The Trials and Tribulations of a Machiavellian and Cunning Thyroid Lesion

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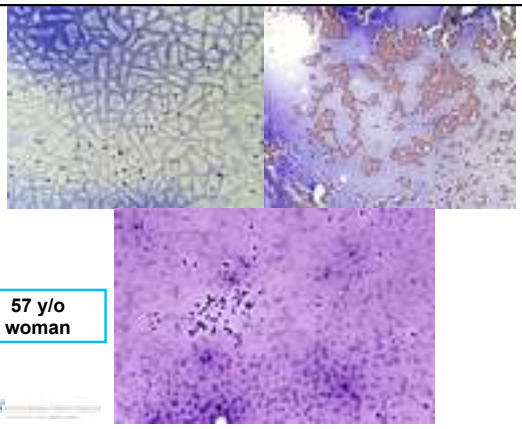
Machiavellian

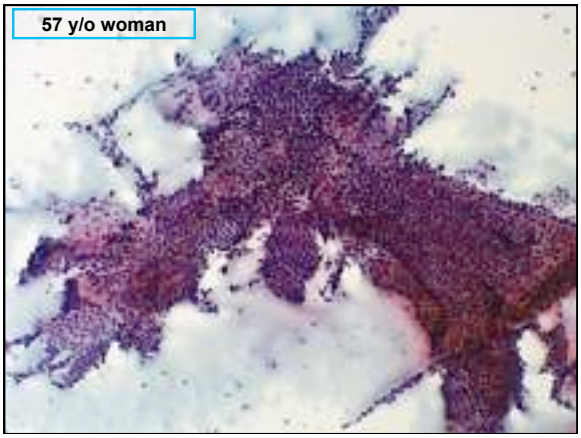
Clever and dishonest methods to achieve a goal

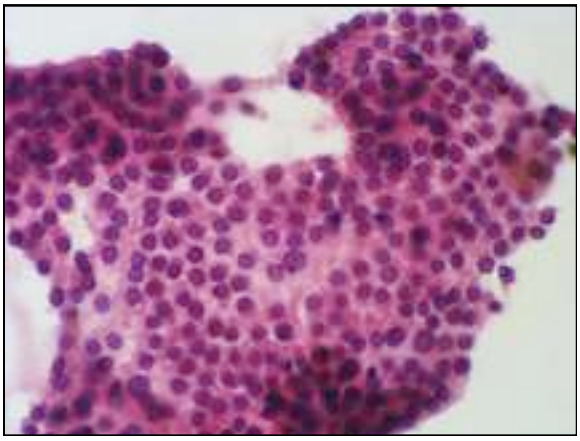
Cunning

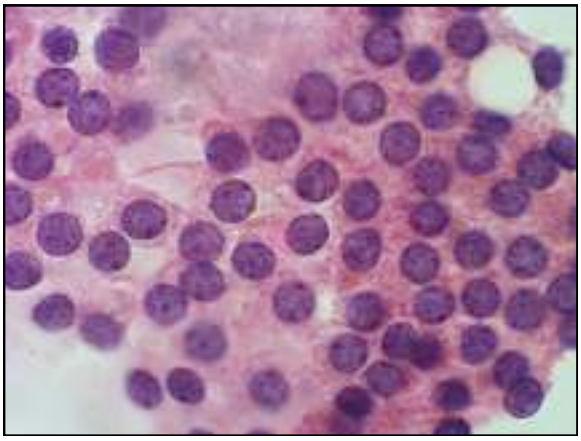
Skill in concealing or disguising the real purposes of one's actions

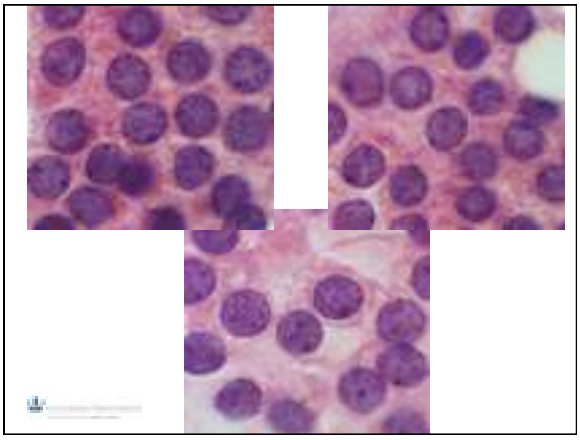


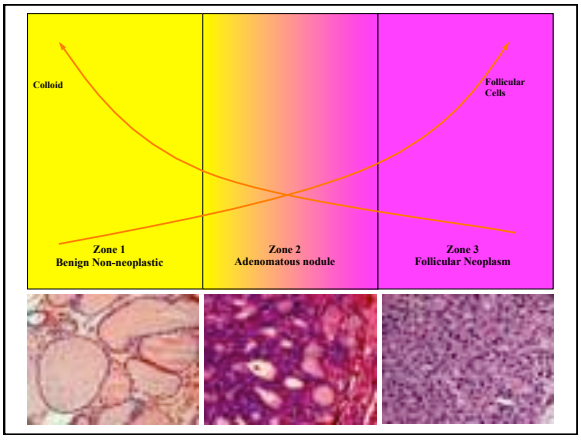
57 y/o woman

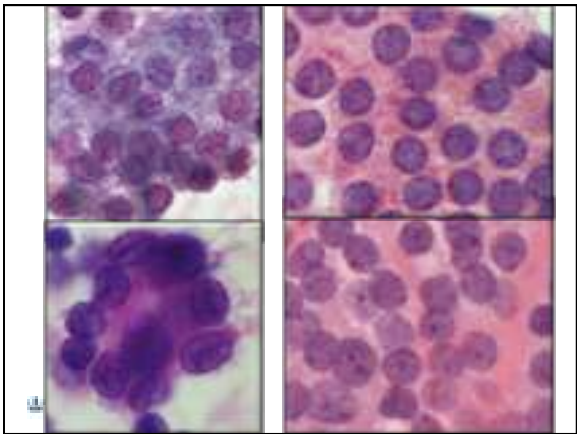


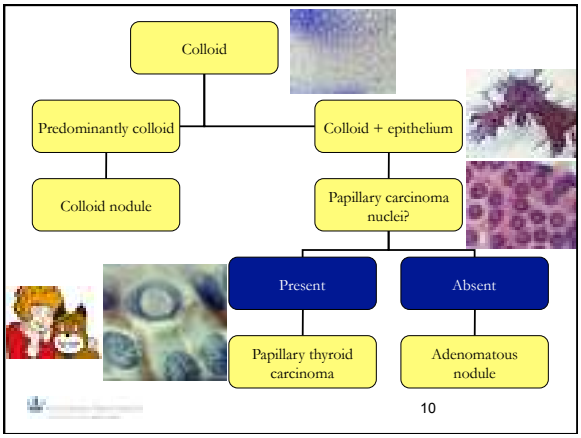










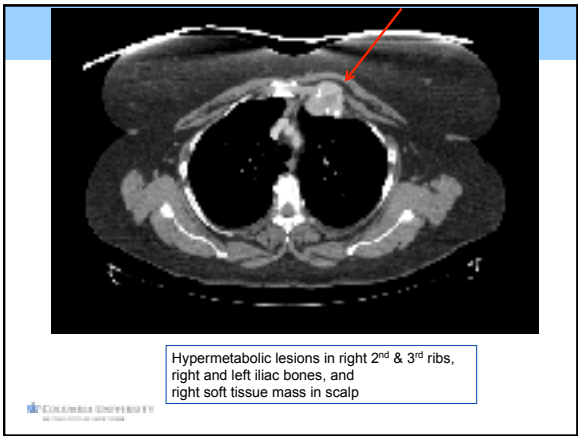


Case Presentation

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

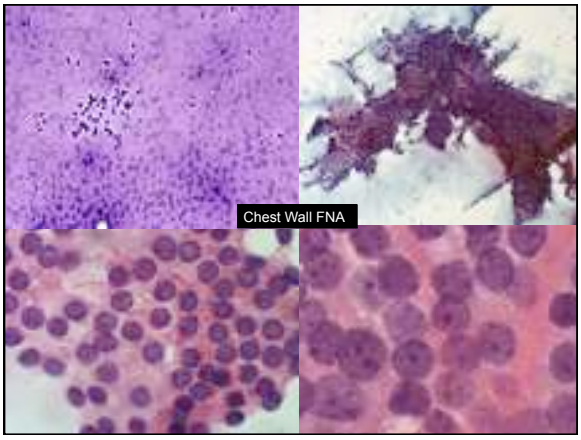
Physical Exam:
- Normal otologic exam
- Normal intranasal exam
- Unremarkable oral cavity and oropharynx
- Neck <u>without</u> discrete masses, lymphadenopathy or thyromegaly

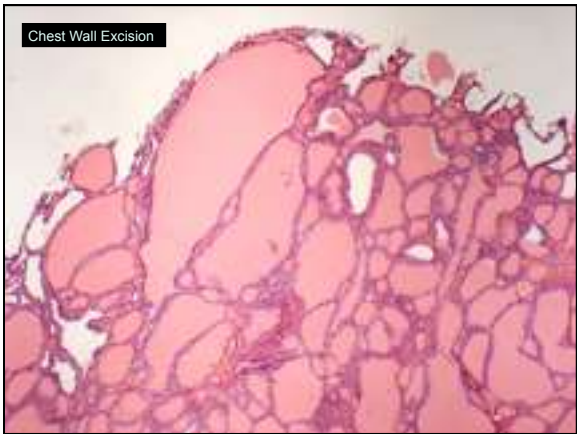


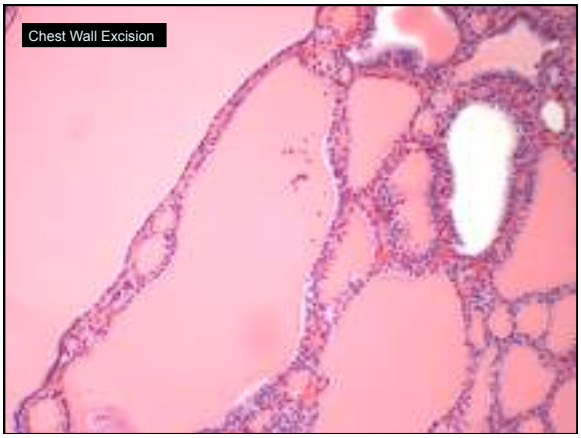
Hypermetabolic lesions in right 2nd & 3rd ribs, right and left iliac bones, and right soft tissue mass in scalp

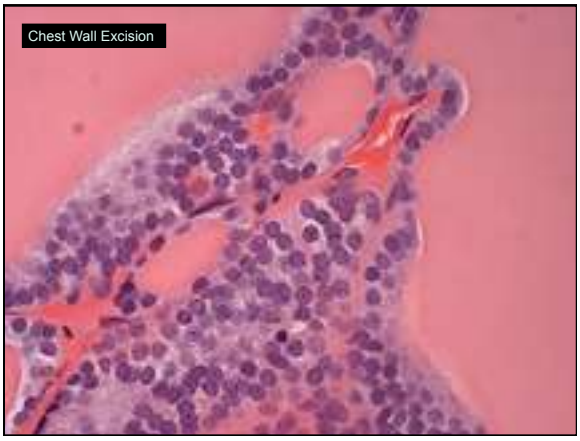
Case Presentation

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

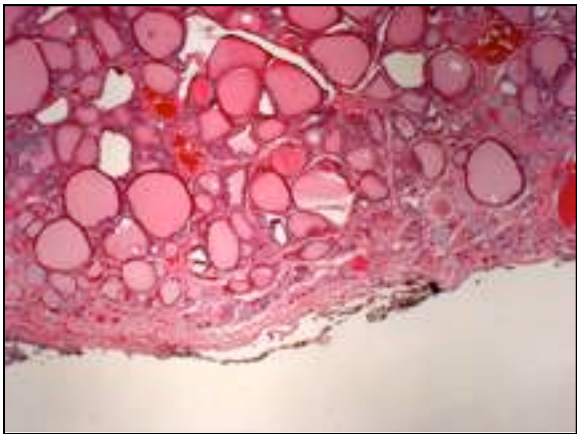
Case Presentation

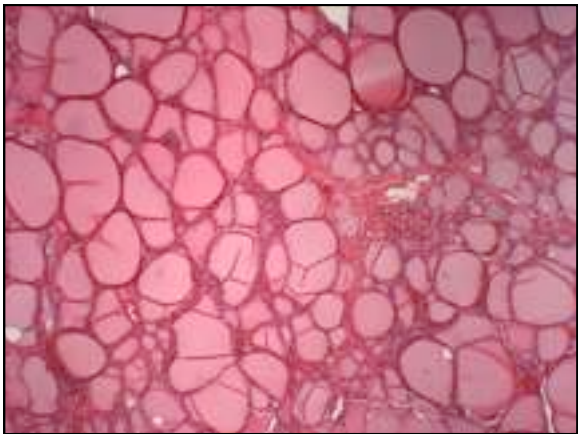
Thyroid Ultrasound

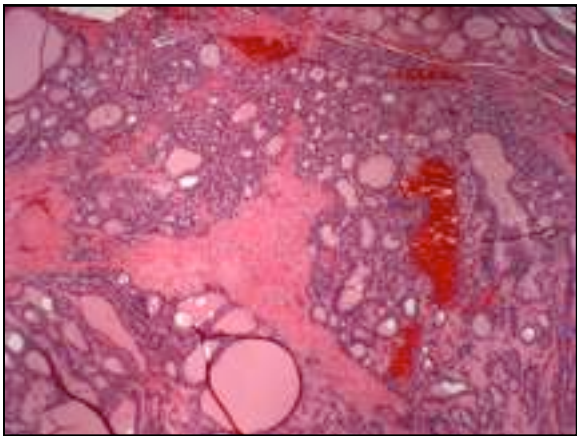
- Right lobe: 4.8 x 2.1 x 2.1 cm
  - Lower pole nodule: **1.9** x 1.1 x 1.3 cm
- Left lobe: 4.7 x 1.4 x 2.1 cm
  - Mid pole nodule: 1.2 x 0.5 x 0.9 cm
  - Adjacent: 0.6 x 0.5 x 0.6 cm
- Isthmus: 2 mm in A-P thickness

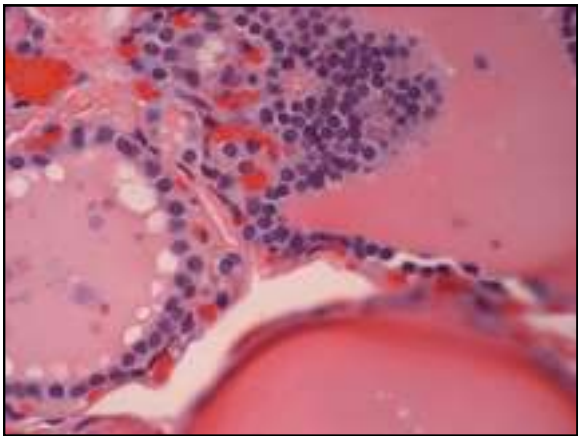
Total Thyroidectomy

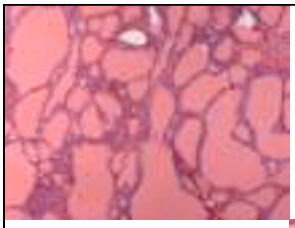
- Total thyroidectomy
  - 19 grams
  - Multiple nodules on the cut surface, largest one measuring 1.3 x 1 x 0.7 cm
  - Entirely submitted



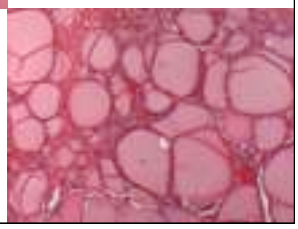








Chest Wall



Thyroidectomy

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

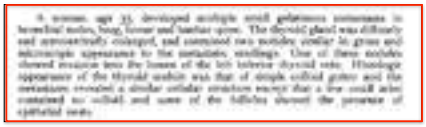
- Tumors ≤ 1 cm or well-differentiated
  - low-risk carcinomas
- Distant metastases extremely rare
- 2 cases of clinically occult carcinoma of the thyroid
  - 2.4 mm carcinoma presenting with distant hematogenous (pulmonary) metastasis
  - Lethal carcinoma with extensive metastasis not diagnosed until 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.

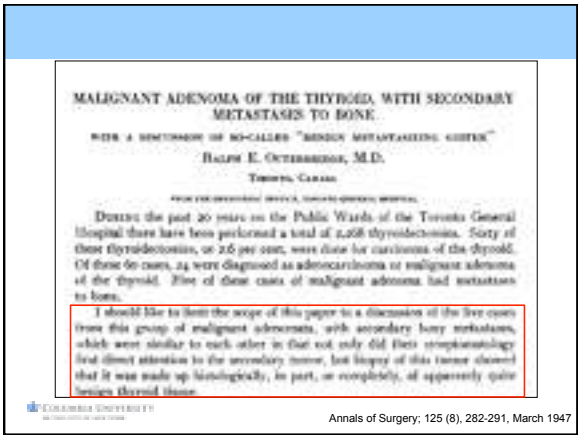
"Tumor Regression"

- 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





MALIGNANT ADENOMA OF THE THYROID, WITH SECONDARY METASTASES TO BONE

WITH A DISCUSSION OF SO-CALLED "BENIGN METASTASIZING GOITER"

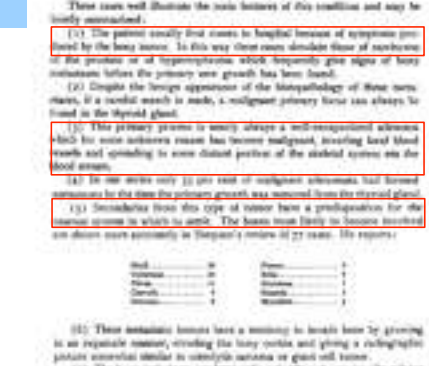
RALPH E. OUTERBRIDGE, M.D.

TORONTO, CANADA

During the past 20 years on the Public Wards of the Toronto General Hospital there have been performed a total of 2,268 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 adenomata, 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 (8), 282-291, March 1947



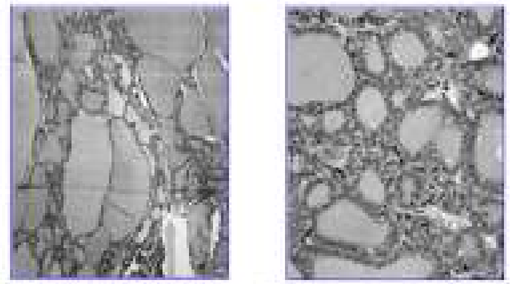
Definition of MFV-PTC

- 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

Two Patients with Highly Aggressive Macrofollicular Variant of Papillary Thyroid Carcinoma



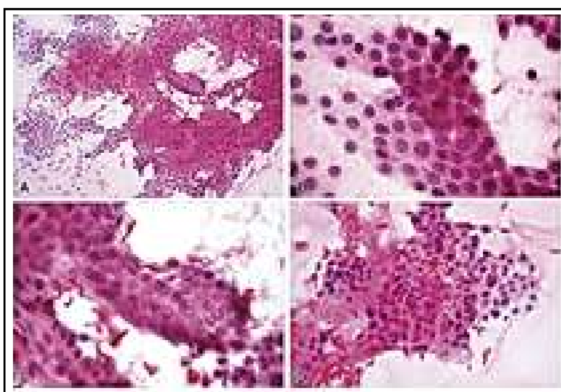
MFV-PTC

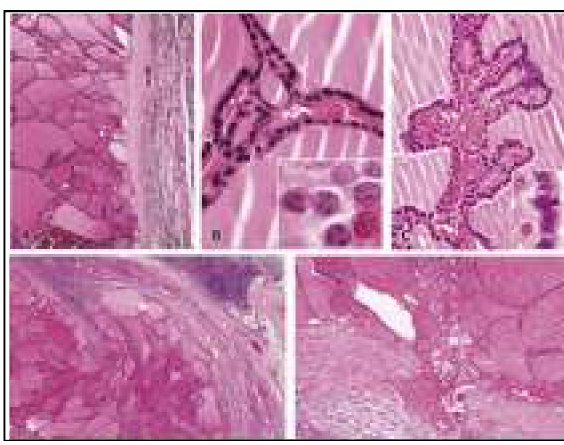
8/64	12/68	3/67	2/67

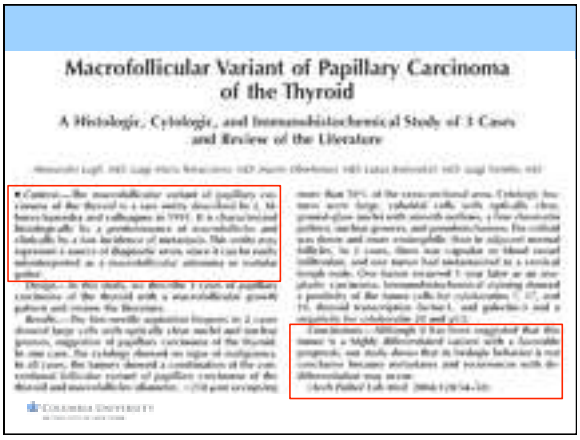
ScienceDirect

Annals of DIAGNOSTIC PATHOLOGY

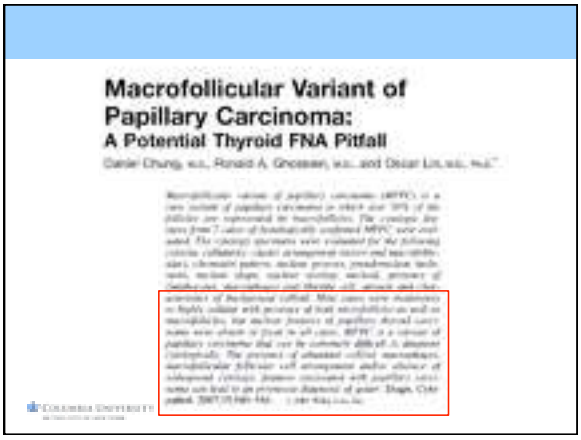
Macrofollicular variant of follicular thyroid carcinoma: a clinical, cytologic, morphologic, and image analysis study of a unique case

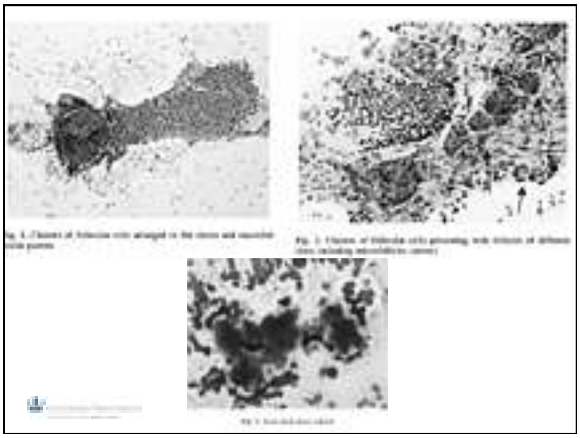





Macrofollicular Variant of Papillary Carcinoma of the Thyroid

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


Macrofollicular Variant of Papillary Carcinoma:
A Potential Thyroid FNA Pitfall



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

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)

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	97-99%

	PTC	FC	PD Ca	ACa
Clinical Prevalence	~80%	~20%	<1%	<1%
Molecular Prevalence (%):				
BRAF	45	-	15	38
RAS	20	40-50	30-54	50
RET/PTC	2-20	-	-	-
PAX8/PPARγ	1-5	30-35	-	-
NTRK1	<5%	-	-	-
CTNNB1	-	-	20	70
TP53	-	-	20-30	50-80
PI3K	-	<10	6	6
PTEN	-	<10	-	-
AKT1	-	-	5-10	5-10
RET	-	-	-	-

Ricarte-Filho JC *Cancer Res* 2009; 69: 4885
Nikiforov YE *Nat Rev Endocrinol* 2011; 7: 569
Theoharis C *Curr Opin Oncol* 2012; 24: 35
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
PAX8/PPARγ	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

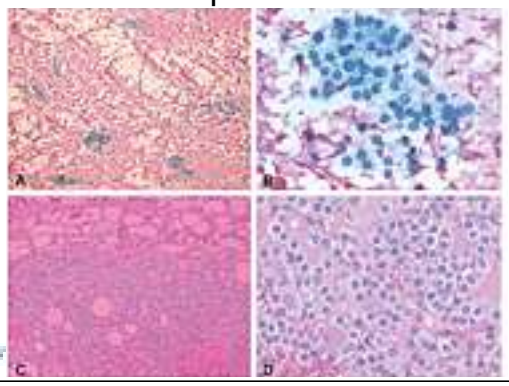
"Colloid-Rich" Follicular Neoplasm/Suspicious for Follicular Neoplasm Thyroid Fine-Needle Aspiration Specimens

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

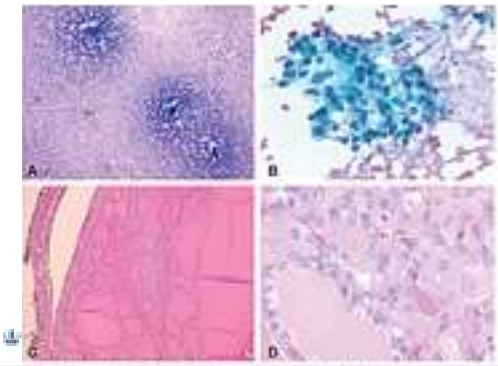
Colloid-rich vs. Colloid-poor FN/SFN

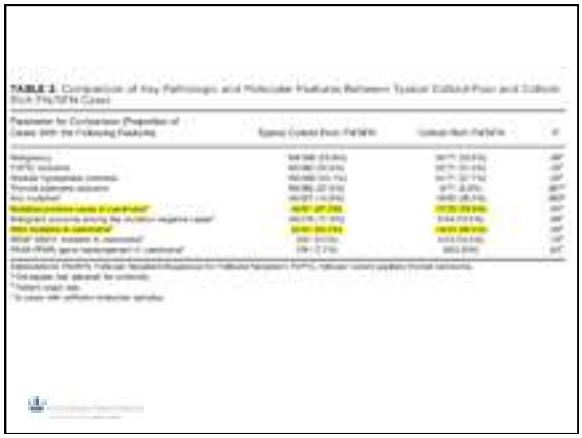
- Risk of malignancy is similar between these 2 groups (28% vs 33%)
- FVPTC most common malignant outcome for both groups
- **Colloid-rich FN corresponded to SP specimens designated as macrofollicular variant of PTC with subtle nuclear changes**
- Resected FVPTC showed well developed nuclear changes 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





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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