

The Predictive Value of the Fine-Needle Aspiration Diagnosis “Suspicious for a Follicular Neoplasm, Hürthle Cell Type” in Patients With Hashimoto Thyroiditis

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Upon completion of this activity you will be able to:

- discuss the role of thyroid fine-needle aspiration (FNA) in the diagnosis and management of thyroid nodules, especially in light of the positive predictive value for malignancy associated with specific cytologic interpretations (eg, “atypia of undetermined significance,” “suspicious for follicular neoplasm,” and “suspicious for follicular neoplasm, Hürthle cell type”).
- list the similarities and differences between follicular carcinomas and Hürthle cell carcinomas of the thyroid.
- describe the findings on a thyroid FNA that would result in a cytologic interpretation of “suspicious for follicular neoplasm, Hürthle cell type.”
- list clinicopathologic findings seen in patients with Hashimoto thyroiditis.

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Abstract

A fine-needle aspiration sample composed exclusively of Hürthle cells is interpreted as “suspicious for a follicular neoplasm, Hürthle cell type” (SFNHCT). Because some nonneoplastic Hürthle cell proliferations in Hashimoto thyroiditis (HT) mimic this cytologic pattern, we examined the positive predictive value (PPV) for malignancy of SFNHCT in patients with HT. Between 1992 and 2007, 401 patients with cytologic findings of SFNHCT were identified at 3 institutions. Histologic follow-up was available for 287 (71.6%), and malignancy was diagnosed in 69 (24.0%). Malignancy was present in 2 (PPV = 9.5%) of 21 patients with HT compared with 67 (PPV = 25.2%) of 266 patients without HT (P = .081). Although the difference in the rate of malignancy between the HT and non-HT cohorts did not reach statistical significance, the lower risk of malignancy in the HT cohort more closely approximates the risk of cases interpreted as “atypia of undetermined significance.” For this reason, it might be appropriate for Hürthle cell–only aspirates from patients with HT to be categorized as either atypia of undetermined significance or SFNHCT.

Hürthle cell neoplasms are relatively rare thyroid neoplasms of follicular cell origin.^{1,2} In particular, Hürthle cell carcinoma (HCC) constitutes only approximately 3% of all thyroid carcinomas.³ Although earlier studies had suggested that HCCs behave more aggressively than follicular carcinomas,^{4,5} a later study found no statistically significant difference in the rate of local recurrence, rate of metastasis, or patient survival.⁶ Thus, HCC has been reclassified by the World Health Organization as an oncocytic variant of follicular carcinoma.¹ On a molecular level, however, the oncocytic variant of follicular carcinoma is distinct from conventional follicular carcinoma. Specifically, the former is associated with increased allelic alterations on chromosomal arms 1q and 2p and with overexpression of p27(kip1) and cyclin D3.^{7,8} In contrast, mutations in RAS and rearrangements at 3p25, which contains the gene locus encoding the peroxisome proliferators-activated receptor γ , are seen in a significant proportion of the latter.^{9,10}

The detection of thyroid nodules has increased with the advent of thyroid ultrasonography. Fine-needle aspiration (FNA) represents a crucial element in their initial evaluation and has improved preoperative assessment significantly.¹¹ A thyroid aspirate that is cellular and consists exclusively (or almost exclusively) of Hürthle cells and lacks the nuclear features of papillary carcinoma raises the possibility of a Hürthle cell neoplasm. Furthermore, the lack of chronic inflammation

or colloid in the background and the presence of transgressing blood vessels have been shown to be significantly associated with Hürthle cell neoplasms on histologic follow-up.¹² Most significant, these cytologic findings raise the possibility of HCC. Nevertheless, Hürthle cell adenomas outnumber HCCs; hence, the specificity of the “suspicious for a follicular neoplasm, Hürthle cell type” (SFNHCT) diagnosis for malignancy is low.¹³⁻¹⁶

The Hürthle cell–only pattern, reported as “follicular neoplasm, Hürthle cell type (FNHCT)” or as SFNHCT¹⁷ can be seen in some nonneoplastic conditions, including multinodular goiter and lymphocytic (Hashimoto) thyroiditis (HT).¹⁸ Hyperplastic nodules in the setting of multinodular goiter and HT can vary in the extent of Hürthle cell metaplasia and occasionally give rise to aspirates so rich in Hürthle cells that the aspirate is interpreted as SFNHCT. As a result, nonneoplastic nodules represent a significant proportion (up to 40%) of the histologic outcome after an interpretation of FNHCT/SFNHCT.^{15,16} For the sake of simplicity, the term SFNHCT will be used for the remainder of this article, with the understanding that FNHCT is equivalent.

The positive predictive value (PPV) for malignancy of the FNA interpretation SFNHCT has been reported to be 15% to 45%.^{15,16,19} Although the overall PPV of SFNHCT has been established, no studies to date have examined the PPV of SFNHCT specifically in patients with HT. Given the high frequency of nonneoplastic Hürthle cell proliferations in patients with HT, we hypothesized that the PPV for malignancy in patients with HT might be lower than in patients without HT. Thus, the purpose of this study was to determine whether the PPV for malignancy of SFNHCT is different in patients with and without a history of HT.

Materials and Methods

After approval by the institutional review boards, electronic pathology databases at 3 institutions—Brigham and Women’s Hospital, Boston, MA; Massachusetts General Hospital, Boston; and University of Virginia Health System, Charlottesville—were searched to identify patients who underwent thyroid FNA between 1992 and 2007 with cytologic findings that were “suspicious” for a Hürthle cell neoplasm. Patients with histologic follow-up after a partial or total thyroidectomy were identified, and the diagnoses for the previously aspirated nodules were noted after the correlation of gross descriptions with ultrasound-guided FNA notes. The sizes of these nodules and the diagnoses of “neoplasia” (adenoma and carcinoma) and “hyperplasia,” specifically, were tabulated based on the original histologic interpretations recorded in the surgical pathology reports. HCCs, papillary thyroid carcinomas (PTCs), and poorly

differentiated carcinomas were diagnosed based on the presence of venous and/or transcapsular invasion, nuclear atypia (demonstrated by irregular nuclear membranes, chromatin clearing, intranuclear grooves, and pseudoinclusions), and insular growth pattern, respectively. Cases without surgical follow-up were excluded from the study.

Thyroid FNAs were processed differently at the 3 institutions. At one, liquid-based preparations (ThinPrep; Hologic, Marlborough, MA) plus optional cell blocks were used (Brigham and Women’s Hospital). At another (Massachusetts General Hospital), ethanol-fixed, Papanicolaou-stained smears were examined in all cases; in a subset of these cases, additional preparations were used: ethanol-fixed, H&E-stained smears; air-dried, Romanowsky-stained smears; and/or ThinPrep slides. At the third institution (University of Virginia Health System), air-dried, rapid Romanowsky-stained smears and ethanol-fixed, Papanicolaou-stained smears with or without ThinPrep slides were examined.

For each case with follow-up, the electronic medical record was searched to determine whether the patient had a history of HT at the time of initial examination of the thyroid nodule before the thyroid FNA and subsequent surgery. This was performed by examining the medical history in clinical notes and determining if the patient was receiving levothyroxine replacement therapy and/or was clinically hypothyroid. In addition, laboratory tests, specifically titers for antibodies against thyroid peroxidase (TPO), along with findings on thyroid ultrasonography were recorded. For the latter, the presence or absence of a “diffusely heterogeneous” thyroid gland, which is highly suggestive of HT, was recorded. Finally, the histopathologic findings were examined to determine which patients had pathologic evidence of lymphocytic thyroiditis in follow-up partial or total thyroidectomy specimens, including diffuse infiltration of the thyroid parenchyma with lymphoplasmacytic infiltrates, formation of lymphoid follicles, and Hürthle cell metaplasia. A patient was classified as having HT if one of the following criteria was satisfied: (1) a clinical history of HT, with elevated anti-TPO titers and documentation of levothyroxine replacement therapy; (2) clinical history of HT, with a diffusely heterogeneous thyroid gland on ultrasound, and documentation of levothyroxine replacement therapy; or (3) diffuse lymphocytic thyroiditis on histologic examination of surgically resected thyroid tissue.

The PPV of the cytologic interpretation of SFNHCT for neoplasia (encompassing adenoma and carcinoma) and that for malignancy were calculated for patients with and without HT based on the follow-up histologic diagnoses as the “gold standard.” The Fisher exact test was used to assess statistical difference between these 2 groups. The Wilcoxon rank sum test was used to assess the statistical difference in nodule sizes between the 2 groups. Statistical significance was determined if the *P* value was less than .05.

Results

Between 1992 and 2007, a total of 401 patients with thyroid cytology suspicious for a Hürthle cell neoplasm were identified. Of these patients, surgical follow-up from thyroid lobectomies or total thyroidectomies was available for 287 (71.6%). Review of clinical patient encounter notes, laboratory tests (specifically, anti-TPO titers), thyroid ultrasonography, and surgical specimens revealed that 21 (7.3%) of 287 patients met our criteria for HT (Table 1). The majority (19 of 21) had a clinically documented history of HT. Of these, 8 had documented elevations in anti-TPO titers, 14 required levothyroxine replacement therapy, and 10 had ultrasonographic findings suggestive of HT. Of the remaining 2 patients, one had ultrasonographic evidence of HT, an elevated anti-TPO titer, and a diffuse lymphoplasmacytic infiltrate with lymphoid follicle formation in the resected thyroid gland. In the other patient, ultrasonographic and laboratory data were not available; however, examination of the surgically resected thyroid gland revealed diffuse lymphocytic thyroiditis consistent with HT.

Of the 287 patients with histologic follow-up, the size of the aspirated nodules was available for 275 (95.8%). The mean \pm SD nodule size for the overall study population was 2.6 \pm 1.4 cm (range, 0.5-10 cm). There was no significant difference between the mean size of the nodules in the HT and non-HT cohorts. For the HT and non-HT cohorts, the mean \pm SD nodule sizes were 2.7 \pm 1.8 cm ($n = 17$; range, 0.7-8.1 cm) and 2.6 \pm 1.4 cm ($n = 258$; range, 0.5-10 cm), respectively ($P = .87$).

Overall, the aspirated nodule with cytologic findings of SFNHCT proved to be a malignant neoplasm in 69 (24.0%) of 287 cases. The majority of these were follicular carcinomas, oncocytic variant/HCCs (41/69 [59%]). Diagnoses of PTC and poorly differentiated carcinoma were made in 26 (38%) and 2 (3%) cases, respectively (Figure 1).

In the follow-up surgical specimens, the previously aspirated nodules represented neoplastic nodules (adenomas and carcinomas) in 9 (42.9%) of 21 and 183 (68.8%) of 266 patients with and without HT, respectively (Table 2). This difference was statistically significant ($P = .016$). The PPV for the cytologic interpretation of SFNHCT specifically for a malignant neoplasm in the non-HT cohort was 25.2% (67 of 266): 39 HCCs, 26 PTCs, and 2 poorly differentiated carcinomas (Image 1). In contrast, the PPV for malignancy in the HT cohort was 9.5% (2 of 21); both malignancies were HCCs (Image 2). Although the PPV of SFNHCT for malignancy was lower in the HT group, the trend did not reach statistical significance ($P = .081$).

Discussion

Hyperplastic nodules in the setting of HT can occasionally yield an aspirate composed exclusively or almost exclusively of Hürthle cells. The Hürthle cell-only pattern, interpreted as SFNHCT, raises the possibility of a neoplasm, specifically Hürthle cell adenoma and, more significant, an HCC. To date,

Table 1
Histopathologic, Clinical, Radiologic, and Laboratory Data for 21 Patients With Hashimoto Thyroiditis

| Case No. | Surgical Follow-up | | | Clinical Manifestations | | | Ultrasound | |
|----------|-------------------------------|------------------|-------------------------|-------------------------|-------------|-----------------------------------|---------------------------------------|----------------|
| | Recorded Pathologic Diagnosis | Nodule Size (cm) | Lymphocytic Thyroiditis | Clinical History of HT | Hypothyroid | Levothyroxine Replacement Therapy | Diffusely Heterogeneous Thyroid Gland | Anti-TPO Titer |
| 1 | HT | 0.7 | Yes | Yes | Yes | Yes | NA | ↑ |
| 2 | LT | NA | Yes | Yes | Yes | Yes | NA | ↑ |
| 3 | MNG, LT | 2.5 | Yes | Yes | Yes | Yes | Yes | ↑ |
| 4 | LT | NA | Yes | Yes | Yes | Yes | Yes | NA |
| 5 | MNG | 4.2 | No | Yes | Yes | Yes | Yes | ↑ |
| 6 | Adenoma | 2.0 | No | Yes | No | Yes | No | ↑ |
| 7 | Adenoma | 4.2 | Yes | Yes | Yes | Yes | Yes | NA |
| 8 | HT | 2.0 | Yes | Yes | Yes | Yes | Yes | NA |
| 9 | HCC | 2.4 | Yes | Yes | No | Yes | Yes | NA |
| 10 | Adenoma | 8.1 | Yes | Yes | Yes | Yes | Yes | NA |
| 11 | MNG | 1.7 | No | Yes | Yes | Yes | Yes | NA |
| 12 | Adenoma | 3.2 | Yes | Yes | Yes | No | No | ↑ |
| 13 | HT | 1.5 | Yes | Yes | Yes | No | Yes | ↑ |
| 14 | Adenoma | 2.3 | Yes | Yes | No | No | NA | ↑ |
| 15 | LT | NA | Yes | Yes | Yes | Yes | No | NA |
| 16 | MNG | 2.5 | Yes | Yes | No | No | Yes | NA |
| 17 | Adenoma | 2.0 | Yes | Yes | Yes | Yes | No | NA |
| 18 | Adenoma, HT | 4.0 | Yes | Yes | Yes | Yes | NA | NA |
| 19 | LT | NA | Yes | Yes | Yes | NA | NA | NA |
| 20 | HCC, HT | 1.3 | Yes | No | No | No | Yes | ↑ |
| 21 | HT | 0.8 | Yes | No | No | No | NA | NA |

HCC, Hürthle cell carcinoma; HT, Hashimoto thyroiditis; LT, lymphocytic thyroiditis; MNG, multinodular goiter; NA, not available (ie, data not in the electronic medical records or test not done); TPO, thyroid peroxidase; ↑, elevated.

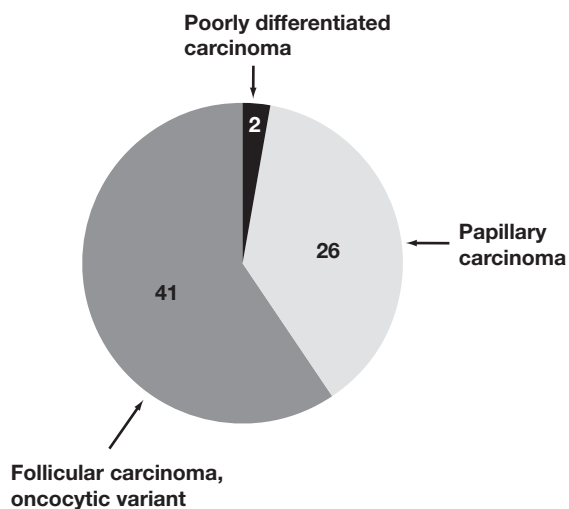


Figure 1 Malignant neoplasms diagnosed on surgical follow-up in patients after a cytologic diagnosis of “suspicious for a follicular neoplasm, Hürthle cell type.” Of the 287 patients with surgical follow-up, a total of 69 malignancies were identified. The number of cases of each histologic subtype of thyroid carcinoma is shown.

however, the significance of a Hürthle cell–only aspirate in the context of HT, especially the PPV of SFNHCT for neoplasia and malignancy in patients with HT, has not been thoroughly investigated. To address this, we first sought to identify patients with HT with cytologic findings SFNHCT. During a 15-year period, we were able to identify 21 patients

Table 2
Corresponding Histologic Findings for the Aspirated Nodules in Patients With and Without HT

| | UVA | BWH | MGH | Total |
|-----------------------------------|-----|-----|-----|--------------------------------|
| Patients with HT | 7 | 10 | 4 | 21 |
| Neoplastic nodules* | 1 | 6 | 2 | 9 (PPV = 42.9%) [†] |
| Carcinomas | 0 | 2 | 0 | 2 (PPV = 9.5%) [‡] |
| Patients without HT | 48 | 155 | 63 | 266 |
| Neoplastic nodules* | 33 | 93 | 57 | 183 (PPV = 68.8%) [†] |
| Carcinomas | 15 | 39 | 13 | 67 (PPV = 25.2%) [‡] |
| No. of FNAs interpreted as SFNHCT | 55 | 165 | 67 | 287 |

BWH, Brigham and Women’s Hospital, Boston, MA; FNAs, fine-needle aspiration samples; HT, Hashimoto thyroiditis; MGH, Massachusetts General Hospital, Boston; PPV, positive predictive value; SFNHCT, “suspicious for a follicular neoplasm, Hürthle cell type”; UVA, University of Virginia Health System, Charlottesville.

* Represents the sum of adenomas and carcinomas.

[†] $P = .016$.

[‡] $P = .081$.

with HT with thyroid cytologic features of SFNHCT. In comparison, the remaining 266 patients with cytologic findings of SFNHCT did not have HT. Next, we sought to determine the frequency of neoplasms diagnosed on histologic follow-up and compare the PPV for neoplasia in patients with and without HT. We found that among the patients with HT, fewer than half of the aspirated nodules were neoplasms (Table 2). This proportion was significantly less than that seen in the non-HT cohort of 266 patients, in which 68.8% of the aspirated nodules were neoplasms ($P = .016$).

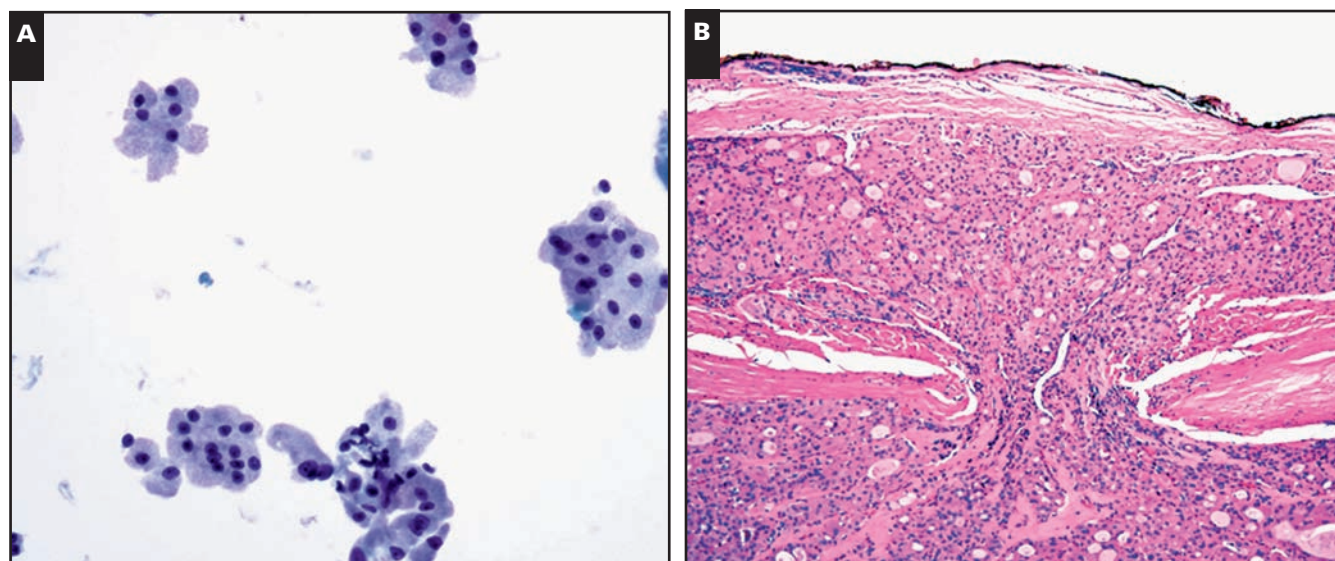
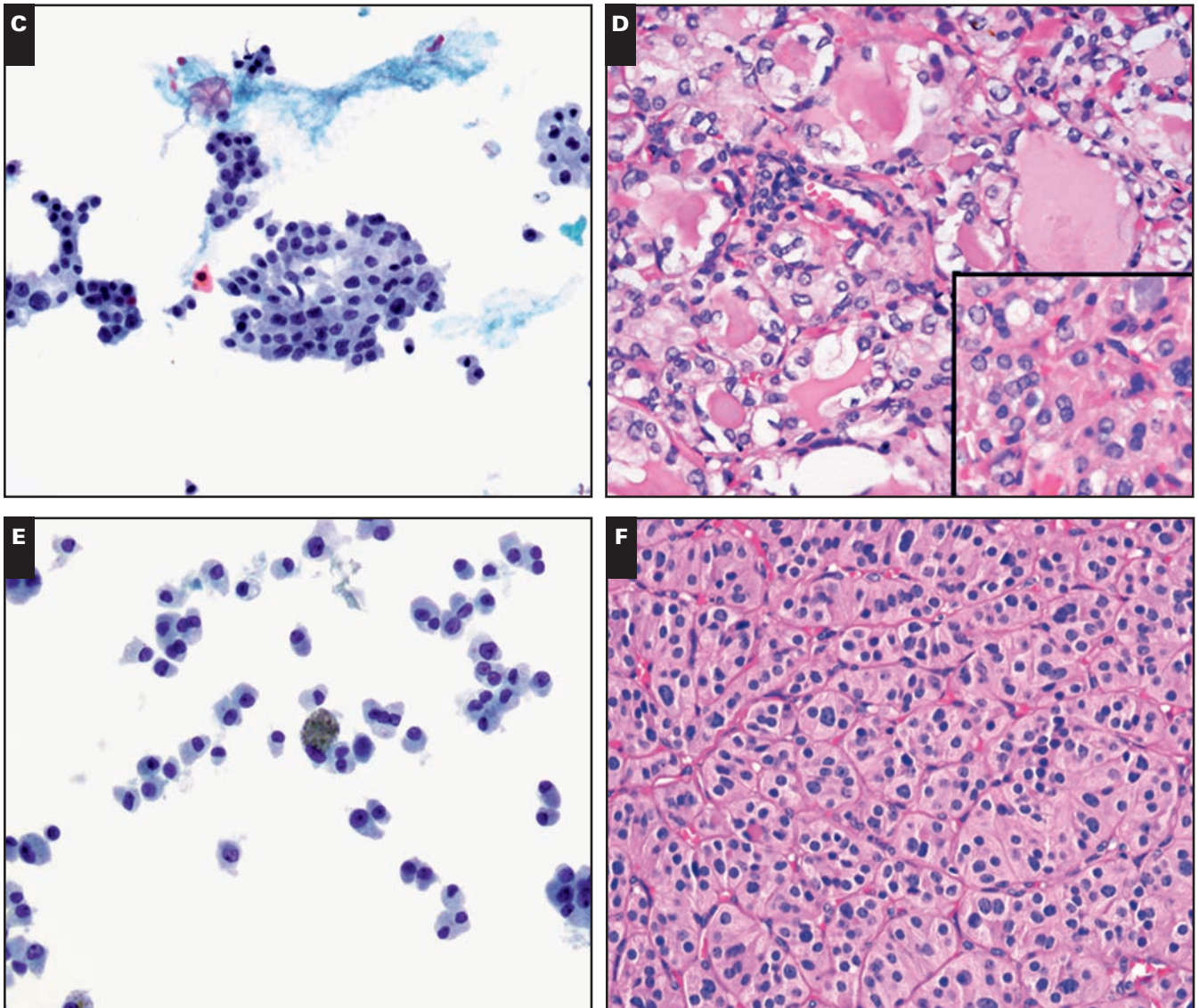


Image 1 Malignant neoplasms in patients without Hashimoto thyroiditis (HT). **A, C, and E**, Representative examples of thyroid fine-needle aspiration cases with cytologic findings “suspicious for a follicular neoplasm, Hürthle cell type” for 3 patients without HT (**A**, Papanicolaou, $\times 400$; **C**, Papanicolaou, $\times 400$; **E**, Papanicolaou, $\times 400$). **B, D, and F**, The corresponding malignant histologic follow-up for each, respectively. **B**, A Hürthle cell carcinoma was confirmed by the presence of transcapsular invasion (H&E, $\times 100$).

If fewer than half of thyroid nodules in patients with HT cytologically interpreted as SFNHCT are neoplasms, what is the PPV for malignancy in the setting of HT? Overall, for the entire study population, the PPV for malignancy was 24%, which is comparable to that seen by Pu et al.¹⁶ The majority of the malignancies were HCCs (Figure 1); however, a significant number of PTCs were diagnosed. Prior reports corroborate this finding,^{15,16} and collectively these data testify to the difficulty in interpreting nuclear atypia of Hürthle cell neoplasms on FNA. After stratifying the cases based on the presence or absence of a history of HT, we found only 2 malignancies in the cohort of 21 patients with HT. In contrast,

25.2% of the patients without HT were found to harbor malignancies on histologic follow-up. It has been reported that HT could be a risk factor for the development of PTC.²⁰ None of the patients with HT in our study, however, was diagnosed with PTC after surgery. This is likely due to our specific analysis of thyroid FNA cases in which the cytologic findings were SFNHCT as opposed to “suspicious for papillary thyroid carcinoma” or “positive for papillary thyroid carcinoma.”

The lower PPV for malignancy of SFNHCT in the HT cohort compared with the non-HT cohort did not reach statistical significance, largely owing to the small patient cohort fulfilling our criteria for HT, despite pooling data



D, An oncocyctic variant of papillary thyroid carcinoma was identified; one portion of the nodule consisted of oncocyctic follicular cells (inset) which merged with an area exhibiting more pronounced nuclear atypia with chromatin clearing, nuclear membrane irregularities, and nuclear grooves (H&E, $\times 400$; inset, H&E, $\times 400$). **F**, Poorly differentiated carcinoma composed of crowded insular nests of follicular cells with oncocyctic cytoplasm (H&E, $\times 400$).

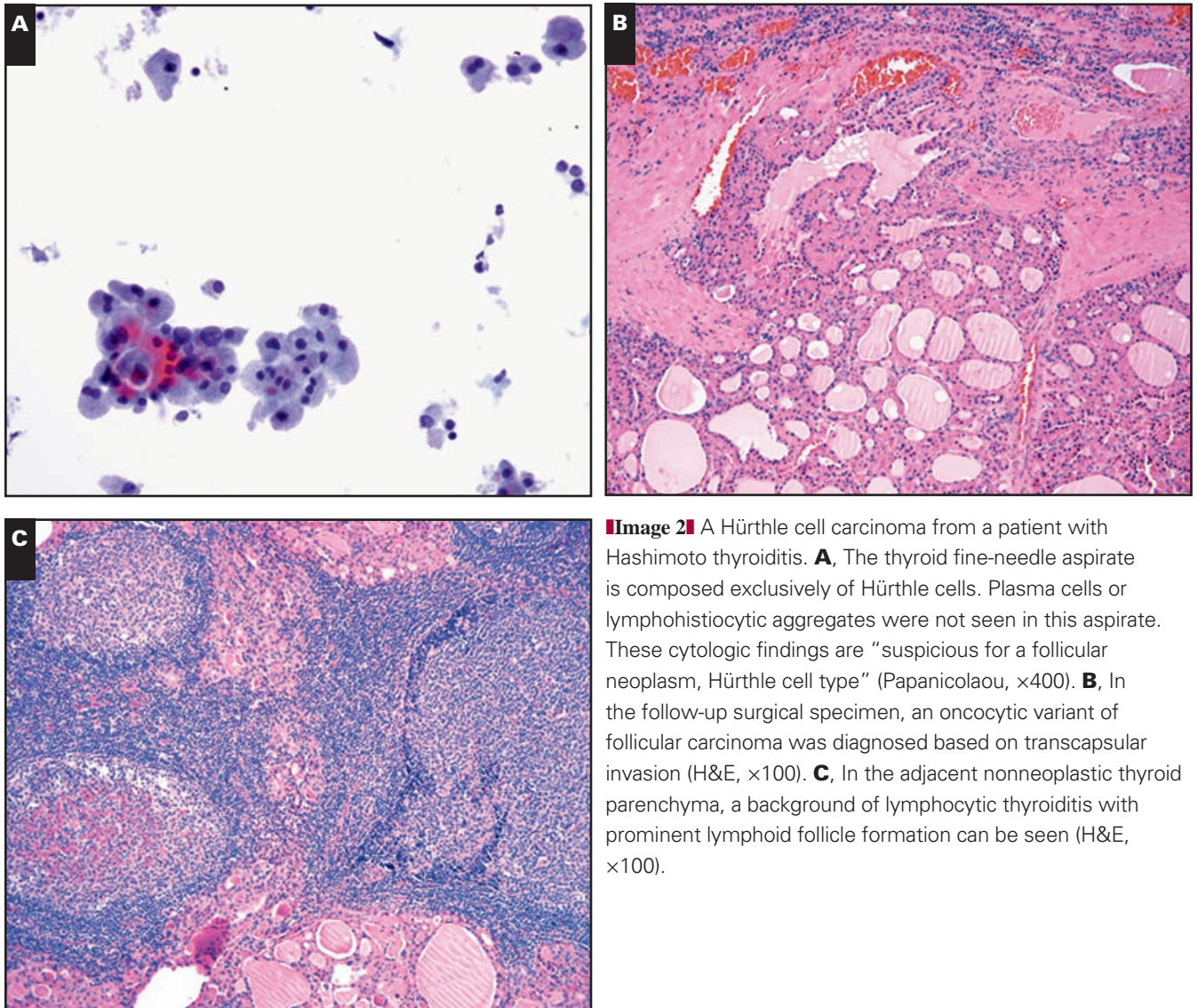


Image 2 A Hürthle cell carcinoma from a patient with Hashimoto thyroiditis. **A**, The thyroid fine-needle aspirate is composed exclusively of Hürthle cells. Plasma cells or lymphohistiocytic aggregates were not seen in this aspirate. These cytologic findings are “suspicious for a follicular neoplasm, Hürthle cell type” (Papanicolaou, ×400). **B**, In the follow-up surgical specimen, an oncocyctic variant of follicular carcinoma was diagnosed based on transcapsular invasion (H&E, ×100). **C**, In the adjacent nonneoplastic thyroid parenchyma, a background of lymphocytic thyroiditis with prominent lymphoid follicle formation can be seen (H&E, ×100).

from 3 large medical centers. The diagnosis of SFNHCT is a relatively infrequent diagnosis; an interpretation of “follicular neoplasm”/“suspicious for follicular neoplasm” is given almost 3 times more frequently than FNHCT/SFNHCT.¹⁶ In our study, we identified 401 patients with thyroid cytologic features of SFNHCT. Different cytopreparatory methods were used at the 3 institutions; nevertheless, the following established criteria were used when interpreting thyroid aspirates as SFNHCT: a cellular specimen composed exclusively or almost exclusively of Hürthle cells, arranged as isolated cells or clusters, with little or no colloid. Plasma cells, lymphocytes, and lymphohistiocytic aggregates were absent or very sparse. A retrospective assessment of the interobserver reproducibility and variability of the SFNHCT interpretation in patients with and without HT was beyond the scope of this study.

Because the PPV for malignancy of SFNHCT in the setting of HT is not zero and because the lower PPV for

malignancy did not reach statistical significance, we do not advocate that a benign interpretation be made in a patient with HT for an aspirate that would be normally interpreted as SFNHCT. On the other hand, the PPV for malignancy of thyroid aspirates interpreted as “atypia of undetermined significance” (AUS) is estimated to be 5% to 15%, in contrast with the PPV of SFNHCT or suspicious for follicular neoplasm, which range from 15% to 45% and 15% to 30%, respectively.^{11,21,22} As the PPV of SFNHCT for malignancy in the HT cohort was approximately 10%, we propose that a thyroid FNA obtained from a patient known to have HT that exhibits predominantly Hürthle cells can be interpreted as AUS or SFNHCT.

An SFNHCT interpretation more accurately reflects the cytologic pattern but overstates the risk of malignancy. If interpreted as SFNHCT, the interpretation can be accompanied by an educational note that the risk of malignancy is

lower than that of SFNHCT in general. On the other hand, an AUS interpretation more accurately reflects the malignancy risk of the nodule. A diagnosis of AUS is typically managed by a repeated thyroid FNA. In this specific setting, however, a repeated FNA is not likely to yield additional information. Although the interpretation of AUS would allow for greater clinical flexibility, permitting, for example, a period of watchful waiting rather than referral for surgical lobectomy, there is still a finite risk of malignancy associated with a Hürthle cell–only pattern in the context of HT. This is illustrated by the 2 patients with HT with HCC identified on follow-up. For these patients, delaying surgical management could have been harmful because HCC has a propensity for lymphovascular space invasion and spread to regional lymph nodes.

Our study results have revealed a discordance between the predicted and the actual risk of malignancy associated with an SFNHCT cytologic interpretation in patients with HT. The best way to report cases that fit this scenario is likely to remain controversial. This underscores the importance of further investigation into the pathology and molecular biology of HCC. In addition, more experience with the application of the Bethesda System to this scenario may lead to a consensus in the future.

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