50 year-old female with 1.8 cm left thyroid nodule: ultrasound-guided FNA

Mike Thrall
The Methodist Hospital, Houston, TX
and Weill Cornell Medical College
The case findings

- The FNA was found to be adequate on immediate assessment
- The features suspicious for papillary carcinoma were seen during screening
- There was a diffuse background of lymphocytic thyroiditis with only very focal suspicious areas
The diagnosis

- Adequacy:
- Satisfactory for evaluation.
- General Diagnostic Category:
- Positive for malignancy
- Descriptive Diagnosis:
- Cytologic features of Papillary carcinoma in a background of Hashimoto’s thyroiditis
Holes
Grooves
Nucleoli
Abundant Granular Cytoplasm
Holes
Abundant Granular Cytoplasm
Nucleoli
Grooves
Atypia

Oncocytic Changes

Nuclear Elongation

Holes
Surgical Follow-up

- A hemi-thyroidectomy was performed with the intention of proceeding to complete thyroidectomy and partial neck dissection.
- The left thyroid was sent for touch preparations and frozen section.
No intranuclear Inclusions!
Touch Preparation Interpretation

- Lymphocytic thyroiditis
- Hurthle cell changes with atypia

- The procedure went on as planned and a completion thyroidectomy was performed with a paratracheal neck dissection
Lymphocytic Thyroiditis
A Wide Range of Nuclear Atypia
Focally Numerous Nuclear Grooves
Rare Pseudo-Inclusions
Final Diagnosis

- Despite complete submission, no papillary carcinoma was identified in the left lobe (the side with prior FNA)
- Diagnosis: Chronic thyroiditis consistent with Hashimoto’s thyroiditis
- In the right lobe, a tiny focus (<1 mm) of papillary carcinoma was found in a distinct fibrotic stroma
- There were 14 negative lymph nodes
Interpreting the Interpretation

- The diagnosis was wrong in the sense that it led to excessive follow-up.
- However, interesting questions can be asked:
  - Could there have been a microcarcinoma that was obliterated by the FNA?
  - Do these cytologic findings represent a premalignant lesion?
  - Did total thyroidectomy mitigate future risk?
Papillary peculiarities

- Papillary carcinoma has no known precursor lesion
- Microcarcinomas are not infrequently seen as incidental findings in thyroid resections
- Variants of papillary carcinoma including the tall cell, oncocytic, and Warthin-like subtypes may simulate Hashimoto’s
- Papillary carcinoma is often associated with chronic inflammation (including Hashimoto’s)
Ancients vs. Moderns

The “Ancient” view: Papillary cancer suddenly emerges like Athena from the head of Zeus

The “Modern” view: Papillary cancer results from cumulative genetic alterations (MAPK)

Nikiforov, Mod Pathol 2008; 21: S37
Molecular explanations?

- RET/PTC recombinations are common in papillary carcinomas and are associated with the characteristic nuclear changes*
- Some authors have found evidence of RET/PTC in the thyroid epithelial cells of Hashimoto’s thyroiditis while others have not, possibly due to differences in testing technique**

Genetic changes in Hurthle cells

- RET/PTC recombinations or other alterations of the MAP-K pathway may explain why occasional Hurthle cells in Hashimoto’s have papillary-like nuclear features.
- Are such Hurthle cells best considered to be pre-papillary or pseudo-papillary?
What about magic markers?

- Hashimoto thyroiditis is a known area of diagnostic difficulty when using immunohistochemistry to distinguish papillary carcinoma from benign thyroid

- Is the overlap in expression of markers such as Galectin-3, CK 19, HBME-1, fibronectin-1 and CITED1* due to overlapping biology or simply an inconvenience to pathologists?

Lessons from this case

- Much is still unknown about the relationship between Hashimoto’s and papillary carcinoma
- Be wary of papillary-like nuclear changes in the setting of Hurthle cell change and/or lymphocytes in the background
- Pulling back to “Suspicious” or even “Atypical” may be the wiser course
Other Hashimoto pitfalls

- Reactive cytologic changes may be the most prominent feature with relatively few lymphocytes present in the smear.
- This can lead to a number of misinterpretations.
An isolated psammoma body in Hashimoto’s thyroiditis
Suspicious for Hurthle Cell Neoplasm?
Follow-up: Adenomatous changes and Hashimoto’s thyroiditis
Suspicious for Follicular Neoplasm?
Follow-up: Hashimoto Thyroiditis
Conclusions

- Hashimoto’s thyroiditis is a major source of pitfalls in thyroid cytology
- Lymphocytes may be rare in some or all smears, compounding the difficulty
- Hurthle cells may have nuclear atypia, including changes that can mimic papillary carcinoma
The patient is a 50 year-old female with a 1.8 cm left thyroid nodule biopsied under ultrasound-guidance. No additional history was provided. The initial check showed adequate material for diagnosis and the case underwent routine screening. Most of the material showed fairly straightforward lymphocytic (Hashimoto’s) thyroiditis with numerous lymphocytes, including many within follicles, and Hurthle cell changes.

Focally, cell clusters were identified with nuclear features highly suspicious for papillary carcinoma. The images of these clusters were provided prior to the conference. There are conflicting cytologic features. The nuclei contain multiple very convincing intranuclear pseudoinclusions with dense margins and central cytoplasm. In addition, many nuclei show nuclear grooves and there is associated nuclear enlargement, elongation, and nuclear contour irregularities. However, many cells show clear oncocyctic change including abundant granular cytoplasm and large round nuclei with some prominent nucleoli. These are Hurthle cells and the nuclear changes must be interpreted with caution. The presence of occasional lymphocytes in the background and the widespread lymphocytic thyroiditis in other areas are also concerning.

Papillary carcinomas may arise in the setting of Hashimoto’s thyroiditis and the possibility must be kept in mind. The original pathologist who signed out this case felt that these cells represented such a carcinoma. A clinical decision was made to proceed with thyroidectomy. Despite a frozen section and intraoperative touch preparations from a hemithyroidectomy specimen that did not reveal papillary carcinoma, the surgeon proceeded with completion thyroidectomy and partial lymph node dissection. The entire thyroid was submitted and only a single microcarcinoma was found in the lobe opposite the site of the FNA. The final diagnosis was lymphocytic thyroiditis. The lymph nodes were all negative.

This case illustrates the pitfalls associated with atypical Hurthle cells encountered in the setting of Hashimoto’s thyroiditis. The nuclei may show convincing nuclear pseudoinclusions that are generally considered to be all but pathognomonic for papillary carcinoma. These pseudoinclusions are very difficult to ignore, especially when they are multiple and in an area with relatively few lymphocytes or are accompanied by other changes typically seen in papillary carcinomas.

Recent investigations into the genetics of papillary carcinoma have revealed that many cases have identifiable alterations in at least one gene related to the MAP kinase (MAPK) pathway. The most common are mutations in BRAF (~40%), followed by RET/PTC translocations (~20% of cases), of which there are many with RET/PTC 1 and RET/PTC 3 being the most frequent. Ras mutations also are sometimes seen in papillary carcinomas (~10%). RET/PTC translocations have been shown to induce the characteristic cytologic changes of papillary carcinoma in cell culture models. Very sensitive PCR studies
have also demonstrated the presence of RET/PTC translocations in follicular cells found in Hashimoto’s thyroiditis, possibly accounting for the rare nuclear changes in associated Hurthle cells that may mimic papillary carcinoma. Not all authors have found these translocations in Hashimoto’s thyroiditis, however, making their presence controversial.

These insights raise the question of whether there is a genetically abnormal, but morphologically normal (or at least not diagnostic), precursor to papillary carcinoma. Although microcarcinomas are well known and not infrequently found as incidental thyroid tumors, with only small metastatic potential, they are not a true precursor. They have all the cytologic and histologic features and are only distinguished by small tumor size. Presumably papillary carcinoma must arise from normal thyroid follicular cells that accumulate a sufficient number of genetic alterations over time to become malignant. Might some of these cause nuclear changes without making the leap all the way to metastatic potential? Could the process happen in reactive oncocytic cells in Hashimoto’s thyroiditis, possibly with an increased frequency? These are interesting speculations without solid answers.

The main lesson to take away from this case is that caution must be exercised when encountering rare nuclear features of papillary carcinoma, especially in the context of lymphocytic infiltration or Hurthle cell change. Nuclear enlargement, atypia, and grooves are common in Hurthle cells. Nuclear pseudoinclusions may also uncommonly be seen, and this is one instance in which they are not pathognomonic for papillary carcinoma. Even in a case with as many impressive pseudoinclusions as this one, it is wise to use the atypical (ACUS/FLUS) or suspicious categories. Outright diagnosis of papillary carcinoma is likely to lead to total thyroidectomy and possibly to lymph node dissection as well.

Hashimoto’s thyroiditis is also associated with a number of other pitfalls. Rarely, psammoma bodies can be seen in this setting. Although like pseudoinclusions they strongly suggest papillary carcinoma, that diagnosis should not be rendered without other features. Reactive hypercellularity and reduced colloid production are also frequent findings in Hashimoto’s. Combined with uniform Hurthle cell changes and atypia, this may lead to a false diagnosis of “suspicious for Hurthle cell neoplasm”. Alternately, the associated presence of numerous microfollicles may suggest a false diagnosis of “suspicious for follicular neoplasm”. Both errors are more likely when lymphocytes are rare on the smears, which may happen when an adenomatous nodule within Hashimoto’s is targeted.

Key Words:
Papillary thyroid carcinoma
Hashimoto’s (lymphocytic) thyroiditis
Hurthle cell
Nuclear pseudoinclusions
BRAF

RET/PTC translocations

References:


Nikiforov YE. “Thyroid Carcinoma: Molecular Pathways and Therapeutic Targets” Mod Pathol 2008; 21: S37.


Prasad ML, Huang Y, Pellegata NS, de la Chapelle A, Kloos RT. “Hashimoto’s Thyroiditis with Papillary Thyroid Carcinoma (PTC)-Like Nuclear Alterations Express Molecular Markers of PTC” Histopathol 2004; 45: 39.


Stephenson TJ. “Papillary Carcinoma of the Thyroid: A Tumor Still With No Benign Neoplastic Counterpart” Histopathol 2001; 39: 536.