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Utility of percutaneous ultrasound guided biopsy in the diagnosis of anterior mediastinal mass lesions

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Abstract---Introduction: mediastinal masses include a broad spectrum of histopathological and radiological entities. Although imaging modalities aid at narrowing the purposed differential diagnosis, accurate categorization is not always possible. Objective: to assess the efficacy as well as safety of percutaneous ultrasound guided biopsy modality in the proper diagnosis of anterior mediastinal lesions. Materials and methods: Forty patients presented with anterior mediastinal masses were enrolled in this study. Each patient was subjected to CT chest with contrast, US guided biopsy from the anterior mediastinal lesions and obtained specimens underwent histopathological examination. Then, patients were observed for possible post-procedural complications. Results: 97.5% of the included cases were symptomatic; with dyspnea [representing 62.5%] was the most frequent complaint among our cases, followed by cough and fever representing 50% and 37%, respectively. The most frequent lesions were lymphoma (40%) followed by metastatic carcinoma (25%) and thymoma (15%). Two cases showed inconclusive results (failure rate 5%). Conclusions: Combined clinico-radiological data can narrow the differential diagnosis of anterior mediastinal masses; yet histopathological examination remains the mainstay of the precise diagnosis. Percutaneous US guided biopsy is claimed to be a useful, minimally invasive cost-effective tool for proper sampling, with minimal complications and low failure rate.

Keywords---ultrasound, biopsy, mediastinal mass, diagnosis.

Introduction

The mediastinum is bounded superiorly by the thoracic inlet, laterally by pleural cavities, and inferiorly by the diaphragm. It is usually further divided into anterior, middle and posterior compartments (Fujimoto et al., 2014).. The mediastinal compartments have traditionally been valuable in the characterization, identification, and hence management of various mediastinal masses (Carter et al., 2017).

Mediastinal lesions include a spectrum of radiological as well as histopathological entities; most frequently encountered are thymic tumors, lymphoma, nerve sheath tumors, germ cell tumors and metastatic tumors as well as benign cysts (Ali, Abd El-Hafeez, Fathallah, & Hamdy, 2016). Among the mentioned settings, lymphomas are treated medically, in contrast to the surgically curable thymomas, and metastatic carcinomas, which are non resectable (Yi, Feng, Wen-Ping, Zheng-Biao, & Fan, 2017). So, a definite diagnosis is a must for adequate as well as prompt therapeutic strategies (Trousse & Avaro, 2010).

The diagnosis of the mediastinal lesions depends largely on imaging. A clinical way to differentiate mediastinal masses is to categorize them in accordance with their prominent CT attenuation values, that are composed primarily of soft tissue, vascular structures, fat, water, and/or calcium. The radiological data in combination with clinical picture and laboratory investigations can warrant the radiologist to provide a fairly confined differential diagnosis and promote needed diagnostic interventions (Trousse & Avaro, 2010).

Some anterior mediastinal tumors (namely non-seminomatous tumors of germ cell nature, thymomas, metastatic carcinomas, carcinomas of thymic gland, seminomas, and lymphomas) can be entirely similar radiologically. Precise histopathologic confirmation of radiologically similar anterior mediastinal lesions is a must for accurate therapeutic decision and remains an essential diagnostic challenge (Mohammad Vaziri, Pazooki, & Zahedi-Shoolami, 2009).

Multiple procedures are available to obtain biopsy from anterior mediastinal lesions like anterior mediastinotomy, video assisted thoroscopic biopsy, cervical mediastinoscopy, endoscopic ultrasound guided biopsy and open surgical techniques (Shrivastava, Devgarha, & Ahlawat, 2006). These techniques require general anesthesia and intubation with increased risk of pleural dissemination and surgical procedures are associated with morbidity. For these causes, surgical procedures are not suitable to obtain biopsy from lesions in the anterior mediastinum (Nasit, Patel, Parikh, Shah, & Davara, 2013). Percutaneous ultrasound guided biopsy has multiple advantages over CT guided as it can be performed in real time which enable monitoring during needle advancement and sampling (Gupta et al., 2005).

Materials and Methods

Patients

This prospective study was conducted during the period from December 2018 to December 2020. The patients were enrolled from Chest Department, Tanta University Hospitals. The study was carried out according to Local Research Ethics Committee of Faculty of Medicine, Tanta University (reference# 34152). Informed written consent from was obtained from each participant in the study.

Forty patients presented with anterior mediastinal lesions (25 males, 15 females; mean age 37.5 years) were eligible for this study.

Inclusion criteria: anterior mediastinal lesions; in either symptomatic or asymptomatic patients; in whom these lesions were accessible for US guidance.

Exclusion criteria: patients with mediastinal lesions which has high vascularity by colour doppler ultrasound (and in whom vessels couldn't be avoided), patients with bleeding tendency, International normalized ratio more than 1.5, prothrombin activity less than 50%, or platelet count less than 40 000/mL.

All patients were assessed for history, clinical features, presenting complaints (dyspnea, cough, hoarseness of voice, fever, hemoptysis, pressure manifestations, and pain). CT chest with or without contrast was performed for all patients before the technique. The US guided biopsy technique was done according to Gupta (10), obtained biopsies were sent for (or in some cases seen for adequacy insitu) histopathological examination, and patients were monitored for post-procedural complications.

Procedure

Pre-procedural preparation:

1. Routine laboratory assessment including prothrombin time and concentration (PT, PC, and international normalized ratio) were investigated in all patients to correct any bleeding diathesis; to minimize possible puncture site bleeding or hematoma which is one of the post-procedural complications.
2. All patients underwent radiological evaluation using chest radiography and CT chest with contrast to obtain proper delineation of the detected lesion and the surrounding anatomical areas in order to choose the safest target lesion.
3. All possible complications were explained to the patients through the written consents.

Ultrasonographic evaluation:

1. All patients performed a preceding US checkup of their entire body [abdomen, pelvis, groin, axilla and neck] to ascertain the diagnosis and to select proper area of sampling.
2. US examination of the chest for accurate localization of the lesion (Figure I).

3. A color-Doppler sonography must be performed to identify the surrounding major vasculature in order to decide a safe and suitable access for each case (Figure II).
4. Sonographic images of the anterior mediastinum were accomplished through parasternal, suprasternal or subxiphoid approaches.
5. Under local anaesthetic drug, a direct mediastinal approach through placement of the biopsy needle through an extra-pleural space medial to the lung to avoid transgression of the lung and pleura or trans-pleural if needed. The needle can be advanced through [1 patient] or lateral to the sternum [37 patients], through the suprasternal notch [2 patients], no cases were done through the subxiphoid space [0 patients].

The methodology of ultrasound examination

1. US device appropriate for thoracic visualization including 3.5, 5, 7.5, and 10 MHz linear, convex, and microconvex transducers (Model: Antares, 2011).
2. Sterile transmission gel was administered to the thoracic skin as a merging medium.
3. The lesion was visualized in grey scale, real-time US imaging with/without color Doppler evaluation.
4. A high frequency (i.e. 5 or 7.5 MHz) linear or convex transducer was used to detect superficial mass lesions located in anterior mediastinum.
5. A microconvex transducer was used for lesions with small US window.
6. 16–18G Tru-cut biopsy needles were used to perform the technique of percutaneous US guided biopsies.

Procedure

1. Accurate visualization of the cutting needle inside the targeted lesion with good accessibility denotes technical success of the procedure (Figure III).
2. To ascertain adequacy of the specimen and to minimize failure rate of the technique; numerous biopsies were usually required.
3. Presence of on-site pathologist for sample adequacy confirmation would help to minimize the multi-puncture sampling.

Post-procedural monitoring

1. Routine assessment of patients to monitor possible post-procedural complications as pain, shock, bleeding or puncture site hematoma.
2. Routine chest radiography was performed half an hour after the technique to exclude possible major complications (as pneumothorax and/or hemothorax).

Histopathological examination

On-site specimen evaluation required rapid technique of frozen section as well as imprint preparation. The on-site technique aimed to evaluate the specimen adequacy rather than obtaining final diagnosis. Further diagnostic histopathological evaluation depended on routinely stained sections using hematoxylin-eosin stain together with immunohistochemical techniques [in

selected cases] "performed in the proper clinical and radiological setting". Tissue specimens were immediately [post-procedural] fixed using neutral buffered formalin (conc 10%); and subjected for microscopic examination. The purposed radiological diagnosis was confirmed or excluded depending on hematoxylin and eosin (H&E) stained formalin-fixed paraffin-embedded tissue sections. In selected cases, in which final diagnosis could not be established by routine examination, a detailed immunohistochemical panel of pan-cytokeratin (pan-CK "for epithelial differentiation"), leucocytic common antigen (LCA "for lymphocytic differentiation" or its alternative name cluster of differentiation 45 "CD 45"), as well as CD 20 [denoting B cell origin], CD3 [denoting T cell origin], CD15, and CD 30 was applied. Immunohistochemical markers specific for certain tissue were also considered in case of metastatic epithelial neoplasm for identifying the possible primary sites. Briefly, Dako automated immune-stainer (Link 48) was used for immunostaining.

Statistical analysis

Collected data were summarized and analyzed by using an appropriate statistical package program (SPSS version 10).

Results

Of the 40 cases included in the current study; there were 25 patients of male gender and 15 females, with male to female ratio around 5:3. The mean patient age was 37.5 years (range 2–61 years), 22 patients (55%) were smokers. Only single case was diagnosed as thymic cyst (2.5%), this case was incidentally discovered without obvious symptomatology, whereas the reminder showed variable symptoms at presentation, dyspnea (62.5%) was the most frequent complain among studied cases, followed by cough and fever representing 50% and 37%, respectively. The clinical presentations of the studied cases were represented in table (I).

Among the studied cases, histopathological examination (table II, III) revealed that 67.5% of the lesions were malignant and only 27.5% were of benign nature. Lymphoma ranked the first among the diagnosed cases representing 40% of cases. Immunohistochemical staining (using CD20, CD3, CD15, CD30) was performed for further immunophenotyping. After both routine H&E; immunohistochemical evaluation which was done when the tissue biopsy was insufficient; Classic Hodgkin lymphoma (including nodular sclerosis variant) were documented in 6 cases, and non-Hodgkin lymphoma (NHL) in 8 cases; 7 cases out of them were of diffuse large cell lymphoma B cell origin (the neoplastic cells showed positive membranous staining for CD20). The remaining 2 cases showed lymphoblastic lymphoma.

The diagnosis of metastatic carcinoma was encountered in 10 cases [representing 25%]; with the pathological examination showed masses and nests of neoplastic hyperchromatic pleomorphic epithelial cells with intervening dense desmoplastic/inflammatory stromal reaction. Immunohistochemistry together with the usual metastatic work up was also considered for proper identification of the primary sites.

A single case was diagnosed as small cell carcinoma [categorized a unique entity, because it may represent a primary versus metastatic mediastinal malignancy]. The histology exhibited dyscohesive small rounded to ovoid hyperchromatic neoplastic cells with wide areas of necrosis and frequent mitotic figures. Among cases of thymoma, the predominant variant was suggestive provisionally for B subtype (cortical) and showed clusters and rosettes of bland looking mildly pleomorphic hyperchromatic epithelial cells exhibiting eosinophilic cytoplasm and centrally located nuclei, embedded within dense fibrous stroma showing lymphocytic infiltration. Excision biopsy was recommended for proper categorization. No cases of thymic carcinoma were detected.

On the other hand, four cases showed prominent epithelioid histiocytic infiltration; two of which were of necrotizing type (necrotizing granulomatous lymphadenitis), and a diagnosis of tuberculous lymphadenitis was given and assured after serological confirmation. The other non-necrotizing epithelioid granulomata (specifically lacked a mantle of surrounding lymphocytes) were suggested to have sarcoidosis. A serum Angiotensin Converting enzyme inhibitor was recommended. Only single case showed thymic cyst on histological examination.

In the present study, false negative diagnoses were obtained in 2 patients (5%) due to sampling necrotic tissue in one case (2.5%) as well as inadequate specimen in the other case (02.5%); which was diagnosed as a lesion of an inflammatory nature. Upon follow up, re-biopsy was performed, and the histopathology revealed malignant lesion with super-added infection.

Post procedure complications were in the form of pain at the site of biopsy in 15 patients (37.5%), only single case (2.5%) had severe pain up to neurogenic shock, which was relieved using potent analgesia. Failure rate of the procedure was 5% as two cases were not finally diagnosed, mortality rate due to the procedure was Nil (table IV).

Discussions

Mediastinal masses can be attributable to a range of benign and malignant lesions. Though differential diagnosis is exceedingly broad, and diagnosis is primarily based on clinico-radiological characteristics, a precise diagnosis would require histopathological evaluation (Safavi, Hosseinian, & FIROUZBAKHS, 2004).

In the current study, 97.5% of the included cases were symptomatic at their presentation; Dubashi et al. and Sharma et al. (Dubashi, Cyriac, & Tenali, 2009; Sharma, Jha, Kumar, Kumar, & Mandal, 2017) reported nearly close figures of 97% and 96.8% of their patients presented with symptoms, respectively. A wide range of 60–88% incidence was shown in various reports (Davis, Oldham, & Sabiston, 1987; Duwe, Sterman, & Musani, 2005). On the contrary, Ganesan et al. (Ganesan et al., 2007) argued that only 40% of mediastinal masses were asymptomatic at presentation; such asymptomatic masses are thought to be more likely benign, whereas symptomatic cases may often harbor malignancies.

An old study by Davis et al. (Davis et al., 1987) showed that only 46% of cases with benign neoplasms had evident complaints, on the other hand 85% of patients having a malignant lesion were symptomatic. In the current study, the single asymptomatic case was proven histologically to be benign (thymic cyst). The differences encountered between various studies may be accounted for the fact that the patients almost always visit the clinic for their presenting symptoms, not for routine check-up.

In the present work, the most frequent symptoms encountered amongst studied patients were dyspnea, cough, and fever. Previous reports by Sharma et al., Shrivastava et al. and Bastos et al. (Bastos et al., 2007; Sharma et al., 2017; Shrivastava et al., 2006) noted similar presentations. In this study, the presence of hoarseness of voice (as a result of recurrent laryngeal nerve paralysis) and compression symptoms were suggestive of malignant etiology; this matched Rice et al. and Ganesan et al. (Ganesan et al., 2007; Rice, Rodriguez, & Light, 2006) stated that the single critical tumor which can be entirely asymptomatic and could be diagnosed incidentally on chest X-rays done for coincidental purposes is thymoma that was reported in 50–60% of cases.

Interestingly, Vaziri et al., (Mohammad Vaziri et al., 2009) encountered some strange associations with particular mediastinal masses, including sternal osteochondroma with Schwannoma, nasopharyngeal carcinoma with intra-thoracic goiter, and neurofibromatosis with ganglioneuroma.

The most essential modality for the assessment of mediastinal lesions is computed tomography (CT), which demonstrates all vital structures of such region and supplies information about the encountered pathologic abnormalities. Imaging using ultrasound waves has assumed greater importance including conventional percutaneous ultrasound of the mediastinum (Dietrich et al., 2015; Koegelenberg, von Groote-Bidlingmaier, & Bolliger, 2012). It can mark both normal and pathological lesions, particularly deeply located lymph nodes in the mediastinal region, but this method is not universal and requisite special competency. Incomparable to CT, studies testing mediastinal ultrasound, published 20-30 years ago, cleared that the parasternal and suprasternal approaches, had a sensitivity of 69–100% for the identification of pathological lesions [specifically lymphadenopathy] in the mediastinal compartments (Wernecke & Diederich, 1994; Wernecke, Vassallo, Rutsch, Peters, & Potter, 1991).

US guided biopsy has superiority over other radiologic techniques, including lower cost, bedside capabilities (suitable for patients with dyspnea who couldn't withstand the recumbent position of the CT), lack of radiation exposure (specifically considered as a disadvantage of CT usage) and time saving, significant morbidity reduction, minimizing chance of pleural dissemination (which is considered as a disadvantage of open biopsy) as well as real time monitoring (Chen, Jiang, & Zhao, 2011). Conventional US is considered an effective modality for real-time guidance of core needle biopsy (Cao, Wu, Li, Deng, & Liao, 2011). With the real-time monitoring of US, the tip of biopsy needle can be observed throughout the technique, the depth of penetration can be monitored,

and the biopsy route can be judged to avoid puncturing any of the great vessels or even the heart (Liao et al., 2000).

In the present study, 67.5% of the studied cases were proved to be malignant on histopathological examination while Vaziri et al. (Mohammad Vaziri et al., 2009) reported that 60% of their cases were malignant. Some studies reported also a higher number of about 72% prevalence of malignancy in their study (Karki & Chalise, 2011). On the contrary, most lesions included in the series of Sharma et al. (Sharma et al., 2017) were benign 73.33%. Karki and Chalise (Karki & Chalise, 2011) recorded a percent of 25–40% of these lesions were malignant.

The most common pathology diagnosed in our series was lymphoma (40%) followed by metastatic carcinoma (25%), this in agreement with Karki and Chalise (Karki & Chalise, 2011) as well as Vaziri *et al.* (Mohammad Vaziri et al., 2009) Yet, this was opposite to Nasit et al. (Nasit et al., 2013) who documented through both cytopathological and histopathological evaluation that metastatic carcinoma was the first among their cases (38%) followed by NHL (32%). Shrivastava *et al.* (Shrivastava et al., 2006) reported that thymic lesions constituted the predominant pathology in their series followed by lymphoma.⁽¹⁵⁾ Previous studies showed that thymoma represented 11% to 38% of primary mediastinal masses (Takeda et al., 2003; Wongsangiem & Tangthangtham, 1996).

The diagnostic rate of US guided biopsy of anterior mediastinal masses is dependent on the total amount of the specimens, which depend on the number of punctures as well as the size of the needles used. In the current search, a failure rate of 5% was reported, this is in contrast to Fang et al. (Fang, Xu, Chen, Chen, & Chen, 2007) who reported a failure rate of 41.7% and considered biopsy through a mini-mediastinotomy a highly effective technique superior to the US guided biopsy. As malignant tumor growth often exceeds its accompanying blood supply of tissue vasculature, necrosis usually marks the malignant masses (Nasit et al., 2013); which should be avoided during biopsy as they usually represent areas of non-vital tissue. With conventional US, the tumor tissue necrosis is radiologically presented as anechoic areas without color flow signal. As the sense of gray-scale echogenicity is operator-dependent and color Doppler flow scanning has numerous artifacts resulting from by heartbeat and breathing, areas of necrosis can be easily overlooked (Nasit et al., 2013).

Clinically, few specimens are often inadequate for proper diagnosis because of tissue necrosis. In this study, false-negative diagnoses were obtained in 2 patients (5%) due to sampling of necrotic tissue in one case (2.5%) and inadequate specimen in the other case (2.5%). Yi et al. (Yi et al., 2017) reported a slightly higher percent of false-negative diagnoses were obtained in four patients (about 8.9%) in the US technique due to necrotic tissue specimens, and in three patients (6.7%) due to inadequate tissue biopsy.

In the current study, the most frequently occurring post-procedural complication was pain in 15 patients (37.5%) who experienced painful sensation ranging from mild transient pain up to neurogenic shock that was reported only in 1 case (2.5%). The latter was managed by centrally acting analgesics. No other major complications were encountered. Ali et al. (Ali et al., 2016) reported also minimal

complications without occurrence of major problems. On the contrary, Nasit et al. (Nasit et al., 2013) found that most common encountered complications within various series were pneumothorax. A significant complication encountered with Vaziri and Mehrasma (M. Vaziri & Mehrasma, 2006) was the occurrence of massive spontaneous hemothorax due to ruptured ganglioneuroma in a young female presented with neurofibromatosis. The low incidence of complications in our study can be explained by proper pre-procedural preparation, real time observation of the needle by ultrasound during biopsy procedure, adjusting needle firing time with patient breath and post-procedural monitoring.

Conclusions

Combined clinico-radiological data can narrow the differential diagnosis of anterior mediastinal masses; yet histopathological examination remains the mainstay of the precise diagnosis. Percutaneous US guided biopsy is claimed to be a useful, minimally invasive cost-effective tool for proper sampling, with minimal complications and low failure rate.

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Tables

Table (I): Clinical presentation of the studied cases

Presentation	Number	Percentage
Dyspnea	25	62.5%
Cough	20	50%
Fever	15	37%
Hoarseness of voice	12	30%
Hemoptysis	12	30%
Pain	10	25%
Weight loss	9	22.5%
Pressure manifestation	5	12%
Asymptomatic [incidentally discovered]	1	2.5%

Table (II): histopathological diagnosis of the included cases; Benign Vs Malignant

Diagnosis	Number	Percentage
Malignant	27	67.5%
Benign	11	27.5%
Inconclusive [failure rate]	2	5%

Table (III): histopathological diagnosis of the included cases

Diagnosis	Number	Percentage
Lymphoma	16	40%
Thymoma	6	15%
Metastatic carcinoma	10	25%
Small cell carcinoma	1	2.5%
Sarcoidosis	2	5%
Tuberculosis	2	5%
Thymic cyst	1	2.5%
Inconclusive [failure rate]	2	5%

Table (IV): post-procedure complications in the studied patients

Complication	Number	Percentage
Mortality	0	0%
Pain	15	37.5%
Neurogenic shock	1	2.5%
Failure rate (inadequate management*)	2	5%

*delayed diagnosis or re-biopsy



Figure (I): Pre-Biopsy Scanning of Anterior Mediastinal Mass With Detected Lateral Displacement of The Lung and High Flow Vessels; Depicted to Avoid Its Injury

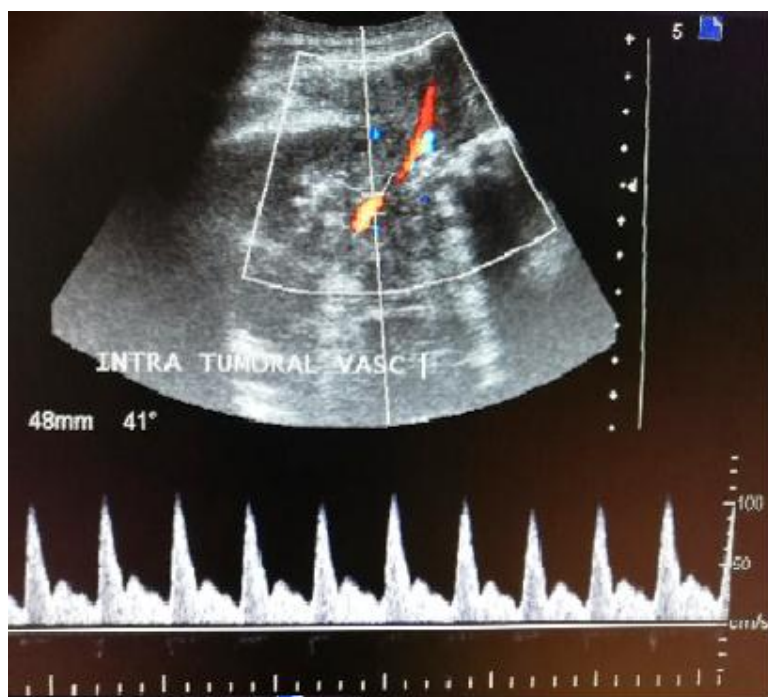


Figure (II): Pre-Biopsy Color Doppler Us Evaluation of Apparently Accessible Anterior Mediastinal Mass Invading Chest Wall with Marked Vascularity of The Tumor and High Velocity Arterial Flow Picked



Figure (III): Tru-Cut Needle Biopsy of Anterior Mediastinal Mass Located Right to The Heart With Detected Pulsation Artifact, US Guidance Assuring The Presence of The Biopsy Needle Inside Mass and Avoiding Injury of The Major Vessels