The Value of Flexible Transbronchial Needle Aspiration in the Diagnosis of Stage I Sarcoidosis*

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Study objectives: Transbronchial lung biopsy (TBLB) during flexible bronchoscopy (FB) is the recommended procedure for diagnosing sarcoidosis in most cases, although its yield in stage I disease is reported to be not as high as when parenchymal involvement is radiologically evident. We undertook this study to assess the diagnostic value of transbronchial needle aspiration (TBNA) in sarcoidosis presenting with hilar and/or mediastinal lymphadenopathy (stage I).

Design: Retrospective review of bronchoscopy procedures performed over a 6-year period for the diagnostic workup of hilar and/or mediastinal lymphadenopathy, as detected by chest radiographs.

Setting: Urban academic hospital.

Patients: Fifty-five patients with hilar and/or mediastinal lymphadenopathy without pulmonary abnormalities were included in the analysis.

Interventions: After chest CT and physical examinations, all patients underwent FB with TBNA. Patients thought to have clinicoradiologic findings highly consistent with sarcoidosis, as assessed by the bronchoscopists performing the procedures, underwent combined TBNA and TBLB.

Results: A diagnosis of sarcoidosis was established in 32 patients. In the remaining 23 patients, other diseases were pathologically diagnosed. Overall, TBNA was diagnostic in 23 of 32 patients with sarcoidosis (72%) by showing nonnecrotizing granulomas in 28 of 39 lymph node stations sampled (72%). Among the 15 patients who were submitted to both TBNA and TBLB, TBNA exclusively established the diagnosis in 7 of 15 patients (47% increase in the diagnostic rate) and its yield exceeded that of TBLB (11 of 15 patients [73%] vs 6 of 15 patients [40%), respectively). The association of TBNA and TBLB increased the diagnostic yield to 87%.

Conclusions: TBNA may be of great value in the diagnostic evaluation of patients with suspected stage I sarcoidosis, and its use in association with TBLB should be strongly encouraged. TBNA may also preclude the need for further surgical diagnostic procedures in several patients with hilar and/or mediastinal adenopathy due to causes other than sarcoidosis.

(CHEST 2003; 124:2126–2130)

Key words: mediastinal lymphadenopathy; sarcoidosis; transbronchial biopsy; transbronchial needle aspiration

Abbreviations: CI = confidence interval; FB = flexible bronchoscopy; TBLB = transbronchial lung biopsy; TBNA = transbronchial needle aspiration

Sarcoidosis is a systemic disorder of unknown cause that primarily involves the lung and lymphatic systems and that can be definitely diagnosed in the presence of a compatible clinical picture and a pathologic demonstration of nonnecrotizing epithelioid-cell granulomas.1 So far, transbronchial lung biopsy (TBLB) is the recommended diagnostic tool when tissue samples are unavailable by less invasive means, although its yield is not optimal (40 to 66%) in the most common mode of the disease presentation, namely hilar and/or mediastinal adenopathy on conventional chest radiographs (stage I).1–5 Transbronchial needle aspiration (TBNA) is a minimally invasive technique that allows adequate lobe sampling by reducing the risk of complications associated with surgical procedures. In the community of sarcoidosis, TBNA has been extensively used for the differential diagnosis of hilar and mediastinal lymphadenopathy.2,6,7,8 We undertook this study to assess the diagnostic value of TBNA in patients with Stage I sarcoidosis presenting with hilar and/or mediastinal lymphadenopathy, as detected by chest radiographs.

We thank the following persons for their help with the data collection: Drs. Trisolini, Lazzari Agli, and Patelli, Department of Pathology (Drs. Cancellieri and Baruzzi), Maggiore Hospital, Bologna; Department of Thoracic Diseases (Dr. Poletti), Forlì; Biometrics Unit (Dr. Tinelli), IRCCS Policlinico S. Matteo, Pavia, Italy. Manuscript received January 29, 2003; revision accepted July 3, 2003.
invasive bronchoscopic procedure used in mediastinal staging of lung cancer. Little data are available in the literature on the yield of flexible TBNA in cases of suspected sarcoidosis.6–9 We undertook this study to assess the diagnostic value of flexible TBNA, a primary tool for mediastinal disease evaluation at our bronchoscopy unit, in the specific setting of stage I sarcoidosis.

**Materials and Methods**

**Study Design**

To assess the diagnostic yield of TBNA in the setting of stage I sarcoidosis, we retrospectively reviewed the records of the bronchoscopic procedures performed between January 1997 and December 2002 in the evaluation of hilar and/or mediastinal lymphadenopathy without pulmonary abnormalities, as detected by chest radiographs. All procedures were performed at a single institution (Unit of Thoracic Endoscopy, Maggiore Hospital, Bologna).

**Bronchoscopic Procedures**

After chest CT and physical examination, all patients underwent flexible bronchoscopy (FB) with TBNA. Combined TBNA and TBLB were performed in patients thought to have clinical and radiologic features highly suggestive of sarcoidosis (e.g., Lofgren syndrome), as judged by the bronchoscopists involved in this study (L.L.A., M.P., V.P., R.T.).

After informed consent, transnasal standard FB was performed under local anesthesia with the patient in a supine position. TBNA was performed with a 19-gauge histology needle (MW-319; Mill Rose Laboratories; Mentor, OH), which allows one to collect both histologic and cytologic material. The technique has already been reported.10 After an accurate analysis of the CT scans, one to four TBNA were performed on one or two lymph node stations before any other sampling procedure, in order to avoid the risk of contamination by secretions or tissue fragments. All TBNA specimens from a single site were used as a combined specimen. After removal of the needle, each specimen was collected on clean glass slides. In those cases in which a histologic core of tissue was obtained, the sample was removed gently from the slide and placed in formalin solution. The remaining cytologic material was smeared on clean glass slides that were subsequently stained with May-Grünwald Giemsa, Papanicolaou, and Ziehl-Neelsen stains.

TBLB specimens were obtained with standard forceps from either of the lower lobes at the discretion of the operator since no pulmonary parenchymal radiograph abnormalities were detectable in any of the patients of this series. The technique has already been described.11

**Pathologic Assessment and Categorization of TBNA Samples**

Samples were classified as adequate or inadequate by the pathologists involved in the study (A.C., G.B.). A TBNA histology core specimen was considered adequate when it showed material consistent with the architecture of lymph nodes. As far as TBNA cytology specimens are concerned, we considered them adequate only if they contained a moderate number of lymphocytes, in agreement with the literature data; however, since no definite quantitative cutoff value has been defined, we required that at least 30% of the cellularity be composed of lymphocytes, as previously proposed.13

**Final Clinicopathologic Diagnosis**

A definite diagnosis of sarcoidosis (stage I) was established in the presence of the following: (1) a compatible clinical, physical and radiologic picture; (2) pathologic evidence of nonnecrotizing epithelioid-cell granulomas, in the absence of identifiable foreign body reaction; and (3) negative stain for acid-fast bacilli and search for fungal organisms. The staging of sarcoidosis was based on conventional chest radiographic findings, although all patients were submitted to a chest CT prior to bronchoscopy. Histology was also required for defining diseases other than sarcoidosis.

Notably, mediastinoscopy was only performed in the following cases: (1) in patients with both sarcoidosis and conditions other than sarcoidosis, when the bronchoscopy sampling procedures proved inconclusive; and (2) in patients with diseases other than sarcoidosis, when the TBNA findings suggested a lymphoproliferative disorder, in order to further confirm and categorize the disease process.

**Statistical Analysis**

Frequencies are reported as proportions with their 95% confidence intervals (CIs). Differences in frequencies were evaluated by means of $\chi^2$ statistics or Fisher exact test, as appropriate; $p < 0.05$ was considered to indicate statistical significance. All tests were two sided. Analyses were performed with Statistica for Windows software (StatSoft; Tulsa, OK).

**Results**

Of the 55 patients enrolled in the study, 23 patients were pathologically proven to have diseases other than sarcoidosis, namely metastatic cancer (n = 10), lymphoproliferative disorder (n = 10), mycobacterial infection (n = 2), and lymphadenopathy in the setting of heart failure (n = 1).14 TBNA proved diagnostic in 8 of 10 cases of metastatic cancer (80%; 95% CI, 44 to 97%), in 6 of 10 cases of lymphoproliferative disorder (60%; 95% CI, 22 to 88%), and in the 3 cases of nonneoplastic disease. All the TBNA findings suggestive of lymphoproliferative disorder were subsequently confirmed and further categorized by mediastinoscopy. Interestingly, among patients with disorders other than sarcoidosis, the TBNA pathologic examination showed the presence of granulomas only in the two patients with mycobacterial infections; in both these cases, the Ziehl-Neelsen stain of the TBNA specimens showed the presence of acid-fast bacilli. The remaining 32 patients (mean age, 45.4 years; male/female ratio = 1) received a pathologic diagnosis of sarcoidosis, either by bronchoscopic procedures or by mediastinoscopy.

Overall, TBNA allowed a pathologic diagnosis of sarcoidosis in 23 of 32 patients (72%; 95% CI, 53 to 86%). Among the 15 patients of this series who were submitted to both TBNA and TBLB, the yield of TBNA (11 of 15 patients [73%]; 95% CI, 45 to 92%) was considerably higher than that of TBLB (6 of 15 patients [40%]; 95% CI, 16 to 68%), although the best diagnostic yield (13 of 15 patients [87%]; 95%
CI, 59 to 98%) was obtained by combining TBNA and TBLB (Table 1). In 7 of these 15 patients, a diagnosis of sarcoidosis was exclusively established by TBNA (47% increase of the diagnostic rate); in 2 of 15 patients, TBLB was the only means of diagnosis (13% increase of the diagnostic rate).

The TBNA results from the 39 lymph node stations sampled in the 32 patients with sarcoidosis in this series are shown in Table 2. A positive TBNA finding was obtained from 28 of 39 lymph nodes (72%). Sensitivity and specificity values were 69% (95% CI, 49 to 85%) and 91% (95% CI, 72 to 99%), respectively, for TBNA cytology specimens, as well as 96% (95% CI, 80 to 99%) and 91% (95% CI, 72 to 99%) for TBNA histology specimens. TBNA performed in the right paratracheal, hilar, and subcarinal lymph node stations yielded the best results (Table 3). Minor, self-resolving bleeding frequently occurring at the puncture site was the only complication observed in the TBNA procedures of this series.

**Discussion**

In the last 2 decades, a growing amount of data have appeared in the literature suggesting that TBNA is a safe, effective, and cost-saving method in the diagnosis and mediastinal staging of lung cancer.13,15–18 Far less information is available on the role of TBNA in the setting of sarcoidosis, and the technique is not even mentioned as a diagnostic tool in the recently published American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and Other Granulomatous Disorders statement on the disease.1 In a review of the literature, only three studies6–8 can be found that specifically addressed the value of TBNA in the diagnosis of sarcoidosis. Pauli et al6 performed TBNA during rigid bronchoscopy in 258 patients with suspected stage I and II sarcoidosis, with a 66% overall yield; among the 152 patients with stage I disease, TBNA showed a 72% yield and was the only diagnostic procedure in 42% of cases. In the first study assessing the value of flexible TBNA in sarcoidosis, Wang et al7 reported an overall 90% sensitivity in a series of 20 patients; notably, TBNA findings were positive in seven of the eight patients with stage I disease (83% sensitivity). Morales et al8 compared TBNA and TBLB in a series of 51 consecutive patients with sarcoidosis; the overall sensitivity for TBLB and TBNA alone were 67% and 51%, respectively. Of the 30 patients with stage I disease, TBNA was positive in 16 (53%) and TBLB in 18 (60%); combining TBLB and TBNA increased the yield to 83% (25 patients).

The present study confirms the diagnostic value of flexible TBNA in stage I sarcoidosis by showing an overall 72% sensitivity. This yield is higher than that reported in stage I disease for TBLB in most studies.1–5 Among the 15 patients of this series who were submitted to both TBNA and TBLB, the yield of TBNA markedly exceeded that of TBLB (73% vs 40%, respectively), although this difference did not reach statistical significance, probably due to the small size of the sample. The combination of TBNA and TBLB was superior to both TBNA alone (87% vs 73%) and to TBLB alone (87% vs 40%: p = 0.02). Furthermore, TBNA alone established the diagnosis in 7 of these 15 patients (47% increase of the diagnostic rate).

An interesting datum emerging from our study is that a TBNA specimen representative of the lymph node tissue—that is, “adequate”—yielded granulomas in a very high percentage of both histologic (96% sensitivity) and even cytologic (69% sensitivity) material, probably because of a high density of granulomas in sarcoid lymph nodes, as already suggested by Wang et al7 (Table 2; Fig 1). Since obtaining adequate samples is mostly a function of

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**Table 1—Sensitivity of TBNA and TBLB Alone and Combined in 15 Patients With Stage I Sarcoidosis Submitted to Both Procedures**

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Patients, No.</th>
<th>TBNA</th>
<th>TBLB</th>
<th>TBNA Plus TBLB</th>
</tr>
</thead>
<tbody>
<tr>
<td>FB with TBNA and TBLB</td>
<td>15</td>
<td>11/15 (73)</td>
<td>6/15 (40)</td>
<td>13/15 (87)</td>
</tr>
</tbody>
</table>

*Data are presented as ratio of positive diagnoses/patients (%) unless otherwise indicated. TBNA vs TBLB: 73% vs 40% (p = 0.12); TBNA plus TBLB vs TBLB: 87% vs 40% (p = 0.02).*

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**Table 2—Overall Results of TBNA From 39 Lymph Node Stations Sampled in 32 Patients With Stage I Sarcoidosis**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cytology</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specimens obtained</td>
<td>39/39 (100)</td>
<td>35/39 (90)</td>
</tr>
<tr>
<td>Adequate specimens</td>
<td>29/39 (74)</td>
<td>25/39 (64)</td>
</tr>
<tr>
<td>Granulomas</td>
<td>20/29 (69)</td>
<td>24/25 (96)</td>
</tr>
<tr>
<td>No granulomas</td>
<td>9/29 (31)</td>
<td>1/25 (4)</td>
</tr>
<tr>
<td>Inadequate specimens</td>
<td>10/39 (26)</td>
<td>10/39 (26)</td>
</tr>
</tbody>
</table>

*Data are presented as No./total (%).*
the skill of the bronchoscopist, the yield of TBNA in sarcoidosis should be expected to improve over time with the education and experience of the examiner.\textsuperscript{19}

The high percentage of granulomas observed among our cytologic TBNA samples has never been reported previously and might be partly explained by the technique of specimen recovery. The direct smearing of the needle content on a slide with rapid fixation and staining, which we used, is likely to have a less negative influence on the architecture and the cellular aggregation of granulomas than the technique utilizing flush solution, which undergoes cytocentrifugation, cell pellet resuspension, and staining.

As already observed in the setting of the mediastinal staging of lung cancer, very satisfactory diagnostic rates were obtained from TBNAs performed in the right paratracheal and subcarinal lymph nodes stations (85% and 65%, respectively), which accounted for > 80% of TBNA procedures of this series.\textsuperscript{13,18} This leads us to suggest, whenever possible, to avoid sampling of the left paratracheal station, which is known to be associated with the worst yields and the major complications.\textsuperscript{13,18,20,21}

In conclusion, our study, which includes a large series of patients with stage I sarcoidosis submitted to flexible TBNA, confirms the diagnostic usefulness of the method in this specific setting. The addition of TBNA to TBLB in patients with suspected stage I sarcoidosis may preclude the need for surgical diagnostic procedures in a considerable number of patients with either sarcoidosis or mediastinal lymphadenopathy due to causes other than sarcoidosis.

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\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
Variables & All Lymph Node Stations & Right Paratracheal (4R) & Left Paratracheal (4L) & Subcarinal (7) & Hilar (10) \\
\hline
Procedures, No. & 39 & 13 & 2 & 20 & 4 \\
Sensitivity & 28/39 (72) & 11/13 (85) & 1/2 (50) & 13/20 (65) & 3/4 (75) \\
\hline
\end{tabular}
\caption{Sensitivity of TBNA According to Lymph Node Station*}
\end{table}

*Results are expressed as ratio of positive diagnoses/procedures (%) unless otherwise indicated.

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{figure1.png}
\caption{Nonnecrotizing epithelioid-cell granulomas are evident in both histologic (\textit{top left}, A [hematoxylin-eosin, original \times 400], and \textit{top right}, B [hematoxylin-eosin, original \times 200]) and cytologic (\textit{bottom left}, C [Papanicolaou stain, original \times 400], and \textit{bottom right}, D [May-Grumwald Giemsa stain, original \times 400]) TBNA samples.}
\end{figure}
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