

 **The Trials and Tribulations of a Machiavellian and Cunning Thyroid Lesion**


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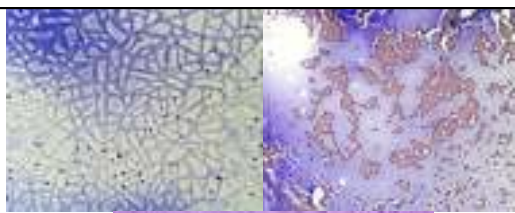
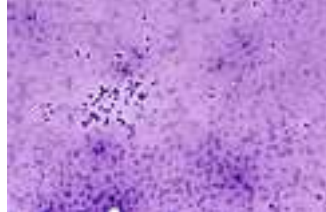


Machiavellian
Clever and dishonest methods to achieve a goal


Cunning
Skill in concealing or disguising the real purposes of one's actions





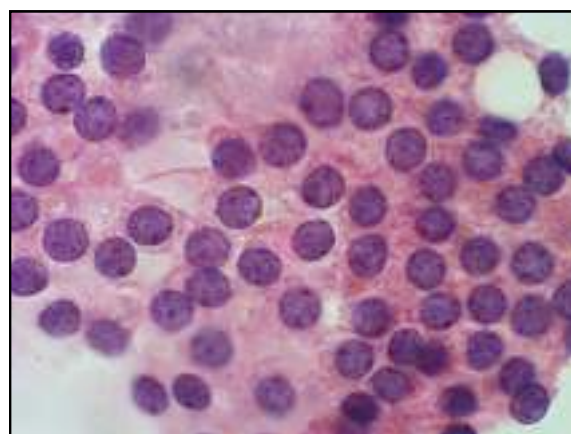
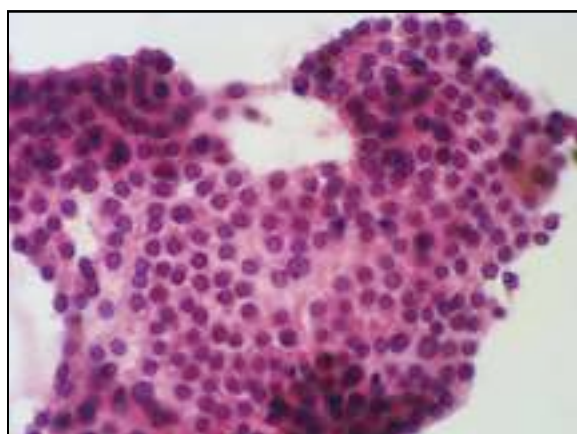



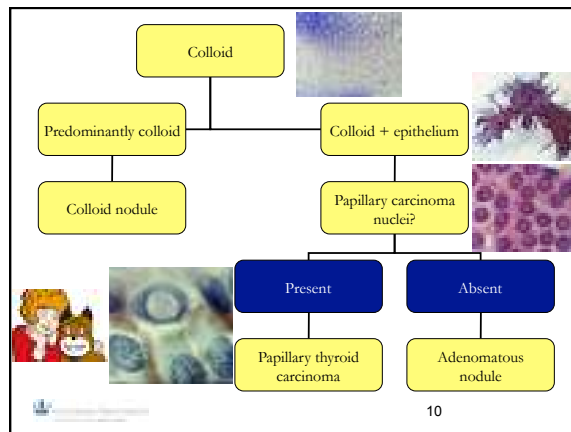
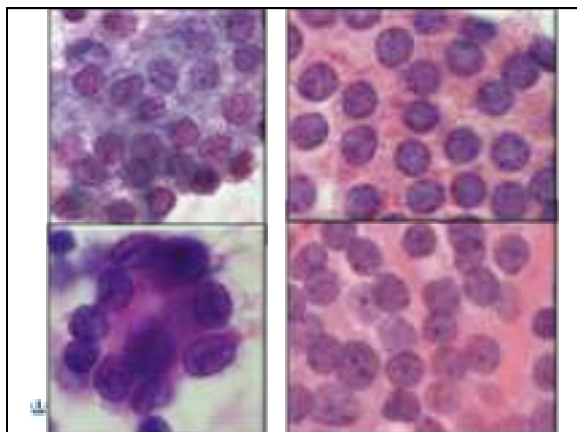
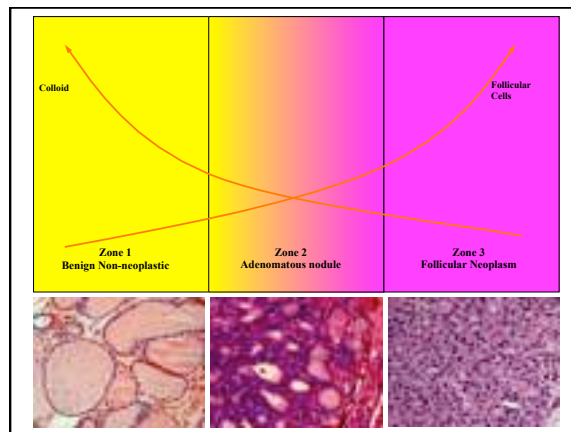
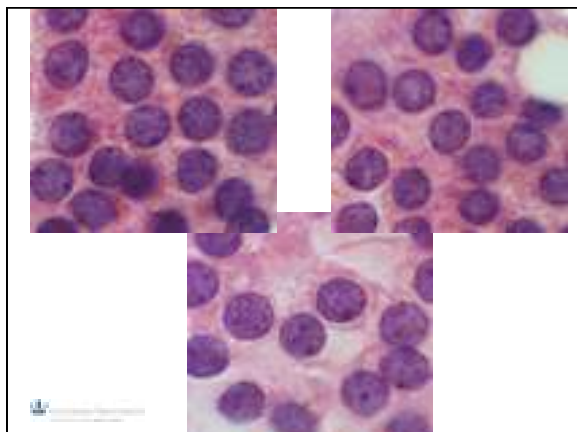
57 y/o woman



57 y/o woman

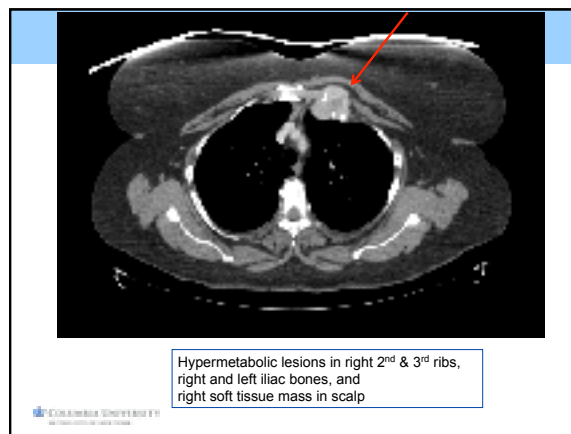






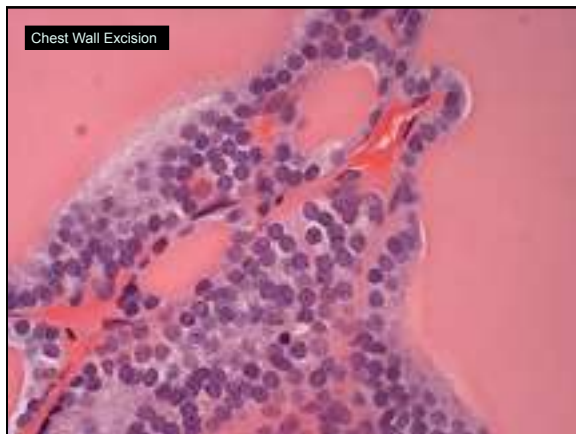
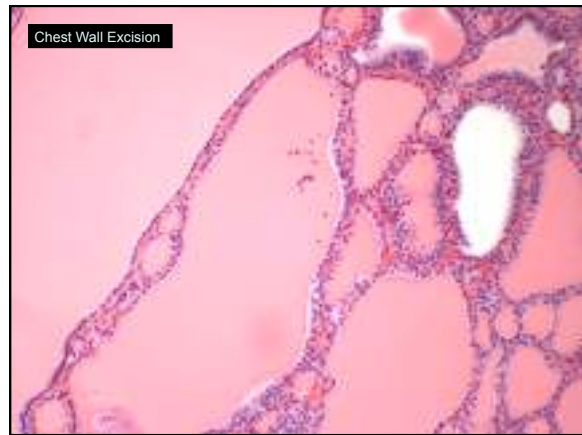
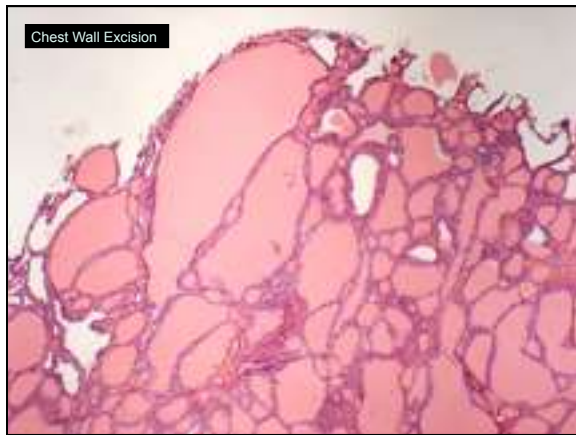
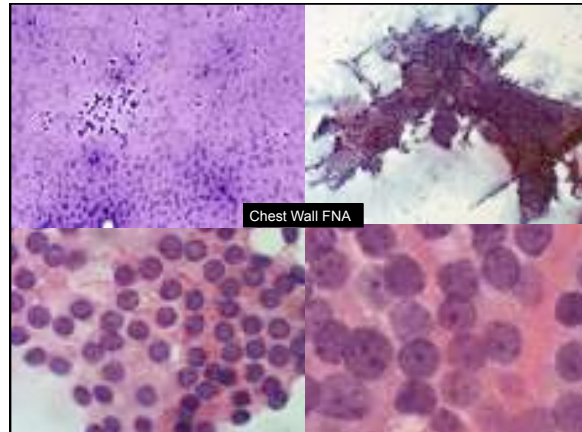
Case Presentation

HPI: 57 y/o woman
 PPD positive, serial CXR's
CXR nodule/mass
 No cough or night sweats
 No hoarseness, dysphagia, stridor, or signs of aspiration
 Physical Exam:
 Normal otologic exam
 Normal intranasal exam
 Unremarkable oral cavity and oropharynx
 Neck *without* discrete masses, lymphadenopathy or thyromegaly



Case Presentation

CT-guided FNA of left chest wall lesion
Excisional biopsy of left chest wall lesion



Pathology Diagnosis

- Chest wall, biopsy
 - **Metastatic papillary thyroid carcinoma, macrofollicular variant**
 - Immunohistochemical markers:
 - Negative for HBME-1, CK19 and Galectin-3

Case Presentation

Thyroid Ultrasound

Right lobe: 4.8 x 2.1 x 2.1 cm

Lower pole nodule: 1.9 x 1.1 x 1.3 cm

Left lobe: 4.7 x 1.4 x 2.1 cm

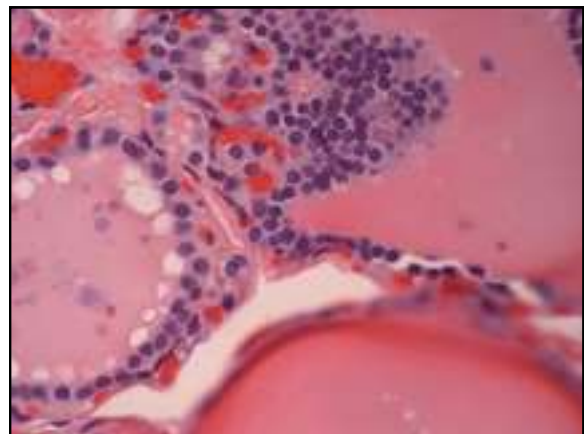
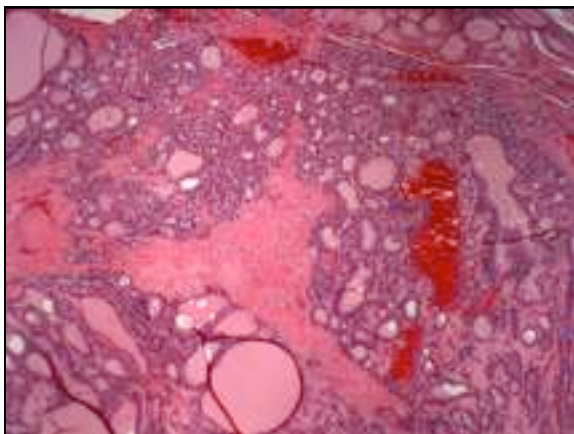
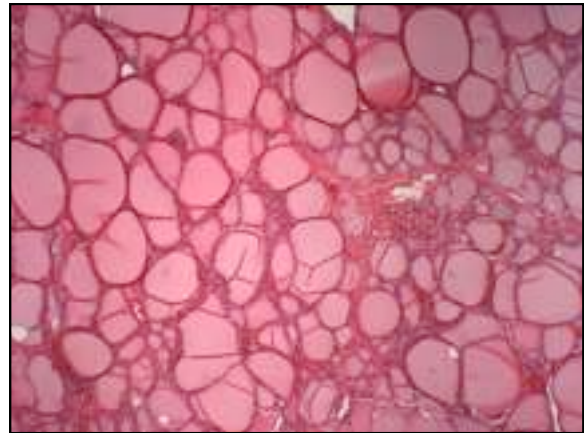
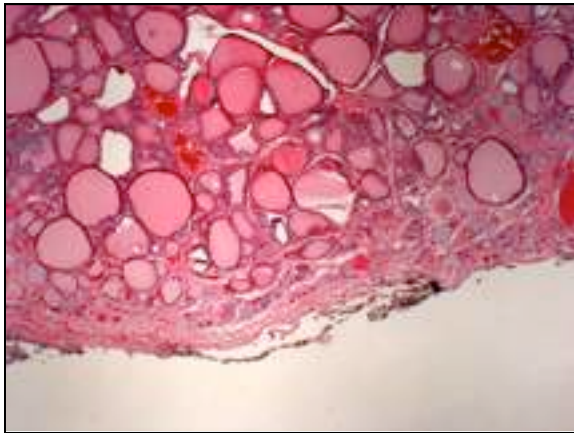
Mid pole nodule: 1.2 x 0.5 x 0.9 cm

Adjacent: 0.6 x 0.5 x 0.6 cm

Isthmus: 2 mm in A-P thickness

Total Thyroidectomy

- Total thyroidectomy
 - 19 grams
 - Multiple nodules on the cut surface, largest one measuring 1.3 x 1 x 0.7 cm
 - Entirely submitted





Pathology Diagnosis

- Thyroid, total thyroidectomy
 - Nodular hyperplasia
- Sent to Dr. Juan Rosai
 - Hypothesis
 - Spontaneous regression of possible primary tumor
 - “Benign metastasizing goiter”
 - Papillary thyroid carcinoma, macrofollicular variant



Papillary Microcarcinoma

- Tumors ≤ 1 cm or well-differentiated
 - low-risk carcinomas
- Distant metastases extremely rare
- 2 cases of clinically occult carcinoma of the thyroid
 - 2.4 mm carcinoma presenting with distant hematogenous (pulmonary) metastasis
 - Lethal carcinoma with extensive metastasis not diagnosed until autopsy
- The absence of a clinically detectable thyroid abnormality does not exclude the possibility of extensive hematogenous and lymphatic metastases from a minute or undetected carcinoma of the thyroid.

“Tumor Regression”

- Papillary microcarcinoma of the thyroid with histologic features suggestive of regression
 - Presented with LN mets without clinical or imaging evidence of primary tumor
 - Thyroidectomy:
 - Microscopic foci measuring <1.5 mm
 - Diffuse sclerosis
 - Significant lymphocytic infiltrate composed of cytotoxic T-lymphocytes



“Benign Metastasizing Goiter”

- First described by Julius Cohnheim (1876)
- Three theories:
 - Misplaced embryonal cells
 - Normal thyroid tissue may break into the blood stream and be carried to bone and metastasize
 - Presence of a “small malignant adenoma” of the thyroid might be the primary source of the metastatic growth



A woman, age 35, developed nodular small gelatinous nodules in her neck, long, hard and vascular. The thyroid gland was diffusely and approximately enlarged, and composed two nodules, coming in gross and microscopic appearance to the metastatic nodules. One of these nodules showed evidence into the lumen of the left inferior thyroid vein. Histologic appearance of the thyroid nodules was that of simple colloid goiter and the metastases showed a similar cellular structure except that a few small cells contained no colloid and some of the follicles showed the presence of epithelial cells.

MALIGNANT ADENOMA OF THE THYROID, WITH SECONDARY METASTASES TO BONE

WITH A REMISSION OF SO-CALLED “BENIGN METASTASIZING GOITER”
 HALPER E. OSTERBERG, M.D.
 TORONTO, CANADA

During the past 20 years in the Public Ward of the Toronto General Hospital there have been performed a total of 2,258 thyroidectomies. Sixty of these thyroidectomies, or 2.6 per cent, were done for carcinoma of the thyroid. Of these 60 cases, 24 were diagnosed as adenocarcinoma or malignant adenoma of the thyroid. Five of these cases of malignant adenoma had metastases to bone.

I should like to limit the scope of this paper to a discussion of the five cases from this group of malignant adenoma, with secondary bony metastases, which were similar to each other in that not only did their symptomatology first direct attention to the secondary tumor, but biopsy of this tumor showed that it was made up histologically, in part, or completely, of apparently quite benign thyroid tissue.

Annals of Surgery, 125 (6), 282-291, March 1947

summary and conclusions

These cases well illustrate the main features of this condition and may be briefly summarized.

- (1) The patient usually first comes to hospital because of symptoms produced by the bone tumor. In this way these cases resemble those of metastases of the prostate or of hypernephroma which frequently give signs of bone metastases before the primary tumor growth has been found.
- (2) Despite the benign appearance of the histopathology of these metastases, if a careful search is made, a malignant primary focus can always be found in the thyroid gland.
- (3) This primary focus is usually always a well-organized adenoma which for some unknown reason has become malignant, invading local blood vessels and spreading to some distant portion of the skeletal system via the blood stream.
- (4) In our series only 11 per cent of malignant adenomas had formed metastases by the time the primary growth was removed from the thyroid gland.
- (5) Secondary foci of this type of tumor form a prelude for the usual course in which it ends. The bones most likely to become involved are those most commonly in the body's center of 27 years. The reports:

Skull	36	Forearm	3
Thyroid	26	Wrist	2
Hand	4	Shoulder	1
Cervical	4	Spine	1
Vertebrae	4	Testicle	1

(6) These metastatic lesions have a tendency to invade bone by growing in an expansive manner, eroding the bony cortex and giving a radiographic picture somewhat similar to osteolytic metastases of giant cell tumor.



Definition of MFV-PTC

- Macrofollicles of >200 microns in more than 50% of the cross-sectional area of the specimen
 - The macrofollicular architecture may represent a phase of differentiation signifying low proliferative activity

MFV-PTC

- Indolent disease
- Good prognosis (?)
- Moderate risk of metastasis
- Regional LN mets 20%
 - Conventional PTC 35-50%
- Lung mets 7%
- Bone mets 0-1%?
- The benign architectural appearance of the macrofollicles, masquerading as normal thyroid tissue, does not predict prognosis

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Two Patients with Highly Aggressive Macrofollicular Variant of Papillary Thyroid Carcinoma

Wenxi G. Chen, MD,¹ Dasha Kim, MD,¹ and Ming Zhu, PhD¹

Background: The macrofollicular variant of papillary thyroid carcinoma (MFV-PTC) is an unusual type of thyroid carcinoma with histological features that can be confused with anaplastic carcinomas. It generally has a good prognosis and low incidence of metastases. We report two patients with highly aggressive MFV-PTC, including two metastases, one of which died of their disease.

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494 LINDQVIST ET AL.

FIG. 1. Section of the thyroid gland containing a characteristic pattern of papillary nodules, nodules, and some papillae. (x40)

FIG. 2. Higher magnification showing the typical morphology of papillary carcinoma characterized by follicular lining, expansion of the colloid, and nuclear features such as nuclear enlargement and some papillae. (x100)

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MFV-PTC

Table 1. Review of Reported Cases of Macrofollicular Variant of Papillary Thyroid Carcinoma in the Literature

Author	No. of cases	Sex	Median age (yr)	Range age (yr)	Median size (cm)	Range size (cm)	Local recurrence	Distant recurrence	Survival (%)
Albano-Rovinsky et al (5)	17	17 F	50	4-69	2.1 ^a	0.5 ^b -5.0 ^b	0.0 ^c	0.0 ^c	0.0 ^c
Carbone-Rodriguez et al (23)	6	4 F	58	3.7	0.4	0.9	0.0	0.0	0.0
Albano-Rovinsky et al (4)	20 ^d	18 F	58	1.8	0.2	6.2 ^e	0.2 ^f	0.2 ^f	0.2 ^f
Hirabayashi et al (18)	7	4 F, 3 M	58	3.5	1.0	6.7	0.7	0.7	0.7
Wang et al (27)	1	1 F	44	4	0.1	0.1	0.1	0.1	0.1
Yokoyama et al (34)	1	1 M	55	5.5	5.5	5.5	0.0	0.0	0.0
Yoshida et al (37)	4	3 M	55	2.3	0.9	5.6	0.0	0.0	0.0
Luigi et al (3)	3	2 F, 1 M	51	2.8	1.3	3.7	0.0	0.0	0.0
Beninato et al (44)	1	1 F	22	2	0.7	0.7	0.0	0.0	0.0
Chen et al (this study)	2	1 F, 1 M	49	7 ^g	5.2	5.0	0.0	0.0	0.0

^aMedian size of tumor with the longest dimension—total of tumor in all cases.
^bMedian size of longest dimension reported.
^cSize of tumor in cm; 0, the tumor size is unknown.
^dNot specified.

8/64 12/68 3/67 2/67

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Annals of Diagnostic Pathology

Macrofollicular variant of follicular thyroid carcinoma: a clinical, cytologic, morphologic, and image analysis study of a unique case

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Abstract: Macrofollicular variant of papillary thyroid carcinoma (MFV-PTC) is a unique variant of papillary thyroid carcinoma (PTC) characterized by the presence of large follicles with a macrofollicular pattern. In this study, we report a unique case of MFV-PTC with a high degree of aggressiveness. The patient had a large primary tumor and a high degree of local recurrence. The patient died of disease 14 months after diagnosis. The histological features of MFV-PTC are similar to those of follicular thyroid carcinoma (FTC) and anaplastic thyroid carcinoma (ATC). The clinical course of MFV-PTC is highly variable. The prognosis of MFV-PTC is poor. The survival rate is low. The overall survival rate is 0%. The overall survival rate is 0%.

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Fig. 1. The macrofollicular variant of papillary thyroid carcinoma. (A) Macrofollicular pattern with crowded cells, expanded colloid, and some papillae. (B) Macrofollicular pattern with crowded cells, expanded colloid, and some papillae. (C) Macrofollicular pattern with crowded cells, expanded colloid, and some papillae. (D) Macrofollicular pattern with crowded cells, expanded colloid, and some papillae.

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Macrofollicular Variant of Papillary Carcinoma of the Thyroid

A Histologic, Cytologic, and Immunohistochemical Study of 3 Cases and Review of the Literature

Shimoda T, et al. J Clin Endocrinol Metab. 2007;97(10):3000-3006. doi:10.1210/2007-0111

Conclusion: The macrofollicular variant of papillary carcinoma of the thyroid is a rare entity described by Li, Li, Hsu, Hsu, and colleagues in 1991. It is characterized histologically by a predominance of macrofollicles and classically by a lack of evidence of papillae. This entity may represent a subset of papillary carcinomas that can be easily misinterpreted as a macrofollicular adenoma or nodular goiter.

Objective: In this study, we describe 3 cases of papillary carcinoma of the thyroid with a macrofollicular growth pattern and review the literature.

Results: The fine-needle aspiration smears in 2 cases showed large cells with optically clear nuclei and nuclear grooves, suggestive of papillary carcinoma of the thyroid. In one case, the cytology showed no signs of malignancy. In all cases, the tumors showed a combination of the conventional follicular variant of papillary carcinoma of the thyroid and macrofollicular adenoma. (J Clin Endocrinol Metab. 2007;97(10):3000-3006.)

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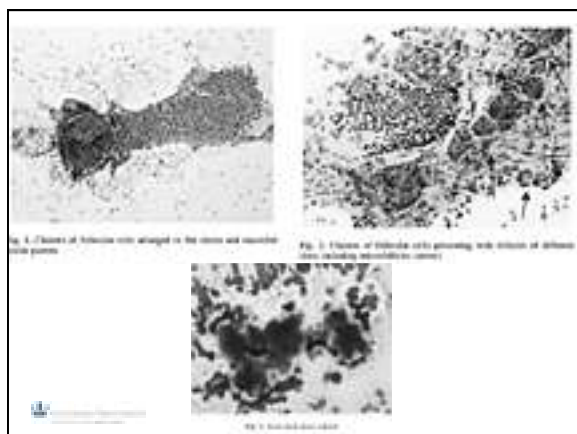
Macrofollicular Variant of Papillary Carcinoma: A Potential Thyroid FNA Pitfall

Darin Chung, M.D., Ronald A. Grossman, M.D., and Oscar Li, M.D., M.Sc.

Macrofollicular variant of papillary carcinoma (MFPC) is a rare variant of papillary carcinoma in which over 50% of the follicles are represented as macrofollicles. The cytologic features from 7 cases of histologically confirmed MFPC were analyzed. The cytologic specimens were evaluated for the following criteria: cytologic details of papillary carcinoma and macrofollicular adenoma patterns, nuclear grooves, pseudoinclusions, nuclear clearing, nuclear overlap, nuclear polarity, presence of nucleoli, macrophages, and watery colloid amount and color.

Conclusion: Although it has been suggested that this tumor is a highly differentiated variant with a favorable prognosis, our study shows that its histologic behavior is not conclusive because anaplasia and recurrence with differentiated tumor may occur. (Arch Pathol Lab Med. 2004;108(1):44-47.)

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Macrofollicular Variant of PTC

- MVPTC is a variant of PTC extremely difficult to diagnose cytologically
- FNAs show:
 - hypocellularity
 - abundant watery colloid
 - macrofollicular arrangement
 - macrophages
 - absence of widespread classic cytologic features of PTC

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Macrofollicular Variant of PTC

- Subtle changes to look for are:
 - Areas of dense colloid
 - Nuclei with grooves
 - Also present in goiters and Hurthle cell lesions
 - Nuclei with small peripheral nucleoli
 - Nuclear overlap
 - Strong degree of clinical suspicion (dominant nodule)

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Bethesda System for Reporting Thyroid Cytopathology and Risk of Malignancy

•Unsatisfactory/Non-diagnostic Specimen	---
•Benign	0-3%
•Atypia of undetermined significance / Follicular lesion of undetermined significance	5-15%
•Follicular Neoplasm/Suspicious for Follicular Neoplasm	15-30%
•Suspicious for Malignancy	60-75%
•Malignant	87-94%



	PTC	FC	PD Ca	ACa
Clinical Prevalence	~20%	~13%	~1%	~2%
Molecular Prevalence (%)				
BRAF	45	15	38	38
RAS	20	40-50	30-54	50
RET/PTC	2-20	-	-	-
FGFR3/PPP4y	1-5	30-35	-	-
NTRK1	<5%	-	20	70
CTNWB1	-	-	20-30	50-80
TSG1	-	<10	6	6
PIK3	-	<10	-	-
PTEN	-	<10	-	-
ACT1	-	-	3-10	5-10
RET	-	-	-	-

Ricarte-Filho *JC Cancer Res* 2009; 69: 4885 Theoharis C *Curr Opin Oncol* 2012; 24: 35
 Nikiforov YE *Nat Rev Endocrinol* 2011; 7: 569 Mourra MM *J Clin Endocrinol Metab* 2011; 96: E863

Adding Molecular Testing Improves Diagnostic Yield

Risk of Malignancy by Indeterminate Category

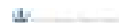
	AUS/FLUS	FN/SFN	SMC
Cytology only	14%	27%	54%
BRAF	100	100	100
FGFR3/PPP4y	100	100	100
RET/PTC	100	100	100
RAS	84	85	88
Any mutation	88	87	95
No Mutation	6	14	28

Nikiforov YE *J Clin Endocrinol Metab* 2011; 96: 3390



Impact of Mutational Testing on the Diagnosis and Management of Patients with Cytologically Indeterminate Thyroid Nodules:

A Prospective Analysis of 1056 FNA Samples
 Nikiforov et al *J Clin Endocrinol Metab*, November 2011, 96(11):3390-3397



Earth from Above by Bertrand - Misiones, Argentina



"Colloid-Rich" Follicular Neoplasm/Suspicious for Follicular Neoplasm Thyroid Fine-Needle Aspiration Specimens

Cytologic, Histologic, and Molecular Basis for Considering an Alternate View

Y. Zhou, MD, PhD, James W. Kim, MD, PhD, Scott L. Harris, MD, PhD, Steven P. Forman, MD, PhD, Sharyn G. Lockhart, MD, PhD, Joseph W. Ho, MD, PhD, & David H. Moon, MD, PhD (University of Michigan, Ann Arbor, MI, USA); Robert S. Suster, MD, PhD (University of Colorado, Denver, CO, USA); and John C. Heffron, MD, PhD (University of Michigan, Ann Arbor, MI, USA)

The 2010 Bethesda System for Reporting Thyroid Cytopathology (BSRTC) defines "colloid-rich" follicular neoplasm/suspicious for follicular neoplasm (FC/FCN) as a category of thyroid fine-needle aspiration (FNA) specimens that are cytologically indeterminate. Although the presence of molecular evidence was not included in the 2010 Bethesda System, a growing number of studies have demonstrated that FC/FCN specimens harbor a higher proportion of benign lesions compared to specimens that are cytologically indeterminate. We performed a retrospective analysis of 1056 FNA specimens that were cytologically indeterminate for FC/FCN and found that 10% (105/1056) were positive for BRAF, 20% (211/1056) were positive for RAS, 40% (422/1056) were positive for RET/PTC, and 60% (363/1056) were positive for FGFR3/PPP4y. The presence of any mutation in the panel of mutations was associated with a higher proportion of benign lesions compared to specimens that were cytologically indeterminate. Our findings support the use of molecular testing to help distinguish between FC/FCN specimens that are cytologically indeterminate and those that are benign.

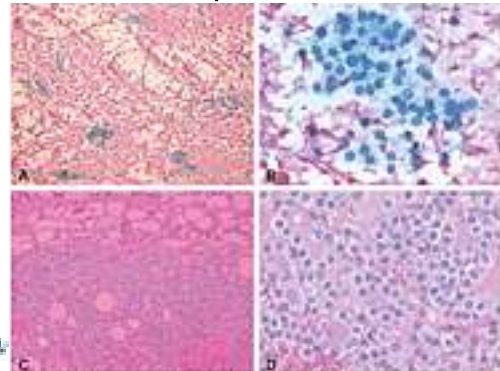


Colloid-rich vs. Colloid-poor FN/SFN

- Risk of malignancy is similar between these 2 groups (28% vs 33%)
- FVPTC most common malignant outcome for both groups
- **Colloid-rich FN corresponded to SP specimens designated as macrofollicular variant of PTC with subtle nuclear changes**
- Resected FVPTC showed well developed nuclear changes of PTC in the subcapsular areas of the nodule, missed by FNA sampling
- **FVPTC is the leading cause of false negative FNA, particularly challenging in colloid-rich FN/SFN**



Colloid-poor FN/SFN



Colloid-rich FN/SFN

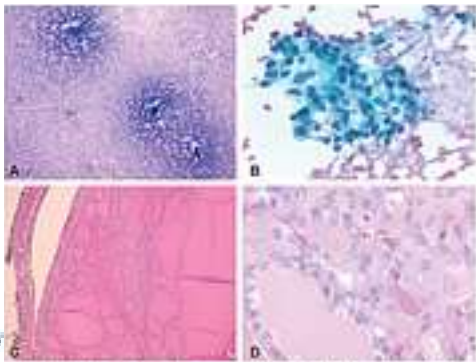


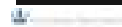
TABLE 2: Comparison of Key Histologic and Molecular Features Between Typical Colloid-Poor and Colloid-Rich FN/SFN Cases

Parameter for Comparison (Proportion of Cases with the Following Feature)	Typical Colloid-Poor FN/SFN	Colloid-Rich FN/SFN	P
Hyperplasia	90/90 (100%)	90/71 (80%)	<.001
PTC nuclear features	90/90 (100%)	90/71 (80%)	<.001
Macrofollicular variant	90/90 (100%)	90/71 (80%)	<.001
Microfollicular variant	90/90 (100%)	90/71 (80%)	<.001
Colloid-rich nuclear features	0/0 (0%)	1/1 (100%)	<.001
Colloid-poor nuclear features	0/0 (0%)	0/0 (0%)	NS



Colloid-rich vs. Colloid-poor FN/SFN

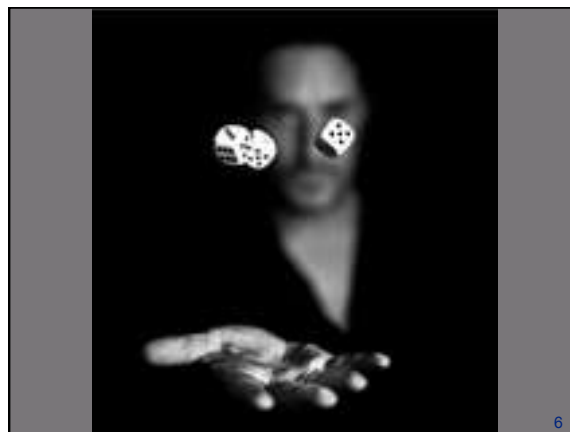
- Colloid-rich FN/SFN had mutations restricted to RAS family (HRAS, NRAS, KRAS) and BRAF
- The presence of a mutation was significantly greater in the colloid-rich than in the colloid-poor (30% vs. 14%)
- **RAS mutations** significantly detected in colloid-rich vs. colloid-poor (**60% vs 35%**)
- **Colloid-rich FN/SFN cases represent a distinct group warranting recognition due to the increased incidence of FVPTC**



Macrofollicular Variant of PTC

- A Machiavellian and cunning thyroid follicular lesion, masquerading deceitfully as a benign follicular lesion (aka "benign metastasizing goiter")
- Morphologic clues:
 - Colloid-rich with areas of dense colloid
 - Subtle nuclear features:
 - Grooves
 - Small peripheral nucleoli
 - Minimal overlap
- Hematogenous spread → Bone metastasis
- Molecular mutations restricted to RAS (60%) and BRAF (2-3%) family

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