Fine-Needle Aspiration Biopsy of the Thyroid

Atypical Cytopathological Features

Moshe Yehuda, MD; Richard J. Payne, MD; Raewyn M. Seaberg, MD, PhD; Christina MacMillan, MD; Jeremy L. Freeman, MD

Objectives: To evaluate the positive predictive value of a thyroid nodule being malignant when categorized as atypical, and to determine the prognostic implications of specific cytopathological features.

Design: Retrospective review of consecutive patients undergoing thyroid surgery following fine-needle aspiration biopsy (FNAB) of thyroid nodules.


Patients: A total of 111 consecutive patients with atypical findings from an FNAB who underwent thyroid surgery from January 2000 to November 2005.

Results: Of 111 patients included in this study, 62 (56%) were diagnosed with a thyroid malignancy on final histopathological examination. The remaining 49 patients (44%) had benign disease. When comparing patients with a postoperative diagnosis of malignancy vs those with benign disease, micronucleoli (71% vs 49%; \( P = .01 \)), nuclear grooves (50% vs 31%; \( P = .03 \)), and powdery chromatin (37% vs 16%; \( P = .01 \)) were more frequently observed in the group with cancer. The probability of malignancy was 83% if all 3 of these features were present; 32% if none of these features was present (\( P = .001 \)).

Conclusions: At our institution, when findings from a thyroid nodule FNAB sample were categorized as atypical, the positive predictive value of the nodule being malignant was 56%. In this series of patients, the presence of micronucleoli, nuclear grooves, and powdery chromatin increased the likelihood that an atypical specimen was representative of malignant disease. These features may help guide treatment of patients with atypical findings from a thyroid nodule FNAB sample.

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Palpable thyroid nodules are estimated to be present in up to 7% of adults in the United States.\(^1\) By the age of 50 years, 50% of the population have thyroid nodules that are detectable on ultrasonographic examination.\(^2\) However, over 90% of these nodules represent benign disease.\(^3\) Fine-needle aspiration biopsy (FNAB) has developed into a critical diagnostic test in the evaluation of a thyroid nodule. It is inexpensive, safe, and yields accurate diagnostic information in 80% of cases.\(^4\) On cytopathological examination, FNAB samples have traditionally fallen into 1 of 4 widely accepted diagnostic categories: malignant, benign, indeterminate, or suspicious for malignancy.\(^5\) These diagnostic categories relate directly to patient treatment. It is generally accepted that malignant nodules are treated surgically, benign nodules are treated more conservatively, and samples categorized as indeterminate merit repeated biopsy.\(^6-8\) Recently, we analyzed FNAB samples reported as suspicious for malignancy at our institution (Mount Sinai Hospital, Toronto, Ontario).\(^9\) The positive predictive value of these patients having a postoperative diagnosis of malignancy was 89%. The presence of psammoma bodies alone was associated with a specificity of 100%; similarly, the combination of nuclear grooves, micronucleoli, pseudo-inclusions, powdery chromatin, and multinucleated giant cells in suspicious FNAB samples, specifically in the detection of papillary thyroid carcinoma, was 100%. These features may help guide treatment decisions in the case of FNAB results that are suspicious for malignancy.

At our institution, the indeterminate category includes “follicular lesion,” “Hürthle cell lesion,” “cellular atypia,” and “suspicious for papillary carcinoma.” The “atypical” diagnosis comprises a spectrum of findings including local atypia in an otherwise benign-appearing aspirate, a
cellular follicular lesion with atypical cells (eg, grooves or crowding), and atypical cells that we cannot differentiate as either reactive atypia or malignant cells (eg, in the case of a cystic lesion, a benign follicular cyst vs a cystic papillary carcinoma). These aspirates may show 1 or several, but not all, of the minimal criteria described by Kini\(^1\) for the diagnosis of papillary carcinoma. These criteria are syncytial-type tissue fragments, enlarged nuclei with very fine dusty or powdery chromatin, multiple micronucleoli and/or macro- nucleoli, intranuclear cytoplasmic inclusions, and linear chromatin ridges or nuclear grooves. In the case of papillary carcinoma, all 5 criteria must be met to make a cytologic diagnosis of malignancy. Meeting 4 criteria results in a diagnosis of “suspicious for papillary carcinoma,” although meeting 3 usually results in a diagnosis of cellular atypia.

We sought to determine the frequency with which atypical FNAB samples correspond to malignant disease and to investigate which commonly reported cytopathological features are most predictive of malignancy. This knowledge will aid clinical treatment decisions for patients with thyroid nodules demonstrating atypical cytopathological features who currently present a diagnostic dilemma.

METHODS

This study involved a retrospective medical chart review of consecutive thyroid FNABs performed at the Department of Pathology at Mount Sinai Hospital from January 2000 to November 2005. All cases reported as atypical and subsequently treated surgically with total or subtotal thyroidectomy were eligible for inclusion in this analysis. Final permanent histopathological diagnosis was available for all cases. The aspirations were carried out by the surgical team using the thin-prep technique. Cells were obtained with a 23-gauge needle affixed to a commercially available 10-ml syringe. The biopsy technique involved a minimum of 2 passes from different parts of the nodule.

The FNAB samples were categorized as atypical if they met 3 of the criteria described by Kini et al\(^1\) for the diagnosis of papillary carcinoma or if they met fewer than 3 criteria but had other types of cytologic atypia. The frequency of various cytopathological features was recorded. These included nuclear grooves, nuclear pseudo-inclusions, powdery chromatin, micronucleoli, psammoma bodies, papillary fragments, multinucleated giant cells, atypical cells, atypical architecture, microfollicular arrangement, macrofollicular arrangement, sheets, and Hurthle cells. Each surgical specimen was classified as either positive or negative for malignancy based on final permanent histopathological analysis. The frequency of each feature present on FNAB was compared between the 2 groups of patients (those with positive vs negative specimens). Statistical analysis was carried out using the Pearson \(\chi^2\) test. A \(P\) value of less than .05 was considered statistically significant. As well, standard sensitivity, specificity, positive predictive value, and negative predictive value calculations were performed for each individual cytopathological feature as well as for a combination of features for atypical FNAB findings. In a multivariate analysis, a logistic regression model was used to identify a combination of features that would best predict malignancy. All statistical analyses were performed using SAS statistical software (SAS Inc, Cary, NC).

RESULTS

This retrospective study identified 111 consecutive patients with thyroid FNAB samples that were adequate for evaluation and classified as atypical. Of these patients, 62 (56%) had a malignant neoplasm identified on histopathological analysis; these diagnoses included 60 patients (54%) with papillary thyroid carcinoma, 1 (0.9%) with medullary thyroid carcinoma, and 1 (0.9%) with undifferentiated thyroid carcinoma. The remaining 49 patients’ surgical specimens (44%) were benign. Sex was not significantly associated with malignancy (\(P = .56\)).

In the 2 groups of patients, micronucleoli (71% vs 49%; \(P = .01\)), nuclear grooves (50% vs 31%; \(P = .03\)), and powdery chromatin (37% vs 16%; \(P = .01\)) were each individually associated with malignancy. Other features that were investigated but not statistically (\(P > .05\)) associated with malignancy included atypical cells, Hurthle cells, multinucleated giant cells, papillary fragments, sheets, macrofollicular arrangement, and microfollicular arrangement (Table 1). The sensitivity, specificity, and positive and negative predictive values for each cytopathological feature were determined (Table 2).

Using a logistic regression model, it was found that the presence of all 3—micronucleoli, nuclear grooves, and powdery chromatin—in a given atypical FNAB sample was associated with an 83% probability of malignancy. Conversely, if none of these features was present, the probability of malignancy was 32% (\(P = .001\)). The sensitivity, specificity, and positive and negative predictive values for combinations of various cytopathological features were determined (Table 3).

COMMENT

Thyroid nodules are common, but only approximately 5% of such nodules represent malignant disease.\(^3\) Thus,
in an effort to avoid unnecessary intervention and associated morbidity, it is critical to accurately identify which nodules require definitive treatment such as surgical resection. Fine-needle aspiration biopsy is an important tool in the treatment of patients with thyroid nodules because it yields an accurate diagnosis up to 80% of the time.4

Although there are currently no standardized reporting guidelines for the cytopathological diagnosis of well-differentiated thyroid cancer by FNAB, there are treatment algorithms that correspond to FNAB results categorized as malignant, benign, and indeterminate. Although the details of these algorithms differ among treatment centers, malignant nodules are generally treated by surgical resection, benign nodules are treated more conservatively, and indeterminate FNAB samples present a challenge that is sometimes resolved by repeated biopsies. Several studies have examined the situation in which FNAB results are categorized as suspicious for malignancy. The treatment recommendations in this case range from surgical resection of all suspicious nodules11 to an individualized approach in which specific cytopathological features and other clinicopathologic factors are considered.7,9

The most appropriate course of treatment is less certain when the FNAB result is categorized as atypical by cytopathological criteria. At our institution, FNAB samples are categorized as atypical if they meet 3 of the criteria of Kini et al10 or if they meet fewer than 3 criteria but have other features of cytologic atypia. We determined the positive predictive value of malignancy in the case of an atypical FNAB result to be 56% at our institution. Further, the particular cytopathological features that were associated with malignancy included micronucleoli, nuclear grooves, and powdery chromatin. When all 3 of these features were present, the probability of malignancy in this series was 83%.

There are few other studies that have examined correlation of atypical FNAB results with thyroid malignancy. Comparisons with the present study are difficult because the criteria for atypia are different; for example, Goldstein et al11 labeled aspirates as “atypical” for follicular neoplasm if individual epithelial cells demonstrated mild abnormalities and low-power criteria were not met, and they found that 20% of atypical samples represented malignant disease. Renshaw12 examined atypical FNAB samples containing fewer than 20 cells with features of papillary carcinoma and found that minimal findings are associated with papillary carcinoma at resection in more than 50% of cases. A recent study at our institution9 revealed that micronucleoli, nuclear grooves, and powdery chromatin were reported with equal frequency in FNAB samples categorized as suspicious for malignancy and those categorized as positive for malignancy. Of the patients in that study, 89% of those with FNAB samples reported as suspicious for malignancy (and 100% of those reported as positive for malignancy) were found to have malignant disease on postoperative histopathological examination. The findings of the present study strengthen the conclusions of Punthakee et al13 regarding the usefulness of these cytopathological features in the prediction of malignant disease. It is important that these conclusions may generalize beyond the confines of our own institution; other study groups have similarly found that micronucleoli, nuclear grooves, and powdery chromatin were highly associated with malignancy.13

Because the FNAB diagnosis of papillary thyroid cancer based on cytopathological features is not standardized, atypical FNAB results should be interpreted in the context of the clinical presentation of thyroid nodular disease, imaging data, and the presence of risk factors for malignancy, including patient age, sex, ethnic background,8 exposure to ionizing radiation, personal, or family history of thyroid malignancy.

The development of new techniques for diagnosis, including immunohistochemical markers,9 telomerase activity,16 and molecular techniques such as differential gene expression,17,18 may prove particularly useful for differentiating benign from malignant disease in the setting of atypical FNAB results. Interestingly, owing to their po-

### Table 3. Sensitivities, Specificities, PPVs, and NPVs of Combinations of Cytopathological Features in Atypical FNAB Samples*

<table>
<thead>
<tr>
<th>Cytopathological Feature</th>
<th>Sensitivity</th>
<th>PPV</th>
<th>Specificity</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>NG, PC</td>
<td>21</td>
<td>94</td>
<td>81</td>
<td>48</td>
</tr>
<tr>
<td>MIN, PC</td>
<td>29</td>
<td>88</td>
<td>75</td>
<td>49</td>
</tr>
<tr>
<td>NG, AA</td>
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<td>86</td>
<td>67</td>
<td>47</td>
</tr>
<tr>
<td>AA, MIN</td>
<td>32</td>
<td>80</td>
<td>67</td>
<td>48</td>
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<td>48</td>
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<tr>
<td>NG, AC</td>
<td>31</td>
<td>76</td>
<td>61</td>
<td>46</td>
</tr>
<tr>
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<td>11</td>
<td>96</td>
<td>78</td>
<td>46</td>
</tr>
<tr>
<td>NG, PC, MIN</td>
<td>15</td>
<td>96</td>
<td>82</td>
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<td>NG, AA, MIN, AC</td>
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<td>58</td>
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</tr>
</tbody>
</table>

*Abbreviations: AA, atypical architecture; AC, atypical cells; FNAB, fine-needle aspiration biopsy; MIN, micronucleoli; NG, nuclear grooves; NPV, negative predictive value; PC, powdery chromatin; PPV, positive predictive value.

*All data are given in percentages.
Thyroid nodular disease is common, but only a small proportion of nodules are malignant. Although FNAB sample results accurately predict diagnosis and are suggestive of appropriate treatment in most cases, the treatment of patients with FNAB results categorized as atypical is less well defined.

Atypical FNAB results need to be considered in combination with clinical presentation, imaging data, and individual patient risk factors. However, the knowledge that the cytopathological features of micronucleoli, nuclear grooves, and powdery chromatin are highly associated with malignancy suggests that a surgical approach may be appropriate when these features are present individually or in combination in atypical FNAB thyroid nodule samples.

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Correspondence: Moshe Yehuda, MD, Department of Otolaryngology, Mount Sinai Hospital, 600 University Ave, Room 401, Toronto, Ontario, Canada M5G 1X5 (moshe@yehuda.com).

Author Contributions: Drs Yehuda, Payne, and Freeman had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Yehuda, Payne, and Freeman. Acquisition of data: Yehuda, McMillan, and Freeman. Analysis and interpretation of data: Yehuda, Payne, Seaberg, and Freeman. Drafting of the manuscript: Yehuda and Seaberg. Critical revision of the manuscript for important intellectual content: Payne, McMillan, and Freeman. Statistical analysis: Yehuda and Payne. Administrative, technical, and material support: Yehuda, Payne, Seaberg, and Freeman. Study supervision: McMillan and Freeman.

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