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Management of "Indeterminate" Cases of Thyroid: A Molecular Signature Approach

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Short Communication

Thyroid nodules, a common diseases of the endocrine system, has 3%-7% prevalence by palpation with annual increasing trends worldwide [1]. The use of sensitive imaging techniques can detect higher percentage of thyroid nodules and 5% to 15% of these are malignant [2]. Thyroid cancer is the 16th most common cancer worldwide with about 2.1% new cases in 2012 [3]. Fine needle aspirate cytology is considered to be the gold standard for diagnosis of progressively increasing thyroid nodules. But the reported sensitivity and specificity falls between a wide range; the sensitivity between 65% and 98% and the specificity between 72% and 100% [4]. Consequently, in a substantial number (20% to 30% of nodules) of cases, the FNA cytology cannot differentiate between benign and malignant leision and these cases are categorized as "indeterminate". The diagnosis of these cases has long been debatable and challenging. In most of the cases, surgery is performed and the definitive diagnosis is made on the basis of histopathology results. Of these 20-30% cases of indeterminate cytology, only 5-30% carry malignancy [5]. Hence a large proportion of indeterminate cases are found to be benign after surgical procedure. These patients may suffer the possible risks of thyroid surgery that could have been avoided if a definitive diagnostic test was available. If the patient has malignant leision, a second surgery, for complete thyroidectomy, must be performed depending on the size and histopathological features. A second surgical intervention poses a higher risk of hypocalcemia and recurrent laryngeal nerve injury, in addition to cost and emotional stress to the patient and the family. Moreover, in follicular thyroid carcinoma, the lesions may be very small or even invisible and by standard guidelines, these small lesions do not merit further analyses. Hence, there is a need to improve the diagnostic accuracy while evaluating thyroid nodules.

Recent advances in molecular biology has unveiled the pathways leading to cancerous transformation. Several studies have evaluated different markers to increase the diagnostic accuracy of thyroid nodules. Mitogen-activated protein kinase (MAPK) signaling pathway plays a central role in uncontrolled cell proliferation and faulty apoptosis. Mutations in BRAF gene are highly specific to PTC and are not found in benign and follicular neoplasms. Greater than 95% of reported mutations are a thymine to adenosine transversion at nucleotide 1799 in exon 15, replacing valine with glutamic acid at amino acid 600 (c.1799T>A; p.V600E) [6-12].This mutation is mostly associated with more aggressive papillary thyroid cancer with highest recurrence [13]. The presence of the V600E mutation in the BRAF gene is usually detected by allele specific oligonucleotide PCR.

RAS family (NRAS, KRAS, HRAS) of GTPases plays a central role in the MAPK signaling pathway. Activating mutations in codons 12, 13, and 61 of NRAS, KRAS have been found in various cancers, including thyroid carcinoma (7%) [7,12].Tumors carrying mutations in codons 12, 13 and 61 of NRAS and KRAS oncogene do not respond to anti-EGFR antibody therapy. Therefore, screening for KRAS mutations is necessary to more accurately identify tumor cells that will not respond to anti-EGFR drugs. These mutations may either be detected by high resolution melt analysis of genomic PCR products followed by DNA sequencing or by next generation sequencing.

Rearrangements involving the *RET* proto-oncogene result in constitutive activation of the RET tyrosine kinase domain These rearrangements are common in PTC (3-60%) and are associated with poor prognosis, more aggressive tumors and higher chance of distant metastasis [13-15].

A chromosomal translocation t(2;3)(q13;p25) results in the production of a PAX8-PPARγ fusion protein found in follicular carcinomas and not in PTC and hence, can be used as a biomarker for differential diagnosis [15-17]. Nested PCR amplification is performed using forward and reverse primers covering major breakpoint regions in RET/PTC and PAX8/PPARγtranslocation product.

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MicroRNAs (miRNAs) regulate gene expression in a number of biological processes including differentiation, cell proliferation and apoptosis [18]. It has been found that the expression of different miRNAs could be associated with differential diagnosis, staging, prognosis, and response to cancer treatment [19]. It has been reported that the expression of miR-221, -222, -146b and -181b is specifically increased 5- to 35-fold in FNAB samples of papillary thyroid carcinoma patients [20], while miR-125b is significantly overexpressed in FTC samples [21]. Moreover, miR-221 is the most favorable miRNA in differentiating benign from malignant thyroid pathology with specificity (100%), negative (96%) and positive (100%) predictive value, and accuracy (98%) respectively [22]. MiRNA signature can also distinguish the degree of PTC aggressiveness [23]. Hence, serum miRNA profiles may be used as novel and minimally invasive diagnostic markers for PTC.

Based on these findings, a Seven Genes Mutational Panel was introduced for "ruling in" malignancy among cytologically indeterminate thyroid nodules [24], hence, eliminating 2-stage surgical procedure. But this 7-gene panel has low NPV and hence is not good enough to "rule out" the probability of malignancy. A second diagnostic test, namely, Afirma Gene Expression Classifier (GEC) based on microarray technology was later introduced. This test evaluates the mRNA expression profiles of 142 genes in cytologically indeterminate thyroid nodules [25].The sensitivity of Afirma test ranges from 83% to 100% and specificity from 7% to 52%. This test has a high NPV (75% to 100%), useful for "ruling out" malignancy, but low PPV (14% to 44%) for malignancy. Both the 7-gene panel and the Afirma GEC are, thus, limited by either low PPV or low NPV [26].

Ideally, an ancillary test for indeterminate thyroid FNAs should have sufficient predictive power to "rule in" and "rule out"malignancy, thereby helping clinicians to improve the management of "indeterminate" cases of thyroid nodules and to avoid many of the currently required surgeries that are associated with significant costs and potential risks. The introduction of Next Generation Sequencing led to the ThyroSeq platform, which tests for point mutations and small insertions/deletions in 14 genes, 42 types of gene fusions, and expression levels of 16 genes. With NPV of 96-97%, and reasonably high (77-83%) PPV, the ThyroSeq v2 can serve the test of choice [26]. Other recently introduced thyroid diagnostic tests use combination of a 7-gene mutation panel and 10 microRNAs (ThyGenX/ThyraMIR) and only 24 miRNA markers (Rosetta GX), remain to be evaluated in large number of samples [27].

In summary, molecular testing of FNA from thyroid nodules has the potential to play a major role in the evaluation of indeterminate thyroid lesions. New insights into the molecular events leading to malignant behavior of thyroid nodules and the introduction of new diagnostic platforms will most likely lead to development of new or improved versions of the current tests. Although the utilization of molecular markers as standalone test is debatable yet it can substantially alter the clinical decision-making process when performed and interpreted within the context of the clinical, radiographic, and cytological findings. We propose algorithm (Figure 1) for management of thyroid nodules showing indeterminate cytology on FNA.

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