Improvement of pulmonary sarcoidosis following sleeve gastrectomy

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ABSTRACT
Pulmonary sarcoidosis is unlikely to resolve if it persists for greater than five years. A growing body of literature supports the involvement of the microbiome in sarcoidosis and a role for sex hormones in pulmonary fibrosis. Additionally, obesity is a risk factor for the development of sarcoidosis. Bariatric surgery is an effective treatment for obesity and can lead to microbial and endocrine changes. Here, we report the clinical improvement of longstanding pulmonary sarcoidosis following sleeve gastrectomy.

Key Words: Sarcoidosis, Bariatric surgery, Obesity, Estrogen, Microbiome

1. INTRODUCTION
Sarcoidosis is a granulomatous disease that can affect any organ, but most frequently affects the lungs. In some patients, the disease resolves over the course of a few years, while about a third of patients progress to develop pulmonary fibrosis. Obesity is an independent risk factor for sarcoidosis incidence and progression. Sarcoidosis treatment often involves corticosteroids which can lead to weight gain, making weight management particularly challenging for sarcoidosis patients. Obesity can be both a consequence of sarcoidosis treatment and a contributor to disease risk likely through the pro-inflammatory environment of obesity. Although the etiology of sarcoidosis progression is still largely unknown, recent studies propose a role for sex hormones and the microbiome in the pathogenesis of fibrotic lung disease. These gaps in knowledge limit the identification of effective treatments. Here, we present a patient with a fourteen-year history of symptomatic pulmonary sarcoidosis who experienced significant clinical improvement in lung function and chest radiographs following sleeve gastrectomy.

2. CASE PRESENTATION
A 43-year-old female had a chest X-ray prior to an elective hysterectomy which revealed hilar adenopathy. A computed tomography (CT) scan was done which revealed bilateral hilar and mediastinal adenopathy and a lung biopsy revealed the presence of non-caseating granulomas. Further clinical and microbiological work-up confirmed the diagnosis of pulmonary sarcoidosis. She remained asymptomatic for five years before she began experiencing a significant cough and shortness of breath. Chest X-ray at this time showed bilateral hilar adenopathy as well as pulmonary parenchymal involvement. She was started on 20 mg oral prednisone, twice daily.
She experienced some improvement, but the side effects of the steroids were intolerable and the medication was discontinued. Over the next eight years, her pulmonary disease was managed with intermittent methotrexate and prednisone. Despite these measures, the patient experienced clinical exacerbations resulting in continued loss of lung function as evidenced by Forced Vital Capacity (FVC) decline from 99% to 84% (see Table 1).

Table 1. Spirometry pre- and post-sleeve gastrectomy

| Year before Surgery | 2006 | 2008 | 2013 | 2017 | 2018 |
|--------------------|------|------|------|------|------|
| Actual FVC (L)     | 4.01 | 3.90 | 3.44 | 3.32 | 3.53 |
| % Predicted        | 99%  | 97%  | 86%  | 84%  | 94%  |
| Actual FEV1 (L)    | 3.11 | 3.02 | 2.64 | 2.59 | 2.66 |
| % Predicted        | 98%  | 95%  | 83%  | 84%  | 91%  |
| Actual FEV1/FVC (%)| 77   | 77   | 77   | 78   | 75   |
| % Predicted        | 99%  | 98%  | 96%  | 99%  | 95%  |
| Actual DLCO (ml/min/mmHg/L) | 26.19 | 26.67 | 24.72 | 24.88 |
| % Predicted        | 88%  | 90%  | 83%  | 84%  |       |

Note. As shown in Table 1, the patient’s lung function declined gradually over time prior to sleeve gastrectomy. Following sleeve gastrectomy, the patient’s lung function began to improve.

Figure 1. CT representation of pulmonary sarcoidosis one year prior to sleeve gastrectomy showing ground glass opacities in the apex (A) and improvement seven months following sleeve gastrectomy (B).

In 2017, one year prior to the sleeve gastrectomy, the patient underwent a routine chest CT scan to monitor her pulmonary sarcoidosis. The CT scan revealed three major abnormalities: 1) a new or increased patchy ground-glass nodule in the right lung base posterior medially measuring approximately 16mm, 2) mild septal thickening in the posterior upper lobes adjacent to the major fissure with faint ground-glass opacities in the lower lobes bilaterally, and 3) stable tiny right lower lobe nodular densities (see Figure 1A, Figure 2A). Pulmonary function tests from this time reveal an FVC and a diffusing capacity of the lungs for carbon monoxide (DLCO) that were both 84%, making them reduced but within normal limits (see Table 1). At this time, she was taking 12.5 mg of methotrexate weekly. In 2018, the patient underwent sleeve gastrectomy to aid with weight loss due to her having a body mass index (BMI) of 37.6. Two months after the sleeve gastrectomy, the patient had lost 22lbs and her BMI was now 34.2. At this time, spirometry was obtained to evaluate her sarcoidosis. Compared to spirometry taken prior to surgery, the spirometry taken after surgery and weight loss showed improved FVC and forced expiratory volume in one second (FEV1). FVC improved from 84% eleven months
before surgery to 94% two months after surgery. FEV1 improved from 84% eleven months before surgery to 91% two months after surgery (see Table 1). Seven months following the sleeve gastrectomy, the patient again had a routine CT scan to monitor her sarcoidosis. The CT scan revealed improvement in all three major abnormalities noted on the CT scan from one year prior to sleeve gastrectomy: 1) there had been clearing of the patchy ground-glass nodule in the superior segment of the right lower lobe, 2) reductions in the fine interstitial changes bilaterally with near complete resolution in the left upper lobe and, 3) the nodular densities in the right lower lobe had diminished. No new infiltrates were seen. (see Figure 1B, Figure 2B). Subjectively, the patient reported “feeling great.” There were no changes in the patient’s medications compared to prior to surgery; she remained on only methotrexate. Eighteen months after sleeve gastrectomy, the patient’s BMI was 26.6. She had maintained a weight loss of 70lbs and reported feeling well with no shortness of breath.

Figure 2. CT representation of pulmonary sarcoidosis one year prior to sleeve gastrectomy showing a ground glass nodule in the right lower lobe (A) and improvement seven months following sleeve gastrectomy (B).

3. DISCUSSION

To our knowledge, this is the first published case of clinical improvement of pulmonary sarcoidosis following bariatric surgery. It is possible that the disease resolved independently of surgery and weight loss since, in about half of sarcoidosis patients, the disease resolves spontaneously within the first two years. However, more than 85% of spontaneous remissions occur within two years of presentation and failure to remit within two years predicts a chronic or persistent course. In a study of 500 patients with sarcoidosis, 43% still required systemic therapy after five years, with 32% experiencing continued or worsening symptoms despite therapy. At the time of surgery, this patient had sarcoidosis for fourteen years, making it unlikely that this case represents a spontaneous resolution. Obesity itself is associated with sarcoidosis clinical progression. Data from the Black Women’s Health Study and the Nurses’ Health Study II show that weight gain and obesity during adulthood are associated with higher sarcoidosis incidence and that higher BMI is prospectively associated with an increased risk of developing sarcoidosis. Obesity can be both a consequence of and a risk factor for the development of sarcoidosis since the corticosteroid therapy used to manage the disease leads to weight gain. Additionally, obesity creates a pro-inflammatory state which may contribute to sarcoidosis pathogenesis. Obesity can also induce restrictive and obstructive lung disease due to increased intrathoracic adiposity. In females, abdominal fat was negatively correlated with FVC and FEV1. In the case reported here, an eleven-point reduction in BMI accompanied the improvement in pulmonary sarcoidosis lung function and radiographs. Much of the data on the relationship between obesity and sarcoidosis comes from female subjects. Sarcoidosis is a disease that predominantly impacts females and new studies suggest a potential role for sex hormones in fibrotic lung disease. Data from the Black Women’s Health Study suggests that later full-term pregnancy and longer exposure to endogenous female hormones may be related to a reduced risk of sarcoidosis. This finding is supported by evidence from animal models showing that ovarian dysfunction may adversely affect
the formation of granulomas in the lung.[9] Apart from sarcoidosis, sex hormones are implicated in other fibrotic lung diseases. In Usual Interstitial Pneumonia, the progesterone receptor has been shown to be expressed within established fibrotic areas.[6] In bronchial epithelial cells, estrogen and transforming growth factor beta1 have been shown to inversely modulate the expression of several genes involved in extracellular matrix turnover, airway smooth muscle cell contraction, and calcium flux regulation.[7] Adipose tissue accounts for the majority of peripheral estrogen synthesis and its contribution to the circulating pool of estrogens increases with body mass and age.[17] It has been shown that bariatric surgery in women can lead to significant decreases in estradiol, total testosterone, and dehydroepiandrosterone sulfate (DHEA-S) as well as significant increases in follicle stimulating hormone, luteinizing hormone, and sex hormone binding globulin.[18] While the relationship between sarcoidosis and sex hormones is emerging, it is possible that a reduction in body fat following bariatric surgery may lead to endocrine changes that favor clinical improvement in pulmonary sarcoidosis. Interestingly, the gut microbiome is another important regulator of circulating estrogens.[19] Recent studies propose a role for the lung and gut microbiome in sarcoidosis and other causes of pulmonary fibrosis. Dysbiosis in the lung or gut may contribute to the development of systemic inflammatory conditions, including sarcoidosis.[11] The lung microbiota has been shown to contribute to pulmonary inflammation and disease progression in pulmonary fibrosis.[12] In sarcoidosis patients, metabolomic profiling has shown changes in energy production, homocysteine, and amino acid metabolism, as well as a potential role of altered gut microbiota.[10] Following bariatric surgery, increased gut microbial diversity and gene richness have been reported.[20–25] While the connection between the gut microbiome and sarcoidosis is developing, their relationship may have contributed to the resolution of sarcoidosis following bariatric surgery reported here.

4. Conclusion
Sarcoidosis is a multifactorial disease about which much remains to be elucidated. The resolution of sarcoidosis following bariatric surgery reported here invites further investigation into the impact of obesity, bariatric surgery, and alterations in the gut microbiome on sarcoidosis pathogenesis. Since sarcoidosis is a complex, multisystem disease, bariatric surgery needs to be carefully and individually considered in sarcoidosis patients, with special consideration given to disease severity and active treatment.[26] Due to the paucity of effective treatments for sarcoidosis, potential innovative therapeutics, such as bariatric surgery, should be investigated.

Conflicts of Interest Disclosure
The authors have declared no conflicts of interest.

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