

REVIEW

Distinguishing Asthma from Sarcoidosis: An Approach to a Problem that is not Always Solvable

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Background. Because pulmonary sarcoidosis often affects the airway, it is commonly confused with asthma. **Methods.** This article reviews the mechanisms of airflow obstruction in sarcoidosis, the symptoms associated with this phenomenon, and the approach to distinguish sarcoidosis from asthma. **Discussion.** Because asthma is highly likely in a patient with wheeze, cough, and chest tightness, sarcoidosis is usually not considered unless the patient has extrapulmonary manifestations of sarcoidosis or a family history of the disease. When pulmonary sarcoidosis is a consideration, a chest radiograph should be performed. A chest radiograph should also be performed in an asthmatic patient when the presentation is atypical, or fails to respond to standard asthma treatment; chest radiography should be performed in this situation to consider not only pulmonary sarcoidosis but also other possible cardiopulmonary disorders. In a patient with confirmed pulmonary sarcoidosis, the diagnosis of concomitant asthma is problematic. The symptoms associated with the two disorders are often identical. Airflow obstruction is common in sarcoidosis so that pulmonary function testing is unlikely to differentiate these two diseases. Demonstration of airway hyperreactivity may fail to distinguish these disorders as this is common in sarcoidosis. Serum IgE, serum angiotensin-converting enzyme levels, sputum eosinophilia, and exhaled nitric oxide measurements show promise as distinguishing tests, although they have not been studied specifically. Pulmonary imaging is probably of limited value unless baseline studies are available for comparison. We suspect that historical information will be more useful in distinguishing these two diseases. Not infrequently, it may be impossible to exclude or confirm an asthmatic component in a confirmed pulmonary sarcoidosis patient. Fortunately, exacerbations of both these diseases are often treated with systemic corticosteroids initially. Significant variability in pulmonary symptoms and airflow obstruction suggest that an asthma component is present, and inhaled corticosteroids and bronchodilators should be considered in these cases. **Conclusions.** Asthma and sarcoidosis share many of the same symptoms, as sarcoidosis commonly affects the airways. Therefore, it is problematic to distinguish these two diseases. In this article, we have outlined an approach to assess the presence of each of these diseases and an approach to therapy.

Keywords asthma, diagnosis, sarcoidosis, treatment

BACKGROUND

Although sarcoidosis is often thought of as an interstitial lung disease causing a restrictive ventilatory defect, it may predominantly affect the airways resulting in airflow obstruction. Sarcoidosis is often misdiagnosed as asthma because the latter disease is a much more common cause of airflow limitation. Even in patients with known sarcoidosis, prominent wheezing and airflow obstruction suggest that the patient might have concomitant asthma.

METHODS

In this article, we describe the varied mechanisms leading to airflow obstruction in sarcoidosis and the asthmatic symptoms that may be present in sarcoidosis patients and outline methods to distinguish these two diseases.

DISCUSSION

Airway Obstruction in Sarcoidosis

Airway obstruction in sarcoidosis can occur via several mechanisms. Endobronchial granulomas from sarcoidosis

may narrow, distort, or completely obstruct the airway (1, 2). Airway involvement in sarcoidosis is very common, as random endobronchial biopsies in pulmonary sarcoidosis show granulomatous inflammation nearly 60% of the time (3). Endobronchial sarcoid granulomas may also lead to endobronchial fibrosis causing further airway narrowing and distortion (4, 5). Airway hyperreactivity has been showed in up to 58% of pulmonary sarcoidosis patients (6–8). This may lead to intermittent airway obstruction from bronchospasm. The mechanism of airway hyperreactivity in sarcoidosis is unclear. It has been suggested that endobronchial granulomata could cause airway hyperreactivity by producing inflammatory mediators or by altering cholinergic mechanisms (9). Because some pulmonary sarcoidosis patients with increased airway hyperreactivity have no clinical evidence of asthma, it has been postulated that some of these patients have a false-positive bronchoprovocation test resulting from endobronchial disease narrowing the airway lumen at baseline (10). Such a false-positive test could occur as follows: since airway resistance is inversely proportional to the fourth power of the airway diameter, a normal degree of airway narrowing from a noxious inhaled irritant in an airway with a reduced baseline airway diameter from endobronchial sarcoidosis could result in an “excessive” increase in airway resistance.

Another common cause of airflow limitation in sarcoidosis is airway distortion and retraction because of

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TABLE 1.—Mechanisms of airflow obstruction in sarcoidosis.

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- **Endobronchial granulomas**
 - **Endobronchial fibrosis** from previous endobronchial granulomatous inflammation
 - **Bronchospasm** from airway hyperreactivity
 - **Airway distortion** from fibrocystic parenchymal lung disease
 - **Extrinsic compression** by hilar adenopathy
-

fibrocystic parenchymal disease (11). Bullae and cysts may also develop in fibrocystic sarcoidosis patients resulting in severe airflow obstruction (12–14).

Finally, hilar adenopathy associated with sarcoidosis may, rarely, extrinsically compress airways (15). This phenomenon is unusual as, typically, even markedly enlarged lymph nodes fail to cause clinically significant airway obstruction (16, 17). Table 1 lists the mechanisms that may cause airflow obstruction in sarcoidosis.

Sarcoidosis Symptoms That Are Also Found with Asthma

Asthma and sarcoidosis share many symptoms so that it is problematic to distinguish these two diseases on that basis. Specifically, cough, wheezing, and chest pain are very common in both the diseases (18).

Cough. There are numerous potential causes of cough in sarcoidosis. Probably, the most common mechanism for sarcoidosis-associated cough is airway irritation or/and mechanical airway damage caused directly by granulomatous inflammation (10). Cough may result from the production of mediators derived from lymphocytes and macrophages within the sarcoid granuloma (19, 20). Bronchial involvement can also cause airway hyperreactivity, as described previously, and lead to cough along with wheezing and dyspnea.

Airway distortion from stage IV fibrocystic disease may also cause cough in sarcoidosis. This airway distortion can alter the activation of certain cough receptors and inactivate c-fibers in the pulmonary interstitium, which have been reported to inhibit the cough reflex (21, 22). The cough associated with sarcoidosis is often nonproductive. A chronic productive cough may occur in a sarcoidosis patient with bronchiectasis that is a common complication of fibrocystic sarcoidosis (23). The acute onset of a productive cough in a sarcoidosis patient suggests an acute bronchitis, pneumonia, and rarely, an acute pulmonary exacerbation of sarcoidosis (APES).

Inhaled corticosteroids (ICSs) may be useful for treating sarcoidosis-associated cough (24). The recommended dose is high: 800–1600 mcg/day of inhaled budesonide in some studies (25) and 800 mcg/day of inhaled fluticasone in others (26). It is unclear whether the alleviation of sarcoidosis-associated cough by ICSs is related to suppression of airway hyperreactivity (25) or a direct effect upon granulomatous airway involvement. Although an initial meta-analysis showed that ICSs are beneficial for treating sarcoidosis-associated cough (27), a more recent meta-analysis did not clearly show a benefit (28). Oral corticosteroids are also useful for treating sarcoidosis-associated

cough and should be used when the cough is severe and fails to respond to ICSs or when cough occurs concomitantly with dyspnea and/or pulmonary dysfunction that require therapy.

Chest Pain. Chest pain is a presenting symptom in over 20% of sarcoidosis cases. It is usually pleuritic and located in the substernal or infrascapular area (29). The location of sarcoidosis-associated chest pain has not been shown to correlate with the location of parenchymal lung involvement or the degree/location of thoracic lymphadenopathy (29). Musculoskeletal irritation from coughing is thought to be a common cause for sarcoidosis-associated chest pain because cough and chest pain are usually present concomitantly and the chest pain is usually pleuritic (29). Sarcoid involvement of the pleura, chest wall, esophagus, myocardium, pericardium (30), and spinal cord (31) can rarely cause chest pain. The treatment of sarcoidosis-associated chest pain depends on its cause. Nonsteroidal anti-inflammatory agents are often used because sarcoidosis-associated chest pain usually has a musculoskeletal origin.

Wheezing. Wheezing is a common presenting symptom of pulmonary sarcoidosis and is common in APES (32). Wheezing in sarcoidosis is directly related to airflow obstruction, which has been discussed previously. Because wheezing is an underappreciated symptom of sarcoidosis, sarcoidosis-associated wheezing is probably a common reason for sarcoidosis being misdiagnosed as asthma. Such an error may cause a significant delay in the diagnosis of sarcoidosis and the initiation of proper therapy.

Differentiating Sarcoidosis from Asthma

Detecting Sarcoidosis in a Patient with Proven or Suspected Asthma. In nonsmoking patients, presenting with typical asthmatic symptoms such as cough, wheeze, dyspnea, and/or chest tightness, the probability of asthma is extremely high. Supportive historical evidence for asthma includes a history of known atopy or exposure to common allergens that may trigger asthma exacerbations. A family history of asthma in one or more first-degree relatives would also support the diagnosis of asthma, as would pulmonary symptoms that vary in severity with or without treatment.

The diagnosis of asthma should be questioned if the clinical presentation is atypical, such as when the disease has no atopic history, minimal variability, and does not respond to conventional treatment. In these situations, it is prudent to obtain chest imaging. If the chest imaging reveals mediastinal lymphadenopathy and/or interstitial lung disease then the diagnosis of sarcoidosis and other alternative diagnoses should be considered (either concomitant with asthma or, alternatively, instead of asthma). Sarcoidosis should also be considered in a presumed asthma patient with a family history of sarcoidosis (33) or who has extrapulmonary manifestations of sarcoidosis such as ocular problems and skin lesions.

The diagnosis of pulmonary sarcoidosis is often delayed. In support of this contention, the time from symptom onset

to the diagnosis of sarcoidosis is longer in patients with pulmonary sarcoidosis compared with skin sarcoidosis (34). It has been postulated that the reason for this delay is that the symptoms of pulmonary sarcoidosis are not specific, and the patient is often assumed to have an alternative lung disease (e.g., asthma and chronic obstructive pulmonary disease (COPD)) if chest imaging is not performed.

Detecting Asthma in a Patient with Sarcoidosis. It is problematic to diagnose asthma in a patient previously diagnosed with sarcoidosis, as pulmonary sarcoidosis may cause asthma-like symptoms and airway obstruction. In one study, 21% of sarcoidosis patients reported that they had been previously diagnosed with asthma (35). It is unclear what percentage of these patients had true concomitant bronchial asthma as opposed to sarcoidosis symptoms that were wrongly attributed to asthma by the patients or their clinicians.

Medical History. The workup of asthma in a sarcoidosis patient should begin with a detailed medical history that should include a history of atopy, an association of exposure to asthma triggers (e.g., pollen and environmental factors) and pulmonary symptoms, previous asthma evaluations, and a family history of asthma. A history concerning the variability of pulmonary symptoms should also be elicited. Most of the mechanisms of airflow obstruction in sarcoidosis outlined above rarely cause rapid variability in symptoms. Therefore, the lack of rapid variability in symptoms or airflow obstruction favors sarcoidosis over asthma.

Pulmonary sarcoidosis can worsen in what is described as APES (36). The criteria for the diagnosis of APES have not been clearly established but worsening pulmonary dysfunction and pulmonary symptoms usually develop over more than 1 month (36). In addition, APES rarely resolves spontaneously. Therefore, the time course of APES is much longer and less variable than with asthma exacerbations; these features may be useful in distinguishing these two diseases. The medical history should also include an evaluation of an association between manifestations of extrapulmonary sarcoidosis and new or worsening pulmonary symptoms because pulmonary and extrapulmonary sarcoidosis often exacerbate concomitantly.

Clinicians need to be cognizant that the use of tumor necrosis factor- α (TNF- α) antagonists for the treatment of pulmonary sarcoidosis may occasionally cause new-onset asthma, asthma exacerbations, and allergic bronchopulmonary aspergillosis (ABPA) (37, 38). It has been proposed that this phenomenon is caused by a TNF- α antagonist-induced disruption of the T helper 1 (Th1)/Th2 balance with a reduction in Th1 cytokines. This entity should be considered in sarcoidosis patients, who develop ABPA and non-ABPA asthma exacerbations after receiving TNF- α antagonist therapy, especially when the asthmatic symptoms correlate with the dosing schedule of these medications.

Laboratory Tests. When a worsening restrictive ventilatory defect is detected in a patient with known sarcoidosis

and worsening pulmonary symptoms, APES is more likely than new onset of asthma. The distinction between APES and new-onset asthma is problematic when a patient presents with pulmonary symptoms and an obstructive ventilatory defect as this may occur in both conditions. As previously mentioned, increased airway hyperreactivity is common in sarcoidosis (6, 7, 39); therefore, a positive test does not confirm the presence of asthma. However, the absence of airway hyperreactivity in this setting is the strong evidence against the presence of asthma.

An exhaled nitric oxide (eNO) level of >16 parts per billion (ppb) has a high specificity (90%) and a positive predictive value (>90%) in asthma (40). Levels of eNO are generally not increased in pulmonary sarcoidosis. Furthermore, in the few studies where some sarcoidosis patients had increased eNO levels, these levels were rarely >16 ppb (41, 42). There appears to be no relationship between the eNO level and the degree of pulmonary function impairment or the activity of the disease (43, 44). These data imply that eNO may be a useful test to determine whether a sarcoidosis patient has concomitant asthma, although no clinical trial has directly assessed this issue.

Serum IgE tends to be elevated in asthma (45), whereas serum IgE levels are significantly lower in sarcoidosis patients than the general population (46). However, the variability of the serum IgE level in healthy individuals, asthmatics, and pulmonary sarcoidosis patients makes the test unreliable to discriminate these two diseases.

TABLE 2.—Distinguishing clinical and laboratory features between asthma and sarcoidosis.

	Supports sarcoidosis	Supports asthma	Does not favor either diagnosis
Clinical examination			
Cough			✓
Wheezing			✓
Chest pain			✓
History of atopy		+	
Family history of asthma		+	
Exacerbations associated with common asthma triggers		++	
Variability of symptoms		+	
Exacerbations associated with worsening extrapulmonary disease	++		
Imaging			
Exacerbations associated with new/worsening infiltrates on lung imaging	+		
Pulmonary function tests			
Obstructive ventilatory defect			✓
Restrictive ventilatory defect	+		
Airway hyperreactivity			✓
Elevated eNO		+	
Laboratory testing			
Elevated serum ACE level	+		
Elevated serum IgE level		+	
Peripheral eosinophilia		+	
Induced sputum eosinophilia		+	

Notes: ACE, angiotensin-converting enzyme; eNO, exhaled nitric oxide; +: Supports the diagnosis; ++: Strongly supports the diagnosis; ✓: Common in both conditions

Peripheral blood eosinophilia is not helpful for discriminating asthma from sarcoidosis exacerbations, since it is shown to be present in up to 21% of sarcoidosis patients (47). Sputum eosinophilia favors a diagnosis of asthma rather than sarcoidosis, since sputum eosinophilia is rare in sarcoidosis patients (48). However, since up to 7% of pulmonary sarcoidosis patients have bronchoalveolar lavage eosinophilia (49), we suspect that sputum eosinophilia will not reliably exclude APES. Although Churg–Strauss syndrome is a rare cause of eosinophilia and asthma, it often has extrapulmonary manifestations similar to sarcoidosis and could possibly be confused with both disorders.

An increase in serum angiotensin-converting enzyme (ACE) levels increases the likelihood of APES over asthma when associated with a reduction in pulmonary

function (50), as serum ACE reflects the patient's granulomatous burden (51). Furthermore, serum ACE levels are rarely elevated in acute or chronic asthma (52). However, the role of serum ACE in distinguishing asthma from sarcoidosis has never been studied specifically.

Chest Imaging. Imaging tests of granulomatous inflammation, such as chest radiography, chest computed tomography, and positron emission tomography scanning, are unlikely to differentiate worsening sarcoidosis from sarcoidosis and concomitant asthma unless baseline studies are available for comparison. Although a chest radiograph showing worsening parenchymal pulmonary disease favors sarcoidosis over asthma, the chest radiograph is not very sensitive or specific in identifying APES (53).

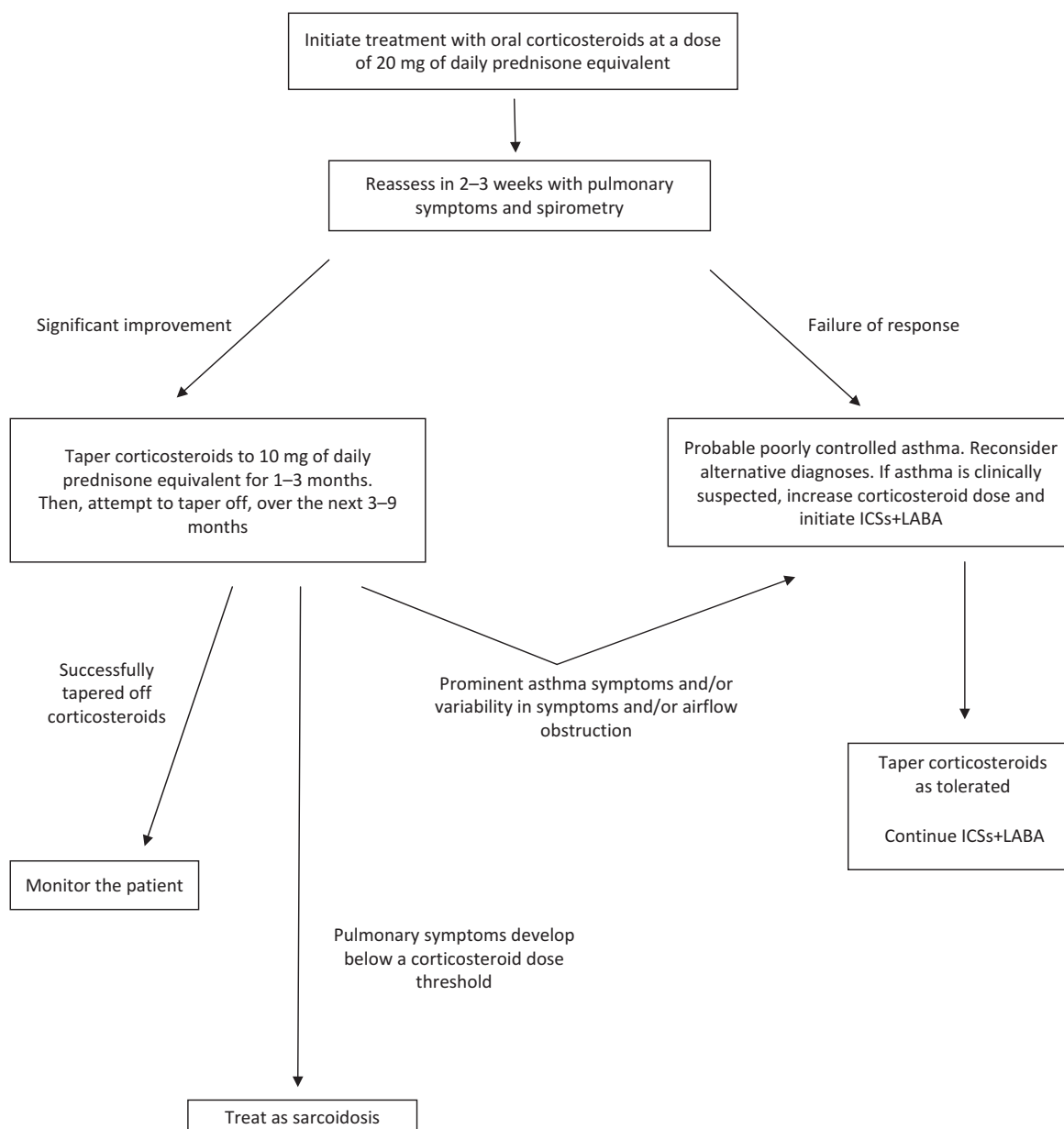


FIGURE 1.—Proposed algorithm for the treatment of a sarcoidosis patient with worsening pulmonary symptoms that could represent asthma. Antibiotics should be additionally considered if a bacterial bronchitis, bronchiectasis, or pneumonia cannot be reasonably excluded. ICSs: inhaled corticosteroids, LABA: long-acting beta-agonist.

Asthma would be suggested if marked hyperinflation was present in the absence of other pulmonary parenchymal abnormalities.

Although the tests described may be useful in distinguishing sarcoidosis from asthma, it may be impossible to clearly make this distinction. We surmise that, in general, the historical information described above is more useful to distinguish these two conditions than relying on any of these aforementioned laboratory tests. Bronchoscopy with bronchoalveolar lavage and/or transbronchial biopsy will rarely be useful and is usually precluded in patients with significant asthma exacerbations. Table 2 outlines the distinguishing clinical and laboratory features between asthma and sarcoidosis.

Using Empiric Therapy to Differentiate Asthma from Sarcoidosis or to Treat Both Conditions. Although anti-sarcoidosis medications other than corticosteroids usually have a slow onset of action and, therefore, are not usually recommended for APES, they may be used as corticosteroid-sparing agents or alternative agents to corticosteroids in recalcitrant cases. Some of these drugs, such as methotrexate, may also be effective in recalcitrant asthma (54, 55) and, therefore, a response to this drug cannot be used to differentiate sarcoidosis from asthma. Other corticosteroid-sparing antisarcoidosis medications, such as azathioprine, have a very limited role in asthma (56); therefore, an improvement in pulmonary symptoms or function with azathioprine would favor a diagnosis of sarcoidosis over asthma.

In situations where the diagnosis of asthma cannot be firmly established or excluded in a sarcoidosis patient, it is often prudent to treat both conditions. Fortunately, the treatment for both the conditions is relatively similar. For these situations, corticosteroids should be initiated at a dose of 20 mg of daily prednisone equivalent. The patient should be reevaluated in 2–3 weeks. Failure of significant response favors poorly controlled asthma, as, although asthma exacerbations may respond to this corticosteroid treatment regimen, APES almost universally responds to this dose of corticosteroids (32). Such patients should have ICSs as well as long-acting β -agonist (LABA) and short-acting β -agonist (SABA) added to their treatment regimen. In patients who respond to the initial oral corticosteroid therapy, corticosteroid tapering should be initiated. The development of significant variability in airflow obstruction (which could be surmised by instructing the patient to regularly use a peak flow meter) as the corticosteroid dose is tapered would suggest an asthmatic component. If pulmonary symptoms consistently develop below a specific corticosteroid dose during tapering, this favors sarcoidosis although this phenomenon may be seen with asthma. Figure 1 outlines an approach to the treatment of a symptomatic sarcoidosis patient, who is thought possibly to have concomitant asthma. Antibiotics may also be considered in addition to the medications

recommended in Figure 1 if bacterial lung infections such as bacterial bronchitis, bronchiectasis, and pneumonia cannot be reasonably excluded.

CONCLUSIONS

Asthma and sarcoidosis share many of the same symptoms, as sarcoidosis commonly affects the airways. This makes it problematic to distinguish these two diseases. On a statistical basis, asthma is overwhelmingly likely in a nonsmoking patient, who presents with wheezing and variable airflow obstruction. However, it may be nearly impossible to exclude an asthma component in a pulmonary sarcoidosis patient with symptoms or clinical data suggesting airflow obstruction. Although laboratory data may favor one disease over the other, often, historical information is more useful in differentiating these two diseases. Fortunately, exacerbations of asthma and sarcoidosis can often be managed in a similar fashion.

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Dr. Kalkanis has nothing to declare. Dr. Judson is a consultant for Centocor, Celgene, and *Pulmonary Reviews*. These two authors received no assistance with the writing of this paper.

REFERENCES

1. Olsson T, Björnstad-Petersen H, Stjernberg NL. Bronchostenosis due to sarcoidosis: A cause of atelectasis and airway obstruction simulating pulmonary neoplasm and chronic obstructive pulmonary disease. *Chest* 1979 June; 75(6):663–666.
2. Hadfield JW, Page RL, Flower CD, Stark JE. Localised airway narrowing in sarcoidosis. *Thorax* 1982 June; 37(6):443–447.
3. Shorr AF, Torrington KG, Hnatiuk OW. Endobronchial biopsy for sarcoidosis: A prospective study. *Chest* 2001 July; 120(1):109–114.
4. Westcott JL, Noehren TH. Bronchial stenosis in chronic sarcoidosis. *Chest* 1973 June; 63(6):893–897.
5. Abehsera M, Valeyre D, Grenier P, Jaillot H, Battesti JP, Brauner MW. Sarcoidosis with pulmonary fibrosis: CT patterns and correlation with pulmonary function. *AJR Am J Roentgenol* 2000 June; 174(6):1751–1757.
6. Mihailovic-Vucinic V, Zugic V, Videnovic-Ivanov J. New observations on pulmonary function changes in sarcoidosis. *Curr Opin Pulm Med* 2003 September; 9(5):436–441.
7. Marcias S, Ledda MA, Perra R, Severino C, Rosetti L. Aspecific bronchial hyperreactivity in pulmonary sarcoidosis. *Sarcoidosis* 1994 September; 11(2):118–122.
8. Bechtel JJ, Starr T 3rd, Dantzker DR, Bower JS. Airway hyperreactivity in patients with sarcoidosis. *Am Rev Respir Dis* 1981 December; 124(6):759–761.
9. Shorr AF, Torrington KG, Hnatiuk OW. Endobronchial involvement and airway hyperreactivity in patients with sarcoidosis. *Chest* 2001 September; 120(3):881–886.
10. Laitinen LA, Haahtela T, Kava T, Laitinen A. Non-specific bronchial reactivity and ultrastructure of the airway epithelium in patients with

- sarcoidosis and allergic alveolitis. *Eur J Respir Dis Suppl* 1983; 131:267–284.
11. Miller A, Teirstein AS, Jackler I, Chuang M, Siltzbach LE. Airway function in chronic pulmonary sarcoidosis with fibrosis. *Amer Rev Respir Dis* 1974 February; 109(2):179–189.
 12. Criado E, Sánchez M, Ramírez J, Arquis P, de Caralt TM, Perea RJ, Xaubet A. Pulmonary sarcoidosis: Typical and atypical manifestations at high-resolution CT with pathologic correlation. *Radiographics* 2010 October; 30(6):1567–1586.
 13. Udawadia ZF, Pilling JR, Jenkins PF, Harrison BD. Bronchoscopic and bronchographic findings in 12 patients with sarcoidosis and severe or progressive airways obstruction. *Thorax* 1990 April; 45(4):272–275.
 14. Judson MA, Strange C. Bullous sarcoidosis: A report of three cases. *Chest* 1998 November; 114(5):1474–1478.
 15. Chambellan A, Turbie P, Nunes H, Brauner M, Battesti JP, Valeyre D. Endoluminal stenosis of proximal bronchi in sarcoidosis: Bronchoscopy, function, and evolution. *Chest* 2005 February; 127(2):472–481.
 16. Sharma OP, Izumi T. Airway obstruction in sarcoidosis. *West J Med* 1988 May; 148(5):568–569.
 17. Polychronopoulos VS, Prakash UB. Airway involvement in sarcoidosis. *Chest* 2009 November; 136(5):1371–1380.
 18. Iannuzzi MC, Fontana JR. Sarcoidosis: Clinical presentation, immunopathogenesis, and therapeutics. *JAMA* 2011 January 26; 305(4):391–399.
 19. O'Connor TM, O'Connell J, O'Brien DI, Goode T, Bredin CP, Shanahan F. The role of substance P in inflammatory disease. *J Cell Physiol* 2004 November; 201(2):167–180.
 20. Xin-Min D, Qin-Zhi X, Yun-You D, Chun-Yan Z, Chao-Sheng P, Hao-Yong N, Yong-Qun L, Ji-Guang M, Zhou-Shan N, Hua-Song F. Impact of tracheal mucosa involvement on clinical characteristics of sarcoidosis. *South Med J* 2011 May; 104(5):315–318.
 21. Jackson DM, Norris AA, Eady RP. Nedocromil sodium and sensory nerves in the dog lung. *Pulm Pharmacol* 1989; 2(4):179–184.
 22. Tatar M, Sant' Ambrogio G, Sant' Ambrogio FB. Laryngeal and tracheo-bronchial cough in anesthetized dogs. *J Appl Physiol* 1994 June; 76(6):2672–2679.
 23. Lewis MM, Mortelliti MP, Yeager H Jr, Tsou E. Clinical bronchiectasis complicating pulmonary sarcoidosis: Case series of seven patients. *Sarcoidosis Vasc Diffuse Lung Dis* 2002 June; 19(2):154–159.
 24. Baughman RP, Iannuzzi MC, Lower EE, Moller DR, Balkissoon RC, Winget DB, Judson MA. Use of fluticasone in acute symptomatic pulmonary sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2002 October; 19(3):198–204.
 25. Alberts C, van der Mark TW, Jansen HM. Inhaled budesonide in pulmonary sarcoidosis: A double-blind, placebo-controlled study. Dutch Study Group on Pulmonary Sarcoidosis. *Eur Respir J* 1995 May; 8(5):682–688.
 26. du Bois RM, Greenhalgh PM, Southcott AM, Johnson NM, Harris TA. Randomized trial of inhaled fluticasone propionate in chronic stable pulmonary sarcoidosis: A pilot study. *Eur Respir J* 1999 June; 13(6):1345–1350.
 27. Paramothayan NS, Jones PW. Corticosteroids for pulmonary sarcoidosis. *Cochrane Database Syst Rev* 2000; (2):CD001114.
 28. Paramothayan NS, Lasserson JT, Jones P. Corticosteroids for pulmonary sarcoidosis. *Cochrane Database Syst Rev* 2005 Apr 18; (2):CD001114.
 29. Highland KB, Retalis P, Coppage L, Schabel SI, Judson MA. Is there an anatomic explanation for chest pain in patients with pulmonary sarcoidosis? *South Med J* 1997 September; 90(9):911–914.
 30. Wyplosz B, Marijon E, Dougados J, Pouchot J. Sarcoidosis: An unusual cause of acute pericarditis. *Acta Cardiol* 2010 February; 65(1): 83–84.
 31. Yanagitani N, Kotake M, Ishizuka T, Iwasaki Y, Sunaga N, Mori M. A case of neurosarcoidosis discovered in a patient complaining of chest pain. *Nihon Kokyuki Gakkai Zasshi* 2009 December; 47(12):1087–1092.
 32. McKinzie BP, Bullington WM, Mazur JE, Judson MA. Efficacy of short-course, low-dose corticosteroid therapy for acute pulmonary sarcoidosis exacerbations. *Am J Med Sci* 2010 January; 339(1):1–4.
 33. Rybicki BA, Harrington D, Major M, Simoff M, Popovich J, Malariak M, Iannuzzi MC. Heterogeneity of familial risk in sarcoidosis. *Genet Epidemiol* 1996; 13(1):23–33.
 34. Judson MA, Thompson BW, Rabin DL, Steimel J, Knatterud GL, Lackland DT, Rose C, Rand CS, Baughman RP, Teirstein AS. The diagnostic pathway to sarcoidosis. *Chest* 2003 February; 123(2):406–412.
 35. Wilsher M, Hopkins R, Zeng I, Cornere M, Douglas R. Prevalence of asthma and atopy in sarcoidosis. *Respirology* 2012 February; 17(2):285–290. doi: 10.1111/j.1440-1843.2011.02066.x.
 36. Panselinas E, Judson MA. Acute pulmonary exacerbations of sarcoidosis (APES). *Chest* (in press).
 37. Judson MA. Allergic bronchopulmonary aspergillosis after infliximab therapy for sarcoidosis: A potential mechanism related to T-helper cytokine balance. *Chest* 2009 May; 135(5):1358–1359.
 38. Guilleminault L, Carré P, Beau-Salinas F, Taillé C, Dieudé P, Crestani B, Diot P, Marchand-Adam S. Asthma unmasked with tumor necrosis factor- α -blocking drugs. *Chest* 2011 October; 140(4):1068–1071.
 39. Ohrn MB, Sköld CM, van Hage-Hamsten M, Sigurdardottir O, Zetterstrom O, Eklund A. Sarcoidosis patients have bronchial hyperreactivity and signs of mast cell activation in their bronchoalveolar lavage. *Respiration* 1995; 62(3):136–142.
 40. Dupont LJ, Demedts MG, Verleden GM. Prospective evaluation of the validity of exhaled nitric oxide for the diagnosis of asthma. *Chest* 2003 March; 123(3):751–756.
 41. Ziora D, Kaluska K, Kozielski J. An increase in exhaled nitric oxide is not associated with activity in pulmonary sarcoidosis. *Eur Respir J* 2004 October; 24(4):609–614.
 42. O'Donnell DM, Moynihan J, Finlay GA, Keatings VM, O'Connor CM, McLoughlin P, Fitzgerald MX. Exhaled nitric oxide and bronchoalveolar lavage nitrite/nitrate in active pulmonary sarcoidosis. *Am J Respir Crit Care Med* 1997 December; 156(6):1892–1896.
 43. Wilsher ML, Fergusson W, Milne D, Wells AU. Exhaled nitric oxide in sarcoidosis. *Thorax* 2005 November; 60(11):967–970.
 44. Choi J, Hoffman LA, Sethi JM, Zullo TG, Gibson KF. Multiple flow rates measurement of exhaled nitric oxide in patients with sarcoidosis: A pilot feasibility study. *Sarcoidosis Vasc Diffuse Lung Dis* 2009 July; 26(2):98–109.
 45. Oettgen HC, Geha RS. IgE regulation and roles in asthma pathogenesis. *J Allergy Clin Immunol* 2001 March; 107(3):429–440.
 46. Hattori T, Konno S, Shigemura M, Matsuno K, Shimizu C, Shigehara K, Shijubo N, Hizawa N, Yamaguchi E, Nishimura M. Total serum IgE levels and atopic status in patients with sarcoidosis. *Allergy Asthma Proc* 2012 January–February; 33(1):90–94.
 47. Renston JP, Goldman ES, Hsu RM, Tomashefski JF Jr. Peripheral blood eosinophilia in association with sarcoidosis. *Mayo Clin Proc* 2000 June; 75(6):586–590.
 48. D'Ippolito R, Foresi A, Chetta A, Casalini A, Castagnaro A, Leone C, Olivieri D. Induced sputum in patients with newly diagnosed sarcoidosis: Comparison with bronchial wash and BAL. *Chest* 1999 June; 115(6):1611–1615.
 49. Allen RK, Pierce RJ, Barter CE. Angiotensin-converting enzyme in bronchoalveolar lavage fluid in sarcoidosis. *Sarcoidosis* 1992 March; 9(1):54–59.
 50. Lieberman J, Schleissner LA, Nosal A, Sastre A, Mishkin FS. Clinical correlations of serum angiotensin-converting enzyme (ACE) in sarcoidosis. *Chest* 1983 November; 84(5):522–528.
 51. Lynch JP3rd, Kazerooni EA, Gay SE. Pulmonary sarcoidosis. *Clin Chest Med* 1997 December; 18(4):755–785.
 52. Mue S, Takahashi M, Ohmi T, Shibahara S, Yamauchi K, Fujimoto S, Okayama H, Takishima T. Serum angiotensin converting enzyme level in bronchial asthma. *Ann Allergy* 1978 January; 40(1):51–57.
 53. Judson MA, Gilbert GE, Rodgers JK, Greer CF, Schabel SI. The utility of the chest radiograph in diagnosing exacerbations of pulmonary sarcoidosis. *Respirology* 2008 January; 13(1):97–102.
 54. Domingo C, Moreno A, Amengual MJ, Comet R, Lujan M. Twelve years' experience with methotrexate for GINA treatment step 5 asthma patients. *Curr Med Res Opin* 2009 February; 25(2):367–374.
 55. Comet R, Domingo C, Larrosa M, Moron A, Amengual MJ, Marin A. Benefits of low weekly doses of methotrexate in steroid-dependent asthmatic patients. A double-blind, randomized, placebo-controlled study. *Respir Med* 2006 March; 100(3):411–419.
 56. Dean T, Dewey A, Bara A, Lasserson TJ, Walters EH. Azathioprine as an oral corticosteroid sparing agent for asthma. *Cochrane Database Syst Rev* 2004; (1):CD003270.