Significance of Repeatedly Nondiagnostic Thyroid Fine-Needle Aspirations

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Abstract

Nondiagnostic thyroid fine-needle aspirations are associated with a risk of malignancy that can be reduced with repeated aspiration. However, the significance of repeated nondiagnostic aspirates is less well studied. This study assessed the risk of malignancy for repeated nondiagnostic aspirates from a large series of cases using the results of histologic follow-up.

From a series of 7,089 aspirates, there were 1,671 nondiagnostic aspirates (23.6%), and 235 of these (14.1%) had histologic follow-up. The risk of malignancy for a single nondiagnostic aspirate was 20.0% (47/235). A total of 51 cases had repeated aspiration. The risk of malignancy for cases with a second nondiagnostic aspirate was 0% (0/23), which was significantly less than for patients with a single nondiagnostic aspirate (20.0%; P = .03).

Patients with 2 sequential nondiagnostic thyroid aspirates have a very low risk of malignancy. Cytologists should strive to better convey this risk in their reports.

Nondiagnostic thyroid fine-needle aspirations remain a source of frustration for patients, clinicians, and cytologists. Beyond the wide range of definitions (6 groups each with 10 or more benign epithelial cells,1,2 10 groups each with 20 or more epithelial cells,3 6 groups on at least 2 of 6 aspirates,4 and 8 groups on at least 2 slides5) and poor reproducibility,6 patients should return and have the aspirate repeated. In some cases, the repeated aspiration is also nondiagnostic, and in some cases clinicians will elect to resect a lesion in which a diagnostic aspirate cannot be obtained.

Although it is well documented that the results of repeated aspiration can significantly change the risk of malignancy in patients who have an initial nondiagnostic aspirate and subsequently have a diagnostic aspirate,7,8 the risk of malignancy in patients with repeatedly nondiagnostic aspirates is less well defined. In 1 study, repeated nondiagnostic aspirates had a risk of malignancy of 4%, which was less than the risk of a single aspirate (8.5%).7 To further examine this issue, a large series of thyroid fine-needle aspirates was reviewed and results were correlated with histologic follow-up.

Materials and Methods

All thyroid fine-needle aspiration reports interpreted at Baptist Hospital, Miami, FL, and Homestead Hospital, Homestead, FL, for the 13-year period from October 1996 through November 2009 were reviewed and the results correlated with the results of histologic follow-up. Histologic follow-up was not available in all cases because these institutions are not tertiary academic medical centers, and some patients had their resections at other institutions. Cytologic cases were classified according to the most recent National Institutes of Health state-of-the-science conference.9 In resection specimens, incidental
papillary carcinomas (≥3 mm) that did not represent the clinical lesion were ignored and not counted as a malignant lesion.

All aspirates were performed by clinicians. Approximately one third of aspirates were performed in clinician’s offices without imaging studies. Between 2 and 8 passes were made. Two thirds of aspirates were performed in the radiology department of the Baptist Hospital, with the aid of ultrasound guidance and immediate evaluation. Direct smears were made in all cases, and all were alcohol fixed and stained with the Papanicolaou or H&E stain. If sufficient material was obtained, cell blocks were also made. Core needle biopsy was also available in approximately 400 cases.

To be adequate, all negative smears had to contain at least 6 groups of epithelial cells with 10 cells per group.\textsuperscript{1,2,8} In addition and in line with the recommendations of the most recent consensus classification,\textsuperscript{9} cases consisting of overwhelmingly abundant colloid and fewer cells than this were classified as a colloid nodule and, for the purposes of this report, were treated as negative and adequate. Also, cases with abundant lymphohistiocytic material and at least some follicular cells, usually with Hürthle cell change, were classified as suggestive of Hashimoto thyroiditis and considered adequate. Cases consisting of hemosiderin-laden macrophages suggestive of cyst contents were not considered adequate.

Repeated aspirates were performed by the same clinician when performed outside the hospital. When repeated aspirations were performed in the hospital, they were performed by the same group but not necessarily by the same physician. While cell blocks showed material that was similar to that in the direct smears, in no case was a case found to be adequate based solely on the basis of material in the cell block. Cases in which the specimen was adequate based solely on the basis of the core needle biopsy were excluded from further analysis. The size of the nodules that were nondiagnostic ranged from 0.5 to 10 cm (median, 1.8 cm). This size was not significantly different from the size of the nodules that were diagnostic (range, 0.4-10 cm; median, 2.0 cm; \( P = .95 \)). The slides from the individual nondiagnostic cases were reviewed as part of another study.\textsuperscript{10}

Categorical analysis was done using a 2-tailed \( \chi^2 \) test. Continuous data (size of nodules) was compared using a 2-tailed binomial proportion model (Instat Plus, Statistical Services Centre, 2005, Reading, England). A \( P \) value of .05 was considered significant.

**Results**

During the study period, a total of 7,089 cases were aspirated, and 1,331 resections were performed \( \text{Table I} \). A total of 425 malignancies were identified at resection, and a total of 906 benign cases were resected. There were 6 false-negative cases and 0 false-positive cases.

Of the cases, 1,671 were diagnosed as nondiagnostic on fine-needle aspiration, and 235 of these cases had histologic follow-up. Of these 235 cases, 54 (23.0\%) consisted primarily of cyst contents (large volume of fluid consisting primarily of hemosiderin-laden macrophages). A total of 47 malignancies (20.0\%) were identified at resection for a single nondiagnostic aspirate (39 papillary carcinomas, 3 Hürthle cell carcinomas, 2 follicular carcinomas, 2 poorly differentiated carcinomas, and 1 parathyroid carcinoma). The risk of carcinoma for patients whose aspirates were composed of predominantly cyst contents (11/43 [26\%]) was not significantly different from the risk for nondiagnostic aspirates of any other type (36/181 [19.9\%; \( P = .55 \)).

There were 51 patients (21.7\%) who underwent repeated aspiration. Of the 51 aspirates, 23 were again nondiagnostic. The risk of malignancy in these 23 cases (0/23 [0\%]) was significantly lower than the risk of malignancy in patients with a single nondiagnostic aspirate (20.0\%; \( P = .03 \)). The risk of malignancy for cases composed of cyst contents (0/9 [0\%]) was not significantly different from that for cases in which the aspirate was nondiagnostic for other reasons (0/14 [0\%]).

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>All Cases</th>
<th>Cases With Histologic Follow-up</th>
<th>Cases With Benign Histologic Findings</th>
<th>Cases With Malignant Histologic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>3,829</td>
<td>361 (9.4)</td>
<td>355 (98.3)</td>
<td>6 (1.7)</td>
</tr>
<tr>
<td>Atypical follicular cells</td>
<td>548</td>
<td>204 (37.2)</td>
<td>154 (75.5)</td>
<td>50 (24.5)</td>
</tr>
<tr>
<td>“Suspicious” for follicular neoplasm</td>
<td>343</td>
<td>179 (52.2)</td>
<td>126 (70.4)</td>
<td>53 (29.6)</td>
</tr>
<tr>
<td>Suspicious for Hürthle cell neoplasm</td>
<td>263</td>
<td>108 (41.1)</td>
<td>81 (75.0)</td>
<td>27 (25.0)</td>
</tr>
<tr>
<td>Suspicious for papillary carcinoma</td>
<td>123</td>
<td>73 (59.3)</td>
<td>1 (1)</td>
<td>72 (99)</td>
</tr>
<tr>
<td>Suspicious for lymphoma</td>
<td>8</td>
<td>2 (25)</td>
<td>1 (50)</td>
<td>1 (50)</td>
</tr>
<tr>
<td>Spindle cell neoplasm</td>
<td>3</td>
<td>1 (33)</td>
<td>0 (0)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Papillary carcinoma</td>
<td>275</td>
<td>160 (58.2)</td>
<td>0 (0)</td>
<td>160 (100.0)</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
<td>16</td>
<td>6 (38)</td>
<td>0 (0)</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Carcinoma, not otherwise specified</td>
<td>10</td>
<td>2 (20)</td>
<td>0 (0)</td>
<td>2 (100)</td>
</tr>
<tr>
<td>Nondiagnostic</td>
<td>1,671</td>
<td>235 (14.1)</td>
<td>188 (80.0)</td>
<td>47 (20.0)</td>
</tr>
<tr>
<td>Total</td>
<td>7,089</td>
<td>1,331 (18.8)</td>
<td>906 (68.1)</td>
<td>425 (31.9)</td>
</tr>
</tbody>
</table>

\* Data are given as number (percentage).
Discussion

The purpose of this study was to determine the risk of malignancy for patients with repeated nondiagnostic thyroid fine-needle aspirates from a large series of cases with histologic follow-up. The results are similar to those of other studies in that patients with a single nondiagnostic aspirate have a relatively high risk of malignancy (20.0% in this series), and the overall risk of malignancy can be altered by repeated aspiration, which often shows results other than nondiagnostic.

However, the risk of malignancy for a patient with repeatedly nondiagnostic aspirates is less well described.

The findings of the present study suggest that patients with at least 2 nondiagnostic aspirates are at a significantly lower risk of malignancy than patients with a single nondiagnostic aspirate. The risk in the present study was 0% and in prior studies was 4%. Both of these values are similar to the estimate of risk for patients with a benign aspirate. Although there were no malignancies in the present series, given the variability in operator skill, nature of thyroid nodules, and criteria for adequacy, I suspect that there certainly are some patients with malignancies who will have 2 sequential nondiagnostic aspirates. However, the data from the present and previous studies suggest that overall this risk is quite low, and, given a thyroid aspiration service with a long history of quality service, such patients may best be served by observation rather than resection, unless specific clinical findings are present that might increase the risk or need for resection.

Given these data, one could argue what the best diagnosis for a nondiagnostic aspirate should be if the cytologist knows that a previous aspirate was nondiagnostic. The data in the present study suggest that the risk of malignancy is similar to that seen in benign aspirates, and one could argue that these aspirates should be diagnosed as benign for that reason. However, another approach would be to diagnose the case as nondiagnostic but then state that the risk of malignancy given 2 such nondiagnostic aspirates is quite low. In my opinion, simply diagnosing the case as nondiagnostic without giving any other indication of the significance of that diagnosis in this setting is not appropriate.

In addition, there remains controversy about the best approach to cystic thyroid lesions. Some cytologists may prefer to diagnose aspirates composed only of cyst contents as adequate and diagnostic, based on the assumptions that such specimens are at relatively lower risk of malignancy and repeated aspiration is less likely to be of use in such a setting. The results of the present study strongly suggest otherwise: the risk of malignancy and the value of a second aspiration (given that a second nondiagnostic result is now much more useful than previously suspected) are essentially the same as those of other types of nondiagnostic aspirates.

I recognize that reporting a nondiagnostic category with a risk of malignancy may make some cytologists uncomfortable. However, the nondiagnostic category has no meaning unless it is shown that the risk of malignancy is different from that of a negative or benign aspirate. Otherwise, there is no usefulness of adequacy criteria. Although I recognize that reporting that 2 nondiagnostic aspirates have a similar risk of malignancy as 1 benign aspirate is a novel concept to many cytologists, the data suggest that it is true and better patient care.

This study has shown that patients with 2 sequential nondiagnostic thyroid aspirates have a significantly lower risk of malignancy than do patients with a single nondiagnostic aspirate. Cytologists should strive to better convey this risk in their reports.

References