Glucocorticoid Treatment of Symptomatic Sarcoidosis in 2 Morbidly Obese Patients

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Corticosteroid management for patients with sarcoidosis requires the need for close monitoring to detect and manage any complications that may arise during treatment.

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Sarcoidosis is a systemic inflammatory condition with pulmonary and extrapulmonary manifestations. The etiology of sarcoidosis remains unknown. Iannuzzi and colleagues hypothesize that an unknown antigen sets off a cycle of chronic granulomatous inflammation in a genetically susceptible host.[1]

DIAGNOSIS

A diagnosis of sarcoidosis is typically based on a patient having an appropriate clinical presentation and a biopsy, often of lungs or skin, showing noncaseating granulomas.

Symptoms

Of the protean manifestations of sarcoidosis, respiratory symptoms are the most common and typically include subacute or chronic cough and progressive dyspnea on exertion.[2] Chest imaging may show only hilar or mediastinal lymphadenopathy, diffuse micronodular lung disease, or signs of chronic inflammation and fibrosis.[2] Upper airway involvement and progressive lung disease may lead to increased risk of sleep-disordered breathing, particularly obstructive sleep apnea (OSA).[3]

Sarcoidosis also can develop in the skin, neurologic system, heart, and other systems. It typically presents as areas of patchy, infiltrative inflammation. In the heart, this can lead to heart failure, often with reduced ejection fraction (EF) and ventricular arrhythmias.[1] Pulmonary hypertension (PH) may result from multiple possible mechanisms, including left-heart disease, parenchymal lung disease, sleep-disordered breathing, and possibly direct inflammation and compression of the pulmonary vasculature.[2-4]

Sarcoidosis in Obese Patients

Emerging evidence shows that sarcoidosis occurs at higher rates in obese patients, suggesting that obesity may be a risk factor for the disease.[5-7] Rates of morbid obesity are increasing in the US. From 2000 to 2010, the prevalence of morbid obesity, defined as body mass index (BMI) > 40, increased by 70%, with even larger relative increases in the number of patients with BMI > 50.[8] Among veterans who receive health care at the US Department of Veterans Affairs (VA) medical centers, 28% are obese.[9] As a result, VA physicians will encounter more patients with morbid obesity and another significant comorbid condition.

Managing symptomatic sarcoidosis in patients with morbid obesity poses a dilemma. Typical treatment for symptomatic pulmonary sarcoidosis is prednisone 20 mg to 40 mg daily.[10,11] Higher doses are suggested for involvement of other organs, such as the heart.[2,12] Associated weight gain from corticosteroid treatment with possible sleep-disordered breathing increases an already high risk of metabolic complications in morbidly obese patients.[13] No clear consensus exists on how corticosteroid doses should be adjusted. We present 2 cases that highlight the complexity of corticosteroid management in the obese sarcoidosis patient.

CASE 1: PULMONARY SARCOIDOSIS

A 43-year-old morbidly obese man presented to his primary care provider with subacute

onset of dyspnea. He had a history of OSA that was diagnosed empirically at another institution without polysomnogram and treated with autotitrating continuous positive airway pressure (CPAP).

The patient was admitted for expedited evaluation. His BMI was 63.2 with declining exercise tolerance and hypoxemia on ambulation. His oxyhemoglobin saturation rate was 85% after walking a short distance. Ongoing CPAP therapy for sleep-disordered breathing made laboratory evaluation for obesity hypoventilation syndrome (OHS) challenging. The patient's serum bicarbonate test result was normal. Serum markers as well as induced sputum stains and cultures were negative for evidence of mycobacterial or fungal infections. A chest radiograph showed bilateral hilar adenopathy and miliary nodularity. Pulmonary function testing revealed severe obstruction and restriction as well as a moderate diffusion impairment. Bronchoscopy with biopsy revealed noncaseating granulomas consistent with sarcoidosis. An electrocardiogram (ECG) was normal. Transthoracic echocardiogram showed evidence of diastolic dysfunction and a mildly dilated right ventricle with normal function, suggestive of possible PH. We were unable to assess his pulmonary artery pressure.

Upon release, the patient began a course of 50 mg (0.24 mg/kg actual body weight) oral prednisone daily and home oxygen.

Six weeks after initiation of steroids, the patient reported that his dyspnea had improved. However, after 6 months of steroid treatment, his weight increased from 462 pounds to 503 pounds. He was evaluated for possible neurosarcoidosis with hypothalamic or pituitary involvement as a possible cause for the weight gain. Brain magnetic resonance imaging and hormonal testing were normal. We considered starting him on a steroid-sparing agent. However, after early efficacy, prednisone was gradually tapered and, after 1 year of treatment, discontinued. At that time, symptoms had substantially improved: His pulmonary function tests had normalized, and he was weaned off oxygen; repeat chest imaging showed only residual enlargement of the hilar lymph nodes. After cessation of steroids, the patient was able to lose 20 pounds.

CASE 2: CARDIAC SARCOIDOSIS

A 57-year-old morbidly obese man presented to the emergency department with subacute increasing dyspnea on exertion. He had a known history of sarcoidosis diagnosed by skin biopsy 28 years earlier but had been without treatment for decades. His history also included prediabetes, heart failure with preserved ejection fraction (HFpEF), OSA with an apnea hypopnea index (AHI) of 114.7 per hour, PH diagnosed by prior echocardiogram, and paroxysmal atrial fibrillation (AF). He required 2 L/m home oxygen and bilevel positive airway pressure (PAP) of 22/17 cm H_2O while sleeping.

On physical examination, the patient's BMI was 54.6. He was tachycardic and hypoxemic on his usual oxygen flow rate. His serum bicarbonate, arterial blood pH, and $PaCO_2$ blood levels were normal. We heard bibasilar crackles over the lungs. Chest radiograph revealed an enlarged cardiac silhouette and bilateral infiltrates concerning for cardiogenic pulmonary edema. An echocardiogram showed a restrictive filling pattern with preserved EF and moderate dilation and dysfunction of the right ventricle, consistent with PH. A positron emission tomography (PET)/computed tomography scan, the preferred study for cardiac sarcoidosis, suggested active infiltrative septal cardiac disease and active hilar and mediastinal adenopathy. This was concerning for both cardiac and pulmonary sarcoidosis. Ongoing treatment of sleep-disordered breathing made laboratory assessment for OHS challenging. Given his intact EF, the absence of ventricular arrhythmias, and improvement with diuretics and bilevel PAP, specific treatment of sarcoidosis was not initiated. He was discharged home with a plan to re-evaluate sarcoidosis symptoms and initiate treatment as an outpatient.

The patient was readmitted 2 weeks later with worsened dyspnea, hypoxemia, and volume overload. A right heart catheterization confirmed PH with a mean pulmonary artery pressure of 44 mm Hg (68/32 mm Hg) and pulmonary vascular resistance of 4.6 Wood units. We also found evidence of left-heart dysfunction with a pulmonary capillary wedge pressure of 16 mm Hg.

Given his recurrent symptoms, evidence of active myocardial inflammation on recent PET, and prior biopsy-proven sarcoidosis, we made the decision to pursue treatment for symptomatic sarcoidosis. He began a course of 40 mg (0.20 mg/kg actual body weight) oral prednisone daily. He now required 6 L/m supplemental oxygen. After IV diuretic therapy during his hospitalization, the patient was discharged on his preadmission oral diuretic dose. Pulmonary vasodilator therapy was not initiated for PH as left heart disease and sleep-disordered breathing needed to be managed first.

One month after steroid initiation, the patient reported that the dyspnea and hypoxemia had markedly improved. His oxygen flow rate was reduced to 2 L/m. He remained normotensive and had no further difficulties with fluid retention or volume overload on a stable dose of oral diuretics. He had elevated blood glucose with a glycated hemoglobin (HbA_{1c}) of 6.4%. He began treatment with glipizide 5 mg daily.

After 3 months, he returned to the emergency department with hyperosmolar nonketotic hyperglycemia due to steroid-induced diabetes mellitus (DM). His HbA_{1c} was now 17.1%. The patient was started on a home insulin regimen, and his blood sugar values subsequently improved. He remained symptomatically better and lost 40 pounds with a guided weight management program and a stable diuretic regimen. He underwent arrhythmia evaluation with a Holter monitor that showed AF without ventricular arrhythmias.

Unfortunately, he did not return for cardiac or pulmonary reevaluation, and was lost to follow-up. Nine months after initiation of treatment, the patient died after an out-of-hospital cardiac arrest.

DISCUSSION

These 2 cases highlight therapeutic challenges that may arise in the management of sarcoidosis with symptomatic vital organ involvement and coexistent extreme obesity. Both patients showed symptom improvement with moderate doses of prednisone (40 mg to 50 mg daily), but serious treatment-related complications developed: further weight gain in the first patient, and severe DM in the second. Although DM may have been a direct treatment complication in our second patient, his HFpEF and PH were high-risk comorbidities; he did not present with acute symptomatic worsening after treatment initiation. His symptoms were never reassessed when he was lost to follow-up.

Sarcoidosis/Obesity Relationship

Recent evidence suggests that patients with obesity are at increased risk of developing sarcoidosis.[5-7] Although the mechanism of association is unclear, several possibilities have been proposed.

Neurosarcoidosis. One known but rare cause of obesity is neurosarcoidosis of the hypothalamus or pituitary.[14] This was investigated in one of our patients.

Proinflammatory responses. Another possible mechanism for the association of sarcoidosis and obesity is the proinflammatory properties of increased fat and adipose tissue.[15] Obesity has been linked to an aberrant expansion of inflammatory cells and mediators, including macrophages, proinflammatory cytokines, T cells, and B cells.[15] Leptin, produced primarily by adipocytes, also is higher in obese patients and has been found to be proinflammatory.[16] These seem to underlie the link between obesity and other inflammatory diseases, including type 2 DM, gout, and atherosclerosis.[15]

Behavioral link. There also is a possible behavioral link between sarcoidosis and obesity: A patient might develop symptomatic sarcoidosis and later become less active due to dyspnea, which could predispose to weight gain.[5]

Management of Comorbid Sarcoidosis and Obesity

Regardless of the exact mechanism of this association, management of the co-occurrence of sarcoidosis and obesity poses a clinical problem, especially in cases of extreme obesity. Corticosteroids are generally considered the treatment of choice for symptomatic sarcoidosis. The initial treatment of symptomatic pulmonary sarcoidosis is 20 mg to 40 mg prednisone daily.[10,11] Higher daily doses such as 60 mg to 80 mg or 0.5 mg/kg are typically used to treat cardiac sarcoidosis, although no clear consensus exists on the appropriate dose.[12,17]

One recent study showed no difference in cardiac outcomes in patients treated with high- and low-dose prednisone.[18]

For patients who are obese and require steroids to treat a medical condition, there is conflicting evidence on whether steroid doses should be increased in proportion to total body weight. Milsap and colleagues found clearance of prednisolone correlated strongly with degree of obesity, suggesting steroid dose should be increased in accordance with actual weight.[19] In contrast, Dunn and colleagues found decreased clearance of methylprednisolone in obese patients, suggesting that ideal body weight dosing is appropriate.[20]

Identifying the appropriate steroid dose is important because corticosteroids place obese patients at higher risk of developing complications. Treatment-related comorbidities include DM, hypertension, fluid retention, osteoporosis, and infection. Further weight gain due to steroid use is a risk for progressive OSA and, even though not generally associated with sarcoidosis alone, OHS. For patients with sarcoidosis, these complications (DM, fluid retention, hypertension, sleep-disordered breathing) may increase the risk of cardiovascular disease and PH.[21-23] Cardiomyopathy, especially with reduced EF and increased PH, can be associated with a poor prognosis in sarcoidosis.[4,24-26] PH also can be challenging to treat patients with sarcoidosis because the response of PH to steroids is unclear.[27] Small trials have shown the benefit of pulmonary vasodilators on hemodynamics, but these have generally been used in patients with stable sarcoidosis who do not have left-heart disease.[28-30]

Our Prescription Model
We empirically prescribed moderate total doses of prednisone—although low on a mg/kg basis—to balance efficacy and the risk of adverse effects in these 2 morbidly obese patients. We also managed treatment-related complications with guided weight-management programs, CPAP, or noninvasive ventilation for sleep-disordered breathing, and DM treatment.

Our cases demonstrate the need for close monitoring of weight, blood pressure, and blood glucose to detect and treat any com-

plications that may arise during corticosteroid treatment. Aggressive treatment of hyperglycemia with insulin or oral alternatives associated with weight loss such as metformin, sulfonylureas, dipeptidyl peptidase 4 inhibitors, or glucagon-like peptide 1 receptor agonists, may help prevent further DM complications. Sleep-disordered breathing should be assessed and treated. Bariatric surgery may be an option to treat obesity and minimize resultant complications. In our patients, and likely many others, the degree of respiratory and cardiac disease coupled with poor wound healing due to chronic prednisone, may increase the procedural risks.

CONCLUSION
Our experiences with these patients illustrate that symptomatic and objective improvement in sarcoidosis may be achieved in morbidly obese patients with doses of prednisone that are generally considered moderate, though quite low on a mg/kg basis.

We believe ours is the first report to describe the use of corticosteroids for the treatment of sarcoidosis in patients with morbid obesity. That 2 patients were treated at a single VA medical center within 1-year likely reflects the rising incidence of morbid obesity in the US veteran population and suggests that other federal practitioners might encounter similar patients.

Further study may show that, as an alternative to initial moderate-dose prednisone, patients with symptomatic sarcoidosis and extreme obesity might be started on antimetabolite or antitumor necrosis factor medication or on low-dose prednisone and a second steroid-sparing agent.

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