Bronchoscopy in sarcoidosis: diagnostic and therapeutic interventions

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Flexible bronchoscopy has revolutionized the evaluation of patients with suspected sarcoidosis and the treatment of sarcoid patients with significant endobronchial disease. The authors explore the diagnostic and therapeutic utility of flexible bronchoscopy by reviewing the pertinent literature with a special interest in recent studies. Bronchoscopy allows multiple diagnostic modalities in suspected sarcoidosis. Recent studies show sometimes surprising results, and the authors review the additive contributions of transbronchial lung biopsy, endobronchial biopsy, transbronchial needle aspiration, and bronchoalveolar lavage to diagnose sarcoidosis. New data specifically show the additive benefit of routine endobronchial biopsy and transbronchial needle aspiration to traditional transbronchial biopsy specimens. In addition, the techniques have been optimized via recent studies and these results are discussed. Endobronchial therapy is reviewed with the recent findings of the superiority of balloon bronchoplasty. Flexible bronchoscopy has a very high diagnostic yield in all stages of suspected sarcoidosis. Transbronchial lung biopsy and endobronchial biopsy should be used routinely, and transbronchial needle aspiration should be considered in cases of significant adenopathy. Bronchoalveolar lavage should be used routinely to exclude alternative diagnoses. Therapeutic bronchoscopy is rarely needed, but when necessary the authors' procedure of choice is bronchoscopic balloon dilatation.

Keywords
sarcoidosis, transbronchial lung biopsy, endobronchial biopsy, transbronchial needle aspiration, therapeutic bronchoscopy

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Abbreviations

BAL	bronchoalveolar lavage
BBD	bronchoscopic balloon dilatation
EBB	endobronchial biopsy
FB	flexible bronchoscopy
TBLB	transbronchial biopsy
TBNA	transbronchial needle aspiration

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Flexible bronchoscopy (FB) has revolutionized the evaluation of patients with sarcoidosis. We explore the utility of several bronchoscopic modalities in diagnosing sarcoidosis. FB has become an accepted therapeutic modality in patients with significant obstruction. We also review the indications and techniques for therapeutic bronchoscopy in sarcoidosis.

Diagnostic bronchoscopy in sarcoidosis

Flexible bronchoscopy has revolutionized the evaluation of patients with suspected sarcoidosis. Before FB, patients underwent rigid bronchoscopy, mediastinoscopy, surgical lung biopsy, scalene node biopsy, skin biopsy, or the Kveim–Siltzbach test (where available), or the diagnosis was established "clinically," without tissue. Many patients were reluctant to undergo invasive biopsies but were also hesitant to take medications with known side effects without a secure diagnosis. Since its introduction by Ikeda *et al.* [1] in 1968, FB has enabled the pulmonologist to diagnose patients with a well-tolerated procedure. We explore the evolution of FB in diagnosing sarcoidosis by reviewing the pertinent literature with a special interest in recent studies.

Flexible bronchoscopy allows tissue sampling from several different anatomic sources. We explore each modality, including transbronchial biopsy (TBLB), endobronchial biopsy (EBB), transbronchial needle aspiration (TBNA), and bronchoalveolar lavage (BAL). TBLB is discussed first because it is the most widely used. We then discuss the utility of performing EBB and TBNA. Lastly, BAL is evaluated for its diagnostic and prognostic efficacy.

Transbronchial biopsy

Transbronchial biopsy was developed to diagnose diffuse lung diseases soon after the fiberoptic bronchoscope became available [2], and its utility for diagnosing sarcoidosis was recognized early as well [3]. Nonnecrotizing granulomas, in the absence of exposure to antigens known to cause hypersensitivity pneumonitis or acid-fast bacilli or fungi on special stains, is the pathologic pattern seen on TBLB.

More advanced stages of disease have a higher rate of diagnostic TBLB (stage I, 55% versus stages II to III, 70%) [4]. Somewhat surprisingly, stage I disease can yield diagnostic granulomas on TBLB. Even patients with normal plain chest radiographs or high-resolution

chest CT, with stage 0 disease can have parenchymal granuloma on TBLB [5,6].

Perhaps even more surprising, prebiopsy disease activity does not influence diagnostic yield of TBLBs. Thus, TBLB has become the accepted standard of care in all patients with suspected sarcoidosis despite variances in radiographic stage and disease activity. Comparing TBLB with more invasive diagnostic techniques is difficult, but it is equal to scalene node biopsy in patients with stage II disease [7].

Variations in the technique used to perform TBLB have been investigated to determine the optimum method for diagnosing sarcoidosis. Most important, biopsy number has been shown to affect diagnostic yield. The probability of making a diagnosis is the same for each TBLB specimen, thus diagnostic yield follows a logarithmic curve, increasing with each successive specimen until a plateau is reached [8]. The plateau varies in different studies, but most investigators think four to six specimens are adequate for stage II disease, but more (perhaps 10) are needed for stage I disease [8–10]. The location of each biopsy is also important, with higher yield seen when biopsies are taken from more than one lobe in all patients and taken from the area of most affected tissue in stage II or stage III disease [10]. Race is also a factor, with blacks more likely to have a positive TBLB than whites (74% versus 50%, $P = 0.0038$) [11].

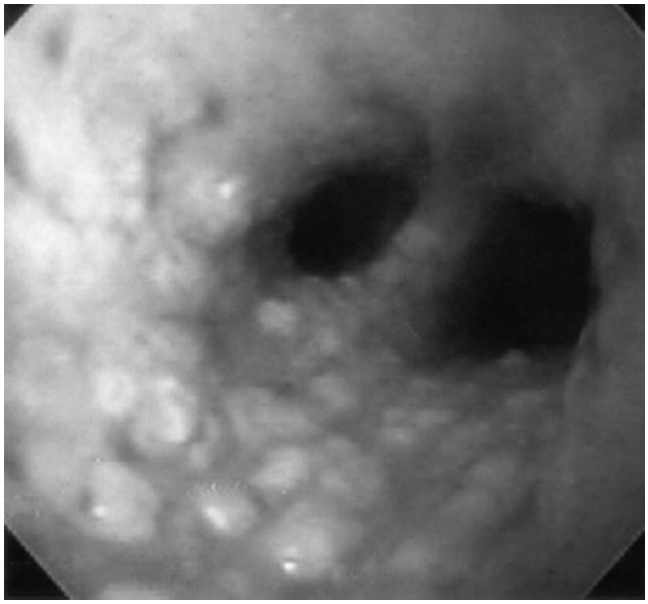
Other determinants of biopsy yield have been investigated. Larger forceps secure bigger specimens that have a higher diagnostic yield, but do not lead to increased risk of bleeding or pneumothorax [12]. Specimen pieces that float when placed in fixative are more likely to contain alveolar tissue and have a higher diagnostic yield than pieces that sink, and are unlikely to contain alveoli [13]. However, pieces that contain only bronchial wall may still contain granuloma and should not be discarded.

Endobronchial biopsy

Sarcoid granulomas can involve any aspect of the respiratory tract. Being aware of mucosal abnormalities can lead to a correct diagnosis, such as when Mariotta *et al.* [14] confirmed sarcoidosis by sampling a patient's abnormal arytenoids during bronchoscopy.

In unusual cases the endobronchial mucosa is markedly abnormal, such as in Figure 1, and EBB is performed by most bronchoscopists. However, in many instances the respiratory mucosa appears normal, but EBB may be diagnostic in these cases as well. Several case series using rigid bronchoscopy demonstrate positive biopsies in 24% to 44% of patients [15–17]. Introduction of FB opened this diagnostic modality to nonsurgeons.

Figure 1. Severe endobronchial sarcoidosis that demonstrated granuloma on biopsy



The utility of EBB has been reported in several studies. Armstrong *et al.* [18] published a case series report describing 101 patients. Most of their patients had abnormal mucosa, with either mucosal nodularity (64%) and/or bronchostenosis (26%). This led to a very high diagnostic yield of 58% for stage I, 62% for stage II, and 46% for stage III. Yield was highest in those with abnormal mucosa (91%) compared with normal mucosa (37%). Another series of consecutive patients reported in 1999 that half of patients with stage I or stage II disease had mucosal abnormalities, whereas those with stage III disease had higher rates of abnormal mucosa at 83% [19]. As would be expected in this patient population, EBB had a high diagnostic yield of 49% in all patients and increased the diagnostic yield of TBLB alone from 52 to 64% when both types of biopsies were used.

A recent case series of consecutive patients reported diagnostic utility in a setting of less frequent mucosal abnormalities [20]. Abnormal mucosa was seen in only one third of patients, but EBB was still useful, being positive in 54% of patients with abnormal mucosa and 20% of patients with normal mucosa. EBB increased the diagnostic yield of TBLB by 10%, from 76 to 86% for the combined procedures.

The Walter Reed Army Medical Center recently reported a prospective study attempting to define the benefit of adding EBB to TBLB in routine clinical practice [21]. A total of 34 patients were enrolled and underwent TBLB, EBB, and mediastinoscopy, if needed. Mucosal erythema or thickening was seen in 70% of patients and

was associated with a higher frequency of positive biopsy than normal mucosa (75% versus 30%). The likelihood ratio of a positive biopsy for abnormal mucosa compared with normal was 7.0 (95% CI, 1.4 to 36.1).

Somewhat surprisingly, EBB had a higher overall diagnostic yield than TBLB alone. The yield for EBB was 62% whereas TBLB demonstrated nonnecrotizing granulomas in 59% of participants. Many patients had positive biopsies from both modalities, but seven patients had positive biopsies only on EBB. Diagnostic yield increased by 21% with EBB.

Further refinements of the benefit and meaning of EBB have been performed by this same group. Racial differences were examined in relation to EBB because other aspects of the disease have racial variation [11]. Black and white patients both had abnormal mucosa in approximately half the patients, but biopsies were positive in 85% of blacks but in only 38% of whites.

We recommend the use of EBB either routinely or when mucosal abnormalities are present. For normal mucosa we recommend six specimens, two from the main carina and two each from bilateral secondary carinae. When an abnormality is present we obtain four biopsies from this area and two from the contralateral secondary carina.

Transbronchial needle aspiration

Patients with sarcoidosis very frequently have enlarged mediastinal and hilar lymph nodes. They are tempting targets for biopsy via FB given the incomplete sensitivity described earlier. TBNA was first developed by surgeons for use during rigid bronchoscopy [22]. French surgeons reported a diagnostic yield of 66% in stage I or stage II patients when a 1.5-mm diameter aspiration needle was used to obtain specimens during rigid bronchoscopy [23]. There was no difference in yield between samples from the paratracheal or hilar nodes.

Wang *et al.* [24] introduced the technique to FB and reported early results in sarcoidosis. When using an 18-gauge needle, the diagnostic yield of TBNA was 90% in the 20 patients reported. Members of our group confirmed this observation, when we reported that the 18-gauge TBNA needle could diagnose sarcoidosis [25]. This is in contrast to the 22-gauge needle that delivers only cytologic specimens that are inadequate to diagnose granulomatous inflammation.

The addition of TBNA to standard TBLB has been delineated. Morales *et al.* [26] reported TBNA specimens in 51 patients. The diagnostic yield for TBNA in stage I and stage II disease was 50%, and most important added 10 to 20% to the yield of TBLB alone. A recent prospective study reported 13 patients with suspected sarcoidosis who underwent TBNA and TBLB [27]. Seven of 13 patients had positive TBNA specimens. Although most patients had diagnostic TBLB, four patients had negative TBLB but diagnostic TBNA tissue, demonstrating a clinically important diagnostic yield. Another recent study demonstrated that seven of eight patients with sarcoidosis had positive TBNA specimens [28•]. These numbers are too small to suggest when to perform TBNA, although they highlight its utility in situations in which the other forms of biopsy may be expected to have a lower yield.

At our center we routinely use TBNA when the main diagnostic consideration is sarcoidosis, and mediastinal or hilar lymphadenopathy is present and malignancy is a strong possibility. Our technique has been described previously and we refer the reader there in the interest of conserving space [29].

Bronchoalveolar lavage

Given that sarcoidosis is a diffuse disease and can involve the alveoli and respiratory bronchioles, one would expect BAL to be a window into the disease. In fact, soon after the application of the technique a key question was answered. It had long been known that patients with sarcoidosis were frequently anergic to common antigens, could convert a previous positive reaction to a negative one, and could have peripheral lymphopenia [30,31]. This was thought to represent decreased immune function and possibly be the cause of the disease. However, BAL fluid analysis demonstrated an increase compared with normal controls in total lung lymphocytes and immune system activation with elevated helper T lymphocytes [32,33]. This revolutionized thinking about the disease and led to BAL as a research and diagnostic tool.

Bronchoalveolar lavage differential cell analysis as a diagnostic tool has been well studied. The location of BAL sampling is not important in this diffuse disease [34,35]. Many investigators have described the classic sarcoidosis BAL fluid cell differential: elevated lymphocytes with a specific increase in helper T cells leading to an elevated CD4-to-CD8 ratio [36]. The positive predictive value of a CD4-to-CD8 ratio of 4:1 is only 50% for separating sarcoidosis from all other lung diseases, but the value increases to 94% when only patients with interstitial lung disease are considered [37]. Unfortunately the sensitivity is low, at 59%. When a ratio greater than 4:1 is coupled with BAL fluid neutrophils and eosinophils less than 1% each, the diagnostic utility is equal to TBLB. Given the variability in differentials, especially in smokers, and the chance of spurious 1% or 2% neutrophils or eosinophils, we do not recommend using this combined differential technique in lieu of TBLB or EBB [38]. Thus, as a diagnostic tool, analysis of differential cell counts function as an adjunct test.

This lack of diagnostic utility contrasts to the sarcoid mimic beryllium lung disease, in which lymphocytes ob-

tained via BAL can be diagnostic for berylliosis if they are reactive to beryllium *in vitro* [39,40]. Because the antigens involved in sarcoidosis are unproved, we cannot use this simple test.

Perhaps an even more difficult task than diagnosing sarcoidosis is predicting who will progress or respond to steroids. BAL fluid differential analysis has been investigated toward this end. Studies have shown that initial BAL fluid lymphocyte counts do not predict disease progression or remission [41,42]. BAL fluid CD4 cell analysis shows, contrary to popular belief, that elevated CD4 lymphocyte counts predict future disease remission [43]. More recently, BAL fluid neutrophilia has been investigated [42]. A total BAL fluid neutrophil count of more than 0.2×10^4 cells mL^{-1} was shown to predict significant worsening in lung function and chest radiographs. However, one needs to note that patients with elevated BAL fluid neutrophils had significantly more advanced disease as assessed by chest radiograph and lung function at study entry than those with low neutrophils. Thus, other tests such as baseline chest radiograph and pulmonary function tests would likely have predicted this group to worsen.

Although BAL fluid differential cell analysis is of questionable use as a clinical tool, BAL cytokine analysis has provided great insights into the pathogenesis of the disease. Although many of these discoveries are beyond the scope of this article, some tests show promise and may one day prove clinically useful and will be described. Two notable cytokines, which are important in granulomatous inflammation, have been found in BAL fluid. Both tumor necrosis factor-α and interferon-γ are present in elevated levels in patients with worsening disease compared with normal control subjects and patients with inactive sarcoidosis [44]. Other BAL fluid cytokine markers (KL-6, tumor necrosis factor-α, granulocyte–macrophage colony stimulating factor, transforming growth factor-β_1) have been shown to correlate with disease severity and activity [45–48]. However promising, these markers have not become the standard of care for making the diagnosis of sarcoidosis or assessing disease activity, but research is ongoing.

Therapeutic bronchoscopy

Significant tracheobronchial obstruction from sarcoidosis is relatively rare and is thought to occur in 2 to 8% of patients with sarcoidosis [49,50], although this percentage is likely an overestimate because far more persons are now diagnosed with early, nonobstructive disease than when these cohorts were reported. Obstruction can occur in relatively advanced stage III and stage IV disease, but has also been reported in stage II disease [51].

The mechanism of stenosis is typically from one of two causes: segmental or lobar obstruction from accumulation of endobronchial granulomas [50]. This occurs most frequently in the right middle lobe and both upper lobe bronchi, but obstruction can occur in all bronchi and even rarely in the trachea [52]. Endobronchial obstruction can improve with corticosteroid therapy and may not require bronchoscopic intervention. However, if obstruction persists, bronchoscopic intervention should be considered.

The other mechanism of obstruction is extrinsic compression of the large airways from enlarged lymph nodes [53]. Systemic corticosteroids can improve this type of obstruction as well, but when it persists, bronchoscopic intervention should be considered.

Several modalities for bronchoscopic intervention exist today. However, laser ablation, electrocautery, and cryotherapy have no utility because of either the diffuse submucosal nature of endobronchial occlusions, or because the compression is from extrinsic nodal compression of the bronchus. Thus, mechanical dilatation with balloons, and stenting are the procedures of choice.

Balloon dilatation

Mechanical dilatation was first performed with bougie catheters via rigid bronchoscopy [54]. This was successful in reducing segmental and lobar intrinsic obstruction in two patients with sarcoidosis. On follow-up examination, one patient had recurrence of obstruction at 10 years, which was redilated with good results. Unfortunately the other patient had frequent restenosis requiring frequent repeat dilatation and oral corticosteroids [55]. Balloon angioplasty catheters applied during rigid bronchoscopy were first used in 1984 to dilate tracheal stenosis, and in 1988 were used to remedy left main bronchus obstruction from sarcoidosis [56,57].

Successful balloon dilatation via FB was initially reported in 1994, when Fouty *et al.* [58] used 5-Fr Fogarty embolectomy catheters to dilate segmental and lobar stenoses in six patients with sarcoidosis. All patients improved subjectively and there were no complications.

Bronchoscopic balloon dilatation (BBD) is our procedure of choice in patients with stenosis. However, BBD can be performed only if the airway is not occluded completely. Our technique has been described recently elsewhere and entails placing the balloon catheter in the stenosed airway either under direct visualization with the bronchoscope or using fluoroscopy and a guidewire if the catheter cannot be placed through the bronchoscope [59]. The various complications of BBD include chest pain, bronchospasm, atelectasis, hemorrhage, bronchial rupture, pneumothorax, pneumomediastinum, or mediastinitis.

Tracheobronchial stents

Placing a prosthetic stent in obstructed airways is an option few patients with sarcoidosis require, but can be very beneficial in select patients. A stent is a cylindrical, hollow prosthesis used to maintain airway patency by opposing extrinsic compressive forces. Two general categories are available: expandable metal and silicone tube. Silicone tube stents require placement via rigid bronchoscopy under general anesthesia and are not discussed further.

The decision to place a stent for sarcoidosis is generally difficult and arrived at after previous treatment failure and recurrence of stenosis. We reserve this technique for when stenosis recurs despite aggressive oral corticosteroid and BBD fails to achieve satisfactory results, when previous inflammation leads to destruction of bronchial cartilaginous architecture, and when extrabronchial compression via enlarged lymph nodes occludes the airway despite oral corticosteroid therapy. We recommend stenting only in these situations because of the possibility of stent-induced granulation, and the relative difficulty of stent removal if complications occur.

There has been significant development of covered and uncovered stents. Our choice in these patients is to use a covered metallic prosthesis if granulation recurrence is expected, and to use an uncovered device if compression is extrinsic or if reestablishment of cartilage architecture is desired. Our group has previously described the technique for stent deployment [60].

Conclusions

Flexible bronchoscopy is an important tool in sarcoidosis for the pulmonary physician. The procedure is safe, well tolerated, and less invasive than alternatives. The diagnostic utility is maximized when EBB and TBLB are used routinely. TBNA and BAL fluid analysis can be helpful in special cases. Bronchoscopic therapy is reserved for patients who have endobronchial obstruction despite corticosteroid therapy. We favor BBD for patients who have significant segmental, lobar, or tracheal stenosis. Stent placement is reserved for recalcitrant cases, or when there is significant destruction of supporting architecture.

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