Risk Stratification of Thyroid Nodules Suspicious for Medullary Thyroid Carcinoma and the Bethesda System for Reporting Thyroid Cytopathology

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BACKGROUND

Medullary thyroid carcinoma (MTC) is a malignant neuroendocrine neoplasm derived from the perifollicular C cells of the thyroid comprising 1-2% of thyroid carcinomas. Its initial presentation can be as a thyroid nodule or a neck mass and fine needle aspiration (FNA) is routinely performed to evaluate these masses. However, MTC can possess diagnostic challenges on FNA biopsy due to variable cytomorphology. The aim of this study is to investigate risk stratification of thyroid nodules suspicious for MTC in the Bethesda System for Reporting Thyroid Cytopathology (BSRTC).

METHODS

After institutional approval, the electronic data in a large academic institution was retrospectively searched for any thyroid FNA cases containing the keywords MTC in the final reports. Cases from 2006-2018 were searched, and only cases with surgical follow-up were included. The cytopathology diagnosis, corresponding histology diagnosis, ancillary studies such as immunohistochemistry (IHC), and patients' demographics were recorded. The BSRTC was applied retroactively for all cases based on their cytology report.

RESULTS

A total of 106 cases were included (46 males and 100 females) with mean age of 52.9 years (17-85 years). The number of histology confirmed MTC cases for each BSRTC category was as follows: III, 1/5, IV, 3/13, V, 12/21 and VI, 59/67, respectively. Combined MTC and papillary thyroid carcinoma (PTC) was reported in seven histology cases. IHC is applied on large number of histology cases as well as on cytology specimens. Multinodular Hyperplasia, Noninvasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features (NIFTP), follicular adenoma with Hurthle cell change, and a fibrosing inflammatory process were benign conditions masquerading MTC on aspirated material. PTC, anaplastic thyroid carcinoma, parathyroid carcinoma, and neuroendocrine neoplasms both low grade and high grade were malignant neoplasms mimicking MTC.

RESULTS (cont.)

Bethesda	Surgical Diagnosis	ROM
III (n=5) (M:F, 1:4)	• MTC and PTC (n=2) • MTC (n=1) • NIFTP (n=1) • Multinodular hyperplasia (n=1)	60% (3/5)
IV (n=13) (M:F, 2:11)	• MTC (n=3) • PTC (n=4) • Parathyroid carcinoma and PTC (n=1) • Anaplastic thyroid carcinoma (n=1) • High grade NEC (n=1) • Hurthle cell carcinoma (n=1) • Low grade epithelial neoplasm with neuroendocrine features (n=1) • Follicular adenoma with Hurthle cell change (n=1)	92.3% (12/13)
V (n=21) (M:F, 10:11)	• MTC (n=12) • MTC and PTC (n=2) • PTC (n=5) • Hurthle cell carcinoma (n=1) • Follicular adenoma with papillary microcarcinoma (n=1)	100% (21/21)
VI (n=67) (M:F, 23:44)	• MTC (n=59) • MTC and PTC (n=3) • PTC (n=3) • Small cell carcinoma (n=1) • Fibrosing inflammatory process (n=1)	98.5% (66/67)

Table 1. Application of Bethesda system for Reporting Thyroid Cytopathology in cases suspicious for medullary thyroid carcinoma, with surgical diagnoses and risk of malignancy for each category

Bethesda	AE1/AE3		Calcitonin		Chromogranin		CEA		Synaptophysin		TTF-1		Thyroglobulin	
	+	-	+	-	+	-	+	-	+	-	+	-	+	-
III (n=5)														
Cytology														
Histology			1											
IV (n=13)														
Cytology					1				2					
Histology			1		1				1		1			1
V (n=21)														
Cytology			3		2		1		1		1			
Histology			10		6		4		5		4			3
VI (n=67)														
Cytology	6		37		14		8		9		9		3	13
Histology	3		23		6		4		7		5			6

Table 2. Immunohistochemistry results from cytology and histology reports for each Bethesda category.

RESULTS (cont.)

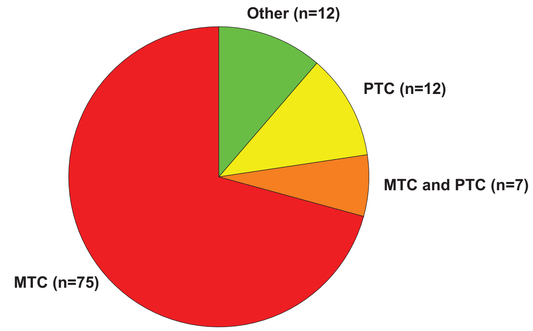

Figure 1. The distribution of the surgical diagnoses for all the cases studied. Around 70% of cases were diagnosed as MTC

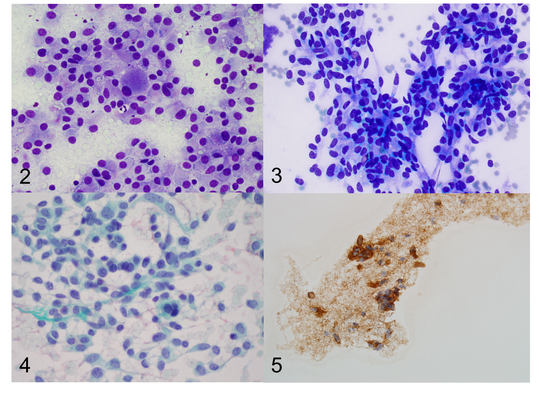

Figure 2. The neoplastic cells of MTC appear with plasmacytoid features including round eccentric nuclei, and abundant granular cytoplasm (X400, Diff-Quik)
Figure 3. The neoplastic cells of MTC appear with spindle cell features elongated nuclei, and granular cytoplasm (X400, Diff-Quik)
Figure 4. Cytomorphology of the neoplastic cells of MTC is variable from round to spindle cells. The nuclei display a coarse chromatin (X400, Papanicolaou stain)
Figure 5. The neoplastic cells exhibit cytoplasmic staining for calcitonin (x200, immunostain)

CONCLUSION

Our study confirms that the BSRTC is a reliable tool for reporting MTC and application of IHC improves the diagnostic accuracy on cytology specimens. Moreover, IHC application in large number of histology cases indicates that the diagnosis of MTC remains a diagnostic challenge due to its variable cytomorphology. There are combined cases of MTC and PTC which requires extra attention and add to the complexity of these entities.