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Bronchoscopy in sarcoidosis: union is strength

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Sarcoidosis is a benign disease of unknown etiology that is characterized by the formation of noncaseating epithelioid cell granulomas. Although a multisystemic disease, it primarily affects the lung and the lymphatic system of the body. When a histological diagnosis is required, bronchoscopy is frequently employed because allows tissue sampling from several anatomic sources, such as airways, lung parenchyma and hilar/mediastinal nodes. Transbronchial lung biopsies (TBLB), endobronchial biopsies (EBB) and conventional transbronchial needle aspiration (cTBNA) have long been the only bronchoscopic techniques to diagnose sarcoid granulomas, until the advent of endobronchial ultrasound guided needle aspiration (EBUS-TBNA). This technique shows excellent yield in sampling mediastinal adenopathies with a higher sensitivity than the conventional technique in sarcoidosis as well. Furthermore, non controlled studies, demonstrated its diagnostic superiority than EBB and TBLB in stages I (hilar adenopathies only) and II (hilar lymph nodes and parenchymal infiltrations) thoracic sarcoidosis. In a recent study, Gupta *et al.,* randomized 130 patients with suspected stage I and II disease to undergo EBUS-TBNA or cTBNA in conjunction with transbronchial and endobronchial biopsies. The Authors demonstrated that the yield of cTBNA added to EBB and TBLB is similar to EBUS-TBNA plus transbronchial biopsies, although ultrasound guided transbronchial needle aspiration shows the best single diagnostic efficacy. In this review article we aimed to discuss the findings by Gupta in the context of medical literature, highlighting the importance of adding nodal aspirations (with or without ultrasound guidance) with bronchial and transbronchial samples to gain the optimal sensitivity in obtaining histological confirmation. We finally pointed out the need for future studies to evaluate the potential role of rapid on-site evaluation (ROSE) of needle aspirates in reducing additional sampling and related costs and complications.

KEY WORDS: Sarcoidosis - Bronchoscopy - Ultrasound guided transbronchial needle aspiration - Conventional transbronchial needle aspiration - Bronchial biopsy - Transbronchial biopsy.

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Sarcoidosis is a benign granulomatous disease of unknown etiology that is characterized by the formation of noncaseating epithelioid cell granulomas. Sarcoidosis is a multiorgan disorder that pri-

marily affects the lung and the lymphatic system of the body. The clinical manifestations depend on several factors such as ethnicity, site and extent of organ involvement and on the activity of granulomatous process. The classification of thoracic sarcoidosis is based on the findings of the chest radiogram and relies on the lung parenchyma and hilar nodes abnormalities. Stage 0 describes no visible intrathoracic changes, stage I is represented by bilateral hilar lymphadenopathies, which may be accompanied by paratracheal nodes. Stage II is bilateral hilar adenopathies accompanied by parenchimal infiltrations while stage III is characterized by parenchimal abnormalities only. Stage IV sarcoidosis consists of advanced fibrosis.

According to the ATS/ERS/WASOG Statement the diagnosis usually entails a compatible clinical and radiological picture, the histologic demonstration of typical granulomas and the exclusion of similar presentating disease such as tuberculosis, lymphomas and lung cancer.

Although in some typical circumstances (such as Loefgren syndrome) clinical and radiological presentation are characteristic and invasive test may be unnecessary, in the vast majority of cases the histologic demonstration of granulomas is required.[1]

In the absence of easily accessibile biopsy sites (such as superficial lymph glands), bronchoscopy is frequently employed in diagnosis, because allows tissue sampling from several anatomic sources, such as airways, lung parenchyma and hilar/mediastinal nodes.[1, 2]

Bronchoalveolar lavage (BAL) has been quite studied in patients with suspected sarcoidosis. A CD4/CD8 ratio >3.5 and differential fluid cells profile may be useful in distinguishing sarcoidosis from most common interstitial lung diseases. Nevertheless, with the current knowledge, BAL examination cannot be considered a substitute for histology and BAL outcomes are supportive but not diagnostic in assessing sarcoid disease.[1-4]

Transbronchial lung biopsies (TBLB) and endobronchial biopsies (EBB) have long been the only bronchoscopic techniques employed to diagnose sarcoid granulomas until conventional transbronchial needle aspiration (cTBNA) allowed bronchoscopists to sample mediastinal nodes with minimal adverse effects. Primarily employed in diagnosing and staging lung cancer, this technique has shown good sensitivity in sarcoidosis and has demonstrated incremental yield over the other bronchoscopic techniques.[2,5]

The introduction of *real time* endobronchial ultrasound guidance for transbronchial needle aspiration (EBUS-TBNA) has revolutioned this sampling method, due to the direct visualization of lymph nodes beyond the tracheobronchial wall. EBUS-TBNA shows excellent yield in diagnosing mediastinal adenopathies and is now widely employed in diagnosing stage I and II sarcoidosis.[6] Moreover, endoesophageal ultrasound guided needle aspiration (EUS-NA) for adenopathies which can be in contact to the upper enteric tract (subcarinal, aortopulmonary window and lower medistinum nodes, according to the international classification), has been utilized with initial success in diagnosing the disease.[3,7,8]

In a recent research paper, Gupta and Collegues studied 130 patients with suspected stage I and II disease requiring a histological diagnosis; they were all randomized 1:1 to undergo EBUS-TBNA or cTBNA in conjunction with transbronchial and endobronchial biopsies.[9]

The study explored some important issues concerning the bronchoscopic diagnosis of sarcoidosis. The primary endpoint was the detection of granulomas by any bronchoscopic technique in patients eventually diagnosed to have sarcoidosis. In secondary analysis they studied the diagnostic yields of individual sampling methods, rate of serious adverse events and the time used for the procedures.

The effectiveness of bronchoscopic sampling techniques in sarcoidosis has been quite studied over the years.

The diagnostic value of cTBNA in diagnosing stages I and II disease was recently

TABLE I.—*Summary of studies adding transbronchial needle aspiration (both conventional and EBUS-guided) to bronchial and transbronchial biopsies in diagnosing sarcoidosis stages I and II.*

Author/Year	Study design	No. of patients	Study protocol	Sensitivity of the bronchoscopic techniques	
				Single	Combined
Morales [10] 1994	PCS	51	cTBNA+EBB+ TBLB	cTBNA: 26/51 (51%) TBLB: 34/51 (67%)	cTBNA+TBLB: 43/51 (84%)
Leonard [11] 1997	PCS	13	cTBNA+TBLB	cTBNA: 6/13 (46%) TBLB: 7/13 (54%)	TBNA+TBLB: 11/13 (85%)
Bilaceroglu [12] 1999	RCR	57	cTBNA+EBB+TBLB	cTBNA: 30/57 (53%) TBLB: 32/57 (56%) EBB: 27/57 (47%)	cTBNA+EBB+TBLB: 51/57 (89%)
Trisolini [13] 2003	RCR	15	cTBNA+TBLB	cTBNA: 11/15 (73%) TBLB: 6/15 (40%)	cTBNA+TBLB: 13/15 (87%)
Trisolini [14] 2004	RCR	32	cTBNA+TBLB	cTBNA: 21/32 (86%) TBLB: 20/32 (93.7%)	cTBNA+TBLB: 30/32 (94%)
Fernandez-Villar [16] 2007	PCS	32	cTBNA+TBLB	cTBNA: 16/32 (61.5%) TBLB: 15/32 (58%)	cTBNA+TBLB: 23/32 (88%)
Trisolini [17] 2008	PCS	53	cTBNA+TBLB	cTBNA: 42/53 (79%) TBLB: 29/53 (55%)	cTBNA+TBLB: 47/53 (89%)
Khan [18] 2011	RCR	215	cTBNA+TBLB	cTBNA: NA TBLB: 139/215 (65%)	cTBNA+TBLB: 151/215 (70%)
Navani [30] 2011	PCS	40	EBUS-TBNA+TBLB+EBB	EBUS-TBNA: 23/27 (82%) TBLB: 8/27 (31%) EBB: 3/27 (11%)	EBUS-TBNA +EBB+TBLB: 25/27 (93%)
Plit [22] 2012	RCR	37	EBUS-TBNA+TBLB+EBB	EBUS-TBNA: 31/37 (84%) TBLB: 29/37 (78%) EBB: 10/37 (27%)	EBUS-TBNA+TBLB: 37/37 (100%) EBUS-TBNA +EBB+TBLB: 37/37 (100%)
Gupta [9] 2014	RCT	130	cTBNA+TBLB+EBB Vs EBUS-TBNA+TBLB +EBB	cTBNA: 30/62 (48%) EBUS-TBNA: 41/55 (74.5%) EBB: 40/111 (36%) TBLB: 78/112 (70%)	cTBNA+EBB+TBLB: 53/62 (85.5%) EBUS-TBNA +EBB+TBLB: 51/55 (93%)

PCS: prospective case series; RCR: retrospective chart review; RCT: randomized controlled trial; cTBNA: conventional transbronchial needle aspiration; EBUS-TBNA: endobronchial ultrasound transbronchial needle aspiration; TBLB: transbronchial lung biopsy; EBB: endobronchial biopsy; NA: not avalilable.

explored in a meta-analysis by Agarwal *et al*. In 21 studies (most of them retrospective), the Authors demonstrated a 62% of pooled sensitivity, with a high range in diagnostic yield (6-90%) and a negligible rate of complications. Nine of the selected studies also reported the performance of TBLB in same patients undergoing TBNA[4,10-18] (Table I).

The diagnostic yield of combined TBNA and TBLB (with a 83% of pooled sensitivity) resulted significantly higher than TBNA alone (53%), with only a small increase in complications number. Furthermore, the sensitivity of transbronchial biopsies was statistically better in patients with stage II compared with stage I (72% *versus* 50%, p <0.001).[4]

The importance of transbronchial biopsies in stages I, II and III sarcoidosis is well recognized. Strikingly, even patients with normal chest radiograph or high-resolution chest CT scans may have parenchymal involvement with granuloma detections on TBLB.[2] The sensitivity of this sampling method ranges between 32 and 100% and may be influenced by many other variables.[2, 12, 19-22] Biopsies taken in patients with

a greater extent of parenchymal disease on the CT scan, from the lobe of greatest involvement and with reticular and ground glass pattern on computed tomography, are more likely to be positive.[2,23] Furthermore, an optimal number of specimens (four to six in stages II and III and probably more in stage I) and the black race rather than white, may augment the diagnostic efficacy of TBLB.[2]

Although sarcoid granulomas can involve any aspect of the respiratory tract, mucosal abnormalities do not represent a frequent finding. However, even when respiratory mucosa appears normal, endobronchial biopsies may reveal underlying granulomas.[2, 24] The utility of this sampling method has been reported in several studies, with a diagnostic yield ranging from 30 to 50% in case of normal appearing mucosa until 71-91% in case of mucosal abnormalities.[2, 25-27]

Some studies showed a significantly increased sensitivity of bronchoscopy by adding EBB to TBLB.[12, 25-28]

Only one small randomized controlled trial (RCT) reported the diagnostic superiority of EBUS-TBNA on conventional transbronchial needle aspiration in sampling hilar and mediastinal adenopathies with a clinical suspicion of sarcoidosis.

Beside showing a longer procedural time with endosonographic needle aspiration, Tremblay *et al.* reported 83% yield with EBUS-TBNA, significantly higher than 54% with cTBNA. Notably, about 50% of the study patients also underwent EBB and TBLB and the cumulative yield of all bronchoscopic techniques was 92% in EBUS-TBNA and 81% in cTBNA arm, which resulted not statistically different.[29]

Few studies have compared the effectiveness of EBUS-TBNA with the other traditional bioptic procedures. In an observational prospective study, Navani *et al.* studied 40 patients with suspected pulmonary sarcoidosis and enlarged hilar and mediastinal nodes (radiographical stages I and II) who underwent EBUS-TBNA and subsequently EBB and TBB.

The Authors observed the significantly greater yield of EBUS-TBNA (85%) *versus* airways and parenchymal biopsies, that showed a very low combined sensitivity (35%), probably due to the high prevalence of stage I patients. Notably, the best diagnostic yield (93%) was obtained by adding all three procedures [30] (Table I).

Similar findings were retrospectively observed by Nakajima *et al.* and prospectively noted by Oki *et al.*, in two separate studies. Both Authors submitted all patients with prevalent stage I disease to EBUS-TBNA followed by TBLB, observing the significantly higher sensitivity of ultrasound-guided needle aspiration (respectively 63% and 94%) than transbronchial lung biopsy (31% and 37%).[21, 31]

Unfortunately, none of these studies reported the cumulative yield of procedures.

Nevertheless, in 37 patients retrospectively studied, Plit *et al.* observed no statistical difference in sensitivity between EBUS-TBNA and TBLB (84% and 78%, p=0.77), and sarcoidosis was diagnosed in all patients by adding the two procedures [22] (Table I).

A large multicenter randomized controlled trial (The Granuloma Trial) randomized 304 patients with suspected thoracic sarcoid disease (stages I/II) to undergo endosonographic needle aspirations (EBUS-TBNA or EUS-NA) or conventional bronchoscopy with transbronchial and endobronchial lung biopsies.

The detection of granulomas was significantly better in endosonography compared to traditional bronchoscopy group (86% yield vs 53%, p <0.001), with a low rate of serious complications in both arms. Interestingly, although the study was not powered for subgroups analysis, for stage II sarcoidosis (about half of all patients) there was only a numeric difference in sensitivity (84% vs 77%) but this was not statistically different.[3]

In this literature context the study by Gupta stands out as the first who looked at the cumulative yield of all three procedures, randomizing patients to undergo EBUS-guided or conventional TBNA. The Authors demonstrated that the diagnostic yield of cTBNA added to EBB and TBLB is similar to EBUS-TBNA plus transbronchial biopsies, highlighting the importance of

adding nodal aspirations (with or without ultrasound guidance) with bronchial and transbronchial samples to gain the optimal sensitivity in obtaining histological confirmation.[9]

The advent of ultrasound guidance for needle aspiration techniques in the last ten years has undoubtely raised their diagnostic yield in sampling mediastinal lymph glands, beside allowing the punction of nodal stations less accessibile to the traditional method.[6,29] As stated before, given the high efficacy of EBUS-TBNA and EUS-NA in diagnosing sarcoidosis, prospective studies demonstrated their greater diagnostic yield compared to the traditional bronchial and transbronchial biopsies. Additionally, they demonstrated a greater prevalence of complications (particularly hemorrage and pneumothorax) associated with TBLB.[3, 32]

On the basis of these experiences, some Authors now seem to consider ultrasound guided needle aspiration techniques as the exclusive sampling method in the first two stages of disease.[3,32-34] However, this technology is still quite expensive; the high costs of equipement as an initial investment and per procedure, are still limiting its diffusion, particularly in developing countries.

Furthermore, including EUS needle aspiration in the diagnostic workup of sarcoidosis may be now considered much more uncertain, due to required competences that are still scarcely widespread.[33]

To this end, the study by Gupta renewed the importance of airways and lung parenchyma biopsies in diagnosing sarcoidosis. By adding these procedures (TBLB in endosonography arm and both EBB and TBLB in the conventional one) to needle aspiration, they significantly improved the sensitivity of bronchoscopy without observing a consensual increase in the rate of adverse events.

No differences in visible abnormalities of bronchial mucosa detected on bronchoscopy were noted between the subgroups. When added to needle aspirations and TBLB, endobronchial biopsies significantly raised the sensitivity of bronchoscopy only in the cTBNA arm. It should be pointed out that the sensitivity of EBB in EBUS-TBNA group was significantly lower than the in cTBNA one (26% *versus* 45%).[9]

Beside showing a longer procedural time, EBUS-TBNA showed a higher sensitivity (74.5%) than conventional transbronchial needle aspiration (48%), confirming the results obtained by Tremblay *et al*. The reported yield by this two procedures are consistent with those reported in literature, while the combined yield of all the sampling methods are comparable to the best reported[5,6,29-31] (Table I).

It is worth noting that more than half of the patients in the study presented pulmonary infiltrates; this issue might explain the high sensitivity of TBLB in detecting granulomas and the lack of superiority of EBUS-TBNA than transbronchial biopsy.

Only two nodal stations (right low paratracheal and subcarinal) and the adenopathies >10 mm in short diameters, were included in the study. In the opinion of the Authors, this could have excluded patients with smaller nodes and other more difficult stations were EBUS-TBNA would have probably been more sensitive than cTBNA. Surprisingly, hilar nodes (stations 10 and 11 of the international classification), that are frequently involved in sarcoidosis and efficaciously sampled also with cTBNA, were ruled out.[8, 17]

Furthermore, it should be pointed out that Authors did not use in their protocol the immediate cytological assessement of needle aspirates. Rapid on-site evaluation (ROSE) in fact guarantees that samples are handled and processed in the best way and offers the opportunity to adjust sampling based on the information provided by the cytopathologist. In case of a non diagnostic sample the operator may perform other needle passes, modifying the technique or the site of sampling. On the contrary the procedure can be stopped by the bronchoscopist when sufficient material has been harvested for diagnosis, avoiding further needle passes or the use of other sampling methods, thus potentially reducing costs and complications.[35, 36]

In a randomized controlled trial, Trisolini *et al.,* failed to demonstrate a significant

increase in yield of ROSE-guided conventional TBNA in hilomediastinal nodes of an unselected population, but reported a significant reduction in the complication rate of bronchoscopy in these patients.[37]

Few studies described EBUS-TBNA with ROSE in patients with sarcoid disease.[21, 32, 38, 39]

In a dual-centre prospective study, Plit *et al.* studied the accuracy of ROSE performed by cytothechnologist during ultrasound-guided transbronchial needle aspiration in patients with suspected stages I and II sarcoidosis. The Authors provided compelling evidence that EBUS-TBNA with ROSE has a good correlation with the final overall pathological assessement and has a high interobserver agreement between cytotechnologist. Given the high and reproducible diagnostic yield of the immediate assessement of the aspirates, they postulated that ROSE be included in the first-line diagnostic algorithm of sarcoidosis.[32]

Future randomized controlled trials are needed to confirm the role of ROSE in transbronchial needle aspiration (with or without ultrasound guidance) of patients with suspected sarcoidosis; these studies should particularly focus on its potential in reducing additional sampling (both endobronchial and transbronchial biopsies) and related costs and complications.

Conclusions

Although EBUS-TBNA is the most sensitive sampling technique in diagnosing thoracic sarcoidosis, the results by Gupta clearly shows that the absence of EBUS should not hamper bronchoscopists to approach patients with suspected sarcoid disease.

No major adverse events were observed in the study, but usually TBLB is more frequently associated with complications than other bronchoscopic sampling technique.[40] However, as suggested by Mehta *et al.*, a non diagnostic bronchoscopy would be more detrimental than the fear of complications.[9]

To this end, clinicians should be aware of the importance of adding all the available bioptic techniques to reach the optimal yield, because literature clearly shows that in the bronchoscopic diagnosis of sarcoidosis union is strenght.

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