Sarcoidal Anemia and Leukopenia Treated With Methotrexate and Mycophenolate Mofetil

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Background: Sarcoidosis is a multisystem granulomatous disease that may involve the bone marrow, with resultant fever, anemia, and leukopenia. Although generally effective in treating the clinical manifestations of bone marrow sarcoidosis, systemic corticosteroids are not warranted for long-term therapy because of their well-known adverse effects. Therefore, alternative corticosteroid-sparing therapeutic regimens are desired.

Observations: A 41-year-old man sought treatment for cutaneous and bone marrow sarcoidosis resulting in fatigue, anemia, and leukopenia refractory to conventional therapies and mycophenolate mofetil. We initiated combination immunosuppressive therapy with methotrexate sodium and mycophenolate mofetil, which resulted in a safe and prolonged quiescence of cutaneous disease and resolution of anemia and leukopenia throughout a 34-month follow-up period.

Conclusions: We present this case to highlight the growing body of evidence supporting combination immunosuppressive therapy to treat refractory sarcoidosis. In our patient, sarcoidal bone marrow involvement responded dramatically to a combined regimen of methotrexate and mycophenolate mofetil with no significant adverse effects, despite previously having been refractory to conventional agents and mycophenolate mofetil alone. This report provides evidence that combination immunosuppressive therapy is a potential treatment of refractory bone marrow sarcoidosis and highlights important issues about combined immunosuppressive therapy.

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SARCOIDOSIS IS A MULTISYSTEM GRANULOMATOUS DISEASE OF UNKNOWN ORIGIN THAT IS BELIEVED TO OCCUR WHEN A GENETICALLY SUSCEPTIBLE INDIVIDUAL IS EXPOSED TO AN UNKNOWN ANTIGEN, RESULTING IN AN EXAGGERATED HELPER T CELL, SUBTYPE 1 RESPONSE, MONONUCLEAR CELL INFILTRATION, AND EPITHELIOID GRANULOMA FORMATION.1,2 ALTHOUGH THE LUNGS AND SKIN ARE COMMONLY INVOLVED, BONE MARROW INFILTRATION, WHICH IS FREQUENTLY ASSOCIATED WITH FEVER, ANEMIA, AND LEUKOPENIA, HAS BEEN IDENTIFIED IN ONLY 10% TO 17% OF PATIENTS WITH SARCOIDOSIS.1,2 WHEN EVALUATING A SUBGROUP OF PATIENTS WITH SARCOIDAL ANEMIA, LOWER ET AL9 IDENTIFIED SARCOIDAL BONE MARROW GRANULOMAS IN 53% OF CASES. SARCOIDAL BONE MARROW INVOLVEMENT IS RARELY REPORTED IN THE DERMATOLOGIC LITERATURE, AND, TO DATE, NO CONSISTENTLY SAFE AND EFFECTIVE LONG-TERM TREATMENT HAS BEEN IDENTIFIED. ALTHOUGH GENERALLY BENEFICIAL FOR TREATING BONE MARROW SARCOIDOSIS, CORticosteroids ARE UNSUITABLE FOR LONG-TERM THERAPY BECAUSE OF WELL-KNOWN ADVERSE EFFECTS.7,8 ACCORDINGLY, ALTERNATIVE SAFE AND EFFECTIVE TREATMENT MODALITIES ARE DESIRED.

We describe an illustrative patient with anemia and leukopenia secondary to sarcoideal bone marrow involvement, refractory to conventional and single-agent immunosuppressive therapies, who exhibited a safe and effective sustained response to a corticosteroid-free regimen of combined methotrexate sodium and mycophenolate mofetil. We discuss the evidence supporting combination therapy for sarcoidosis and the associated concerns.

REPORT OF A CASE

A 41-year-old African American man with a 7-year history of sarcoidosis sought ongoing treatment of sarcoideal cutaneous and bone marrow infiltration, which manifested symptomatically as fatigue and lack of endurance. Flesh-colored to hyperpigmented smooth papules and plaques, some annular, were noted, particularly on his head and neck and on tattooed areas of his upper extremities (Figure 1A). Analysis of a bone marrow biopsy specimen revealed that most normal hematopoietic tissue had been replaced with sarcoideal granu-
lomas; special stains did not identify any infectious organisms (Figure 2). Laboratory evaluations revealed the following abnormalities: hemoglobin concentration, 10.4 g/dL (reference range, 14.0-18.0 g/dL); hematocrit, 31.3% (42%-52%); mean corpuscular volume, 78.8 µm³ (80-94 µm³); mean corpuscular hemoglobin concentration, 26.3 pg/cell (27-31 pg/cell); red blood cell distribution width, 18.6% (11.5%-14.5%); white blood cell (WBC) count, 3.7 x 10³/µL (4.8-10.8 x 10³/µL); segmented neutrophils, 42% (50%-70%); immature neutrophils (bands), 6% (0%-5%); monocytes, 10% (1%-6%); eosinophils, 7% (1%-5%); lactate dehydrogenase level, 809 U/L (300-650 U/L); total protein level, 9.0 g/dL (5.8-8.1 g/dL); angiotensin-converting enzyme (ACE) level, 159 U/L (12-68 U/L); and erythrocyte sedimentation rate, 57 mm/h (0-15 mm/h). Serum protein electrophoresis identified a polyclonal increase in γ-globulin. Results of the following laboratory evaluations were within the reference range: platelet count, iron level, ferritin level, transferrin level, folate level, vitamin B₁₂ level, reticulocyte count, lymphocyte proportion, basic metabolic panel, alanine aminotransferase level, aspartate aminotransferase level, calcium level, and albumin level. Other than calcification of hilar lymph nodes and a mild decrease in pulmonary diffusion capacity (60% of the reference predicted value with a preservation of lung volume), there was no evidence of other organ involvement. (To convert ACE to nanokatals per liter, multiply by 16.667; to convert hemoglobin, mean corpuscular hemoglobin concentration, and total protein to grams per liter, multiply by 10; to convert lactate dehydrogenase to microkatal per liter, multiply by 10; to convert hemoglobin, mean corpuscular hemoglobin concentration, and total protein to grams per liter, multiply by 10; to convert lactate dehydrogenase to microkatal per liter, multiply by 10; and to convert mean corpuscular volume to femtoliters, multiply by 1.)

Previous treatment with topical and intralesional corticosteroids, as well as a 7-month oral course of 100 mg of doxycycline hyclate twice daily, was unsuccessful. A 6-month trial of 200 mg of oral hydroxychloroquine sulfate twice daily improved the patient's cutaneous sarcoidosis, but was discontinued because of worsening ane-

Figure 1. Clinical appearance of a 41-year-old African American man with a 7-year history of sarcoidosis. Before initiating combined immunosuppressive therapy, flesh-colored to hyperpigmented smooth papules and plaques, some annular, are visible on the face and tattooed portions of the upper extremities (A). Marked improvement is noted after combined immunosuppressive therapy with methotrexate sodium and mycophenolate mofetil (B).

Figure 2. A bone marrow biopsy specimen revealed partial replacement of hematopoietic tissue with epithelioid granulomas (hematoxylin-eosin, original magnification ×100 [inset, ×200]).
mia. His most recent regimen, consisting of 2500 mg of oral mycophenolate mofetil in daily divided doses for 4 months, also failed to treat his cutaneous lesions or alter his hemoglobin level, WBC count, or ACE level.

We recommended that the patient continue his existing dosage of mycophenolate mofetil and initiated oral therapy with 7.5 mg weekly of methotrexate sodium and 1 mg daily of folic acid. For the next 8 months, he was monitored closely throughout a gradual dose escalation until he reached a stable therapeutic oral regimen of 3 g daily of mycophenolate mofetil in divided doses, 17.5 mg weekly of methotrexate sodium, and 1 mg daily of folic acid. Seven months after beginning treatment with methotrexate, the patient's cutaneous lesions had improved significantly. Two months later, his hemoglobin level and WBC count began to increase slowly but progressively, his fatigue began to be relieved, and his ACE level decreased. Because the declining ACE level seemed to correlate well with clinical improvement, we elected to continue monitoring ACE levels for additional therapeutic guidance. After the patient maintained improved hematological parameters and remained free of active cutaneous involvement for 4 months, his mycophenolate mofetil dosage was decreased and subsequently discontinued; he continued to take 15 mg of methotrexate sodium once weekly with folic acid supplementation. Most recently, methotrexate was increased to 17.5 mg once weekly, a change in dosage prompted by an increase in the patient's ACE level with a concurrent decrease in hemoglobin level and WBC count. Hemoglobin level, WBC count, and ACE level responded favorably to this small increase in dosage. Presently, the patient remains asymptomatic with an overall significant improvement in his quality of life, stemming from resolution of anemia-related fatigue and quiescence of cutaneous sarcoidal involvement (Figure 1B). His medication regimen and hematological parameters, as well as the timing of significant clinical events, are detailed in Figure 3.

Throughout the 34-month regimen of combined immunosuppressive therapy, our patient experienced only minor and limited adverse effects. Despite improvement in his hematological parameters and only limited residual cutaneous involvement, with smooth violaceous papules and plaques after 14 months of combined therapy, he developed a transient, self-resolving 4-month episode of bilateral asymptomatic parotid enlargement (Figure 4). Histological and flow cytometric analysis of a fine-needle aspiration biopsy specimen revealed a benign, nonclonal, lymphocytic infiltrate in the parotid gland. The patient's only other complication was a solitary mild cutaneous flare-up concurrent with tapering of methotrexate; the flare-up resolved with subsequent dose escalation.

**COMMENT**

Systemic corticosteroid treatment, generally effective for cutaneous and pulmonary sarcoidosis, has proven beneficial for sarcoidal bone marrow involvement. Lower et al. reported that, in 12 of 12 patients, anemia from sar-
Later, Kouba et al.15 reported the safe and effective treatment of sarcoidal uveitis by Kilmartin et al.14 in 1998. Mycophenolate mofetil, was first described as beneficial in the treatment of sarcoidosis. However, the well-known adverse effects of chronic systemic corticosteroid therapy preclude its widespread use in treating chronic cases of sarcoidosis, which has led to the search for effective corticosteroid-sparing therapeutic regimens. Excellent comprehensive reviews of sarcoidosis therapy exist in the literature.8,9

Methotrexate was first reported effective in treating sarcoidosis by Lacher10 in 1968 and has since become a commonly used immunosuppressive agent for treating this disease.8,11 A double-blind, randomized, placebo-controlled trial demonstrated that methotrexate is an effective corticosteroid-sparing agent for treating sarcoidosis and confirmed prior reports of delay (approximately 6 months) in onset of therapeutic effects.7,12 It has been suggested that the efficacy of methotrexate for treating sarcoidosis and the therapeutic latency period may be owing to the slow accumulation of intracellular polyglutamate derivatives required to stimulate release of adenosine extracellularly, which is thought to mediate the anti-inflammatory properties of low-dose methotrexate.13 Methotrexate toxicity, however, can complicate sarcoidosis therapy because it can be difficult to differentiate sarcoidosis-induced and methotrexate-induced cytopenia, hepatitis, and pneumonitis. For these reasons, additional immunosuppressive agents have been evaluated for use in sarcoidosis treatment.

A newer cytotoxic immunosuppressive medication, mycophenolate mofetil, was first described as beneficial for treating sarcoidal uveitis by Kilmartin et al.14 in 1998. Later, Kouba et al.15 reported the safe and effective treatment of 5 patients who had cutaneous and systemic sarcoidosis, and several other reports detailing the safety and efficacy of mycophenolate mofetil for treating sarcoidosis have since been published.16,17 However, to date and to our knowledge, there are no reports documenting the efficacy of mycophenolate mofetil in treating sarcoidal bone marrow involvement. Mycophenolate mofetil is thought to be beneficial for treating sarcoidosis because it inhibits inosine monophosphate dehydrogenase with resultant inhibition of de novo purine synthesis, preferentially targeting lymphocytes, in addition to its anti-inflammatory effect via suppression of cytokine and cell surface adhesion molecule production.18 Other than the potential cytotoxic effects of anemia and leukopenia, mycophenolate mofetil appears to be a relatively safe alternative to methotrexate and chronic corticosteroid use for the treatment of sarcoidosis.

More recently, combination therapies have been demonstrated to be relatively safe and efficacious in treating sarcoidosis. Presumably, combination therapies optimize immune system alteration and anti-inflammatory effects through different mechanisms and minimize adverse cytotoxic effects by using lower doses of individual agents.5,10 Combinations of methotrexate and prednisone, with or without cyclosporine; methotrexate and azathioprine; and methotrexate and leflunomide have been reported.19,20 However, concern exists regarding the long-term effects of combination immunosuppressive therapy on the risks of developing malignancy and opportunistic infection. In addition, not all immunosuppressive agents combine in a synergistic manner: the combination of methotrexate and cyclosporine is suboptimal, in our opinion, because of concerns that cyclosporine nephropathy affects methotrexate excretion. To date, combination cytotoxic immunosuppressive therapy has not been reported as a treatment for sarcoideal bone marrow involvement.

Our patient sought treatment with cutaneous and bone marrow sarcoidosis refractory to conventional therapies. Mycophenolate mofetil was chosen as the initial immunosuppressive agent in an attempt to avoid potential confounding issues of hepatitis and pneumonitis associated with methotrexate and sarcoidosis. Yet while the patient’s cutaneous disease and hematological parameters remained stable, neither improved throughout the 4 months he was treated with mycophenolate mofetil. His clinical stability and high functional status did not warrant the associated adverse effects of chronic systemic corticosteroid therapy. Therefore, we selected a combination immunosuppressive regimen of mycophenolate mofetil and methotrexate with the goal of suppressing the sarcoideal bone marrow granulomas with subsequent improvement in hemoglobin and white blood cell counts before experiencing iatrogenic suppression of his remaining hematopoietic tissue. Four mechanisms have been described by which sarcoidosis results in cytopenia: granulomatous replacement of bone marrow, sequestration of cells into areas of inflammation, splenic sequestration, and immunological destruction.6,12,21 We believe the primary mechanism causing anemia and leukopenia in this patient was direct replacement of hematopoietic tissue by sarcoideal granulomas. This is supported by the parallel upward trending of his hemoglobin level and WBC count with a concurrent decrease in ACE level, which, although not specific to sarcoidosis, has been proven a reliable indicator of granuloma burden.22,23

Figure 4. Clinical appearance of residual smooth, indurated, violaceous papules and plaques. The transient, self-resolving 4-month episode of bilateral asymptomatic parotid enlargement occurred during the fourth month of combined immunosuppressive therapy. Arrows indicate parotid enlargement.
Despite obvious concerns regarding infection, malignancy, and suppression of remaining hematopoietic tissue function in this patient with preexisting anemia and leukopenia from sarcoidal bone marrow infiltration, the patient experienced only mild and transient adverse effects throughout this 34-month course of combined methotrexate and mycophenolate mofetil therapy. Although we were not able to identify the cause of his transient bilateral parotid enlargement, the differential diagnosis included sarcoidal granulomatous deposition, infection, and malignancy. Parotid tissue evaluation failed to identify any clonal population among the lymphocytic infiltrate; however, this episode highlights the potentially increased risk of malignancy when combining immunosuppressive medications and motivated our conversion to monotherapy with methotrexate. The unfavorable character of the patient’s hematological parameters following discontinuation of mycophenolate mofetil suggests it was indeed contributing to clinical and hematological improvement and underscores the synergistic response achievable with combination immunosuppressive therapy.

We have described a patient with cutaneous and bone marrow sarcoidosis, refractory to conventional and single-agent immunosuppressive therapy, who experienced a safe, effective, and sustained response to a corticosteroid-free combined immunosuppressive regimen of methotrexate and mycophenolate mofetil. Only mild and transient adverse effects were encountered throughout the 34-month therapy period. To our knowledge, this is the first report detailing combined immunosuppressive therapy to treat sarcoidal bone marrow involvement. We hope this report helps raise awareness of the potential benefits and safety of combined immunosuppressive therapy while highlighting the need for careful clinical monitoring.

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REFERENCES