Is Cytology Necessary in Diagnosis of Mediastinal Mass?

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Background: *Mediastinal mass is an uncommon abnormality found in clinical practices of respiratory physicians. The diagnosis of a mediastinal mass arises from a clinical suspicion, and more commonly, by a check- up chest x-ray. Definite diagnosis is necessary because the managements are different in various etiologies of the masses.*
Objective: *Adequacy of cellular sample recovered from small needle aspiration is the point of question among pathologist and physician in the diagnosis of mediastinal mass. Many centers recommend fine needle aspiration biopsy for cytology (FNAB) as an adequate procedure in this situation[1-3]. This study is aimed to find the value of cytology and histological examination in the diagnosis of a mediastinal mass.*
Materials and Method: *The study was done by prospective collected data of patients who were consulted for needle aspiration biopsies of their mediastinal mass since 1999 to 2006 at the Respiratory Diagnostic Unit, Division of Respiratory disease and Tuberculosis, Faculty of Medicine Siriraj Hospital. The protocol in evaluating mediastinal mass was to obtain both cytologic slides and tissue for histology from lesions in the mediastinum by ultrasonic guidance when they were possible.*
Results: *During 1999 to 2006, there were 35 patients who had mediastinal masses referred for needle aspiration procedures. Their mean age and standard deviation were 42.37 $\pm$ 16.97 year-old. Among these patients, 22 were men and 13 were women. The mean age ($\pm$ standard deviation) of male patients was 40.47 $\pm$ 17.17 years and 45.5 $\pm$ 16.79 year- old for the female. The histology could make diagnosis in a significantly higher number of patients as compared to cytology (88.57% compared to 40%). There was statistically different higher diagnostic rate of UG-CNB than UG-FNA in non-carcinomatous group. The complications were mild.*
Conclusion: *Since most lung mass are carcinomatous in origin, depending on various factors (age, sex, smoking habit and size), the recommendation of FNA as the first line investigation are warranted because of high yield to risk for complication ratio, but in mediastinal mass in which many etiologic cells of origin cannot be diagnosed accurately by retrieved cytological cell, the CNB for small histology section is recommended as an initial investigation method without the loss of time required for cytological aspiration.*

Keywords: *Biopsy, Fine-needle, Cytology, Cytological techniques, Mediastinal neoplasms, Ultrasonography*

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Mediastinal mass is an uncommon abnormality found in clinical practices of respiratory physicians. The diagnosis of a mediastinal mass arises from clinical suspicion and more commonly by a check-up chest x-ray. Definite diagnosis is necessary because the managements are different in various etiologies of the masses.

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The diagnosis of mediastinal mass warrants study of cell or tissue obtained from many kinds of procedures. From the less to the more invasive procedures are fine needle aspiration with small needle either from transthoracic route or inside the bronchus for cytologic examination, histological section by using a larger cut needle, mediastinoscopy, mediastinotomy and thoracotomy.

Adequacy of cellular samples recovered from small needle aspiration is the critical point of question among pathologists and physicians. Many centers

recommend fine needle aspiration biopsy for cytology (FNAB) as an adequate procedure in this situation[1-3]. This study is aimed to find the value of cytology and histological examination in diagnosis of a mediastinal mass.

Material and Method

The study was done by prospective collected data of patients who were consulted for needle aspiration biopsies of their mediastinal mass since 1999 to 2006 at the Respiratory Diagnostic Unit, Division of Respiratory disease and Tuberculosis, Faculty of Medicine Siriraj Hospital. Since 1999, the Respiratory Diagnostic Unit has used ultrasonic scanner with Doppler flow detector (Toshiba model SSA-550A , Tokyo, Japan) using 3.75 or 4.0 MHz convex or linear probe to guide transthoracic needle aspiration of intrathoracic lesions. The protocol used in evaluating mediastinal mass was to obtain both cytologic slides and tissue for histology from lesions in the mediastinum when they were possible. The procedure was started with through examination of the mediastinal region with ultrasonic probe using the convex type and the mediastinal mass was localized with its relation to great vessels and heart. The internal echogenic appearance of the mediastinal mass was described. The blood supply of the mediastinal mass was evaluated by Doppler flow and only masses with low to moderate flow of blood supply proceeded to biopsies. The area from skin to the mass was evaluated for vessels, especially internal mammary vessels and the distance from the skin to mass was determined. The area of superimposition of normal lung over the mass was avoided. The puncture probe, having central channel guidance (4.0 MHz linear puncture probe, Toshiba, Japan), was prepared and the point on skin was marked for puncture by the needles. Routinely a 21-gauge fine needle constructed of steel and consisting of an inner stylet and an outer sheath (15 cm in length) was first used to obtain cells for cytologic examination, and a 16-gauge semi-automated cut needle, length 15 cm (Quick-core disposable biopsy needle, Cook Incorporated, USA) was used to obtain histological tissue. The number of needles passed depended on adequacy of the cell and tissue retrieved usually one to three passes were enough. The cytologic slides were immersed in 95% ethanol and histological tissue was put in formalin solution before being sent to the pathological department. A repeated ultrasonic examination was performed to evaluate immediate complication such as localized hematoma or pneumothorax. In case of suspicion of pneumothorax, a chest x-ray was done for confirmation. The patients were observed at least one to two hours post-procedures for vital signs and bleeding complications until stable.

The patients were followed up for their definite diagnosis either by noting their response to definite therapy or by surgical resection of the masses. Pathological sections and cytological slides were reviewed by a certified pathologist and cytologist for their concordance to the original reports.

The diagnostic rates for needle aspiration for cytology and histology (the number of positive or correct diagnoses divided by the total number of patients examined) were calculated and compared. The final results of the tumors were also divided into a carcinomatous group (epithelial in origin) and a non-carcinomatous group (other tumor including benign lesions) using the same comparison. In comparing diagnostic results, chi-square test was used. The $p < 0.05$ was considered significant different. Every complication was recorded.

Results

During 1999 to 2006, overall of 412 procedures of needle aspiration of thoracic lesions were done at the Respiratory Diagnostic Unit, Division of Respiratory disease and Tuberculosis, Faculty of Medicine Siriraj Hospital. The methods of guidance were computerized tomography, ultrasonic, plain chest x-ray or pictures from patient's previous computed tomography of the lesions and only by physical examination when lesions could be obviously demonstrated. Most of them were done only FNAB for cytology. There were 35 patients who had mediastinal masses referred for needle aspiration procedures. Their mean age and standard deviation were 42.4 ± 17 year-old. Among these patients, 22 were men and 13 were women. The mean age ($\pm$ standard deviation) of male patients was 40.5 ± 17.2 years and 45.5 ± 16.8 year-old for the female. The locations of the mediastinal mass were anterior in 28 patients and superior in 9. All lesions were guided biopsies by ultrasound per protocol described and both FNA for cytology and cutting needle for histology.

Cytology was able to make the definite diagnosis of mediastinal masses in 40% (14 out of 35) of cases as compared to histology which could make the diagnosis in 88.57% (31 out of 35) of cases. These numbers had statistically significant difference ($p < 0.001$). There was only one case of metastatic carcinoma in which cytology revealed positive

malignant cells, but that histologic section demonstrated only skeletal muscle and fatty tissue. There were 17 cases of carcinoma in this study in which metastatic adenopathy of the mediastinal nodes were involved, including non-small cell lung cancer (11), small cell lung cancer (2), renal cell carcinoma (1) and unknown primary (3). The prevalence of carcinoma in mediastinal masses was 0.48. Diagnosis could not be made by either ultrasonic-guided fine-needle aspiration (UG-FNA) or ultrasonic guided cutting needle biopsy (UG-UCB) in one case of metastasis squamous cell carcinoma and thoracotomy was need for diagnosis. There was a statistically different higher diagnostic rate of UG-CNB than UG-FNA in the non-carcinomatous group (Table 1).

In non-carcinomatous group (Table 2), there were 16 tumors including thymoma (6), lymphoma (4), seminoma (2), yalk sac tumor (2), primitive neuroendocrine tumor (1) and malignant fibrous histiocytoma (1). The only two benign lesions were organized arteriovenous malformation and chronic lobar atelectasis mimic mediastinal mass. UG-FNA could only accurately diagnose 2 out of 6 (33.3%) cases of thymoma and none of the rest. UG-CNB could be used to diagnose all non-carcinomatous tumors. Both methods could not diagnose cases of organized arteriovenous malformation that required thoracotomy for final diagnosis.

There were four complications related to the procedures. One patient developed hypotension immediately after UG-CNB was done without external or internal bleeding. The hypotension was recovered after intravenous fluid administration and vagovasal reaction was diagnosed. Two patients developed minor bleeding from the puncture sites on the chest wall and required prolong compression time. A small pneumothorax was detected in one patient without drainage being needed.

Table 1. Diagnostic rate of mediastinal masses by cytology and histology in carcinoma group compared to non-carcinoma group

Groups of diagnosis number	Diagnosed by UG-FNA number (%)	Diagnosed by UG-CNB number (%)	p-value
Carcinoma 17	11/17 (64.7)	15/17 (88.2)	0.225
Non-carcinoma 18	3/18 (16.7)	16/18 (88.9)	<0.001

Table 2. Number of cases categorized in groups and results of UG-FNA and UG-CNB in 18 cases of non-carcinoma group

Final diagnosis 18	Diagnosed by UG-FNA (%)	Diagnosed by UG-CNB (%)	Diagnosed by UG-FNA and / or UG-CNB (%)
Thymoma 6	2 (33.3)	6 (100)	6 (100)
Lymphoma 4	0 (0)	4 (100)	4 (100)
Germ cell tumor 4	0 (0)	4 (100)	4 (100)
Other malignancy 2	0 (0)	1 (50)	1 (50)
Benign lesions 2	0 (0)	0 (0)	0 (0)

Discussion

Most of the abnormalities detected from radiological finding of thoracic region especially lung and mediastinum warrant definitive diagnosis either by methods of sampling specimens for organisms detection, cytologic diagnosis and histological characteristic examination. Only in a minority diagnosis be made by other means such as antibody detection in serum or by therapeutic diagnosis. The non-surgical sampling methods of thoracic lesions were numerous but usually required some methods of guidance[4]. Except when the lesions could be visualized directly by bronchoscopy, the other guidance methods used were arbitrary and included physical examination, fluoroscopy, computed tomography[5] and ultrasound.

Doppler ultrasound is a valuable tool in evaluating thoracic lesions. Information of the content inside the lesion, relationship to the surrounding vessels and characteristic blood flow could be obtained from ultrasonic examination and real time biopsy guidance could be done with cost-benefit outcomes[6,7]. The prerequisite for ultrasonic guidance of thoracic lesion is the close contact of the lesion to the chest wall which makes most of the mediastinal mass ideal for this method and, because the mediastinal mass is usually not covered by pleura and lung tissue, the risk of pneumothorax is even less than for lesions in the lung parenchyma and chest wall.

The main limitation of ultrasonic guidance transthoracic needle aspiration biopsy is the limited window of access to the lesion in which either the lesion is not in close contact to the chest wall or there is a vessel in between the lesion and the puncture site. In the situation that occurs when the mediastinal mass is beneath the lung, the puncture can be done under ultrasound-guidance by passing the alveoli with the

risk of pneumothorax, or be better done under CT guidance using protective pneumothroax described by Scalzetti[8] .

The diagnostic rate of needle aspiration of intra-thoracic lesions depended on the amount of the specimens, which depend on the size of the needles used and number of passes. Not only does the risk of complication depend on the correct selection of the suitable lesion for biopsy, but it also depends on the diameter of the needle used.

The present study is the first report as far as literature surveyed in comparing UG-FNA and US-CNB in the diagnosis of mediastinal masses that include high number of cases. The prevalence of carcinoma in mediastinal masses was 0.48. The UG-FNA could make a diagnosis in 40% in spite of UG-CNB that yielded the diagnosis of 88.57% which different statistically. UG-CNB had statistically significant higher diagnostic rate in the non-carcinomatous lesions. There were only 3 cases whose diagnosis could not be made by both methods and they required more invasive approaches. Among these 3 cases, two of them were malignant fibrous histiocytoma and metastatic squamous cell carcinoma, only one benign case of arteriovenous malformation was missed by both procedures. The false negative results probably came from failure to sample the lesions[9] .

Schubert et al[10] found comparable results of US-guided fine-needle aspiration biopsies for cytology and histology specimens from cutting-needle biopsies with fewer special investigations and recommended US-FNA as a first line investigation. In his study, there were 97 recruited patients and mediastinal biopsies were done in only 4% of cases. Diacon AH et al[11] studied comparing the diagnostic yields of ultrasound assisted cutting needle biopsy(CNB) and fine-needle aspiration biopsy (FNAB)in 155 chest lesions in which again mediastinal lesions comprised only 17 (11%). The overall diagnostic yield was 87%. FNAB was superior to CNB in lung carcinoma but CNB was superior in non-carcinomatous tumors and benign lesions.

In the study of Hsu WH et al[12] that included 33 patients with anterior mediastinal masses underwent ultrasonically guided aspiration biopsy. UG-FNA was done on all patients but UG-CNB was done on only 13 patients who were negative from results of UG-FNA. The diagnostic rate of UG-FNA was 52% (17/33). The number was slightly higher from this reported study. The over all diagnostic rate was 79% (26/33). With different methodology they found that carcinomatous group was more easily diagnosed by UG-FNA than the non-carcinomatous group and UG-CNB was more valuable and helpful than UG-FNA in the diagnosis of non-carcinomatous mediastinal masses.

We are aware of the study by Watanabe M et al[13] which reported a 50% (5 in 10 patients) difference in diagnosis of histologic tissue obtained from histology needle and larger tissue. There were three patients in which management changed and only one in which diagnosis was made by a more invasive diagnostic procedure such as mediastinotomy. In our opinion, the use of UG-CNB is recommended before more invasive procedures in studying mediastinal mass lesions.

The rate of complications from this study was low and their severity was mild. Reversible hypotension occurred in one case from vagovasal reflex and mild bleeding from puncture sites in two patients. Minimal pneumothorax occurred after biopsy of collapsed lung without further management. Other studies also showed low complication rate but accidental puncture of the aortic wall could have occurred[12]. This uncommon episode might be due to insertion of the needle deeper than was measured therefore; real time observing of the needle during biopsy is necessary.

From the fact that most lung masses are carcinomatous in origin, depending on various factors (age, sex, smoking habit and size), the recommendation of FNA as the first-line investigation is warranted because of a high yield to risk for complication ratio, but in a mediastinal mass, in which many etiologic cells of origin cannot be diagnosed accurately by retrieved cytological cell, the CNB for small histology section is recommended as an initial investigation method without the loss of time required for cytological aspiration.

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การวินิจฉัยโดยใช้เซลล์จำเป็นสำหรับการหาสาเหตุของก้อนใน mediastinum หรือไม่

แจ่มศักดิ์ ไชยคุนา, ปานเทพ สุทธินนท์

ภูมิหลัง: *ก้อนใน mediastinum เป็นความผิดปกติที่พบได้ไม่บ่อยในทางคลินิก การให้การวินิจฉัยมักพบจากการเอกซเรย์ทรวงอกจากเหตุอื่นหรือจากการตรวจร่างกาย การหาสาเหตุของก้อนมีความจำเป็นในการให้การรักษา โดยปกติแล้วสาเหตุของก้อนมักต้องการตัวอย่างของเซลล์หรือชิ้นเนื้อเพื่อการวินิจฉัยซึ่งทำให้ผู้ป่วยต้องรับการผ่าตัดมากน้อยขึ้นกับปริมาณชิ้นเนื้อที่ใช้ การศึกษานี้เพื่อดูวิธีการที่เหมาะสมในการได้ชิ้นเนื้อเพื่อการวินิจฉัย*

วัสดุและวิธีการ: *เป็นการศึกษาแบบไปข้างหน้าเปรียบเทียบประสิทธิภาพของการใช้เข็มเจาะดูเซลล์และการใช้เข็มตัดตัวอย่างชิ้นเนื้อจากก้อนใน mediastinum เพื่อการวินิจฉัยโดยการใช้เครื่องอัลตราซาวด์เป็นตัวนำ โดยทำระหว่างปี พ.ศ. 2542 ถึง พ.ศ. 2546 ในผู้ป่วยที่มารับการรักษาด้วยโรคนี้ที่สาขาวิชาโรคระบบการหายใจและวัณโรค ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ศิริราชพยาบาล*

ผลการศึกษา: *ในช่วงเวลาดังกล่าวมีผู้ป่วยทั้งหมด 35 ราย อายุเฉลี่ย 42.37 ปี เป็นชาย 22 ราย หญิง 13 ราย การวินิจฉัยสาเหตุของก้อนได้จากการตัดชิ้นเนื้อมากกว่าจากการดูดเซลล์ไปตรวจอย่างมีนัยสำคัญทางสถิติ (88.57% เทียบกับ 40% ตามลำดับ) โดยพบความแตกต่างนี้ในกลุ่มที่มีสาเหตุจาก non-carcinomatous ผลแทรกซ้อนพบได้น้อยมาก*

สรุป: *เนื่องจากสาเหตุของก้อนใน mediastinal อาจไม่ใช่กลุ่ม carcinomatous ซึ่งการวินิจฉัยอาจทำได้ง่ายกว่าโดยการดูจากเซลล์เป็นส่วนใหญ่ การตัดชิ้นเนื้อจากก้อนโดยการใช้เข็มมีความปลอดภัยค่อนข้างสูงและสามารถให้การวินิจฉัยได้มากกว่าจึงแนะนำให้ใช้เป็นขั้นตอนแรกในการวินิจฉัยสาเหตุของก้อนใน mediastinum*