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CLINICAL REVIEW

Sarcoidosis in Lambert-Eaton Myasthenic Syndrome – Culprit or Disguise? Two Cases and a Literature Review of EBUS-TBNA/Forceps Biopsy of Lymph Nodes

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Introduction

Lambert-Eaton myasthenic syndrome (LEMS) is a neuromuscular junction disorder characterized by presynaptic defect of neuromuscular transmission. This is in contrast to myasthenia gravis which has a postsynaptic defect. Pathogenic autoantibodies against the voltage-gated calcium channel (VGCC) on the presynaptic nerve terminals can be detected in a majority of cases of LEMS. They interfere with the calcium influx through VGCCs and impair transmitter release causing typical symptoms. More than half of patients with LEMS have cancer, with small cell lung cancer (SCLC) the most common. These cancer cells often express functional VGCCs on cell membrane serving as immunologic targets, producing VGCC antibodies that cross-react with the host native presynaptic VGCCs.[1,2] For those without cancer, conditions such as sarcoidosis have been associated with LEMS.[3,4] We present two cases of LEMS, in which sarcoidosis and lymphoma with sarcoid-like reaction were the most likely etologies. The diagnostic approach in both cases demonstrated different diagnostic yields endobronchial ultrasound-guided needle aspiration (EBUS-TBNA) and EBUS-transbronchial forceps biopsy (EBUS-TBFB) of intrathoracic lymph nodes. We reviewed the literature on EBUS-TBNA or EBUS-TBFB for lymph node biopsy in patients with sarcoidosis and lymphoma, both of which are believed to require tissue sample with intact architectural/histologic information compared to non-small cell lung cancer (NSCLC), and performed a systemic review and mini meta-analysis.

Patients

Patient A is a 52-year-old previously healthy female presented with lower extremity weakness and bulbar symptoms including Bell's palsy, phonophobia, photophobia, hearing loss and swallowing difficulty. These symptoms resolved with prednisone treatment. Two distinct relapses occurred over five months and showed unequivocal responses to prednisone and symptomatic recurrences on discontinuing or reducing the prednisone dose. Extensive testing revealed the presence of VGCC autoantibodies (both N- and P/Q types). MRI of the brain was negative, however Chest CT showed extensive intrathoracic lymphadenopathy.

Patient B is a 54-year-old male, who presented to a neurologist for gait unsteadiness, ataxia, frequent falls, and weakness in lower extremities for 18 months. He has a history of polycythemia with negative gene mutation testing (including JAK2 V617F, JAK2 exon 12 and MPL). Physical examinations revealed reduced tendon reflexes. Extensive blood testing showed elevated VGCC autoantibodies (N-type but not P/Q-type). An electromyogram study was normal, and he was diagnosed with "paraneoplastic neuropathy and cerebellar syndrome." Neuroimaging studies of the brain and spine with MRI and CT did not show abnormalities. However, the PET/CT revealed extensive intrathoracic lymphadenopathy with intense FDG avidity.

Both patients were referred to Interventional Pulmonology for biopsy. EBUS-TBNA was performed in both in bilateral hilar and subcarinal lymph nodes. 19-gauge needles were used to puncture the bronchial wall to access the targeted lymph nodes. Three to five passes were taken on each lymph node and each pass consisted of 20 jabbing motions of the needle with suction applied. Rapid on-site evaluation was available to assess the sample adequacy. Additionally, EBUS-TBFB was done to biopsy the right hilar lymph node for patient A and the left hilar lymph node for patient B, immediately after the EBUS-TBNA of the corresponding station, a forceps with an outer diameter of 1.2mm was fitted into the working channel of the bronchoscope and passed through the track created by the needle puncture from TBNA.

In patient A, both the TBNA and TBFB biopsies in all stations showed prominent non-caseating granulomas. In patient B, only crushed and scattered lymphocytes in all TBNA biopsies were seen. However, pronounced clusters of non-caseating epithelioid granulomas from the TBFB samples were presented and were confirmed with mediastinoscopy with lymph node biopsy.

Based on the clinical picture, lab testing, biopsy results and the dramatic response to prednisone, it was believed sarcoidosis was most likely responsible for Patient A's symptoms. For patient B, a similar conclusion was reached initially as in patient

A. However, review of lymph node samples revealed some uniform small lymphoid cells positively stained for CD 23, suggesting possible chronic lymphocytic lymphoma/ small lymphocytic lymphoma and that the non-caseating granulomas obtained with TBFB may have been a sarcoid-like reaction. After multidisciplinary discussion, a concensus of starting a trial with Rituximab was concluded and treatment is undergoing.

Systematic Review and Mini Meta-Analysis Results

These two cases raised our interest in investigating the diagnostic performance of lymph node biopsy between using needles and forceps for sarcoidosis and lymphoma, both of which requires architectural information from the samples for diagnostic purposes. Therefore, we performed a systematic review and a mini meta-analysis. A bibliographic search for medical literature published through November 2017 was done in MEDLINE via PubMed and Google. The following search terms were used: (Endobronchial Ultrasound OR EBUS OR EBUS TBNA OR TBNA OR Forceps) AND (Sarcoidosis OR Lymphoma), as well as "forceps" AND "needle" AND ("endobronchial ultrasound" OR "EBUS" or "TBNA"). Additionally, references of the included articles and relevant review articles were reviewed individually for relevant publications (Figure 1). Given the scarce literature on 19G needles, we combined it with that of forceps and comparison was made between using 22G needles versus using 19G/forceps. Exclusion criteria were pediatric population, review articles, studies without comparison arms and studies for conditions other than sarcoidosis and lymphoma. There was no language restriction.

The articles were reviewed by two authors, T.H. and S.O. The process included study selection, data extraction and quality assessment. Any disagreement was resolved by consensus among all authors. Extracted data included design characteristics and parameters from studies.

We focused on the diagnostic yield (ability to achieve a clinical diagnosis) rather than the diagnostic accuracy (diagnosis made via current gold standard), due to the lack of such outcomes in the included studies. Specifically, the main outcome of interest was the diagnostic yield achieved by 22G needles versus that by 19G needles or forceps for sarcoidosis and lymphoma, respectively. Assuming the outcomes being evaluated from different studies were not identical but showed a certain distribution, a random effect model was used for the meta-analysis with RevMan 5.3 software. A p-value of < 0.05 was considered significant. Inverse variance weighing was applied to analyze diagnostic yield proportions among studies. Heterogeneity on the pooled effects of the outcome was assessed using the τ^2, I^2 index and the Cochran Q statistic; $\tau^2 > 1.0$ or $I^2 \geq 50\%$ with a $p < 0.1$ was considered to have significant heterogeneity.

Systematic review resulted in Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram[5] (Figure 1). Seven studies[6-12] for sarcoidosis and five[6,7,9,10,12] for lymphoma were identified (Table 1). The quality of the studies was variable but most were of good quality (Table 2). For sarcoidosis, the pooled diagnostic yields using 22G needles and 19G/forceps were 49.6% (95% CI: 28.5%-70.7%) and 83.7% (95% CI: 71.6%-95.7%), respectively, with an odds ratio of 4.83 (95% CI, 2.40-9.75). For lymphoma, the yields were 22.3% (95% CI: -32.0%-76.6%) and 62.5% (95% CI: 48.6%-106.4%), respectively, with an odds ratio of 6.71 (95% CI, 1.50- 30.02). Both odds ratios were statistically significant. There was clinical heterogeneity in the characteristics of the studies, such as the type (prospective vs. retrospective), the use of ROSE and the difference in forceps external diameters, although there appeared to be no significant statistical heterogeneity (I^2 14% and 22%, and τ^2 0.13 and 0.71 for these two conditions, respectively) (Figures 2 and 3).

Discussion

We reported two cases of LEMS, one of which was likely associated with sarcoidosis, whereas the other was possibly lymphoma with sarcoid-like reaction. The diagnosis of LEMS can be made based on clinical signs and symptoms with autoantibodies against VGCCs or an abnormal electromyogram. The autoantibodies are directed against P/Q-type VGCC in greater than 85% of LEMS patients, with 30-40% of patients having co-existing antibodies to N-type VGCC.[2] The presence of only N-type VGCC antibodies is rare (as in our patient B) but has been reported.[4,13,14] There only have been two cases that report a possible association between LEMS and sarcoidosis.[3,4] Whether this rarely reported association is due to under-reporting or rare occurrence is unknown. Immunologically, LEMS and sarcoidosis may share some common features, such as the down-regulation of regulatory T lymphocyte (T_{reg}) population or function and a hyperimmune state.[15,16] No causal relationship has yet been established. The association of LEMS and lymphoma has been relatively well established.

In the diagnosis and staging of NSCLC, EBUS-TBNA to provide tissue for cytologic assessment is recommended by the American College of Chest Physician (ACCP) because of its minimal invasiveness and high accuracy[17] Smaller needles such as 22G are most commonly used. This is less certain in conditions such as sarcoidosis, low-grade lymphoma, well-differentiated carcinomas and those with microscopically discrete foci, which required considerable amount of tissue to provide architectural information for diagnosis. Smaller-gauge needle samples are likely insufficient since this information may be lost when tissue is aspirated and packed into the needle during sampling.

19G needle (outer diameter of 1.1 mm) is considered a "histology" needle since it can obtain core samples for histologic examination, in addition to cellular aspirates for cytology. Clinical implication with larger needles has mostly been studied in gastroenterology because 19G needles have been used in EUS since 2005, whereas it was only introduced to Interventional Pulmonology in 2015. Gauge-up needles such

as 19G were shown to be superior in obtaining samples for accurate histologic diagnosis than thinner needles in EUS-FNA.[18] A major disadvantage of 19G needles and forceps with a similar outer diameter is the difficulty passing through the bronchoscope when the tip of the bronchoscope is angulated, for instance, when one is trying to sample lymph node station 10 or 4L. The use of these "histology" needles appears to produce higher diagnostic yields than those with smaller needles.[19]

The diagnostic yield of EBUS-TBNA for sarcoidosis has been shown to be around 80% from the two largest meta-analyses.[20,21] This can be affected by the prevalence and the staging of the disease. The higher the prevalence and the earlier the stage of the disease, will have higher yields.[21] A majority of the studies included in these two meta-analyses used 22G needles for biopsy. The diagnostic yield using smaller needles such as 22G for lymphoma is much less certain, varying widely from 29% to 91%.[22-25] The disagreement is likely due to the differences in technical aspects (operator's experience, needle size, use of rapid on-site evaluation, etc) and disease characteristics (lymph node size and station, pre-test probability, etc). Higher diagnostic yields appear to be related to more passes per lymph node (up to five), use of ROSE, and use of flow cytometry.[22]

In this mini meta-analysis, transbronchial biopsy of lymph nodes using larger-gauge needles of 19G and forceps appear to have significantly higher diagnostic yields for sarcoidosis and lymphoma than that using smaller needles such as 22G. The diagnostic yields of using 22G needles for both sarcoidosis and lymphoma were lower than that reported in the literature. Other conjectural explanations, include the clinical heterogeneity in study design and mixed population, as well as the very small number of patients in each study. Despite this, we believe this study suggests the potential advantages of 19 gauge needles and forceps in obtaining tissue with preserved architectural and histologic information for a more confident diagnosis using direct comparison. Additionally, in the two cases presented here, biopsy with TBFB resulted in a tissue diagnosis in both whereas TBNA with 19G needles only established one diagnosis. There may be additional advantage of forceps biopsy over needle aspiration even with 19 gauge needles. In our institution, we have started routinely using transbronchial forceps biopsy following EBUS-TBNA with a 19G needle in patients with clinical suspicion for sarcoidosis and lymphoma. This approach minimizes the time added to the procedure since the forceps enters the target lymph nodes through the hole created by the proceeding needle puncture. Data collection to delineate the potential advantage of using forceps in these conditions is ongoing.

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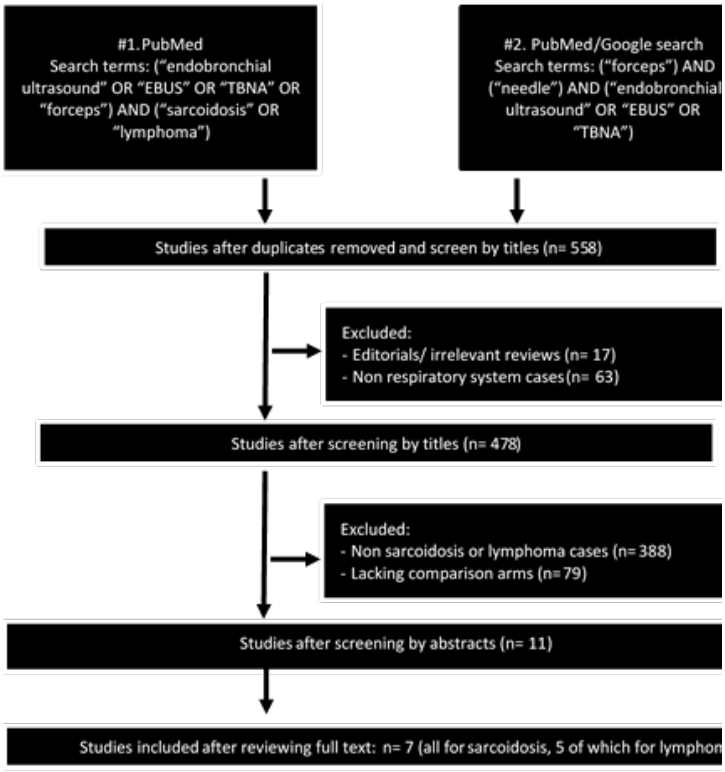

Figure 1: Flow of study selection.

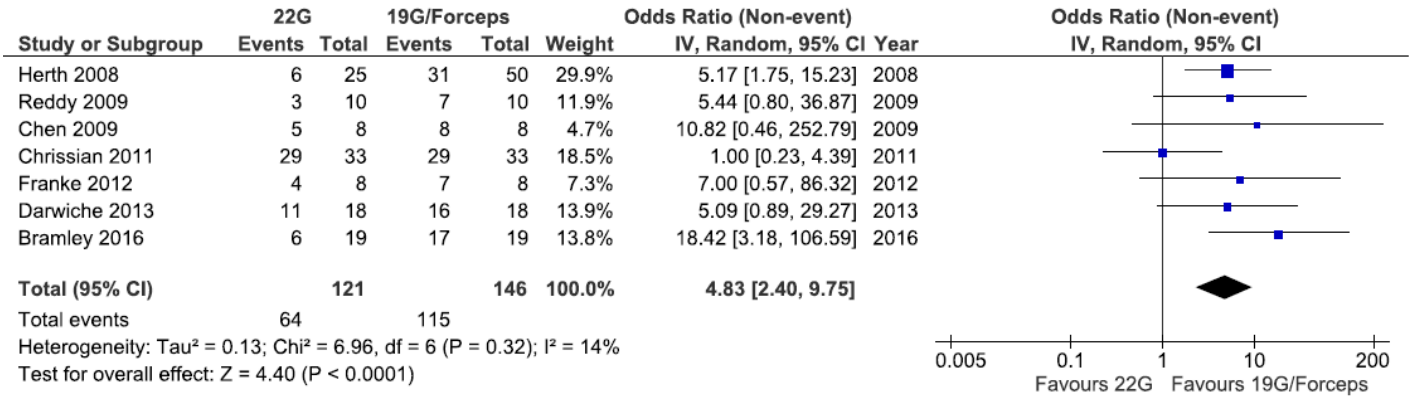

Figure 2: Comparison of the diagnostic yields between 22G needles and 19G needles/forceps combined for sarcoidosis.

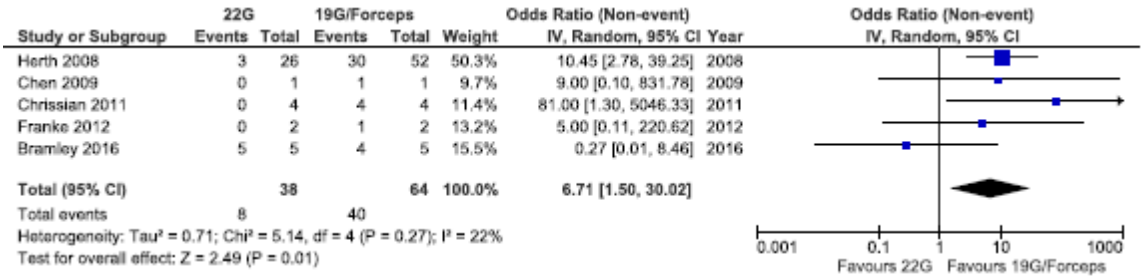

Figure 3: Comparison of the diagnostic yields between 22G needles and 19G needles/forceps combined for lymphoma.

Table 1 Characteristics of studies.

Author	Year	Method	Study type	ROSE	Time spent on TBFB	Needle gauge	Forceps external diameter	TBNA 22G (Diagnostic/total) Sarcoidosis	Lymphoma	TBNA 19G+ TBFB (Diagnostic/total) Sarcoidosis	Lymphoma
Herth[&]	2008	EBUS/ conventional	Prospective	No	Not reported	22G	1.15mm	6/25	3/26	31/50	30/52
Chen[&]	2009	EBUS	Retrospective	Yes	Not reported	22G	1.0mm	5/8	0/1	8/8	1/1
Reddy[&%]	2009	EBUS	Prospective	Not reported	Not reported	22G	1.2mm	3/10	0/1	7/10	0/1
Chrissian[#]	2011	EBUS	Prospective	No	2.25-2.75 min per LN with 3 passes	22G	1.0mm	29/33	0/4	29/33	4/4
Franke[&]	2012	EBUS	Retrospective	Not reported	Not reported	22G	0.8mm	4/8	0/2	7/8	1/2
Darwiche[&]	2013	EBUS	Prospective	No	6 min for one LN with 3 passes	22G	N/A	11/18	n/a	16/18	n/a
Bramley[#]	2016	EBUS	Prospective	No	4 min 12 sec for one LN with 2 passes	22G	1.9mm	6/19	5/5	17/19	4/5

*: two patients in whom the forceps was not able to penetrate the wall were excluded from analysis.
[&]: number of patients.
[#]: number of lymph nodes.
[%]: not included for the lymphoma group

Table 2. Checklist for assessing the quality of qualitative studies.

	Herth 2008	Chen 2009	Reddy 2009	Chrissian 2011	Franke 2012	Darwiche 2013	Bramley 2016
Question/objective well described	2	2	n/a	2	2	2	2
Study design evident and appropriate	2	2	n/a	2	2	2	2
Context for the study clear	2	2	n/a	2	2	2	2
Connection to a theoretical framework/wider body of knowledge	2	1	n/a	2	2	2	2
Sampling strategy describe, relevant and justified	1	2	n/a	2	2	2	2
Data collection methods clearly described and systematic	2	2	n/a	2	2	2	2
Data analysis clearly described and systemic	2	2	n/a	2	1	2	2
Use of verification procedure(s) to establish credibility	1	1	n/a	1	1	1	1
Conclusions supported by the results	2	n/a	n/a	2	2	2	2
Reflexivity of the account	1	1	n/a	1	1	1	1
Total score	17/20	15/18	n/a	18/20	17/20	18/20	18/20