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EBUS- the minimally invasive tool for evaluation of systemic sarcoidosis

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I. Introduction

Sarcoidosis is a multisystem disease of unknown origin which is characterised by non caseating granulomas at the sites of the disease. It can affect more than one organ at a time amongst which mediastinal lymph node and pulmonary sarcoidosis are the most common clinical presentation. The definitive diagnosis of sarcoidosis can only be made with the clinical features and the histopathological finding of non caseating granuloma, so that all the other differential diagnosis are excluded.[(1)]As the clinical presentation of sarcoidosis is similar to tuberculosis and malignancy (which are also systemic diseases, can present with mediastinal lymphadenopathy), proper histopathological examination is necessary to diagnose the condition precisely. The clinical presentation and diagnostic evaluation of sarcoidosis is briefly described in the table below.

Table 1

SYSTEM	CLINICAL PRESENTATION	INVESTIGATION	DIFFERNTIAL DIAGNOSIS
OCULAR	Uveitis Pars planitis Optic disc nodule Choroid nodule	Conjunctival biopsy (low yield)[(13)]	Tuberculosis Vasculitis
CARDIAC	Arrythmia Heart block Valvular disease	Cardiac MRI Positron Emission Tomography Speckle tracking Echo	Restrictive cardiomyopathy Infarction Pericardial disease
RENAL	Nephrolithiasis Nephrocalcinosis Interstitial nephritis	Renal biopsy	Tuberculosis Berylliosis Coccidiodomycosis
LIVER	Hepatomegaly Hepatic nodule	Liver biopsy	Infections Drug induced liver injury Malignancy
METABOLIC	Hypercalcemia Lymphopenia with CD4 depletion		Tuberculosis GPA Berylliosis Candidiasis
SKIN	Erythema nodosum Papular sarcoidosis Lupus pernio	Skin biopsy (except erythema nodosum)	Tuberculosis Malignancy Antibiotics(pencillin , sulphonamides) Cat scratch fever
PULMONARY	Hilar lymphadenopathy Reticulonodular opacities	EBUS TBNA TBB	Tuberculosis Lymphoma Malignancy

Despite the varied clinical presentation of systemic sarcoidosis, Hilar and /or paratracheal lymphadenopathy is present in almost 90% of the patients, which are almost always an incidental finding in CT thorax. [(2)] All these patients can be subjected to EBUS guided TBNA of the enlarged lymph nodes, in order to confirm the histopathological diagnosis of sarcoidosis and to rule out the other differentials. Studies have shown that EBUS TBNA is a safe and useful tool in the diagnosis of Stage 1 and 2 sarcoidosis with sensitivity of 83% to 93% and specificity of 100%.[(3)]. The sole purpose of this study is to highlight the importance of real time Endobronchial ultrasoundguided Trans bronchial needle aspiration(EBUS-TBNA) in the diagnosis of systemic sarcoidosis as it is minimally invasive and is associated with less incidence of complications.

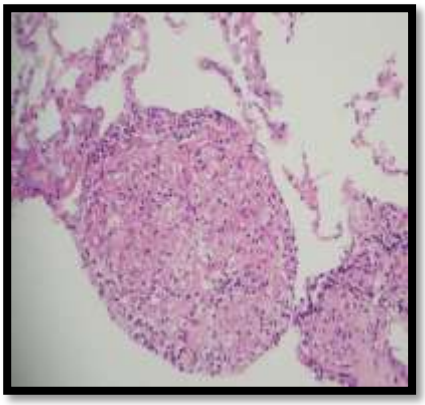
II. Methods

This is a retrospective study which includes11patients who presented to our institution, Aster RV hospital, JP Nagar, Bangalore over a period of 1 year 6 months.These patients were referred to us by different speciality doctors, all these patients had presented with a variety of clinical symptoms and signs like watering of eyes, blurring of vision, facial puffiness,pedal edema, breathlessness, cough, fever and weight loss. All these patients who presented with a clinical suspicion of sarcoidosis underwent CT thorax which revealed hilar or mediastinal lymphadenopathy. With informed consent, Conventional flexible bronchoscopy was performed first followed by EBUS TBNA using the ultrasound probe in the presence of ROSE (Rapid pathological Onsite evaluation)cytopathologist .A diagnosis of sarcoidosis was made by demonstrating the histopathological feature of sarcoidosis (non caseating granulomas)in biopsy. Other granulomatous diseases were excluded after reviewing the patient's history, Tuberculin Skin test and following up with the microbiological results of the TBNA sample like smear, Xpert MTB and cultures. The clinical presentation of these patients and the management has been described in the table below.

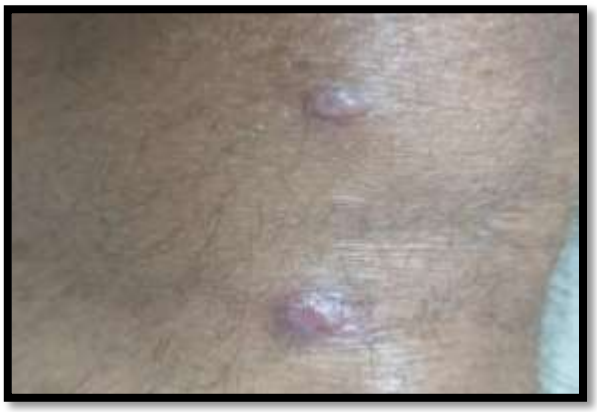
Table 2

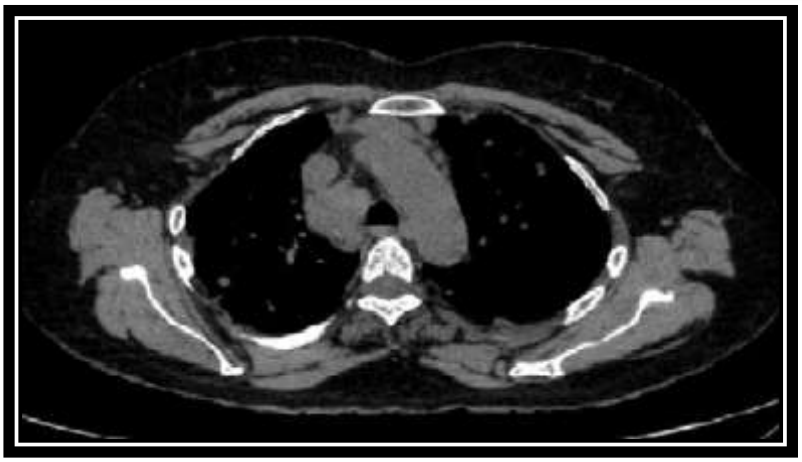
Sr.No	Clinical Presentation	Diagnosis	ACE levels	TST	EBUS-histopathology	Treatment	Follow up Reports
1	B/l anterior uveitis	Systemic sarcoidosis(lymphnode + uveitis)	58	negative	Granulomatous inflammation Fundoscopy - Optic disc granuloma, Multiple chorio retinal lesions	steroids	ACE- 28
2	Cough, SOB	Pulmonary sarcoidosis	33.7	negative	Granulomatous inflammation	Steroids MMF	PFT with DLCO-FVC-2.33(75), FEV1-1.56(64), FEV1FVC-0.669, DLCO-44%
3	Cough, SOB	Pulmonary		negative	Granulomatous inflammation	Steroids	After 1 month
4	Fever, weight loss	Systemic sarcoidosis(mediastinal lymphnode+Uretric calculi)	1.37	negative	Granulomatous inflammation		
5	cough	Mediastinal lymphnode sarcoidosis	28	negative	Granulomatous	Steroids MMF	PFT with DLCO-FVC-3.04(50),FEV1-2.67(56),FEV1FVC-87%,DLCO-65%
6	Cough, SOB	Mediastinal lymph node sarcoidosis	15.3	negative	Granulomatous Inflammation	Steroids	Serum Ca- 10.20
7	Cough, SOB, fever on ATT	Mediastinal lymphnode sarcoidosis	94	negative	Granulomatous inflammation	Steroids	ACE- 60 FVC- 2.58(62), FEV1- 2.21(66), FEV1/FVC-0.855, DLCO-74%
8	Cough, fever ,wt loss on ATT	Pulmonary	152	negative	Granulomatous inflammation	Steroids	Calcium – 9.8
9	Cough, fever ,wt loss	Lymphnode sarcoidosis (generalize lymphadenopathy)	164.5 Calcium 9.5 Creatinine- 3.3	negative	Granulomatous inflammation	steroids	ACE- 54 Calcium- 9.4 FVC-3.32(64),FEV1-2.75(66),FEV1FVC-0.828,DLCO-45% Creatinine-1.0
10	Wt loss, watery eyes	Systemic sarcoidosis	57	negative	Garnulomatous inflammation	Steroids	ACE-47.8
11	Cough ,wt loss	Mediastinal lymphnode sarcoidosis	190	negative	Granulomatous inflammation	Steroids	

Granuloma on HPE



Erythema Nodosum





CT picture of Right Paratracheal Lymph node

Procedure

EBUS is a minimally invasive and extremely safe procedure to diagnose infections, malignancy and other diseases causing enlarged lymph nodes in the mediastinum. Convex probe EBUS was performed in all these patients with a convex transducer probe, which is integrated at the tip of the flexible bronchoscope. The diameter of the bronchoscope was 6.9 mm. The field of view of the scope was 80^0 and forward oblique view was $35^{0.}$. Images can be obtained by scanning with the probe and filling the balloon at its tip with saline for keeping the probe in contact with the bronchial wall while sampling of the lymph node. The image was given by the ultrasound scanner (Olympus BFUC180F EBUS scope) along with a bronchoscopy image also. This system has an inbuilt colour Doppler which helps in identifying the blood vessels and prevents puncturing of the blood vessels while sampling the lymphnodes. This bronchoscope has a working channel diameter of 2.2 mm and we used a conventional 21 gauge needle for the core biopsy of the lymph node.

Bronchoscopy procedures were done orally under general anaesthesia. Initially Fibre optic bronchoscopy was done to see the anatomy and the patency of the airways. Then EBUS scope was introduced and the lymph node station was identified by the surrounding anatomical landmarks. The station was then fixed with the saline inflated balloon at the tip of the scope and the lymph node is then sampled with a 21 gauge needle under ultrasound guidance. Initially the anatomy of the lymph nodes were assessed and samples were taken from the lymph nodes with abnormal morphology. The aspirated material were then smeared in glass slides, allowed to air dry and fixed with alcohol. These slides are immediately examined by the Cytopathologist (ROSE- Rapid Onsite Evaluation) . FNAC aspirate were taken in saline and sent for culture, AFB smear and Xpert MTB. The core biopsy samples were taken in formalin and sent for Histopathological examination. The diagnosis of sarcoidosis is made after demonstrating non caseating granulomas in histopathological examination in the background of clinical and radiological picture.

III. Results

This is a case series of 12 patients, who presented with a variety of clinical presentation as mentioned in the table above. These patients were referred from different speciality clinics of our hospital. All these patients were evaluated with CT Chest which revealed multiple mediastinal lymphadenopathy. All these patients were evaluated with Tuberculin skin test, Serum ACE levels, Serum calcium and other differentials like tuberculosis was ruled out. All these patients underwent EBUS guided TBNA which revealed non necrotising

granulomatous inflammation on Histopathological examination and the tissue was negative for Xpert MTB, AFB Cultures .The procedure was performed in all these patients under general anaesthesia and the procedure was uneventful. There were no intraoperative or postoperative complications.

IV. Review of literature

In the earlier days, patients with mediastinal lymphadenopathy/ suspected sarcoidosis with lung parenchymal changes usually undergo a transbronchial lung biopsy, when negative were referred to Mediastinoscopy and conventional lymph node biopsy. With the availability of Endobronchial ultrasound, TBNA has become much easier, less invasive, safer and more economical alternative with less number of complications and minimal hospital stay, especially for sampling mediastinal lymph nodes. Also immediate ROSE(Rapid Onset Evaluation) of the aspiration sampling can completely obliviate the need of lung biopsy which definitely comes with severe complications like pneumothorax and bleeding.

There are several studies that highlight the efficacy of EBUS TBNA in the diagnosis of sarcoidosis because of its minimal invasiveness, less cumbersome as compared to conventional TBNA/ mediastinoscopy.

One study conducted a RCT to compare the efficacy Conventional versus EBUS guided TBNA which showed that the diagnostic yield of EBUS guided TBNA was superior to conventional TBNA for stage 1 and 2 sarcoidosis (83.3% vs 53.8%)[4]

EBUS guided TBNA has been accepted as a sensitive and minimally invasive tool in the diagnosis of sarcoidosis, however there are few studies [5]whichdescribecertain factors which would increase the diagnostic yield,including number of passes . The diagnostic yield is 80% for the first 5 passes, but no increase more than 7 passes. Also, in this study, the diagnostic yield of EBUS-TBNA was 85%, amongst which 94% in stage I, and 80% in stage II disease .This study confirms that the yield of EBUS guided TBNA in the diagnosis of systemicsarcoidosis is almost similar to mediastinoscopy and also it can a preferred option because it is minimally invasive and there is a less incidence of complications.

There are factors contributing to the diagnostic yield of sarcoidosis by EBUS TBNA. One study[6]examined the correlation between the cytologicalpreparations, number of aspirates per node, lymph node location and size to the diagnostic yield, however no correlation was found.

One study published in JAMA 2013, an RCT which was done across 6 countries in 14 centres, over a period of 2 years confirms that the diagnostic yield is better with EBUS guided TBNA in patients with Stage1/2 sarcoidosis[(8)]

V. Discussion

Sarcoidosis is a multisystem disorder, but 90 % of the patients shows evidence of hilar enlargement in the chest radiograph. [(7)]It has a varied mode of clinical presentation like fever, weight loss and cough, vision loss, skin rashes whereas some patients maybe asymptomatic. Since it is a multisystem disorder it can also present with uveitis, erythema nodosum, chest pain and breathlessness as in case of cardiac sarcoidosis, facial puffiness and anasarca as in case of renal sarcoidosis. Despite of its varied clinical presentation , precise diagnosis is possible by EBUS guided biopsy of the mediastinal lymphnodes as it is the most common presentation of sarcoidosis. It is also a minimally invasive tool in the diagnosis of sarcoidosis even in asymptomatic patients who present only with hilar enlargement as an incidental finding(stage 1) . The incidence of complications like pneumo mediastinum, hemothorax, haemoptysis and pneumothorax are very less when compared to mediastinoscopy.

VI. Conclusion

Systemic sarcoidosis is one of the most common underdiagnosed diseases in India. The Clinical presentation of systemic sarcoidosis overlaps with other diseases as shown in table 1,hence is almost always falsely diagnosed and treated in certain peripheral centres due to lack of tissue diagnosis . This study highlights the importance of EBUS guided TBNA in the histopathological definitive diagnosis of sarcoidosis, thereby other differentials can be excluded and can be treated accordingly. EBUS is most accepted diagnostic tool for systemic sarcoidosis because of its high sensitivity, it is minimally invasive , less number of complications and also shorter learning curve compared to mediastinoscopy. Hence it is ideal to get a pathological diagnosis for all patients presenting with symptoms associated with hilar enlargement before falsely starting them on empirical anti tubercular treatment, which is still being followed in many peripheral centres in India.

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