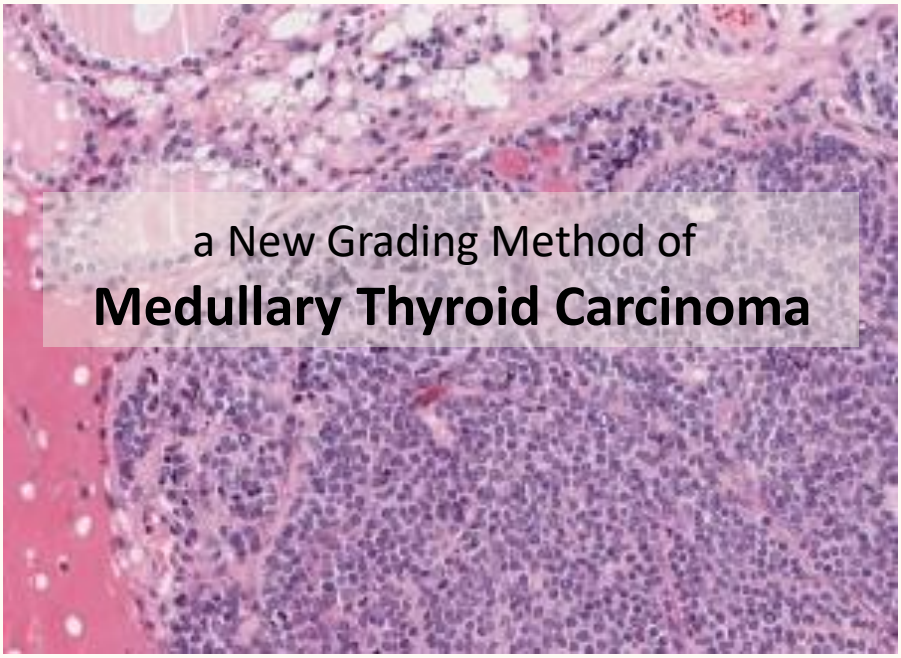
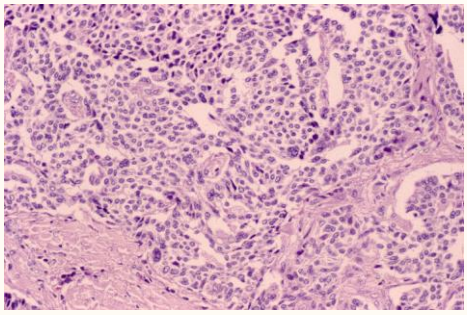


Medullary thyroid carcinoma

- *5 – 10%*
- *Familial or sporadic*
- *Middle third of each lobe*
- *50% - nodal Mts, 15 % - distant Mts*
- *Calcitonin serum levels are elevated*
- *Other peptide products may be produced.*

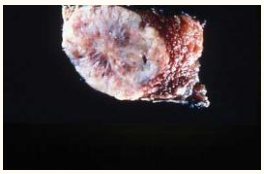


Diagnostic Methods

- **Bio-markers**
  - **Calcitonin** – screening test
  - CEA, VIP – prognostic factors
- **Imaging** :
  - **US –** initial assessment of the nodule
  - MRI, CT – distant metastases
- **Genetic diagnosis**
  - **Sporadic \ inherited** (germline mutation in RET)
  - Sporadic tumors with mutation in RET – **worse prognosis**
- **FNA** (cytopathology)
  - Sensitivity - only **60%**

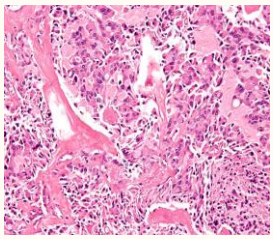
Pathological Features of MTC

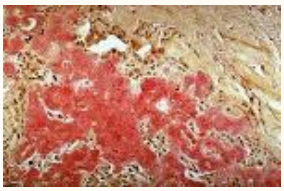
- **Macroscopic features**:
  - Usually in the **lateral upper two-thirds of the thyroid** – highest C-cell concentration
  - Tumor size – **variable**
  - Solid, granulated
  - color: **grey-white**
  - **Well circumscribed**, but without fibrotic capsule



Pathological Features of MTC

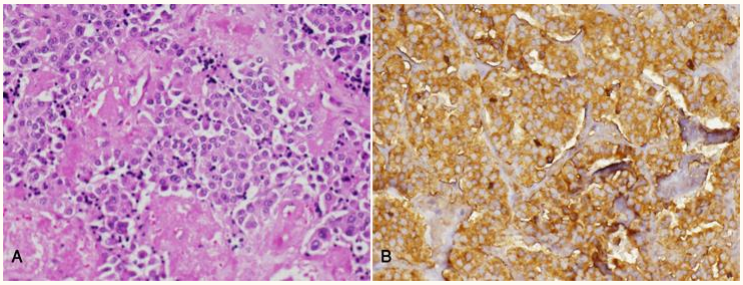
- **Microscopic features**:
  - **Variable**
  - Nests and sheets of **round or polygonal cells**
  - **Fibrovascular stroma**
  - **Well circumscribed,** but not encapsulated.
  - **Amyloid deposits** (80%)





Immunohistochemical features of MTC

- Positive for:
  - **Calcitonin** (95%)
  - **Neuroendocrine Markers**: Synaptophysin, chromogranin
  - **TTF1**
  - **CGRP, CEA:** frequently positive in MTC which are negative for calcitonin.

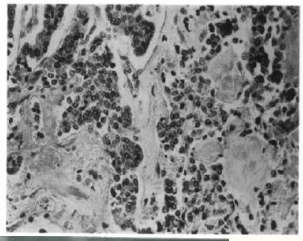


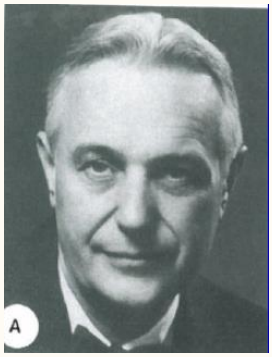
1959, Hazard JB, Hawk W, Crile G, J Clin Endocrinol Metab 19: 152-161

MEDULLARY (SOLID) CARCINOMA OF THE THYROID—A CLINICOPATHOLOGIC ENTITY*

JOHN B. HAZARD, M.D., WILLIAM A. HAWK, M.D. AND GEORGE CRILE, JR., M.D.

The Department of Anatomic Pathology, and the Department of General Surgery, The Cleveland Clinic Foundation, and The Frank E. Bunts Educational Institute, Cleveland, Ohio



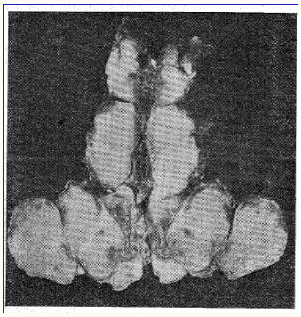


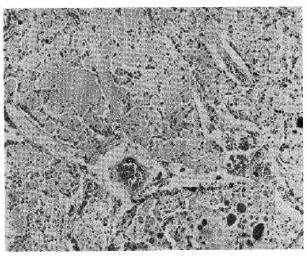
1957, J Laskoswki “carcinoma hyalinicum thyreoidase

Józef Laskowski

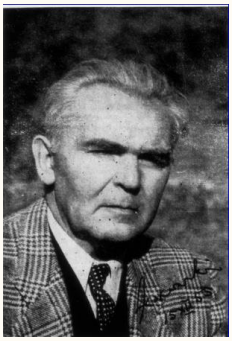
CARCINOMA HYALINICUM THYREOIDEAE
(ODRĘBNA JEDNOSTKA NOWOTWOROWA)

Z Zakładu Patologii Instytutu Onkologii
im. Marii Skłodowskiej-Curie w Warszawie
Dyrektor: Prof. dr med. *Fr. Łukaszczyk*
Kierownik Zakładu Patologii: prof. dr med. *J. Laskowski*



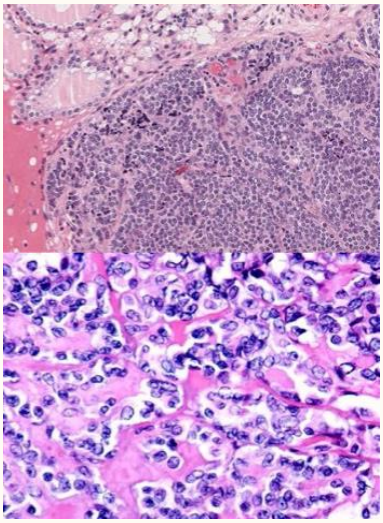


Ryc. 7. *Carcinoma hyalinicum thyreoideae* (M/619 — H/29118) — szkliście zmienione zraziki rakowe. W dolnej części zdjęcia zawapnienia w postaci kulistych złogów



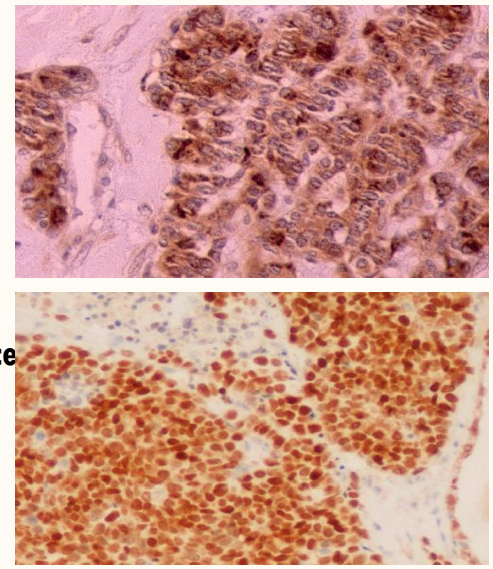
Medullary thyroid carcinoma – Variants

- Papillary or pseudopapillary
- Glandular (tubular or follicular)
- Giant cell
- Spindle cell
- Small cell/neuroblastoma-like
- Paraganglioma-like
- Oncocytic-cell
- Clear cell
- Angiosarcoma-like
- Squamous cell
- Melanin-producing
- Amphicrine.



Medullary thyroid carcinoma – IHC

- Calcitonin
- CEA
- Chromogranin A
- Synaptophysin
- TTF-1
- Keratins
- Neuroendocrine substance



Medullary thyroid carcinoma

Not sensitive to Radioactive Iodine

Chemotherapy – very limited effect

Angioinvasion – aggressive behavior & adverse prognostic effect

Lymphatic invasion - ???

VEGFR1, 2, and 3, PDGFR, and KIT -*partial*

Bcl-2, SSTR-2 and SSTR-5 etc. – perspective

Motesanib, Cabozantinib etc. -

BM Erovic et al. Prognostic and Predictive Markers in MTC.- End Path.-2012.-23 (4).-p.232-242

Medullary thyroid carcinoma – Variants

- Papillary or pseudopapillary
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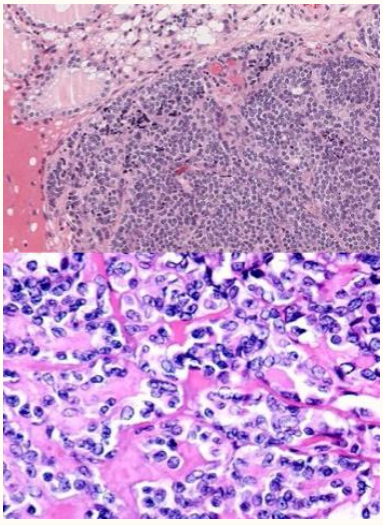


MTC – Papillary variant

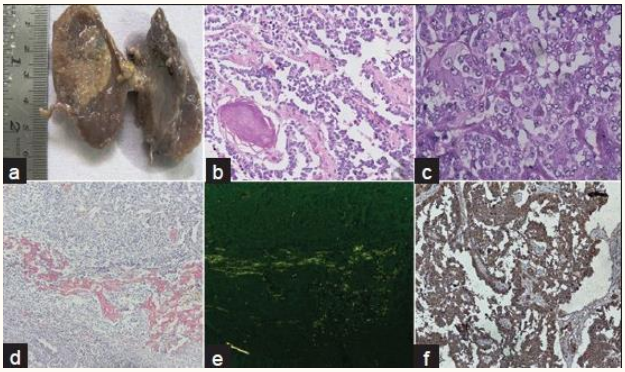
Indian Journal of Pathology & Microbiology

LETTER TO EDITOR

Year : 2014 | Volume : 57 | Issue : 1 | Page : 151-152

Papillary variant of medullary carcinoma thyroid

Saumya Shukla, Namrata P Awasthi, Nuzhat Husain



MTC – Papillary variant

Rare variant of MTC

Papillae formation

PTC nuclear features - 20-25%

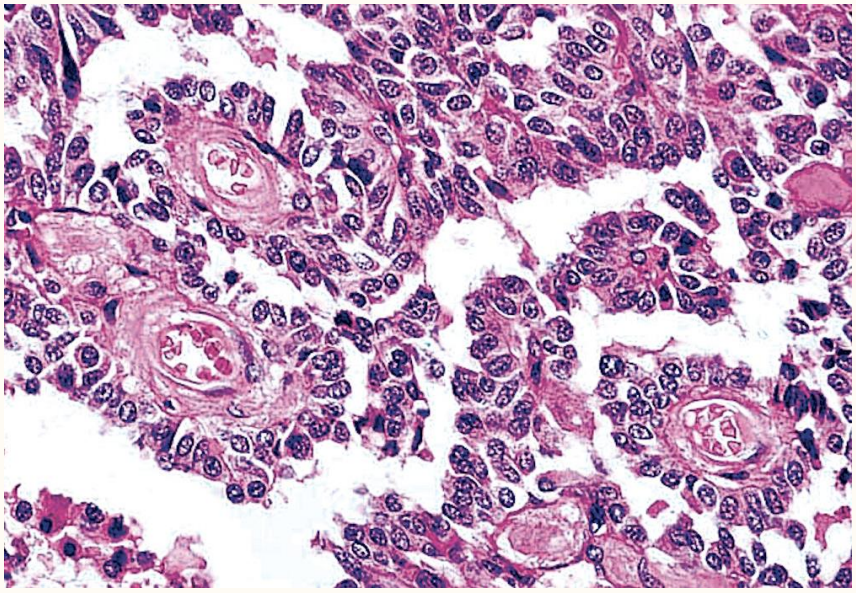
Amyloid frequently presents

Lymph nodes involvement rare (< PTC)

Encapsulation – often (about 1/3 cases)

SS Desai et al.2005

MTC – Papillary variant

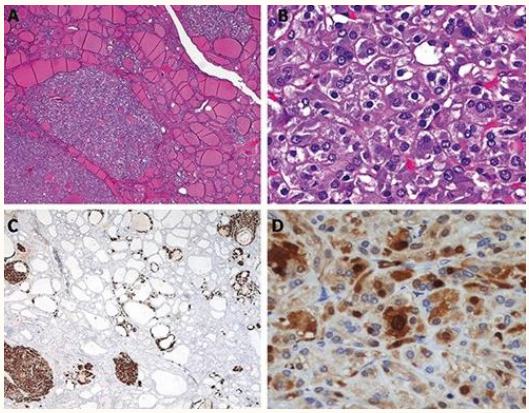


MTC – Oncocytic variant

Rare Tumors 2016; volume 8:6537

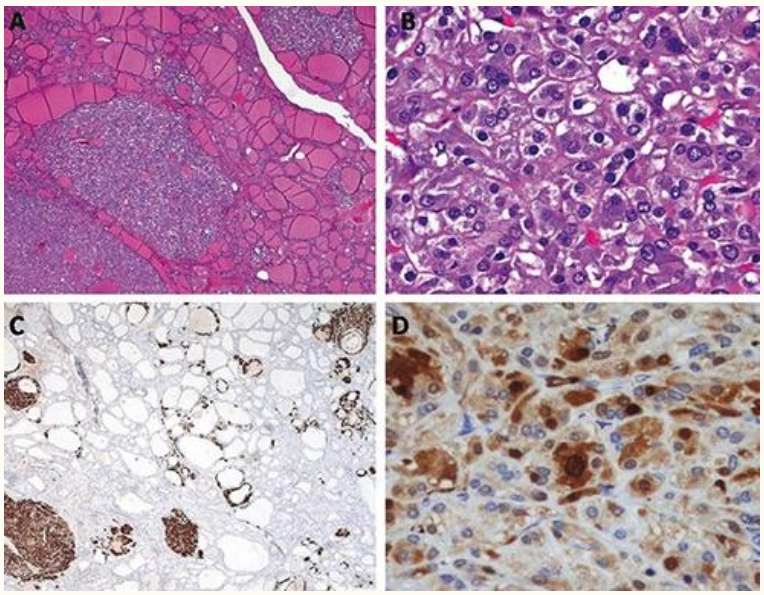
Oncocytic variant of medullary thyroid carcinoma: a rare case of sporadic multifocal and bilateral *RET* wild-type neoplasm with revision of the literature

Gian Luca Rampioni Vinciguerra,[1] Niccolò Noccioli,[1] Claudia Cippitelli,[1] Angelo Minucci,[2] Ettore Capoluongo,[2] Armando Bartolazzi[1]



- **Rare variant – about 17 cases reported**
- **Sporadic**
- **Bilateral or multifocal**
- **RET –mutations**

MTC – Oncocytic variant



Vinciguerra GL, et al. Rare Tumors. 2016.- 20;8:6537

MTC – Melanotic variant

Diagnostic Pathology

BioMed Central

Case Report

Open Access

Melanotic medullary carcinoma of thyroid – report of a rare case with brief review of literature

Kamaljeet Singh[1], Mehar C Sharma*[1], Deepali Jain[1] and Rajinder Kumar[2]

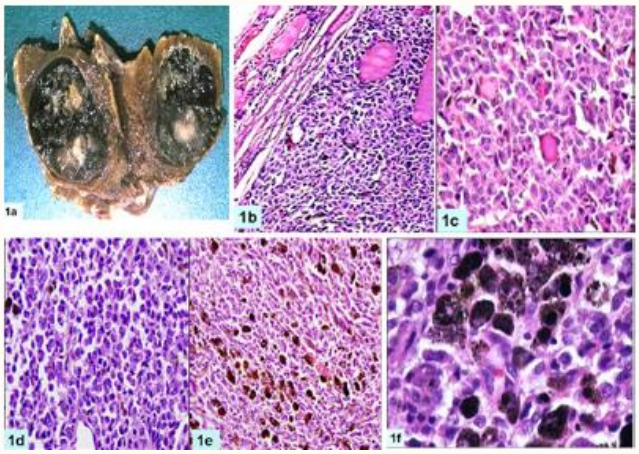
Address: [1]Department of Pathology, All India Institute of Medical Sciences, New Delhi, India and [2]Department of Surgery, All India Institute of Medical Sciences, New Delhi, India

Email: Kamaljeet Singh - kjsingh@yahoo.co.in; Mehar C Sharma* - sharmamehar@yahoo.co.in; Deepali Jain - deepalijain76@gmail.com; Rajinder Kumar - rajinderk@yahoo.com

* Corresponding author

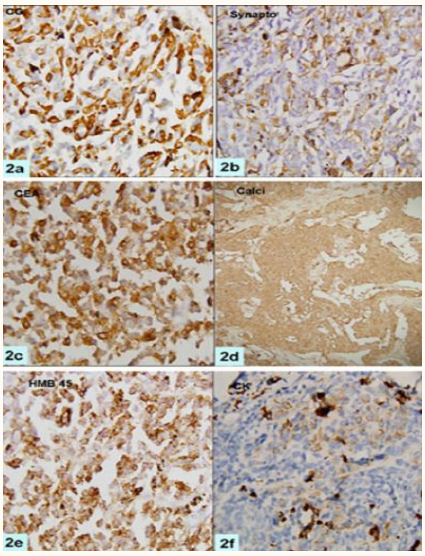
First description -1982 (Marcus et al.)
Extremely rare entity, M = F, (Age - 20-72)
About 10 cases in English-spoken literature
Neural crest – melanocytic features
IHC and EM – dual features

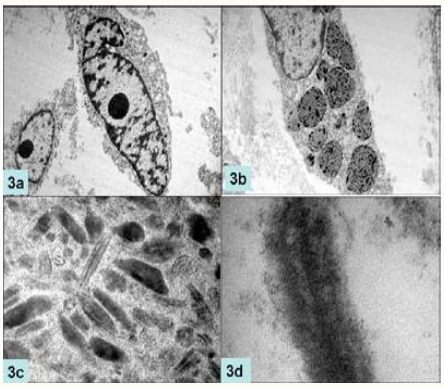
MTC – Melanotic variant



K. Singh et al. Diagnostic pathology.-2008.-Vol.3

MTC – Melanotic variant



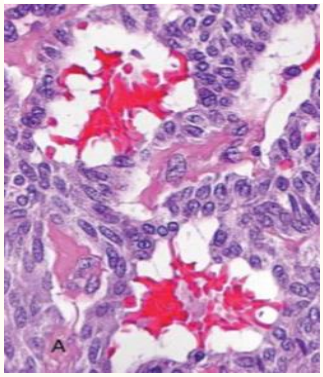


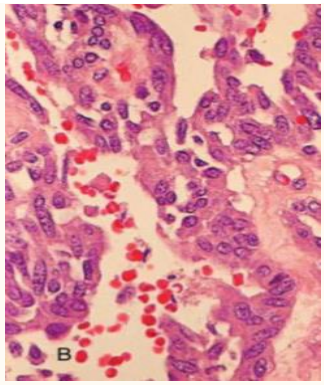
K. Singh et al. Diagnostic pathology.-2008.-Vol.3

MTC – Angiosarcoma-like variant

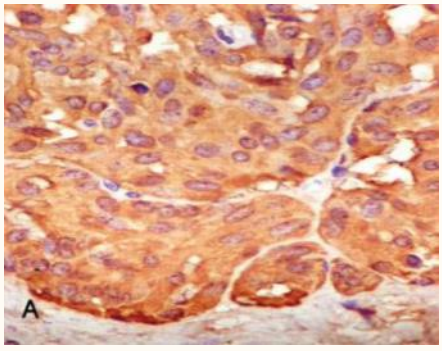
Pseudoangiosarcomatous Features in Medullary Thyroid Carcinoma Spindle-Cell Variant. Report of a Case Studied by FNA and Immunohistochemistry

Juan B. Laforga, M.D.[1*] and F. Ignacio Aranda, M.D.[2]





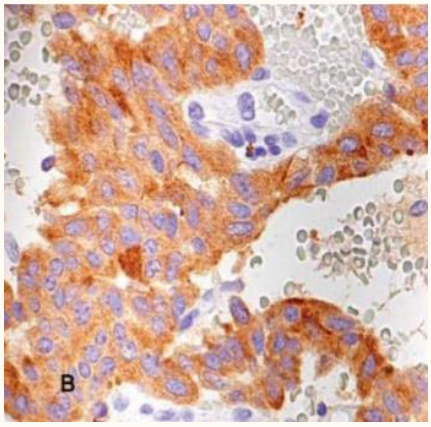
MTC – Angiosarcoma-like variant



CD31 –
CD34 –
TTF-1 +
Serotonin +
CK+

Calcitonin

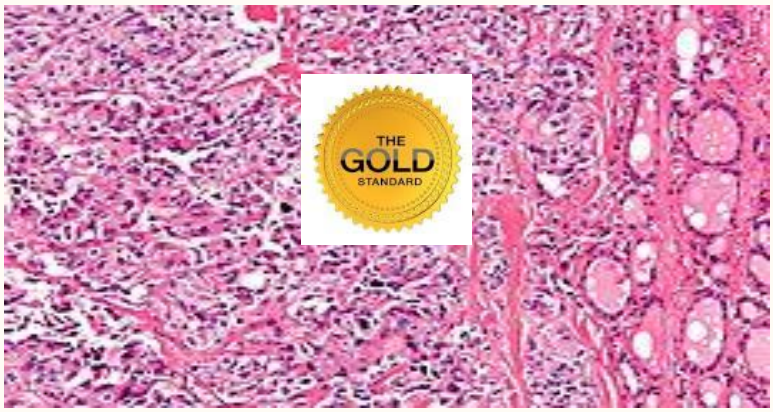
Synaptophysin



Pathology

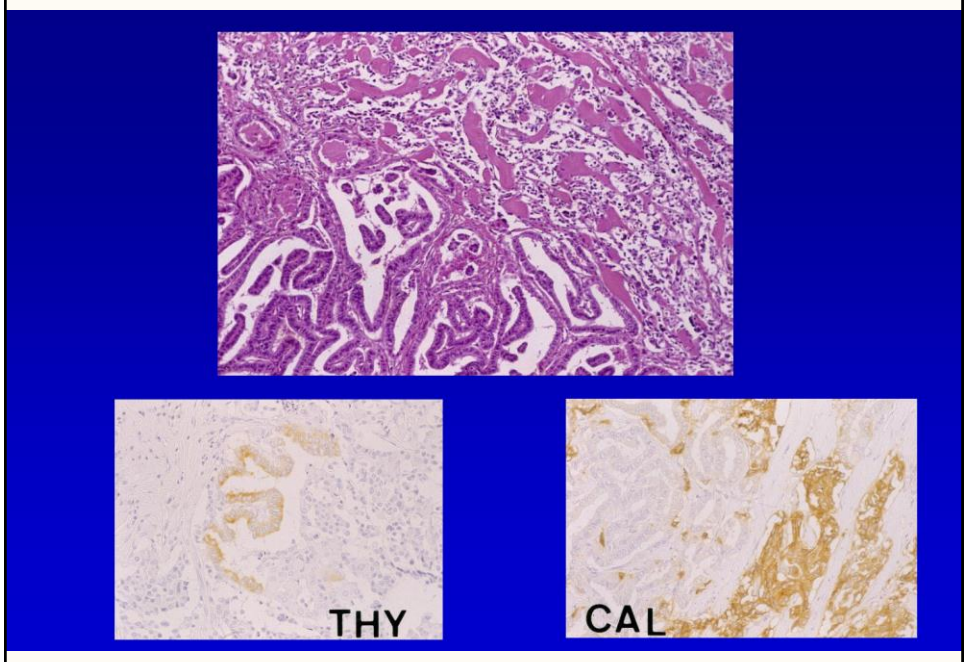
pathologic examination -

gold standard for diagnosis



Mixed medullary and follicular cell carcinomas (Definition)

A tumour showing morphological and immunophenotypical evidence of coexistence of follicular and parafollicular cell derived tumour populations within the same lesion.


THY
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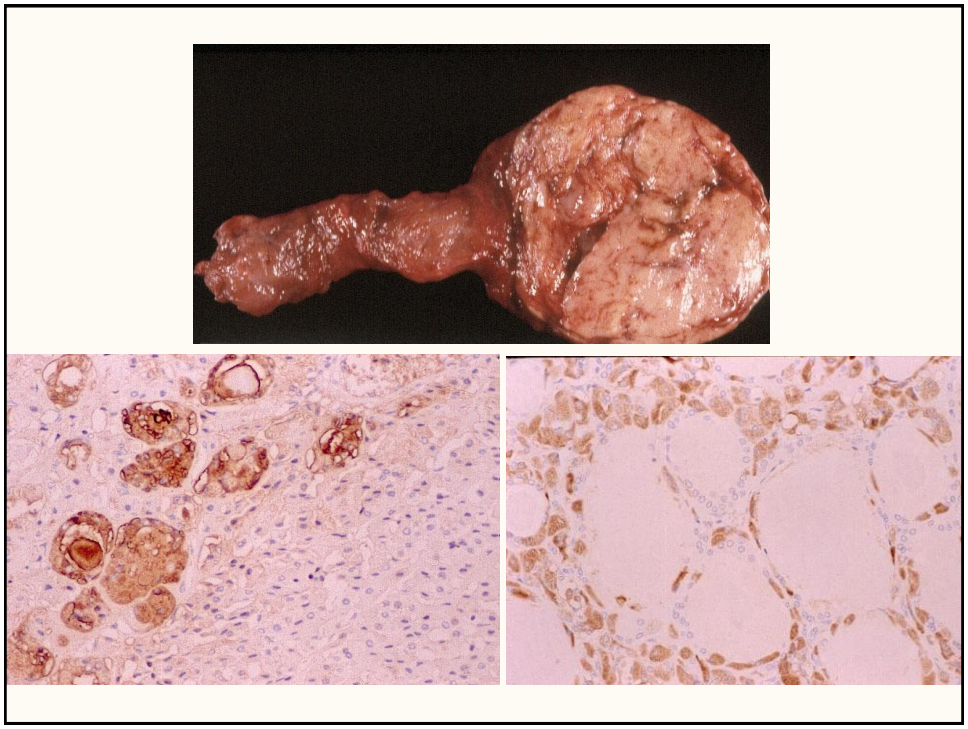


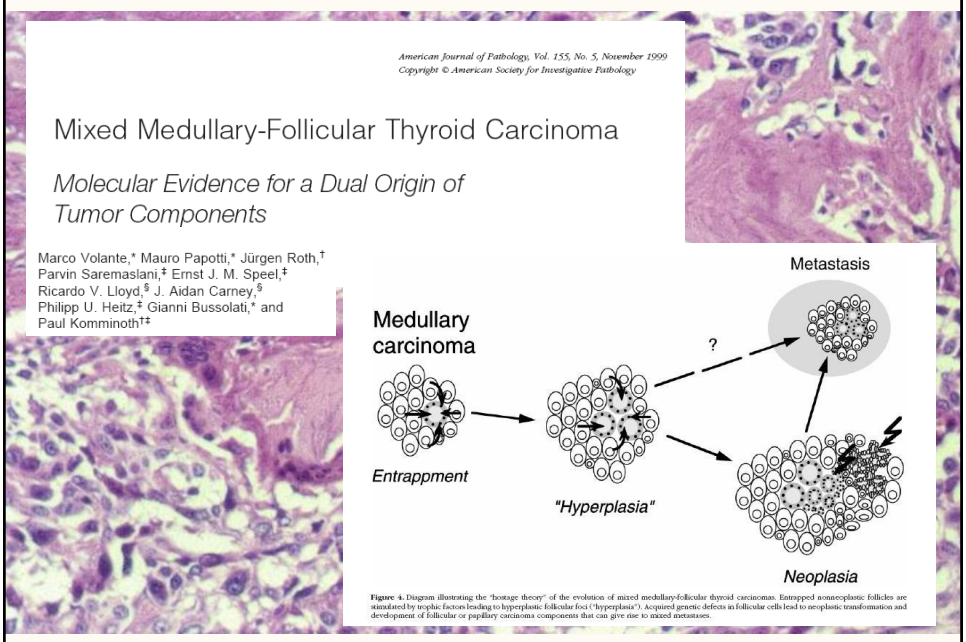
Simultaneous MTC-PTC (Germany)

3.6% of PTC

2.6% of familial MTC

4.1% of sporadic MTC

Machens and Dralle Ann Surg Oncol 2012



Molecular features of MTC

- **Mutation in RET proto-oncogene**:
  - Germline mutation in the **inherited syndromes** (MEN2, FMTC).
  - Worse prognosis if found in **sporadic tumors**.
- **RET**: tyrosine-kinase receptor, which **activates several signaling pathways in the cell** – STAT, NFkB and beta-catenin.
- **Types of mutations**:
  - Extracellular region: independent dimerization of two receptors (activates the tyrosine kinase).
  - Intracellular region: independent activation of the intracellular tyrosine kinase, without dimerization.

Prognostic Factors of MTC

- Age and Gender
- Tumor size (micro/macro-carcinoma)
- Level of invasion
- Distant metastases
- Calcitonin and CEA doubling time

No pathological grading system for a more accurate prognosis

Research Question and Hypothesis

- Can we use pathological or immuno-histochemical feature for **grading and prognosis**?
- **Hypothesis**: Pathological and immuno-histochemical features which are **used for grading other Neuroendocrine Tumors**, **can also be used for grading in MTC.**

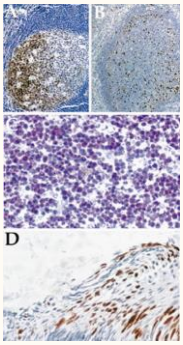
Neuroendocrine Tumors

- **Neoplasms that originate from neuroendocrine cells.**
- **Neuroendocrine cells**: cells that **release hormones,** as a result of a **direct neural stimulation.**
- Secrete **specific hormones**, such as Calcitonin, ACTH, Epineprine and Norepineprine**.**
- **Grading Methods:**
  - **KI67%**
  - **Mitotic count**
  - **Presence of necrosis**

Can we use these methods in MTC?

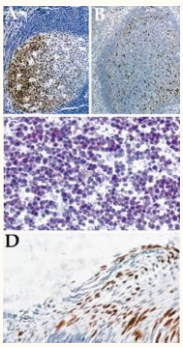
KI67

- **Very large protein:** 395 kDa, 30,000 BP.
- **Specific localization pattern**, changes during cell cycle.
- The amount of the protein during the cell cycle is **highly regulated**.
- Functions:
  - Mostly **unknown**
  - **Vital for cell proliferation** (removal of KI67 prevents proliferation).
  - May have a roll in **producing ribosomal RNA**.



KI67

- **KI67 is present during active phases of the cell cycle** (G1, S, G2), but is absent from resting cells (G0).
- Used as a **<u>cellular marker for proliferation</u>.**
- **Several methods** of KI67% determination:
  - Expert eye
  - The Aperio automated computer-assisted manual count.
  - Computer-assisted manual count.



What have we done so far?

- **Reviewed the literature** ✓
- **Collected relevant cases** ✓
- **Located the samples of the tumors** ✓
- **Collected and tabulated the pathological features and clinical outcomes of the relevant cases** ✓

Remains to be done

- **Perform KI67 Immunohistochemical staining on the tumor samples.**
- **Choose our main outcome:**
  - 5 year survival?
  - distant metastases?
  - Involvement of lymph-nodes?

- **Hopefully:** find a **statistically significant connection** between the **KI67% staining and a worse clinical outcome.**

THANK YOU!