Case Report
Thyroseq V3 Molecular Profiling for Tailoring the Surgical Management of Hürthle Cell Neoplasms

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1. Introduction

Thyroid nodules with a predominance of Hürthle cells often confound the diagnostic utility of fine needle aspiration biopsy (FNAB) with cytology often interpreted as a Hürthle cell lesion with an indeterminate risk of malignancy, Bethesda category (BC) III or IV. Molecular diagnostics for Hürthle cell predominant nodules has also been disappointing in further defining the risk of malignancy. We present a case of a slowly enlarging nodule within a goiter initially reported as benign on FNAB, BC II but on subsequent FNAB suspicious for a Hürthle cell neoplasm, BC IV. The patient had initially requested a diagnostic lobectomy for a definitive diagnosis despite a higher risk of malignancy based on the size of the nodule > 4 cm alone. To better tailor this patient’s treatment plan, a newer expanded gene mutation panel, ThyroSeq® v3 that includes copy number alterations (CNAs) and was recently found to have greater positive predictive value (PPV) for identifying Hürthle cell carcinoma (HCC), was performed on the FNAB material. Molecular profiling with ThyroSeq® v3 was able to predict a greater risk of carcinoma, making a more convincing argument in favor of total thyroidectomy. Surgical pathology confirmed a Hürthle cell carcinoma with 5 foci of angioinvasion and foci of capsular invasion.
difficult clinical management of Hürthle cell thyroid nodules. Diagnostics, specifically, ThyroSeq v3 was able to predict a greater risk of HCC, making a finding alone could not reliably predict a HCC, the patient had initially requested a diagnostic lobectomy for a definitive pathologic diagnosis despite a higher risk of malignancy based on the size of the nodule > 4 cm alone. To better tailor this patient's treatment plan, the ThyroSeq v3 panel, recently found to have greater positive predictive value (PPV) for identifying Hürthle cell malignancies, was performed on the FNA material. Molecular profiling with ThyroSeq v3 was able to predict a greater risk of HCC, making a more convincing argument in favor of total thyroidectomy. This case report illustrates the important role of molecular diagnostics, specifically, ThyroSeq v3 in tailoring the often difficult clinical management of Hürthle cell thyroid nodules for optimal surgical treatment.

2. Case Presentation

This patient was a generally healthy 62-year-old male with a left lobe complex nodule within a nontoxic multinodular goiter that had been enlarging for approximately 3 years. In 2015, the patient had a FNAB reported as benign, BC II. Because of continued growth, he had a second FNA biopsy approximately six months later reported as a Hürthle cell neoplasm or suspicious for a Hürthle cell neoplasm, BC IV with Oncocytic / Hürthle cells dispersed mostly singly and in small fragments in a background of lysed blood. CKAIE/AE3, TTF-1, and thyroglobulin immunostains were positive (Figure 1(a)). Molecular testing with ThyroSeq v2 revealed an absence of gene mutations or fusions but overexpression of the MET gene. Since this finding alone could not reliably predict a HCC, the patient had initially requested a diagnostic lobectomy for a definitive pathologic diagnosis despite a higher risk of malignancy based on the size of the nodule > 4 cm alone. To better tailor this patient's treatment plan, the ThyroSeq v3 panel, recently found to have greater positive predictive value (PPV) for identifying Hürthle cell malignancies, was performed on the FNA material. Molecular profiling with ThyroSeq v3 was able to predict a greater risk of HCC, making a more convincing argument in favor of total thyroidectomy. This case report illustrates the important role of molecular diagnostics, specifically, ThyroSeq v3 in tailoring the often difficult clinical management of Hürthle cell thyroid nodules for optimal surgical treatment.

3. Discussion

In the past, cytologic assessment, with or without molecular profiling, of Hürthle cell nodules failed to accurately predict the risk of HCC. The presence of Hürthle or oncocytic cells in cytologic specimens from FNA samples is often seen in a wide range of thyroid pathologies, the majority of which are benign. The finding of predominance of Hürthle cells is usually interpreted as suspicious for a follicular neoplasm,
Hürthle cell type, BC IV, conferring a positive predictive value (PPV) for malignancy of approximately 15-30%. The high frequency of nonneoplastic Hürthle cell proliferation in patients with Hashimoto’s thyroiditis can be a diagnostic dilemma for the cytopathologist [3]. With the advent of molecular profiling, the hope was to minimize the need for diagnostic thyroid lobectomy for benign nodules, for tumor prognostication to tailor the extent of thyroid surgery for optimal cure and to prevent tumor recurrence. The Afirma® Gene Expression Classifier developed by Veracyte, Inc. (South San Francisco, CA) has been shown to have a high negative predictive value (NPV) for most benign thyroid nodules but with a poor PPV for malignancy and renders a large number of FNA samples with various proportions of nonneoplastic Hürthle cells as suspicious for malignancy, thus triaging most of these patients to thyroid surgery [4].

ThyroSeq is a multigene next-generation sequencing-based test for thyroid nodules. The early version, ThyroSeq v2, utilized the analysis of 56 genes predominantly for point mutations and gene fusions, as well as for limited gene expression alterations [2]. The expanded version of the test, ThyroSeq v3, interrogated 112 genes and is based not only on the analysis of point mutations, gene fusions, and gene expression alterations, but also on copy number alterations (CNAs) [5]. The latter is particularly important for predicting Hürthle cell carcinomas, which are known to have a characteristic pattern of CNAs with almost complete genome haploidization [6]. Taking advantage of the analysis of CNAs, in the validation study, ThyroSeq v3 showed reliable performance in Hürthle cell cancers, offering 93% sensitivity and 69% specificity [5]. In a preliminary report from a recent multicenter study which included 10 Hürthle cell carcinomas,
34 Hürthle cell adenomas, and 5 hyperplastic nodules with Hürthle cell predominance, the performance of ThyroSeq\textsuperscript{v3} allowed for the detection of all HCCs (sensitivity, 100%; 95%CI: 69.2-100%), with all 5 hyperplastic nodules with Hürthle cell predominance classified as negative and overall test specificity of 66.7% (95%CI: 49.8-80.9%) [7].

In an era of patient-guided decision-making and the ability to tailor the extent of surgery based on preoperative FNA biopsy prognostication, molecular profiling of thyroid nodules has become increasingly utilized. Despite the limitations of molecular testing and the variance in both PPV and NPV with a varying prevalence of malignancy in different populations, its utility in selecting patients for active surveillance, thyroid lobectomy, and total thyroidectomy will likely increase, especially as their overall accuracy improves over time. The particular advantages of ThyroSeq\textsuperscript{v3} over ThyroSeq\textsuperscript{v2} in guiding the extent of thyroid surgery for indeterminate Hürthle cell cytopathology are illustrated by this case report and helped tailor the best treatment for this patient with a Hürthle cell carcinoma who would otherwise have likely needed a completion thyroidectomy.

Conflicts of Interest

Dr. Nikiforov reports an IP related to Thyroseq. The University of Pittsburgh Medical Center (UPMC) has a service agreement with CBLPath/Sonic Health Care Company to offer Thyroseq for commercial use. The other authors declare that they have no conflicts of interest.

References
