difficulty with treatment [36].

As a result of evidence of TNF-alpha involvement in the pathogenesis of sarcoidosis [39, 40], alternative therapies for cutaneous sarcoidosis such as the TNF-alpha antagonists have been proposed [2, 3]. Reports on the efficacy of TNF antagonists used for cutaneous sarcoidosis are increasing, although at this time this treatment modality remains off label by the standards of the US Food and Drug Administration. Although there have been no comparative trials between the biologic agents for sarcoidosis, infliximab is the most heavily reported medication in the literature [6–11], and overall has shown great promise in the treatment of sarcoidosis patients refractory to more conventional therapies [6, 7, 12, 26]. Favorable outcomes of infliximab therapy in patients who have renal sarcoidosis [13], vertebral sarcoidosis [14], joint sarcoidosis [15], optic neuropathy [16], pulmonary sarcoidosis [6, 17], retinal vasculitis [18], cutaneous sarcoidosis [3–5, 22], neurosarcoidosis [19], and cardiac sarcoidosis [20] have also been reported.

For sarcoidosis patients reported in the literature, the usual dose of infliximab has been 3–10 mg/kg per dose at 0, 2, and 6 weeks, followed by every 8 weeks for maintenance [25, 34]. If patients respond insufficiently to 5 mg/kg, reducing the treatment interval has been shown to lead to higher trough levels than increasing the dose [25]. A randomized, double-blind, placebo controlled study on the efficacy of infliximab in 36 sarcoidosis patients with cutaneous and pulmonary involvement used a 6-week maintenance regimen. After 24 weeks of treatment, patients overall showed improvement in cutaneous findings compared with placebo, although this was not statistically significant ($P = 0.09$) [12]. In addition, a retrospective review of lupus pernio (13 courses of treatment with infliximab in nine patients) reported the success of a 6-week maintenance regimen, which was statistically more efficacious than corticosteroids used with and without other non-steroid immunosuppressive agents ($P = 0.0015$) [5]. All three patients in the current case study were able to control their cutaneous sarcoidosis, although doses had to be tailored to the severity and variably refractory nature of their diseases. However, it should be noted by the prescribing physician that increased doses of immunosuppression can of course lead to an increased tendency toward infection, and can also be associated with demyelination and worsening of multiple sclerosis lesions [41]. Increasing doses of infliximab should not be given lightly.

While TNF inhibitors have been shown to be of benefit in treating sarcoidosis, it is of some interest that a few cases have been reported

wherein patients developed sarcoidosis while undergoing treatment with anti-TNF therapy. In the largest reported series of sarcoid-like granulomas developing during TNF inhibitor therapy [42], three of 10 patients treated with infliximab for ankylosing spondylitis developed pulmonary sarcoidosis 14–51 months after the initiation of treatment. All three patients improved within 6 months of discontinuation [42]. Other case reports of infliximab-treated patients include one patient with ankylosing spondylitis who developed pulmonary sarcoidosis after 5 years of therapy [43], and patients with psoriatic arthritis who developed pulmonary sarcoidosis [44] and cutaneous sarcoidosis [45]. The mechanisms of sarcoidosis development during anti-TNF-alpha therapy are unclear.

In an article by Saleh et al. [21], the following were offered as indications to initiate treatment with infliximab for refractory sarcoidosis:

- unsuccessful treatment with systemic corticosteroids;
- intolerant to systemic steroids side effects;
- unsuccessful treatment or intolerance to other systemic therapies;
- requirement for additional systemic therapy but intolerant to alternative agents.

CONCLUSION

In summary, the authors report three cases of patients with refractory sarcoidosis successfully treated with infliximab. Their clinical outcomes were good, sustained, and there was no associated morbidity from the medication. Definite indications, dosage, interval, and duration of treatment for cutaneous sarcoidosis are not firmly established, although altering the dose and schedule of infusions can be useful in bringing the disease under optimal control. Larger randomized controlled trials are warranted to validate the efficacy of infliximab in patients with cutaneous sarcoidosis.

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Dr. Gaspari is the guarantor for this article, and takes responsibility for the integrity of the work as a whole.

Conflict of interest. The authors report no conflicts of interest.

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