

# Distinguishing Carcinoid Tumor of the Mediastinum From Thymoma

## Correlating Cytologic Features and Performance in the College of American Pathologists Interlaboratory Comparison Program in Nongynecologic Cytopathology

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• **Context.**—The cytologic features of carcinoid tumor in mediastinal fine-needle aspiration are well described. Nevertheless, this tumor may be difficult to distinguish from thymoma in this site.

**Objective.**—We sought to correlate the cytologic features of carcinoid tumor of the mediastinum in the College of American Pathologists Interlaboratory Comparison Program in Nongynecologic Cytopathology with the frequency of misclassification as thymoma.

**Design.**—We reviewed 446 interpretations from 18 different cases of carcinoid tumor in mediastinum and correlated the cytologic features with performance.

**Results.**—Cases were more frequently classified as thymoma (158 responses, 35%) than as carcinoid tumor (126 responses, 28%). The best-performing case was classified as carcinoid tumor only 56% of the time. Three cytologic patterns were identified. Four cases consisted of isolated

round cells with salt-and-pepper chromatin. Four cases consisted of isolated spindle and round cells with salt-and-pepper chromatin. The remaining 10 cases consisted of cohesive fragments of crowded cells with finely granular chromatin showing numerous pyknotic cells mimicking lymphocytes. Prominent vasculature patterns were not a feature of any of the cases. There was no correlation between any pattern and the rate of classification as carcinoid tumor or thymoma ( $P > .05$ ).

**Conclusions.**—Carcinoid tumor of the mediastinum is frequently misclassified as thymoma in this program. Although some cytologic patterns resemble thymoma, the lack of correlation of these patterns with performance suggests that at least part of the reason for misclassification may be failure to consider the correct diagnosis or a lack of familiarity with discriminating cytologic criteria.

(*Arch Pathol Lab Med.* 2006;130:1612–1615)

Carcinoid tumor can occur in a variety of sites, including the mediastinum.<sup>1–9</sup> Histologic variants can occur in the mediastinum and include typical, spindle cell, and oncocyctic patterns. Although the cytologic features of carcinoid tumors in general, and especially in the lung, have been well described,<sup>10–16</sup> reports of the cytologic features of fine-needle aspiration of carcinoid tumors of the mediastinum are limited to case reports.<sup>17–20</sup> Nevertheless, the described cytologic features are similar to those of carcinoid tumor in other sites and include either round or spindle-shaped cells with a “salt-and-pepper” chromatin pattern, variable nucleoli, and variable amounts of cytoplasm.

The College of American Pathologists (CAP) Interlaboratory

atory Comparison Program in Nongynecologic Cytopathology is an educational peer-comparison program that includes cases of fine-needle aspiration biopsy of carcinoid tumor in the mediastinum. We recently noted that the performance of cases of carcinoid tumor in the mediastinum was quite poor, and these cases were frequently misdiagnosed as thymoma. To identify causes for misdiagnosis, the cytologic features of the individual cases of carcinoid tumor of the mediastinum were reviewed and correlated with the performance in the program.

### MATERIALS AND METHODS

The Interlaboratory Comparison Program in Nongynecologic Cytopathology is a quarterly mailed, glass slide, quality improvement exercise. Cytology laboratories of all types participate, with the largest number (approximately 60%) being hospital based. In addition, independent, federal and government, university, and other types of laboratories, such as those associated with a group practice or physician's office, also participate. The large number of participants from a diverse range of practice settings suggests that the results may be indicative of cytology practice in the broader population.

Slides are submitted by the members of the CAP Cytopathology Resource Committee. All types of nongynecologic cytology sites are included. Slides are reviewed by at least 2 experienced

Accepted for publication May 1, 2006.

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The authors have no relevant financial interest in the products or companies described in this article.

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**Table 1. Summary of the Morphologic Features of the 3 Presentation Patterns of Carcinoid Tumor Involving the Mediastinum**

Pattern 1. 10 cases, Cohesive fragments of crowded cells with finely granular chromatin with numerous smaller pyknotic cells mimicking lymphocytes (Figure 1, A through C)
Pattern 2. 4 cases, Isolated round and spindled cells with salt-and-pepper chromatin pattern (Figure 2)
Pattern 3. 4 cases, Isolated round cells with salt-and-pepper chromatin pattern (Figure 3)

cytopathologists from the committee. Before acceptance into the program, each slide must be judged to be of good technical quality and an excellent example of the reference diagnosis. All reviewers must agree on the exact target diagnosis, and this must agree with the submitted and biopsy diagnosis prior to accepting a slide for circulation.

Mediastinal fine-needle aspirates with a reference diagnosis of carcinoid tumor were identified, and the performance of individual slides was reviewed. These cases were retrieved and then reviewed by 3 of the authors to identify features that might be responsible for the frequent misinterpretation as thymoma by participants.

Statistical analysis of categorical data was performed using a 2-tailed Fisher exact test or chi square test as appropriate. A *P* value of  $<.05$  was considered significant.

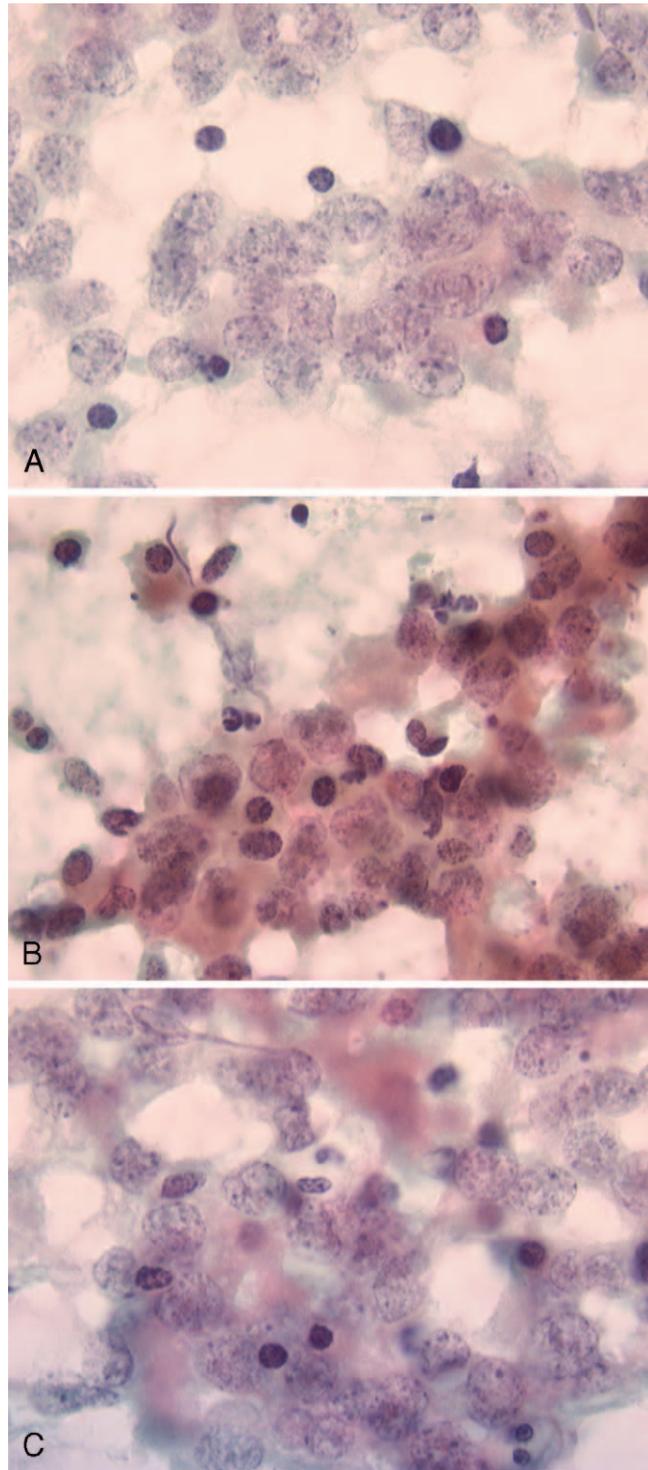
## RESULTS

A total of 446 interpretations from 18 different cases of carcinoid tumor in mediastinal fine-needle aspiration specimens was reviewed. Overall, cases were more frequently classified as thymoma (158 responses, 35%) than as carcinoid tumor (126 responses, 28%). The best-performing case was classified as carcinoid tumor only 56% of the time. The remaining interpretations were scattered at lower percentages as benign processes, carcinoma, germ cell tumor, and lymphoma. All slides reviewed in this study consisted of direct smear specimens stained with either Papanicolaou or hematoxylin-eosin stains.

On review, 3 cytologic patterns were identified in individual cases, as summarized in Table 1. Ten cases consisted of cohesive fragments of crowded large cells with finely granular chromatin showing numerous smaller pyknotic cells that mimicked lymphocytes (Figure 1, A through C). Four cases consisted of isolated round and spindled cells with salt-and-pepper chromatin (Figure 2). The remaining 4 cases consisted of isolated round cells with salt-and-pepper chromatin (Figure 3). There was no correlation between any pattern and the rate of classification as carcinoid tumor or thymoma ( $P = .66, >.99, = .58$  for the 3 presentation patterns, respectively). Other features evaluated included prominence of the vascular pattern, frequency of mitoses, and prominence of solid areas; there was no clear correlation with any of these patterns and the participants' classification. None of the cases reviewed showed well-developed vascular strands with adherent tumor cells, a reported feature of carcinoid tumors from other sites.<sup>12,21</sup>

## COMMENT

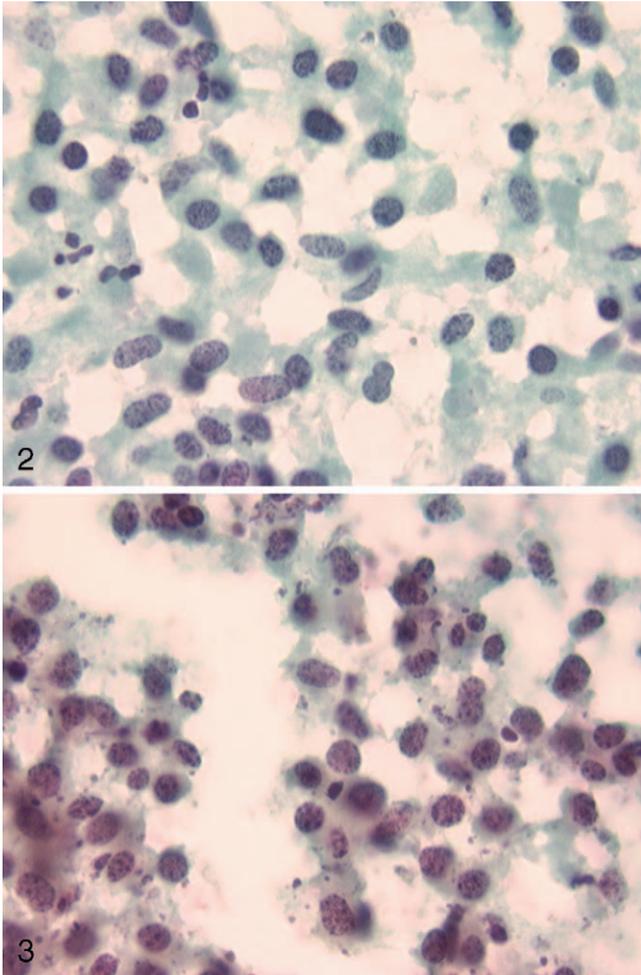
The College of American Pathologists Interlaboratory Comparison Program in Nongynecologic Cytopathology provides a unique opportunity to correlate the cytologic features of individual cases with particular diagnoses and the diagnostic opinions of numerous cytologists with a broad range of backgrounds and in a wide variety of prac-



**Figure 1.** A, B, and C, Carcinoid tumor aspirates of the mediastinum consisting of cohesive groups of epithelial cells with fine chromatin with scattered smaller pyknotic cells mimicking lymphocytes (A, B, and C, Papanicolaou stain, original magnifications  $\times 1000$ ).

tice settings. This exercise therefore might mimic the expected performance of a larger cross section of cytologists. The results of this program are unique, and there are no results available from similar programs of comparable size.

When discrepancies in diagnoses are found in the pro-



**Figure 2.** Carcinoid tumor aspirates of the mediastinum, consisting of a mixture of isolated round and spindle-shaped cells (Papanicolaou stain, original magnification  $\times 1000$ ).

**Figure 3.** Carcinoid tumor aspirates of the mediastinum consisting of monotonous, isolated, well-preserved round cells (Papanicolaou stain, original magnification  $\times 1000$ ).

gram, there are 2 principal possibilities. First, they could represent an error on the part of the participant. Certainly, if an individual participant makes a significantly greater number of errors than others do, this most likely is the case. However, if the discrepancy is made by a number of different pathologists, such discrepancies may reflect something about the individual cases involved or about the state of knowledge of participants regarding rare entities or uncommon presentations.

In the current study, there was considerable misclassification of carcinoid tumor in the mediastinum as thymoma, interpretations that reportedly do not share many cytologic features. In thymoma, the epithelial cells are typically polygonal with abundant cytoplasm, bland regular nuclei with evenly dispersed chromatin, and prominent and distinct nucleoli. The cells can be arranged in islands or clusters or can be scattered and dyscohesive. Backgrounds contain abundant polymorphous lymphocytes that can be intermingled with the epithelial cells. In the present study, however, it was noted that in some of these cases, carcinoid tumors presenting in the mediastinum did share (or mimic) several cytologic features associated with

thymoma. Specifically, as illustrated in Figure 1, A through C, and seen in the majority of these cases (10/18), carcinoid tumor can very closely mimic epithelial-predominant thymoma. In these cases, the cohesive clusters of carcinoid cells resembled the epithelial component, and the pyknotic tumor cells resembled intermixed lymphocytes. The frequent occurrence of pyknotic cells in aspirates of carcinoid tumor was also noted and previously reported in carcinoid tumors of the lung in this program.<sup>21</sup> In that setting, the pyknotic cells may have been responsible for participants misdiagnosing the aspirate as small cell carcinoma. In the mediastinum, these pyknotic cells may also be a potential cause of misdiagnosis, with misinterpretation of the cells as lymphocytes. Hence, interpretation is almost certainly driven in these 2 circumstances by "disease prevalence bias," with outcomes being in the direction of the more common entities noted in these sites.

The second pattern, as seen in 4 cases, with a characteristic example noted in Figure 2, was a combination of round and spindle-shaped dyscohesive cells. Although mixed epithelial and spindle-type thymoma exists, this variant is unusual. One would also expect the epithelial cells to be more cohesive than in the aspirates of carcinoid tumor, since it is well known that these cells have extensive desmosomal cell junctions.

It is unclear to us why aspirates with the third pattern, as noted in Figure 3, consisting of isolated round cells, could be confused with thymoma. Although thymoma certainly does have round cells, these are typically extensively cohesive, unless they are occurring in the setting of a lymphocyte-predominant thymoma, in which case the epithelioid cells are difficult to discern behind the dense lymphoid infiltrate. Finally, vascular strands with adherent tumor cells are a reportedly classic pattern for carcinoid tumor in lung fine-needle aspiration specimens.<sup>12,21</sup> This pattern was essentially absent in all cases reviewed in the mediastinum. Again, the lack of this classic pattern seen elsewhere as a feature of carcinoid tumor may be another potential driver of a noncarcinoid interpretation at this site.

Although we found that the 3 most common patterns differed in how well they resembled aspirates of thymoma, there was no correlation between the type of pattern in the aspirate and whether a correct or incorrect diagnosis was rendered. While we cannot know for sure, it is suspected that at least part of the reason for the frequent misinterpretation of these cases as thymoma is that the participants simply did not consider the diagnosis of carcinoid tumor in this site, since it is relatively rare. This circumstance, combined with the partial features present suggestive of thymoma, may account for interpretation bias when participants evaluated the specimens in the program. Increased awareness of the occurrence of carcinoid tumor at this site, along with routine immunocytochemical evaluation in real-life cases, would be expected to aid in the correct identification of carcinoid tumor in aspiration material. If adequate tissue or cell blocks are available, immunocytochemical markers of lymphoid tissue (T cell) and epithelium (cytokeratin) should be helpful in investigating the origin of the small pyknotic cells in the slide background. Markers of neurosecretory differentiation, such as chromogranin and synaptophysin, may assist in the assignment of an origin from carcinoid tumor, although it should be pointed out that some thymomas may show areas of neurosecretory activity with these markers. Other

**Table 2. Most Useful Points for the Distinction of Carcinoid Tumor Involving the Mediastinum from Thymoma**

1. It should be recognized that carcinoid tumors, although rare in the mediastinum, must be considered in the differential diagnosis with thymoma.
2. The presence of small pyknotic cells within islands of epithelial cells may represent degenerated tumor cells and not lymphocytes.
3. The presence of classic patterns of either epithelioid or epithelioid and spindled cells may be seen in carcinoid tumors.
4. Prominent background vascular structure may not be present in carcinoids of the mediastinum.
5. Immunocytochemical markers (lymphoid, epithelial, and neurosecretory markers) may be useful in the distinction of carcinoid tumors vs thymomas.
6. Consideration of clinical history is always important; the presence of myasthenia gravis or other immune-mediated process may be associated with thymoma.

markers that can be useful in this discrimination are p63, cytokeratins 5/6, and CD5. Studies have shown that thymoma and thymic carcinoma are typically positive for p63 and cytokeratin 5/6, but carcinoid tumors are generally negative. CD5 has been shown to be positive in about 50% of thymic carcinomas and may be useful in the case of more poorly differentiated tumors<sup>22</sup> (Table 2). Close attention to clinical history, cytologic detail, and knowledge and recognition of the similarities in the morphologic patterns between carcinoid tumors and thymomas presenting in the mediastinum are the most important details in reliable final interpretation.

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