The Role of Fine Needle Aspiration Cytology in the Diagnosis and Management of Thymic Neoplasia

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Background: Fine needle aspiration biopsy is commonly used to document the metastasis to the mediastinum. It is less often used to make the primary diagnosis of tumors, particularly thymic neoplasms. This is due to fear of sampling error, rarity of thymic tumors, multiplicity of lesions in the mediastinum, and inexperience on the part of the cytopathologist. We show that needle aspiration sampling of thymic tumors, both thymoma and thymic carcinoma, is an accurate method of diagnosis.

Methods and Results: In our series of 22 thymic tumors aspirated preoperatively and compared with the subsequent surgical resection, the accuracy of a diagnosis of thymoma was 100%, and the accuracy of a diagnosis of carcinoma was 100%. Difficulties were encountered when vague terminology was used, and insufficient information was conveyed. Immunohistochemical stains can be applied to cytologic material to aid in the identification of the epithelial and lymphocytic components of thymoma.

Discussion: Correlation with clinical and radiographic information is necessary, and wording of the cytology report should be as complete and clear as possible.

Key Words: Thymoma, Thymic carcinoma, Fine needle aspiration biopsy, Preoperative, Surgical resection, Immunohistochemical stains.

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The diagnosis of mediastinal lesions can be challenging in surgical pathology material because of the numerous benign and malignant processes occurring at this site. The use of fine needle aspiration (FNA) cytology as a diagnostic tool is even more challenging. Accurate and reliable diagnostic procedures are necessary in the management of mediastinal lesions to facilitate timely treatment. FNA is commonly used to sample tumors in all compartments of the mediastinum, especially in the setting of metastatic disease, but its utility in the diagnosis of thymic neoplasm is not well studied. We have undertaken a retrospective review of thymic neoplasms diagnosed by FNA and subsequently excised, with an emphasis on the accuracy and usefulness of cytology in the diagnosis and management of thymic epithelial tumors.

Thymoma is a distinctive biphasic tumor containing neoplastic epithelial cells and benign reactive, immature T-cell lymphocytes; it is the most common primary malignancy of the anterior mediastinum,[1,2] although it can occur in other compartments and anatomic sites as well. The possibility of thymoma should be considered in any patient presenting with a mediastinal mass. Thymomas are slow growing tumors with the potential for local extension and late recurrence. When metastases occur, they are most frequent in the pleura, pericardium, and diaphragm.[3] Clinically, thymomas are generally regarded as malignant with varying degrees of aggressiveness. They are often classified using the WHO system, although several systems, often overlapping, are in use. Thymomas are stratified by the WHO into six groups (types A, AB, B1, B2, B3, and C)[4] on the basis of the morphology of epithelial cells and the lymphocyte-to-epithelial cell ratio. Final pathologic staging is usually done using the Masaoka staging system on resected tumors. Histologic classification systems do not correlate well with cytology findings, and Masaoka staging cannot be applied to a cytology specimen because of the inability of cytology to determine capsular invasion.[5–7]

Thymic carcinomas are aggressive epithelial malignancies presumed to arise from the native epithelial cells of the thymus gland. They are not biphasic and are not classified in a similar fashion to thymomas; rather, they are identified descriptively according to their morphologic appearance, such as squamous carcinoma and mucoepidermoid carcinoma. Confusingly, thymic carcinomas are also called as type C thymomas in the WHO system.

The cytologic features of thymomas have been described previously,[5,7–10] but few studies describe the use of FNA as the primary diagnostic modality. The two components of thymoma, epithelial cells and lymphocytes, may vary in quantity, and the epithelial cells may show inconsistency in size and shape as well as number. Recognition of the biphasic nature of thymomas is necessary for making the correct diagnosis, especially in cytologic preparations where the material may be limited or sampling suboptimal. Failure to do so can lead to the incorrect interpretation of thymoma as benign or malignant lymphoid lesions; similarly, an epithelial predominant thymoma may be incorrectly diagnosed as a carcinoma or even a sarcoma. Immunohistochemical (IHC) studies are helpful in supporting the cytomorphologic impression, both by characterizing the epithelial component as

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thymic in origin and by demonstrating the immature T-cell phenotype of the admixed reactive lymphocytes.

Because of the rarity of these tumors and the subsequent inexperience of cytopathologists, the confusing morphologic picture, and the inability to apply Masaoka staging to cytologic material, FNA biopsy may be underused in the diagnosis and treatment of thymic neoplasia. The lack of understanding or confidence of the clinician as to the usefulness of mediastinal FNA to establish primary disease may also be a limiting factor. Nevertheless, we consider FNA to be an accurate and useful tool in the clinical setting of thymoma.

MATERIALS AND METHODS

Twenty-two mediastinal fine needle aspirations (FNAMs) and corresponding surgical resections from 22 patients were retrieved from the files of the Pathology Department of Memorial Sloan-Kettering Cancer Center. Cases were identified by searching the files from 1997 to 2006 for surgically resected thymic tumors with antecedent corresponding cytology specimens. All procedures were performed at a single institution. Consultation cases received from outside institutions were not included in the series. Only untreated primary tumors in the mediastinum identified by prior imaging were included, thus the FNAM represented the initial diagnostic procedure. FNAMs were performed by image-guided transthoracic FNA. Diff-Quik (Baxter Diagnostics, Miami, FL) -stained smears were prepared, and specimen adequacy was determined at the time of procedure by on-site cytotechnologists. Additional smears were fixed in 95% alcohol, and the aspiration needle was rinsed in CytoLyt fixative (Cytyc Corporation, Boxborough, MA). Alcohol-fixed smears were stained either by the Papanicolaou technique or with hematoxylin and eosin. A Papanicolaou-stained ThinPrep slide was prepared from the CytoLyt-fixed needle rinse. A cell block was prepared if sufficient material was present. Immunohistochemistry was performed on either additional ThinPrep slides or cell block material. The surgical specimens were fixed in 10% formalin, processed in the routine fashion, and embedded in paraffin. Four-micrometer thick sections were cut and stained with hematoxylin and eosin.

All cytology slides were blindly reviewed by a senior cytopathologist (M.F.Z.), and the surgical slides were reviewed by a senior thoracic pathologist (M.F.Z.). The surgical resections were reclassified in accordance with the 2004 WHO guidelines. The cytology slides and surgical slides were compared in cases of diagnostic discrepancy. Both the original and review diagnoses were recorded for each case (Table 1).

RESULTS

The age range in the series was 42 to 82 years, and the mean age was 60 years; 12 patients were women, and 10 were men. Eighteen cases were thymoma and four were thymic carcinoma: three squamous cell type and one lymphoepithelial carcinoma. For the four cases of thymic carcinoma, there were four male patients and one female patient; average age was 58 years. Both the youngest (42 years) and the oldest patients (82 years) in the series had thymic malignancies. The thymomas included WHO type A (one), B2 (six), B3 (two), B1/B2 (four), AB1 (two), AB2 (two), and micronodular type (one) by final reviewed histologic diagnoses. No pure type B1 was identified. These diagnoses were almost in exact concordance with the original histologic diagnoses.

The original cytologic diagnoses were less specific and never included the WHO subtype.

On review of the cytology, 17 cases were called thymoma/suspect thymoma. Of these 17 cases, all were confirmed thymoma by histology. Three cases called squamous cell carcinoma/suspect squamous cell carcinoma on cytology were confirmed as thymic carcinoma, squamous cell type on histology. One case diagnosed as "malignant neoplasm with necrosis" on cytology proved to be a B1/B2 thymoma on resection, and one case called "B3 thymoma v well differentiated adenocarcinoma" on cytology was a tissue-confirmed B2 thymoma.

This cytology diagnoses, made on blinded review, did not differ significantly from the original cytology interpretations. The cytology review diagnoses were more specific than the original interpretations.

There were six cases that were discordant in part or whole between initial cytology diagnosis and cytology review/surgical pathology diagnosis. Case 9 called "negative for malignancy," not further specified, was called consistent with thymoma on cytology review and proved to be a B1/B2 thymoma on histology. Case 11 called "suspect spindle cell neoplasm" was a spindle cell thymoma on review and on subsequent resection (Figure 1). Case 14 called originally "atypical lymphoid population" was misclassified on cytology review as "suspect thymoma" and tissue proven to be a lymphoepithelial carcinoma. Case 17 was called "neoplastic cells present" on the original cytology, and diagnosis was deferred to the concurrent core biopsy. The core biopsy demonstrated a thymic carcinoma, squamous cell type. Case 18 was called "malignant epithelial neoplasm" originally and reviewed as a thymoma. The original cytology description of case 20 favored "carcinoma over thymoma" and was diagnosed as thymoma on review of the cytology and by tissue (Figure 2). Of the six discrepant cases described above, there was only one case (9) that was actually incorrect, where cytology was not helpful in achieving a preoperative diagnosis, making the usefulness of a cytologic diagnosis 95%. The specificity of the cytologic diagnoses was lower. Case 17 was diagnosed as neoplastic and as such, provided correct, albeit, limited information to the clinician.

On the basis of our blinded review of the cases, the predictive value of a cytologic diagnosis of thymoma was 100%, and the predictive value of a diagnosis of carcinoma was 100%; however, there were several cases where the exact classification was not made on the cytologic specimen.

Difficulties arose with the correct identification of tumor type when necrosis, which is correlated with malignancy,[7] was present (case 2), and with an epithelial-rich thymoma (case 12) where the epithelial component was predominately aspirated and the lymphoid component was overlooked, case 14 was misdiagnosed originally and on review, perhaps due to

TABLE 1. Cytologic and Histologic Diagnoses of Cases Studied

Case	Gender	Age (yr)	Specimen	Original Cytology Diagnosis	Cytology Diagnosis on Review	Original Surgical Diagnosis	Surgical Diagnosis on Review
1	F	52	FNAM	Suspect thymoma	Thymoma	B3 thymoma	B3 thymoma
2	F	57	FNAM	Suspect malignant neoplasm	Malignant neoplasm with necrosis	B1 thymoma	B1/B2 thymoma
3	F	55	FNAM	Suspect spindle cell neoplasm	Spindle cell thymoma	A thymoma	A thymoma
4	F	59	FNAM	Suspect thymoma	Thymoma	B2 thymoma	Micronodular thymoma with lymphoid hyperplasia
5	F	74	FNAM	Suspect thymoma	Thymoma	B2/B3 thymoma	B3 thymoma
6	M	68	FNAM	Suspect thymic neoplasm	Thymoma	AB thymoma	AB1B2 thymoma
7	M	53	FNAM	Thymoma	Thymoma	AB thymoma	AB2 thymoma
8	M	54	FNAM	Suspect thymoma	Thymoma	B2 thymoma	B2 thymoma
9	F	75	FNAM	Negative for malignancy	Consistent with thymoma	B1 thymoma	B2/B1 thymoma
10	F	42	FNAM	Suspect malignant neoplasm	Suspect squamous cell carcinoma	Poorly differentiated carcinoma	Squamous cell carcinoma with squamoid features
11	F	46	FNAM	Suspect spindle cell neoplasm	Suspect thymoma	AB1 thymoma	AB1 thymoma
12	F	46	FNAM	Adenocarcinoma	B3 thymoma versus well	B2 thymoma	B2 thymoma differentiated adenocarcinoma
13	M	71	FNAM	Suspect thymoma	Thymoma	B2 thymoma	B2/B1 thymoma
14	M	82	FNAM	Atypical lymphoid population	Suspect thymoma	Thymic carcinoma,	Lymphoepithelioma lymphoepithelial type
15	F	71	FNAM	Atypical, suggestive of thymic	Suspect thymoma	A thymoma	A/B2 thymoma tissue, cannot rule out thymoma
16	M	66	FNAM	Squamous cell carcinoma	Squamous cell carcinoma	Squamous cell carcinoma	Squamous cell carcinoma
17	M	44	Neoplastic cells present	Squamous cell carcinoma	Squamous cell carcinoma	Squamous cell carcinoma	
18	M	67	FNAM	Malignant epithelial neoplasm	Thymoma	B2 thymoma	B2 thymoma
19	F	74	FNAM	Suspect thymoma	Thymoma	AB thymoma	A/B1 with micronodular thymoma with lymphoid hyperplasia
20	F	42	FNAM	Favor carcinoma over thymoma	Thymoma	lymphocyte-rich thymoma	B2 thymoma
21	M	76	FNAM	Thymoma	Thymoma	Mixed type thymoma	B2 thymoma
22	M	49	FNAM	Thymoma	Thymoma	B2 thymoma	B2/A thymoma

FNAM, mediastinal fine needle aspiration.

the difficulty in recognizing the appearance of a tumor as rare as a lymphoepithelial carcinoma. The original cytology interpretations, made by at least six different cytologists with varying degrees of experience, were less specific than the review diagnoses and, therefore, less clinically useful but not technically incorrect.

DISCUSSION

Multiple techniques have been used for the pathologic diagnosis of thymic tumors, including computed tomography-guided core biopsy, mediastinoscopy, mediastinotomy, and thoracoscopy. These techniques, although effective, are relatively invasive, with complication rates ranging from 1 to 3%.[11] With image guidance, it is possible to perform FNA biopsy of mediastinal lesions (FNAM) with reduced complication rates and avoidance of a diagnostic thoracotomy.

Although FNA biopsies are widely accepted for visceral organs, they are not generally well accepted in the mediastinum. As noted earlier in the text, this may be due to the inexperience of cytologists and/or the lack of confidence on the part of the clinician with the usefulness of mediastinal FNA to establish primary disease. FNAM is better accepted in the documentation of suspected metastatic disease to the mediastinum in the setting of a known primary.[6]

The literature suggests a fairly wide range of reliability for FNAM. Published accuracies range from 77 to 100%,[2,6,11]

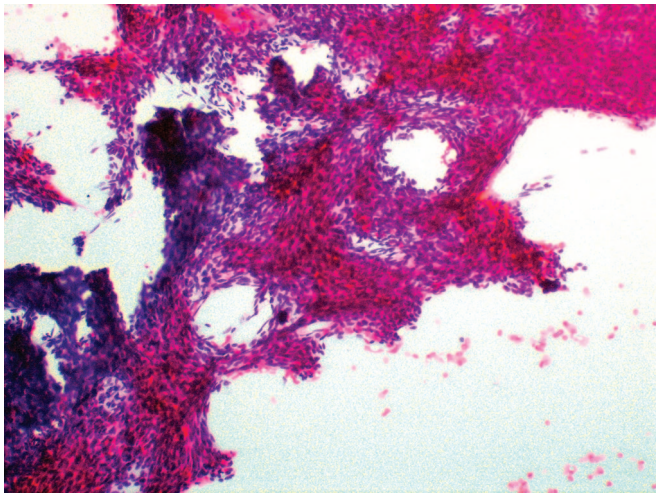

FIGURE 1. Case 11: Fine needle aspiration (FNA) of an AB1 thymoma originally diagnosed on cytology as a spindle cell neoplasm. Note the predominance of cohesive spindle-shaped epithelial cells and the relatively inconspicuous lymphocytes. Hematoxylin and eosin (H&E) stain.

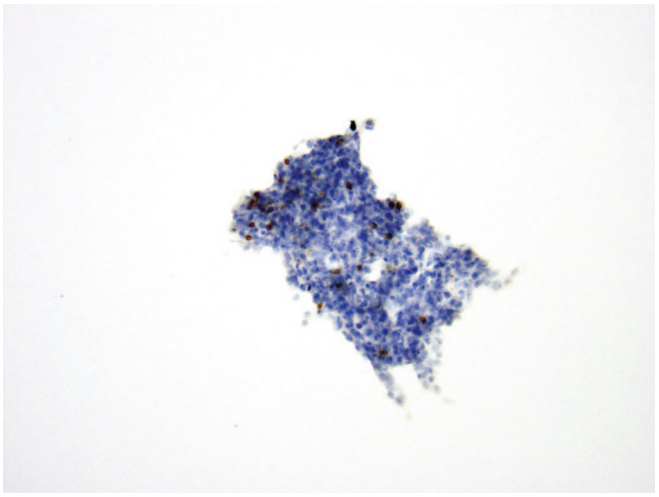

FIGURE 3. Case 12: Immunohistochemical (IHC) stain for cytokeratin on an fine needle aspiration (FNA) specimen demonstrating the (brown) positivity for keratin in the background of reactive lymphocytes.

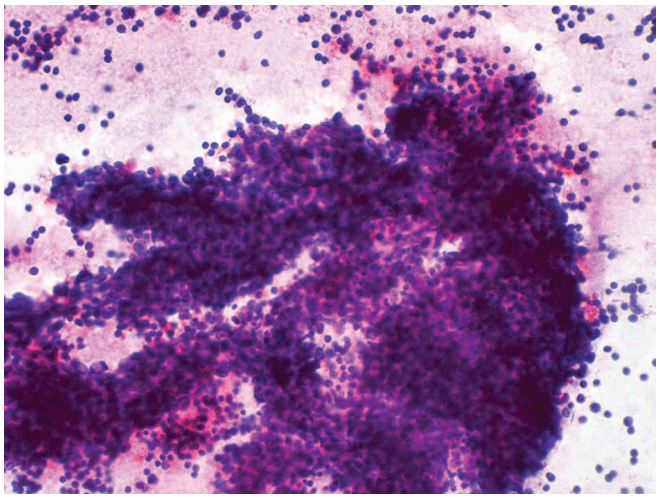

FIGURE 2. Case 20: Fine needle aspiration (FNA) of a lymphocyte-rich thymoma, type B2 where the majority of the cells are reactive lymphocytes, and fewer epithelial cells are seen. Diff-Quik stain.

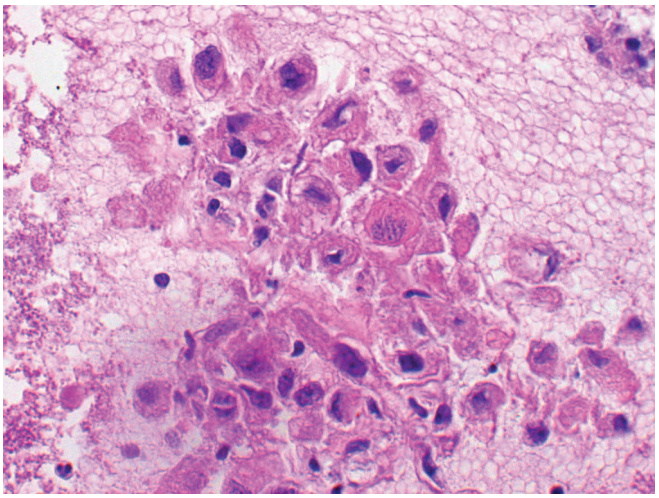

FIGURE 4. Case 16: Cell block preparation showing large eosinophilic cells of thymic carcinoma, squamous cell type. Hematoxylin and eosin (H&E) stain.

sensitivities range from 71 to 87%,[2,5] and positive predictive values range from 69 to 100%.[2]

Diagnostic pitfalls have been previously noted in the evaluation of thymic neoplasms by FNAM. Many of these pitfalls can be overcome by proper sampling and the appropriate use of ancillary studies. If the epithelial component of lymphocyte-rich thymomas (such as WHO type B1) is not identified, the specimen may seem to represent a benign lymph node, a reactive process, or even a lymphoma. This problem can occur if the epithelial component is scant and overlooked, or misinterpreted as germinal centers or granulomas. In some cases, the epithelial component may be absent due to poor sampling. When the presence of epithelial cells is suspected, a cytokeratin IHC stain should be used (Figure 3). Spindle cell thymomas (WHO type A or AB) can be misidentified as another spindle cell lesion, such as carcinoid, low-grade sarcoma, or misinterpreted, as the sclerosis seen in a large cell lymphoma.

Thymic carcinomas are often morphologically and immunohistochemically indistinguishable from a metastatic carcinoma. An example of this is an FNAM showing a squamous carcinoma (Figure 4). In this case, the tumor may represent a primary thymic carcinoma or perhaps a lung carcinoma with either local extension into the mediastinum or metastasis to a mediastinal lymph node. In many cases, the origin of the carcinoma cannot be determined on morphologic or IHC grounds alone. Another area of difficulty in FNA

biopsy of mediastinal tumors is the misidentification of a germ cell tumor as a thymic carcinoma. In this case, proper sampling combined with IHC stains should clarify the distinction.

We agree with the literature that FNA is vastly underused as a diagnostic technique for mediastinal masses in general and for thymic epithelial neoplasms specifically.[5,11] Percutaneous FNAM is diagnostic in a sufficiently large number of cases[11,12] to make it the primary modality in the work up of suspected thymomas. Attempts at subtyping thymomas on cytology are probably not worthwhile, and if a pathologist is able to confidently issue a diagnosis of thymoma on FNA, this information should suffice to direct management.[2]

According to our experience and that of others, we believe that thymic neoplasms are distinguishable from the majority of other lesions of the mediastinum by FNA biopsy,[2,7] especially when it is correlated with clinical and radiologic findings.[8]

Of note, in all but two of our cases (2 and 13), the FNA diagnosis on review was accurate and correlated well with the surgical sample.

Interestingly, difficulty in diagnosis due to sampling error played a minor role in our series. Therefore, it is assumable that the experience of the pathologist played a role.

We recommend that FNAM be the first diagnostic test performed in the scenario of a mass occupying mediastinal lesion, including cases where thymic neoplasia is a clinical consideration. The accuracy of the diagnosis of thymic neoplasia rests in part on the experience of the cytopathologist, and a central registry or review of such specimens is not an unreasonable proposition. Nevertheless, as we have shown, the confidence level of a report of thymoma is high, and the use of FNA should be encouraged in this setting. Furthermore, we believe that cytopathologic terminology should be as specific as possible to convey an accurate picture to the treating physician. The use of vague terminology such as "neoplasm," not further described, is to be discouraged. Clinical and radiographic correlation with the FNAM is essential. Cytology plays little, if any, role in the WHO subtyping or the Masaoka staging of thymomas.

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