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## CASE REPORT

# Treatment of refractory sarcoidal parotid gland swelling in a previously reported unresponsive case

LOUIS MANDEL, D.D.S.; BARRY WOLINSKY, D.D.S.; ELIZABETH C. CHALOM, M.D.

**P**reviously in this journal, we<sup>1</sup> reported diagnosing a case of bilateral parotid gland swelling caused by sarcoidosis in a 13-year-old African-American girl (Figure 1). We validated the diagnosis on the basis of a positive ocular finding of sarcoidal uveitis, the microscopic

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finding of a classic granulomatous lesion in a labial salivary gland biopsy specimen and the presence of bilateral parotid gland swelling. The patient's elevated serum angiotensin-converting enzyme (ACE) levels that were consistent with, but not specific for, sarcoidosis, supported the diagnosis. Chest radiographs revealed no pulmonary involvement or hilar lymphadenopathy. Because uveitis can lead to visual impairment and because the patient was concerned about the discomfort

and deformity associated with the bilateral parotid gland swelling, we initiated steroid therapy.

The patient's uveitis rapidly went into remission. However, despite the patient's receiving various systemic immunosuppressive agents at different dosages for three years, the parotid gland swellings increased significantly, causing her to be apprehensive about her appearance.

**Background.** Sarcoidosis is a multi-system granulomatous disease that is seen occasionally in patients with characteristic bilateral parotid gland swelling. Conventional therapy has involved either no treatment because of spontaneous remission or corticosteroids when organ involvement is severe.

**Case Description.** The authors describe a previously published case report of a patient with sarcoidosis with parotid gland swellings who did not respond to standard therapy. Despite the use of various immunosuppressive agents, the swellings failed to resolve over a three-year period. It was only after a newly recommended agent, infliximab, was used that the patient's condition was treated successfully.

**Clinical Implications.** It is important for dental practitioners to be familiar with manifestations of sarcoidosis, particularly its salivary gland aspects. Inherent in the knowledge of the disease is the therapeutic approach to both routine and recalcitrant cases.

**Key Words.** Parotid; sarcoidosis; infliximab.

Fortunately, we found a medication called infliximab that has allowed us to treat this refractory case of gross bilateral parotid gland swelling caused by sarcoidosis successfully. Our follow-up use of infliximab serves as the impetus for a case report, which is a sequel to our previously published case.<sup>1</sup>

## CASE REPORT

We authenticated the diagnosis of sarcoidosis for a 13-year-old patient in February 2001 at Columbia University's Salivary Gland Center in New York City. A pediatric rheumatologist prescribed for her steroid eye drops for the uveitis and systemic prednisone (20 milligrams daily) for the parotid gland swelling.

With the aim of avoiding steroid toxicity, over the next three years the pediatric rheumatologist added the

immunosuppressive agents cyclosporin and hydroxychloroquine to the patient's drug regimen and decreased the prednisone prescription to 5 mg daily. The uveitis went into remission, and the parotid gland swellings decreased in size but did not completely disappear.

By June 2002, the pediatric rheumatologist discontinued all of the medications except the prednisone. Unfortunately, within a month, the patient's parotid gland swellings rapidly increased in size. The rheumatologist then increased the patient's prednisone prescription to 20 mg each day, but there was no improvement. Methotrexate was then added to the patient's drug regimen but soon was stopped because the patient developed an allergic rash. The parotid gland swellings continued to increase in size despite the increased prednisone therapy.

Next, the rheumatologist introduced etanercept into the therapeutic mix. However, the patient developed a new rash, so it was discontinued and cyclosporin was started again. Unfortunately, no decrease in parotid gland swellings resulted, and the glands continued to enlarge.

In February 2004, we saw the patient again at the Salivary Gland Center. During the interim three years, the patient's parotid gland swellings had become larger (Figure 2). We prescribed an alternative pharmacological approach: we administered one bolus of 1,000 mg of methylprednisolone sodium succinate intravenously. However, the therapy did not result in a decrease in the size of the parotid gland swellings. In April 2004, the pediatric rheumatologist administered infliximab (5 mg/kilogram) intravenously. The parotid gland swellings resolved during the first week. The treatment was repeated two weeks and then six weeks later.

Although parotid gland swellings no longer are evident (Figure 3), the patient will continue to receive infliximab infusions every two months. She is not taking prednisone.

## DISCUSSION

Sarcoidosis is a multisystem granulomatous disease. In the United States, black adults younger than 40 years of age are most susceptible to experiencing this disease, which has a population incidence of 35.5 in 100,000.<sup>2</sup> The incidence in children is unknown,<sup>3</sup> with most cases developing in



**Figure 1. Bilateral parotid gland swellings (arrows) in a patient with sarcoidosis (February 2001).**

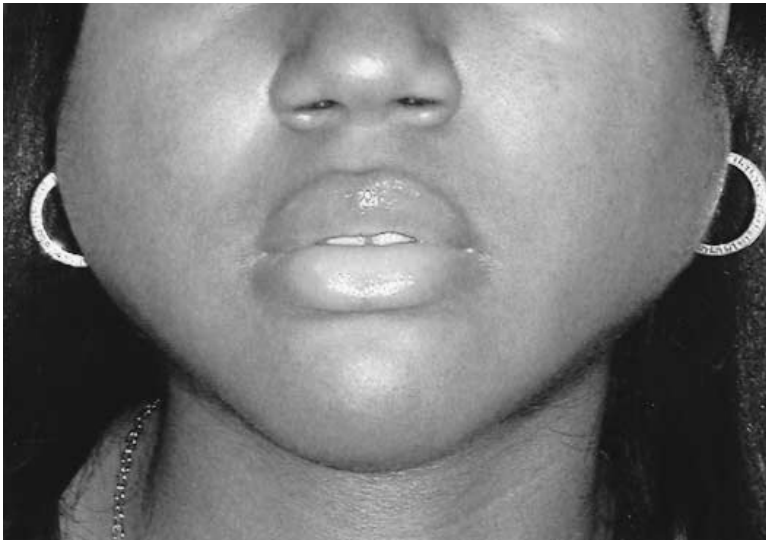
children between 8 and 15 years of age.<sup>4</sup>

Manifestations of sarcoidosis are diverse, but pulmonary infiltrations and hilar lymphadenopathy are most common.<sup>5</sup> Eyes, skin, liver, salivary glands and heart frequently are involved. Despite aggressive treatment with immunosuppressive agents, sarcoidosis may be progressive and debilitating.<sup>6</sup> The disease's long-term effect on lungs can be life-threatening,<sup>7</sup> with mortality approaching 12 percent.<sup>2</sup>

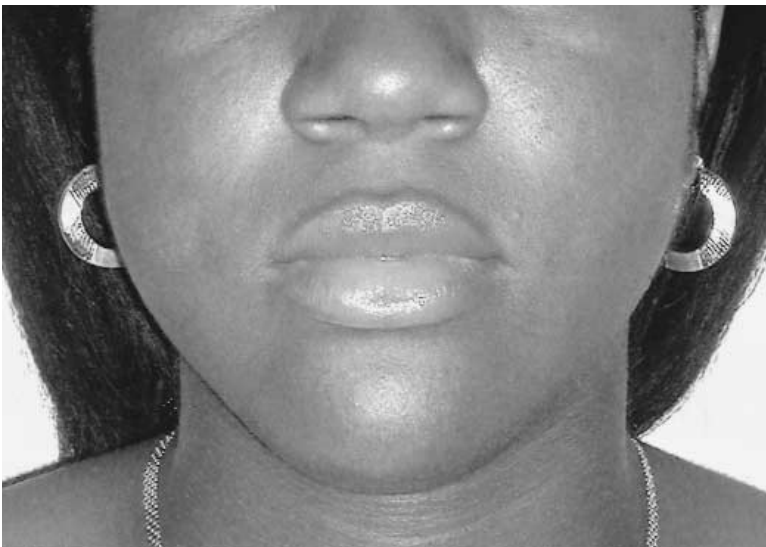
Of significance to the dental profession is the fact that sarcoidosis involves the salivary glands.<sup>8</sup> Parotid gland swellings have been reported in 4 to 6 percent of patients with sarcoidosis.<sup>9,10</sup> Submandibular salivary gland swelling is not as common as parotid gland swelling. Minor salivary glands also are involved, and a histologic examination will demonstrate the hallmark granulomas found in 58 percent of the patients.<sup>8,11</sup>

Parotid sialadenopathy can be seen in children with sarcoidosis.<sup>10-12</sup> Besides the clinical involvement of the salivary glands and other organs, 80 percent of these children have elevated serum ACE levels.<sup>13,14</sup> This enzyme is secreted by endothelial cells of the pulmonary vasculature and by alveolar macrophages. It also is produced by epithelioid cells present in the granulomas of sarcoidosis.<sup>15</sup> An elevated ACE level is consistent with sarcoidosis, but the serologic test is nonspecific. Other conditions, such as tuberculosis, leprosy and Gaucher's disease, also are associated with elevated ACE levels.<sup>16</sup>

The etiology of sarcoidosis is unknown, but a transmissible agent is suspected. Familial<sup>2</sup> and environmental<sup>17</sup> groupings have been observed, and racial and ethnic clustering also has been



**Figure 2. Bilateral parotid gland swellings in a patient with sarcoidosis (February 2004).**



**Figure 3. Resolution of bilateral parotid gland swelling in a patient with sarcoidosis (April 2004).**

noted and is suggested as a genetic cause.<sup>2</sup>

The granulomas of sarcoidosis are non-caseating. They consist of tightly packed epithelioid cells that are macrophages, which take on an epithelial-like appearance. Giant cells are scattered throughout the granuloma. At the periphery of and surrounding the granuloma, accumulations of lymphocytes may be seen.

### TREATMENT

Conventional therapy for sarcoidosis includes either no treatment because of spontaneous remission or corticosteroids when the severity

of organ symptomatology indicates the need for medication.<sup>17</sup> Corticosteroids usually are effective.<sup>18</sup> Other agents, such as methotrexate, azathioprine, cyclosporin and hydroxychloroquine, may be used in chronic sarcoidosis as steroid-sparing agents or steroid substitutes to avoid steroid toxicity.<sup>17</sup> Chronic steroid use may lead to problems such as osteoporosis, impaired growth in children, skin reactions, insulin-resistant diabetes, weight gain and hypertension.<sup>6,19-21</sup>

Infliximab is advocated for patients with sarcoidosis who do not respond to standard steroid therapy.<sup>6,18,20,21</sup> Infliximab is a monoclonal antibody against tumor necrosis factor-alpha (TNF- $\alpha$ ). Inflammation is accelerated and intensified with the release of TNF- $\alpha$  by macrophages.<sup>17,18,22</sup> Circulating TNF- $\alpha$  levels are increased in sarcoidosis, and TNF- $\alpha$  also is found in the sarcoid nodules.<sup>20,23</sup> Infliximab acts by binding to TNF- $\alpha$  and blocking its interaction with TNF- $\alpha$  receptor sites.<sup>17,19,24</sup>

Patients whose sarcoidosis does not resolve within two years with standard corticosteroid therapy are considered to have chronic disease. Patients with refractory sarcoidosis may benefit from a course of infliximab. The usual therapy requires a two-hour intravenous infusion of infliximab (5 mg/kg) followed by similar doses two and six weeks after the first dose, and every eight weeks thereafter as indicated.<sup>6,17,25</sup>

After discussing the recalcitrant behavior of the parotid gland swellings with us, the pediatric rheumatologist instituted this regimen for the patient featured

in our case report. It resulted in the patient's going into total remission after the first infusion with simultaneous cessation of the need for steroids. The successful use of infliximab in our patient was both dramatic and startling.

Complications can occur in relation to the use of infliximab. As it is an immunosuppressive agent, it can increase the risk of infection. Granulomatous infection has been reported to develop in 239 of 100,000 patients who have received infliximab.<sup>26</sup> Activation of latent tuberculosis is the most common problem, and it has been suggested that skin testing for inactive tuberculosis should be performed before infliximab therapy is

initiated.<sup>26-28</sup> Infusion reactions such as chills, fever, hypertension and flushing also can occur. Malignancy is a possible complication and requires patient monitoring.<sup>6,21,29</sup>

Infliximab has given medical practitioners a potent tool for the management of sarcoidosis, particularly for recalcitrant cases. In the case we report, not only did infliximab resolve the persistent and large bilateral parotid gland swelling in the patient, but it also allowed us to eliminate steroid therapy and the patient to avoid the toxicity associated with prolonged systemic steroid use. It is interesting to note that in pediatric patients who received steroid therapy for Crohn's disease, steroid independence was achieved in as much as 73 percent of the patients treated with infliximab.<sup>29</sup> Such success is the therapeutic goal for refractory sarcoidosis.

## CONCLUSION

In this report, we reviewed the clinical symptomatology of sarcoidosis. The presence of bilateral parotid gland swelling can be a significant diagnostic clue. Various commonly prescribed immunosuppressive agents failed to reduce the progressive and gross parotid gland swellings that developed in our patient. It was only when we tried the newly recommended medication infliximab that rapid regression of the patient's gland swellings occurred. ■

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