Laryngeal Sarcoidosis

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Summary: Sarcoidosis is a chronic granulomatous disease that tends to involve the lungs, hilar and mediastinal lymph nodes, liver, eyes, skin, bones, and nervous system. Sarcoidosis involves the larynx less commonly than it afflicts these other sites. Laryngeal sarcoidosis may occur in isolation or as a component of systemic sarcoidosis and it may produce hoarseness, dysphagia, and dyspnea. Life-threatening airway obstruction can occur. Treatments used for laryngeal sarcoidosis have included tracheotomy, low-dose radiation, surgical excision, systemic steroids, and intralessional steroids. An autoimmune etiology has been suggested. The patient reported in this manuscript showed marked, sustained improvement following the use of inhaled steroids prescribed for obstructive pulmonary disease. The possible efficacy of steroid inhalers for treatment of laryngeal sarcoidosis warrants further investigation. Key Words: Sarcoidosis—Laryngeal sarcoidosis—Hoarseness—Steroid inhaler.

INTRODUCTION

Sarcoidosis is a chronic granulomatous disease of undetermined etiology that can involve any organ system of the body. It is characterized by the presence of epithelioid cell tubercles without caseation; causes little or no round-cell reaction; and in older lesions converts into fibrous hyaline tissue.1 Sarcoidosis does not usually involve the larynx. The most commonly affected sites are (in decreasing frequency) the lungs, hilar and mediastinal lymph nodes, liver, eyes, skin, bones, and the nervous system.2 Symptoms are generally mild despite extensive tissue involvement. The disease tends to progress slowly and is characterized by many relapses and remissions. After many years, the disease tends to “burn out.”3 The end result of sarcoidosis may be clinical recovery with roentgenographic evidence of residual disease, impaired function of the organs involved, or a continued chronic progression of the disease.1

CASE REPORT

A 64-year-old African American female with a long history of sarcoidosis involving the hands, nasal cavity, and lungs was referred for treatment of new onset laryngeal sarcoidosis. The diagnosis of systemic sarcoidosis had been established in 1965, and a diagnosis of laryngeal sarcoidosis was made 34 years later in 1999. She presented with progressive hoarseness over a few weeks and difficulty breathing
when lying down. Her physical examination revealed the supraglottic involvement seen typically with laryngeal sarcoidosis (Figure 1), but her airway was not compromised. She was treated with systemic steroids; and subjectively she noted improvement in her breathing and decreased hoarseness. Her laryngeal examination improved also. We evaluated her in January 2000, one year following steroid therapy; she again complained of progressive and worsening hoarseness and increasing shortness of breath upon exertion over the previous six months. She was reluctant to undergo further treatment with systemic steroids because of side effects she had experienced previously. Nasopharyngeal examination revealed a sarcoid nodule at the base of her nose and strobovideolaryngoscopic evaluation revealed severe diffuse laryngeal sarcoidosis involving the epiglottis, posterior larynx, and supraglottic tissues. There was also irregularity along the vibratory margin of both vocal folds and her voice was moderately hoarse. She also had signs of reflux laryngitis.

A comprehensive workup including a pulmonary evaluation, was completed. Magnetic resonance imaging (MRI) of the larynx revealed thickening of the epiglottis, aryepiglottic folds, and arytenoid complexes. Computed tomography (CT) of the chest showed calcified hilar and mediastinal adenopathy and chronic right middle lobe collapse, related to sarcoidosis. A radionucleotide whole-body gallium scan showed findings consistent with sarcoidosis, including uptake in both parotids and both hilar regions. Pulmonary function tests showed an obstructive pattern with normal diffusion and lung volume.

Treatment options were discussed with the patient. Since she was unwilling to take steroids orally, treatment with intralesional steroid injections was proposed, and antireflux therapy was initiated. She noted slight improvement in voice quality on antireflux therapy. However, approximately one month later, she was started on a steroid inhaler by the pulmonologist because of her obstructive lung disease. Within 2 to 3 weeks, she had marked improvement in voice quality. Strobovideolaryngoscopy approximately 3 months later confirmed improvement in hoarseness and diminished supraglottic fullness and vocal fold irregularity. Over one year following initial strobovideolaryngoscopy, she remains improved and has developed no complications from use of the steroid inhaler.

**DISCUSSION**

Jonathan Hutchinson described the skin lesions of sarcoidosis in 1875, and the histology was reported by Boeck in 1899,1,2,4 and the disease was subsequently referred to as Boeck’s disease. The first case of laryngeal sarcoidosis with a confirmed histopathologic diagnosis was reported by Poe in 1940.4 Sarcoidosis occurs predominantly between the ages of 20 and 40 and afflicts women more than men. In the United States, the disease has a predilection for African Americans and Hispanics,2 but worldwide, it occurs most commonly in the Scandinavian and Northern European populations.4 The pathogenesis of sarcoidosis remains obscure. However, there appears to be a host response to an unknown stimulus, possibly an infectious agent or a chemical such as zirconium or beryllium. Sarcoidosis also has characteristics of autoimmune disease, possibly due to abnormal immune regulation or multiple disordered defense reactions that may be triggered by a variety of stimuli. Individuals who have sarcoidosis are not able to develop and maintain delayed-type hypersensitivity, have reduced lymphocyte blastogenesis, possess circulating immune complexes, and have a variety of other immunologic perturbations. It is thought that these immunologic abnormalities may be a pre-
requisite to the development of the disease, but they are more likely a secondary phenomenon. Histopathologically, the characteristic sarcoid granuloma occur as clusters or crops of tubercles at the same stage of development, composed of epithelioid cells, a few giant cells, and various numbers of lymphocytes and plasma cells. There is no necrosis or caseation. Regression by fibrosis begins as a fibrotic process between and around the individual granulomas. The fibrous tissue becomes compact, hyalinizes, and forms a dense scar in which only a suggestion of the previous tubercle remains. Consequently, it is far more difficult to obtain histologic confirmation of late-stage sarcoidosis because it may only show nonspecific fibrosis. Fletcher’s observation of the tendency for the tubercles of sarcoidosis to remain stable and unchanged for long periods of time without breaking down, ulcerating, or caseating is one of the most important factors in distinguishing sarcoidosis from tuberculosis.

In 1982 Neel and McDonald reported that 9% or 220 of 2,319 patients with sarcoidosis seen at the Mayo Clinic from 1950 to 1981 had sarcoidosis involving the head and neck. Of those, 13 patients had laryngeal sarcoidosis. However, it is doubtful whether any definitive statement can be made concerning the frequency of sarcoidosis of the larynx. Perhaps more cases would have been detected if every patient with sarcoidosis had undergone a laryngeal examination (laryngeal examination was not performed in a great many cases). Currently, various authors have estimated the incidence of laryngeal involvement in patients having sarcoidosis to be between 1% and 5%.

In the presence of chronic laryngeal edema or pseudoedema and thickening, the laryngologist must rule out lymphoma and other malignant neoplasms, cartilaginous tumors, benign myxomatous polypoid thickening of the vocal folds due to smoking, and specific infections such as tuberculosis, syphilis, histoplasmosis, coccidiomycosis, blastomycosis, and actinomycosis, as well as such entities as amyloidosis or lipoid proteinosis. The clinician should also exclude other causes such as myxedema, previous radiation therapy to the neck, and various systemic connective tissue diseases. When first seen by the laryngologist, one must also keep in mind that this kind of edema may have an acute etiology such as epiglottis, allergic reaction, Reinke’s edema, trauma, or other miscellaneous conditions. However, a comprehensive clinical evaluation will give clues to the acute nature of the problem. If the main area of involvement is the subglottis, one must exclude the causes of nontraumatic, non-neoplastic subglottic stenosis such as relapsing polychondritis, amyloidosis, and Wegener’s granulomatosis. The diagnosis is established by biopsy showing noncaseating granuloma and negative culture stains for mycobacteria and fungi of the biopsied material.

Sarcoid reaction is a histologic diagnosis made by the pathologist. Sarcoid granulomas in the larynx are often very scarred. Multiple tissue resections may be necessary for diagnosis and biopsied specimens may only reveal nonspecific lymphocytic inflammatory infiltrative reactivity. Sarcoidosis is a clinical diagnosis made after demonstration of consistency with sarcoid histologic changes, and clinical, laboratory, and roentgenologic evidence, and often careful exclusion of the diseases that simulate sarcoidosis.

Sarcoidosis usually involves multiple systems. Yet, many patients are asymptomatic, and often their disease is detected through routine chest radiography. Occasionally, constitutional symptoms such as fever, weight loss, and arthralgia are presenting features. The features of laryngeal sarcoidosis have been well described. The most common symptoms often include a combination of hoarseness, dysphagia, and dyspnea. Other symptoms described in the literature include sensation of a lump in the throat, and mild pain in the throat. According to Bower et al’s review of 44 cases of laryngeal sarcoidosis (4 of his cases and 40 from the literature) the presenting symptoms of patients with laryngeal sarcoidosis were as follows: hoarseness (63%), dyspnea or stridor (47%), dysphagia (85%), cough (13%), and no laryngeal symptoms (18%). The larynx is affected by sarcoidosis in such a characteristic manner that some laryngologists feel that the disease can almost be diagnosed by the appearance alone. Although subglottic involvement does occur, sarcoidosis of the larynx has a predilection for the supraglottic area, most commonly involving the epiglottis followed by the arytenoids, aryepiglottic folds, and ventricular folds (false vocal folds). Involvement of the true vocal cords and epiglottis occurred in 70% of the cases and most commonly present a combination of hoarseness, dysphagia, and dyspnea. Other symptoms described in the literature include sensation of a lump in the throat, and mild pain in the throat. According to Bower et al’s review of 44 cases of laryngeal sarcoidosis (4 of his cases and 40 from the literature) the presenting symptoms of patients with laryngeal sarcoidosis were as follows: hoarseness (63%), dyspnea or stridor (47%), dysphagia (85%), cough (13%), and no laryngeal symptoms (18%). The larynx is affected by sarcoidosis in such a characteristic manner that some laryngologists feel that the disease can almost be diagnosed by the appearance alone. Although subglottic involvement does occur, sarcoidosis of the larynx has a predilection for the supraglottic area, most commonly involving the epiglottis followed by the arytenoids, aryepiglottic folds, and ventricular folds (false vocal folds). Involvement of the true vocal cords and epiglottis occurred in 70% of the cases and most commonly present a combination of hoarseness, dysphagia, and dyspnea. Other symptoms described in the literature include sensation of a lump in the throat, and mild pain in the throat.
fold is rare in sarcoidosis. This may be explained by the fact that the disease is one of the reticuloendothelial system; there are few lymphatics and very little lymphoid tissue in the true vocal folds. However, Bower et al reported abnormalities of the true vocal folds in 8 of 34 (24%) of the patients who underwent laryngoscopy. According to most authors, edematous, pale, and diffuse enlargement of the supraglottic structure is the most common laryngeal manifestation of laryngeal sarcoidosis and, in fact, is considered pathognomonic of sarcoidosis of the larynx. There is turbanlike thickening of a full and rounded rim of the epiglottis, aryepiglottic folds, and arytenoids. Occasionally, red or granular areas and punctate nodules may appear, particularly in the subglottic larynx. The true vocal folds appear nearly normal but may have erythema or thickening of the anterior or inferior portion, particularly if there is more extensive subglottic disease. Pain and ulceration rarely occur. Vocal fold mobility is usually not impaired. However, vocal fold paralysis due to peripheral neuropathy involving the recurrent laryngeal nerve also has been reported. In most cases, the laryngeal nerves were involved in a polyneuritis affecting cranial nerves I, VII, VIII, X, and XII. Reduced mobility of the vocal folds in the absence of polyneuritis is most often due to gross distortion of normal anatomy by local infiltration of sarcoid tissue.

Laryngeal sarcoidosis can occur as an isolated phenomenon or in association with systemic disease. As stated by Devine “a careful history may reveal evidence that the disease is or has been systemic, has involved other organs in the past, may do so in the future and often requires long-term follow up to reveal its true, chronic relapsing systemic nature.” According to Bower et al’s review, 12 of the 44 cases had isolated laryngeal sarcoidosis, and their laryngological presentations and responses to treatment were indistinguishable from those with documented systemic disease who also had laryngeal involvement. Neel and McDonald reported 6 cases with isolated laryngeal sarcoidosis documented by laryngeal appearances typical of laryngeal sarcoidosis, laryngeal biopsies showing noncaseating granulomas, and a long period of observation and exclusion of the systemic form of the disease.

EVALUATION

When the diagnosis of laryngeal sarcoidosis is suspected, a complete workup is necessary to rule out evidence of systemic disease and it may help monitor the activity of the disease. However, there is no single laboratory study that will confirm the diagnosis of laryngeal sarcoidosis. Laboratory studies should include CBC, sedimentation rate, serum and urinary calcium level, protein electrophoresis, liver function tests, and ACE (angiotensin converting enzyme) level. The usual abnormalities include hypercalcemia and hypercalciiuria, hyperglobulinemia in 45%–70% of cases, abnormal protein electrophoresis (elevated alpha-2 and beta globulin, marked elevation of gamma globulin, and decreased albumin). Serum ACE levels are useful for monitoring the course of the disease, because the serum level seems to parallel the clinical course with elevated levels often a precursor to exacerbations of the disease. However, it is not as useful for diagnostic purposes because of its low sensitivity (60%), and it may be elevated in other granulomatous states and in nongranulomatous states.

A PPD skin test should also be administered to rule out tuberculosis. An electrocardiogram (EKG), chest x-ray, and pulmonary function tests should be included in the basic workup. Maximal effort flow-volume curves will demonstrate a characteristic truncation of peak flow rates in the presence of upper airway obstruction and the degree of truncation is proportional to the severity of the airway obstruction.

Kveim’s test employs an intradermal injection of antigenic extract from the spleen of patients with known sarcoidosis. The test is interpreted as positive after four to six weeks if a nodule develops at the site of injection. The nodule is excised and should show noncaseating granuloma. The test is no longer used because an antigen of reliable consistency is difficult to procure and there has been controversy over its accuracy. A gallium 67 citrate scan may define clinically nonapparent granulomatous inflammation in other organs such as the lacrimal and salivary glands.

As previously stated, the diagnosis of sarcoidosis is made by assembling a constellation of clinical, radiological, and laboratory findings, and confirmed with biopsy showing noncaseating granuloma. The pres-
ence of laryngeal sarcoidosis can be established by laryngoscopy with laryngeal biopsy. However, Neel and McDonald\(^3\) have reported two cases of laryngeal sarcoidosis without biopsy. Both patients had the typical supraglottic appearance found in all the patients with supraglottic sarcoidosis and they both had systemic sarcoidosis, confirmed by biopsies elsewhere in the body revealing noncaseating granuloma.\(^3\)

**TREATMENT**

Early diagnosis and proper management of laryngeal sarcoidosis are important to prevent upper airway obstruction and tracheotomy.\(^2\) Treatment depends on the degree of the symptoms.\(^2\) No therapy for sarcoidosis of the larynx is required if the patient is asymptomatic.\(^1,6,8\) Meticulous follow-up is mandatory since the disease may resolve spontaneously or may progress to cause severe airway obstruction\(^2\) and is potentially life threatening.\(^9\) Because of the natural evolution of the disease with its frequent spontaneous remissions, little can be said regarding the efficacy of the various treatment modalities.\(^8\)

Systemic corticosteroid therapy is the treatment of choice in most cases. In the series by Bower et al,\(^7\) it appeared efficacious in 11 of 13 patients. As reported by Neel and McDonald,\(^3\) the indications for the use of systemic glucocorticoids are controversial and their effect is difficult to assess because, by nature, sarcoidosis is a disease with frequent spontaneous remissions and exacerbations. Corticosteroids are always recommended for impending laryngeal obstruction. Sarcoidosis of the larynx occasionally does not respond well to systemic corticosteroids and the disease may progress relentlessly, leading to airway obstruction.\(^2,9\) Also, some patients may experience recurrence of their symptoms when their steroid dosage is decreased and thus require maintenance therapy.\(^7\) Long-term steroid therapy is associated with complications, and the laryngologist must have other options when the complications outweigh the benefits.\(^8\)–\(^10\)

Intralesional steroid injections of the larynx have been successful for selected patients with well-circumscribed disease. It may be accomplished by direct or indirect laryngoscopy. In the series by Bower et al,\(^7\) symptomatic relief was obtained in 5 of 5 patients; Neel and McDonald\(^3\) obtained improvement in 2 of 4 patients. Krespi et al\(^2\) reported that of 6 patients treated with intralesional injections, 4 did not need further treatment after the injection; 2 of the 6 continued to take oral steroids for systemic sarcoidosis and 3 of the 6 patients, who had required tracheotomy prior to the injections, were successfully decannulated. The follow-up period was 14 months to 7 years. Also, the response occurred fairly early in 3 of the 6 patients, with significant improvement in the airway apparent within 36 to 48 hours. According to Devine, interlesional injection of steroids should be used when laryngeal sarcoidosis is of the diffusely infiltrative edematous type that tends to cause airway obstruction.\(^1\)

Tracheotomy must be performed when mandated by airway compromise.\(^5\) In the series by Neel and McDonald\(^3\) 6 of 13 patients needed tracheotomy for airway obstruction. One of those patients required a tracheotomy on 3 separate episodes of exacerbation of the laryngeal disease.\(^3\) As noted by Bower et al,\(^7\) high-grade upper airway obstruction and asphyxiation may occur if the disease remains untreated. Three of their 44 patients reviewed required tracheotomy and one asphyxiated before tracheotomy could be performed. Tracheotomy may also be an appropriate treatment option for a patient who develops marked side effects from systemic corticosteroids,\(^10\) although intralesional steroids are often a more attractive alternative.

Surgery has been advocated for patients with well-localized mass lesions producing high-grade airway obstruction and has proven effective.\(^1,4,7\) Transoral resection, supraglottic laryngectomy, and laryngofissure with excision of subglottic tissue and skin grafting have produced good results in highly selected patients.\(^1,3\) Gallivan and Landis\(^4\) reserved surgery for patients who failed systemic steroid therapy, and performed intralesional steroid injections and transoral microendoscopic-limited surgical excision of the affected areas. The goals of surgery must be to create an adequate airway, avoid aspiration, avoid tracheotomy, and preserve the voice.\(^4\)

Low-dose external beam radiation therapy (3000 rads over 6 weeks) has also been used in selected patients. It has been proposed as an alternative treatment modality in adults in whom intralesional steroids or local excision of granulomatous tissue are not feasible and who are refractory to systemic
steroids. The proponents of radiation therapy state that subcutaneous fibrosis and chondronecrosis are highly unlikely long-term sequela in this dose range. However, because of the risk of thyroid and other malignancies, it is not recommended for children. In 1974, Carasso presented a case of a woman with airway obstruction who failed systemic steroid therapy. She was treated with radiation therapy in order to avoid tracheotomy. The patient was without evidence of disease five years after treatment. Fogel et al reported a well-detailed case of a patient whose symptoms were controlled following radiation therapy, but the follow-up period was short (16 months). Ridder et al presented a case of isolated laryngeal sarcoidosis with impending airway obstruction unresponsive to 6 months of prednisone at therapeutic level. A trial with clofazimine resulted in significant improvement in the patient’s signs and symptoms. However, this represents an isolated use of this antileprosy agent to treat laryngeal sarcoidosis, and further study is needed before any conclusions can be drawn regarding its advocacy.

Spontaneous remission may occur. In the series by Bower et al only 2 of 20 patients had spontaneous remission. Due to the risk of upper airway obstruction from laryngeal sarcoidosis, an active medical/surgical treatment is preferable to observation for the symptomatic patient.

CONCLUSION

Sarcoidosis of the larynx is a chronic granulomatous disease that may occur in isolation, or as a manifestation of systemic sarcoidosis. It can cause not only hoarseness, but life-threatening airway obstruction. Active treatment is often advisable, rather than observation alone; intralesional or systemic corticosteroids are the mainstays of therapy. Our case suggests that there may be a role for topical or inhaled steroids, but no conclusion can be drawn on the basis of one case. Considering the potential complications, such as laryngeal candidiasis, we recommend cautious further investigation of the safety and efficacy of inhaled steroids in these patients. Tracheotomy, low-dose radiation, and surgical excision may also be appropriate in the management of selected patients with laryngeal sarcoidosis; and considering the possibility of an autoimmune etiology, it may also be reasonable to investigate the use of cytotoxic medications for the treatment of this challenging laryngeal malady.

REFERENCES