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Review Article:
Approach to Intrathoracic Lesions in areas with high prevalence of Histoplasmosis and Sarcoidosis

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Short Title: Intrathoracic lesions

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ABSTRACT
Differential diagnoses of patients presenting with lung lesions and/or mediastinal lymphadenopathy are primary malignancy, lymphoma, germ cell tumors, metastatic disease, granulomatous lesions, fungal infections such as histoplasmosis, hamartomas, and other benign neoplasm. Despite being a significant and frequent problem, there are few management guidelines recommending the approach to these lesions. Large size and positron emission tomography (PET) positivity of benign lesion is a common finding in areas with high prevalence of histoplasmosis and sarcoidosis. The current guidelines do not specifically address these problems. So, clinicians in these areas face a dilemma on deciding aggressiveness of diagnostic tests. Current diagnostic modalities including serology, imaging, bronchoscopy, etc. have limitations on classifying these lesions into benign vs. malignant. This exposes patients to multiple invasive procedures including surgical biopsy that might be unnecessary in many cases. In this review article, we have analyzed the role of various diagnostic modalities in these patients and proposed a clinico-radiological approach based on current literature. We believe this approach will lead to a decrease in health care costs by limiting the number of invasive diagnostic procedures and may also decrease morbidity and mortality associated with invasive procedures.

INTRODUCTION
Patients presenting with lung lesions and/or mediastinal lymphadenopathy are common problems for pulmonologists and thoracic surgeons. Differential diagnoses of these lesions are primary malignancy, lymphoma, germ cell tumors, metastatic disease, granulomatous lesions, and fungal infections such as
histoplasmosis, hamartomas, and other benign neoplasm. Despite being a significant and frequent problem, there are few management guidelines recommending the approach to these lesions. These cases are even more challenging in areas with high prevalence of histoplasmosis and sarcoidosis for the following reasons.

Firstly, the current recommendation for pulmonary lesions more than 3 cm in diameter is to presume malignancy until proven otherwise. Also, the prevalence of malignancy is presumed to increase with the size of the lesion that persuades clinicians to pursue aggressive diagnostic tests. However, both Histoplasmosis and Sarcoidosis commonly present with multiple lung lesions, occasionally large in size (up to 5-7 cm), and can also have significant mediastinal involvement. Thus, the management plan based on the size of the lesion could be unnecessarily aggressive in these areas (specifically the Mississippi and Ohio River valleys).

Secondly, the current recommendation for Fluorodeoxyglucose positron emission tomography/Computed tomography (FDG-PET/CT) positive lesion is to pursue until final histological diagnosis. However, many of the intrathoracic lesions due to histoplasmosis and sarcoidosis are FDG-PET/CT scan positive. So, following this recommendation in the areas with high prevalence of histoplasmosis and sarcoidosis will expose patients to unnecessary invasive diagnostic and therapeutic procedures.

Current management guidelines do not specifically address above mentioned problems in management. Due to this and also because of the limitations of various diagnostic modalities in these situations (as explained later), patients are required to undergo myriad of invasive procedures including surgical lung biopsy to obtain the final diagnosis. The fear of losing an opportunity for a curative resection is one of the justifications for these extensive, and costly interventions in pursuit of tissue. Patients with benign lesions usually will improve with treatment or may not even need a therapy or imaging follow-up. Since most of the studies included in current guidelines are not from areas endemic for histoplasmosis and very few are from areas with high prevalence of sarcoidosis, we don’t know the true incidence of malignancy in patients presenting with lung and/or mediastinal lesions in these specific areas. We need specific guidelines on the approach to lung and/or mediastinal lesions in these areas. These recommendations will help to decrease the number of invasive tests, serial imaging and the need for patient follow-up.

In this review, we analyze the common diagnostic modalities used in these clinical scenarios, their usefulness, and limitations. We propose a clinical-radiological approach for these patients based on current evidence in the published literature. We believe this recommendation for endemic areas will offer a guide for clinicians for better management in this group of patients.

ROLE OF PRETEST PROBABILITIES

Several models of pretest probabilities have been developed to assist clinicians in decision-making and also in selection and interpretation of the diagnostic tests. These tests help clinician divide patients into high risk, moderate risk and low risk of malignancy. In addition to dividing patients into different categories (low, moderate and high risk), recommendations regarding further management have been provided as per the malignancy risk and have been incorporated into current guidelines. The size of the lesion has been included in determining pretest probability and positivity in PET/CT scan has been used to determine pretest probability as well as further management decision. When the pretest probability is very low or very high, the management path is clear for clinicians. For patients with moderate probability of malignancy, unfortunately, no such clear path exists.

Most of the studies on determining pretest probability are from areas non-endemic for histoplasmosis and sarcoidosis and have included lesions less than 30 mm in size. In addition, PET positivity in non-malignant lesions is not a common occurrence in the areas of above studies. However, in the Mississippi and Ohio River valley areas, and specifically in our practice area of Memphis and its
outlying areas, large size and PET positivity in benign lesion is a common finding (due to high prevalence of histoplasmosis and sarcoidosis). Using size and PET positivity as a feature of malignancy may put many of our patients in higher risk category falsely.

DIAGNOSTIC MODALITIES; USES VS. LIMITATIONS
We are going to review the diagnostic modalities and procedures commonly utilized while evaluating patients with lung and mediastinal lesions.

Serological Tests:
In case of fungal diseases presenting with lung and/or mediastinal lesions without systemic symptoms, the cultures and antigen tests are usually negative, presumably due to lower number of viable organisms in the lesions. Antibodies will not be detected in most of the cases and even when detected they are usually present in low titers (1:8 - 1:16 by Complement fixation). However, the fungal stain may show organisms in the biopsy specimen. Similarly, we do not have any specific serologic test that is diagnostic for sarcoidosis. Serum ACE level has little utility for diagnosis in case of sarcoidosis due to its limitations.

Chest X-ray:
There are no specific patterns on chest X-ray described for lesions due to histoplasmosis, although multiple calcified lung nodules and mediastinal nodes are frequently seen in these patients. In the absence of calcification, chest X-rays are not very helpful in endemic areas except for initial detection and sometimes, for follow-up. However, chest X-ray has been helpful in cases of sarcoidosis (with typical appearance) in appropriate clinical scenario. Also, when lesions show typical calcifications described for a benign lesion (diffuse, central, laminated and popcorn patterns), further investigations can be prevented.
CT Chest:
Computed tomography (CT) has become an important tool in the management of lung lesions; both for initial evaluation and subsequent follow-up. CT scan gives information on characteristics of lesions (size, shape, calcification, attenuation, border, etc), number, location and associated findings. Size more than 3 cm, irregular border, rapid rate of growth, multiplicity, lower mean density, inhomogeneity, indistinct edges, presence of bronchus and vessel sign, presence of spicules are characteristics suggestive of malignant process whereas lack of growth for two or more years and presence of calcification are suggestive of benign process. Cavitations associated with thick and irregular wall is highly suggestive of malignancy. Similarly, CT halo sign has been defined in relation to benign lesions. However, studies have shown that the prevalence of malignancy could be up to 60% in nodules less than 2 cm, eccentric calcifications are seen in malignant lesions, even lesions with smooth borders have around 20% likelihood of being a malignant and some malignant processes like alveolar cell carcinoma grows very slowly. Also, the time to calcification in benign lesions is variable and cannot be used alone to distinguish absolutely from malignancy and many nodules never calcify. In addition to this, the lesions due to histoplasmosis do not have any special features in CT chest that would help clinicians to diagnose them and limit or plan further investigations. Thus in our geographic area, CT scan of the chest has limited value in diagnosing lesions due to histoplasmosis and sarcoidosis except when the presentation is typical (in case of sarcoidosis), and lesions have typical calcification.

The Fleischner Society guidelines on follow-up of lung lesions are limited when the lesions are larger (> 1 cm) in size and patients are younger. In areas endemic with histoplasmosis and sarcoidosis, you can routinely see patients (even younger age group) with lesions up to 5 cm being ultimately diagnosed as histoplasmosis or sarcoidosis. Hence, in endemic areas this guideline may not be very helpful.

PET/CT Scan:
PET/CT Scan helps clinicians in differentiating benign from malignant lesions as well as in staging the disease once the lesion has been diagnosed with cancer. At present, in cases of solitary pulmonary nodules (SPNs), a cut off standardized uptake value (SUV) of 2.5 is used to separate benign (lower SUVs) and malignant (higher SUVs) lesions with high sensitivity and good specificity. However, in lesions due to fungal and granulomatous diseases, the SUVmax can be significantly higher than this cut-off value. This is one of the dilemmas faced by physicians in this area in the utilization of PET/CT scan. Delayed PET/CT scan (where initial PET scan is followed by another PET scan in 1-2 hrs) has shown some promise in this situation. In malignant diseases, the SUVmax of lesions are expected to remain same or increase in delayed scan, whereas, in cases of benign lesions, the SUVmax can decrease, remain stable or increase.

In our recently published study on patients from this area endemic in histoplasmosis and sarcoidosis, we found that the decrease in SUVmax in delayed scan had a 100% negative prediction value in ruling out cancer. Dual time point PET/CT has also been found useful to evaluate the persistence of pulmonary involvement in sarcoidosis.

In areas endemic for tuberculosis, current literature reports no advantage or help of delayed PET/CT in differentiating it from malignant lesions.

So, in patients presenting with lung and/or mediastinal lesions from these areas, the decrease in SUVmax of lesions in delayed scan can help clinicians to decide when to stop further investigation. However, PET/CT scan can be of limited use in cases of adenocarcinoma, carcinoid or bronchoalveolar cell carcinoma since many times these lesions do not light up.

Bronchoscopy with biopsy, Transbronchial Needle Aspiration (TBNA):
Although a valuable tool in the diagnosis of malignant lesions, its utility in cases of fungal lesions like histoplasmosis is limited due to the low organism burden in these lesions. For sarcoidosis, the diagnostic yield depends on the experience of the operator, stage of disease and also a number of biopsies taken\textsuperscript{12}. The diagnostic yield of TBNA in sarcoidosis ranges from 40-90\% with increased yield if transbronchial lung biopsy is performed, in addition, with the caveat of increased complications.

**Endobronchial Ultrasound (EBUS)/ Esophageal Ultrasound (EUS):**
There is ample evidence of the superiority of EBUS/EUS in the diagnosis of malignant lung and mediastinal lesions as compared to bronchoscopy with conventional TBNA, especially in the mediastinum. We do not have data on sensitivity and specificity of diagnosis of histoplasmosis with EBUS TBNA. In case of sarcoidosis, however, the diagnostic yield in mediastinal lesions has been reported between 54-93\%\textsuperscript{12,13}.

**Transthoracic Needle Aspiration (TTNA):**
The diagnostic sensitivity of transthoracic needle aspiration is very high in patients with carcinomatous malignancy. However, the high incidence of non-diagnostic biopsy results in patients with benign lesions. In addition, mediastinal lesions are not generally accessible with transthoracic needle aspiration.

**Surgical Lung biopsy:**
Surgical lung biopsy is usually diagnostic for these lesions as the appropriate stain might show the organisms in the biopsy specimen. Also, it will rule out malignancy in suspicious lesions. Mediastinoscopy is almost 100\% sensitive in sarcoidosis but is expensive and thus is not recommended routinely. Also, the location of nodule will decide on approach; if subpleural we can readily use Video-assisted thoracoscopic surgery (VATS), while if in a central or peri-hilar location, thoracotomy may be indicated. However, surgical biopsy is associated with increased morbidity and mortality as compared to other diagnostic modalities in addition to increased costs. Thus, the overall burden in health care system will be high if every patient is referred for this procedure.

**DISCUSSION**
*Histoplasma Capsulatum,* the causative agent of histoplasmosis, is found worldwide, particularly in North and Central America. In the United States, *H. Capsulatum* is most prevalent in the midwestern and central states along the Ohio and Mississippi River valleys, but also occurs in microfoci in several states along the East Coast. It is also found throughout Mexico, Central, and South America, as well as in parts of eastern and southern Europe, Africa, eastern Asia, and Australia\textsuperscript{3,4}. Our clinical practice area (Memphis, TN, and adjoining areas) is endemic for histoplasmosis and with significant presence of African American population in the area; it also has a high prevalence of sarcoidosis. Both of these diseases presents with bulky intrathoracic lymphadenopathy with or without lung lesions.

Differentiating malignant from benign chest lesions has always been a difficult task for the clinicians. The problem lies in the fact that most of the criteria or features defined are for malignant lesions. Except for stability of lesions for two years and characteristic calcification patterns, there are no other features assigned specifically to benign lesions. Mostly lack of features defined for malignant lesions has been used to define the benign lesions.

If patients fall into low probability group for cancer, they can be followed with serial CT and/or PET scan as per current guidelines. However, in patients with moderate risk of cancer (based on clinical evaluation and pretest probability criteria), clinicians might not feel comfortable to wait and usually decides on getting invasive procedures early. The current approach for patients who fall in the moderate probability of cancer is to proceed with either PET/CT scan, contrast-enhanced CT or
The problem in following this in areas endemic for histoplasmosis and sarcoidosis is the high incidence of patients with PET positive benign lesions of significant size (5-7cm) which may never calcify. So, in these areas decision to proceed with further invasive biopsy based on size and PET scan result will lead to increase number of invasive procedures including surgical lung biopsy increasing not only the cost of health care but also morbidity. Therefore, the major question is which group of patients who has moderate risk of having malignant lesions can be safely observed without surgical biopsy when less invasive measures fail??

In case of sarcoidosis, bronchoalveolar lavage, transbronchial biopsy, and increased use of EBUS has lead to increased success in getting a diagnosis.

With histoplasmosis, the situation is different. We do not have much evidence on the utility of EBUS. Since the problem is low organism burden in lesions, there is doubt if it will be any more helpful than conventional bronchoscopy. As mentioned before, serological tests, bronchoscopy, TTNA are usually not very helpful. The findings on imaging like chest X-ray and CT chest are also not very distinctive in these cases. Due to the size of these lesions, they are usually pushed towards a higher probability of malignancy per the current guidelines.

There is a potential role for delayed PET/CT scan with dual point imaging in this scenario3. We found that if the SUVmax of a lesion is decreased in delayed scan, its chance of being malignant is very low (negative predictive value 100%). However, if the SUVmax increases or remains stable in the delayed scan, the lesion is indeterminate in nature as we found that some of the benign lesions can have an increase in SUVmax in the delayed scan. The decrease in SUV max in delayed scans in benign lesions has also been shown in other studies15. The timing of delayed PET/CT scan depends on clinical decision. It can be performed after detecting the lesion on a CT Chest or after interventional bronchoscopic procedure (either conventional or EBUS) and transthoracic needle aspiration has failed to reveal any diagnosis. The need for interventional bronchoscopic procedure (either conventional or EBUS) and transthoracic needle aspiration will be more especially if clinical suspicion is high for sarcoidosis (for possible treatment). If the clinician decides to start with delayed PET/CT scan, then the decision to do above mention procedures (like bronchoscopy, EBUS, and transthoracic needle) will solely base on clinician’s decision. However, even if clinician decides to do one of above procedure, with the delayed PET/CT result, they will still be able to avoid surgical lung biopsy

Thus, in patients with moderate probability of cancer, in whom the bronchoscopic or transthoracic intervention has failed to provide any diagnosis and the delayed PET/CT scan shows decrease in SUVmax, we recommend the lesions should be considered benign. In this scenario, further evaluation with surgical lung biopsy can be avoided (Fig 1). With this approach, we will be able to decrease a significant number of surgical lung biopsy decreasing overall morbidity, mortality and health care cost associated with the procedure.

This approach will be best in areas with high prevalence of granulomatous disease like histoplasmosis and sarcoidosis. We will need further studies to see if it will help in areas with other granulomatous diseases.

The difference in percentage increase in SUVmax in delayed scan between benign and malignant lesions, though suggested to be of help in previous studies, was not found to be of any aid in diagnosis in our study.

Further studies are needed on approach to lung lesions from areas with high prevalence of granulomatous diseases to help clinicians make better decisions. Increased knowledge and understanding will lead to better approach; decrease the number of invasive procedures and imaging studies. This will help decrease morbidity, mortality and also the overall cost of healthcare.

CONCLUSION
In areas with high prevalence of histoplasmosis and sarcoidosis, patients can present with PET positive lung and/or mediastinal lesions of significant size. In these patients, we suggest a different approach from the commonly practiced aggressive invasive interventions. In patients with moderate probability of cancer, in whom the bronchoscopic or transthoracic intervention has failed to provide any diagnosis and the delayed PET/CT scan shows decrease in SUV max, we suggest that the lesions should be considered benign. Our approach should lead to a decrease in the number of invasive diagnostic procedures (especially surgical lung biopsy) and thereby will decrease morbidity and mortality and health care costs associated with those procedures.
Legends of Figure:

Figure 1: Approach to the management of lung and/or mediastinal lesion with moderate probability of cancer. DTP- Dual time point, SUV- standard uptake value
References:


