Adrenal Disorders for the USMLE Step One…

…the Adrenal Medulla:

Pheochromocytoma (Pheo) and MEN2 Syndrome

Howard J. Sachs, MD
www.12DaysinMarch.com

Adrenal Medulla: Background

- Key facts to know about the Medulla
  - Derived from neural crest
  - Function as modified autonomic ganglion
  - Stimulated by SNS (Acetylcholine) to release catecholamines
    - Principle product: Epinephrine

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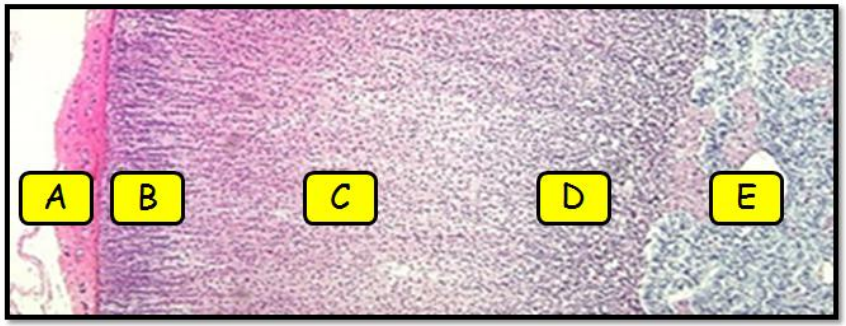

In the diagram above, choose the appropriate stimulus to hormone release at the region designated by letter E.

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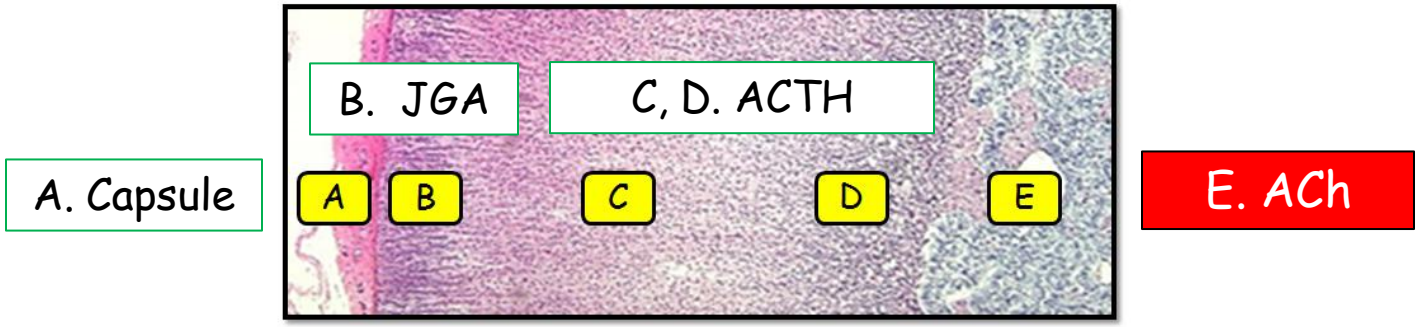

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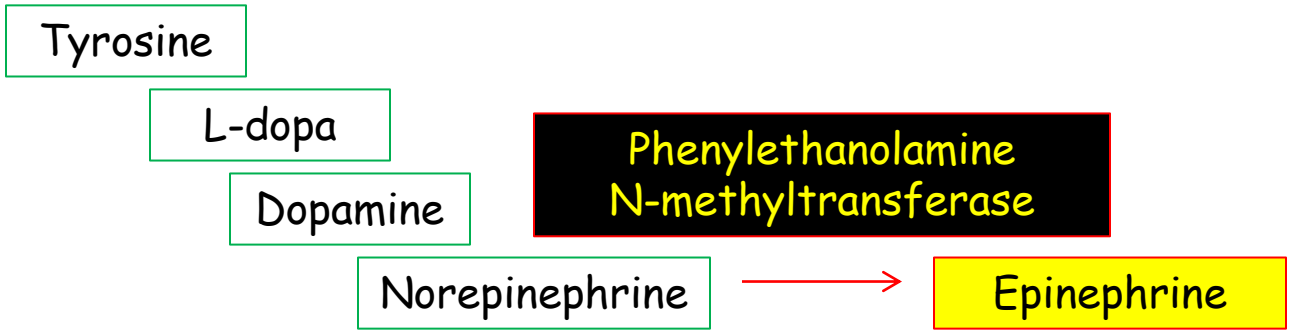

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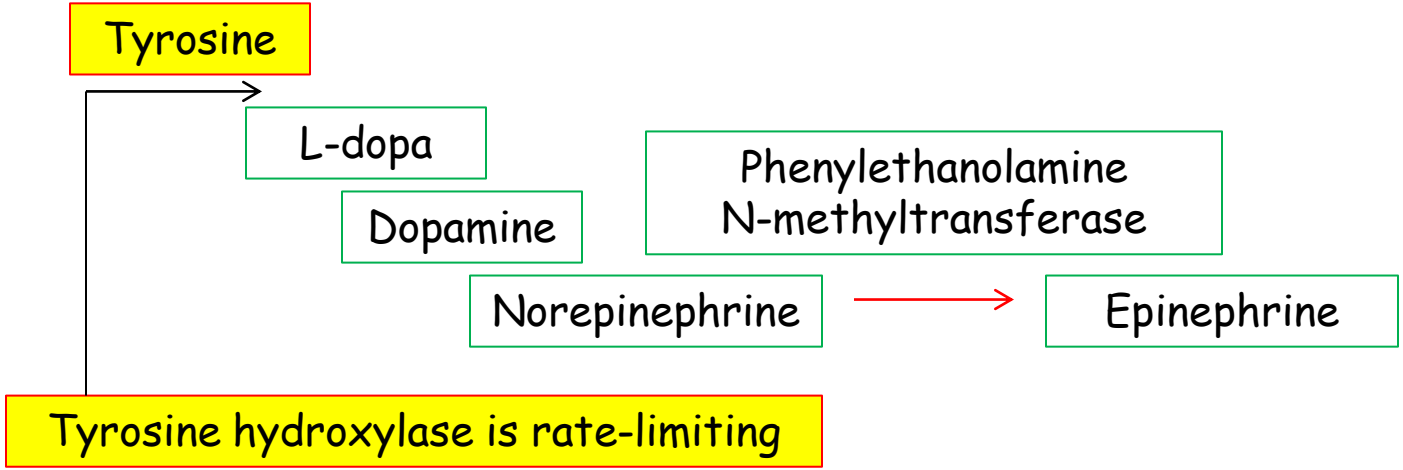
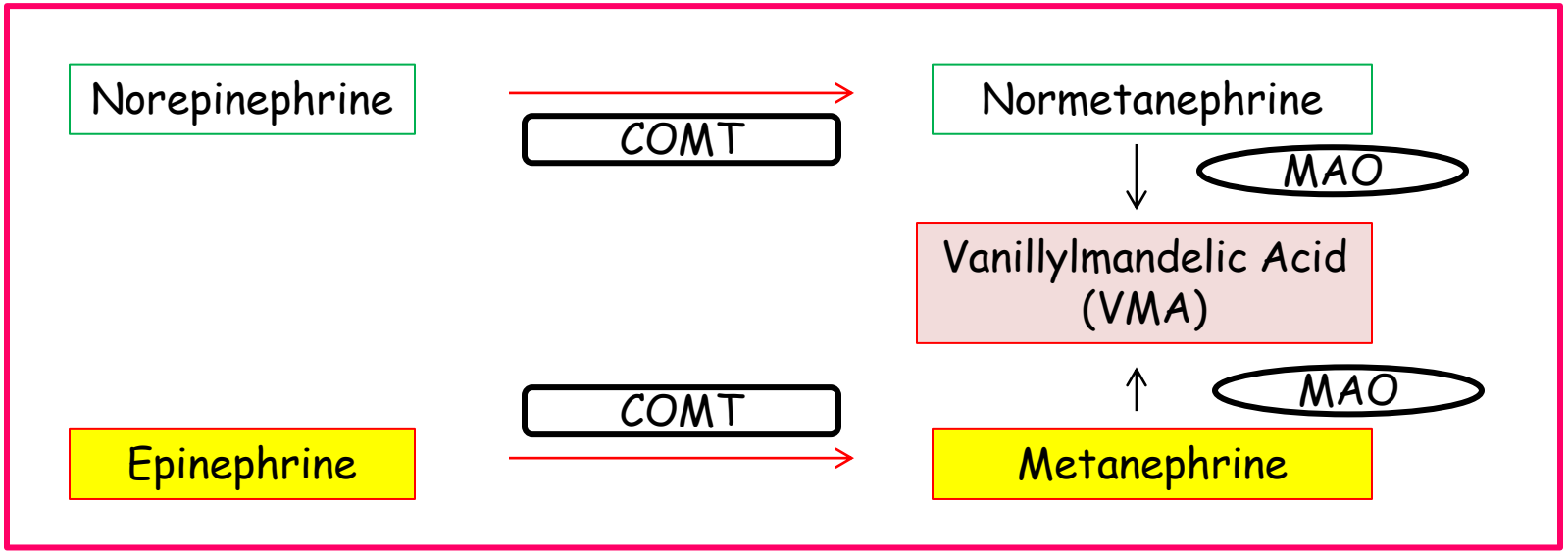
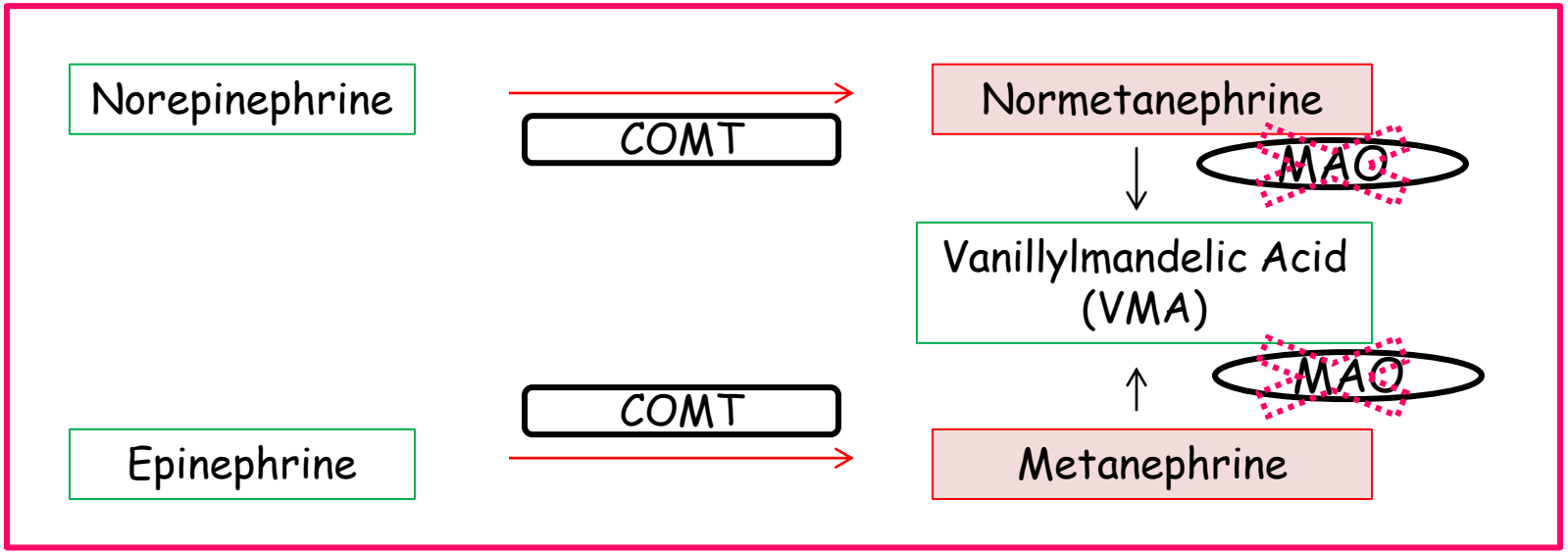


Adrenal Medulla: Metabolism



MAO: monoamine oxidase
COMT: catechol-O-methyltransferase

Adrenal Medulla: Metabolism



Implications:

1. In assessing medullary hyperfunction, biochemical metabolites are the diagnostic test of choice (metanephrines and VMA)
2. MAO inhibitor results in increased levels of catecholamines

Pheochromocytoma/MEN 2

- Background
  - Catecholamine-secreting tumor of the adrenal medulla
    - Only 10% malignant
  - Majority are sporadic but the familial syndromes capture the imagination of the NBME
    - AD: MEN 2, VHL (Von Hippel-Lindau), Neurofibromatosis (NF-1)
- Pathology
- Clinical
- Data
- Treatment

Pheochromocytoma/MEN 2

- Background
- Pathology
  - Composed of chromaffin (neuroendocrine) cells
  - EM: neurosecretory granules
  - Tumors are generally small circumscribed lesions but can get pretty enormous
  - No histologic features that predict malignant behavior.
    - They are malignant if they metastasize
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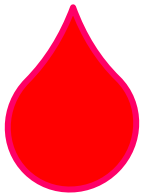
Pheochromocytoma/MEN 2

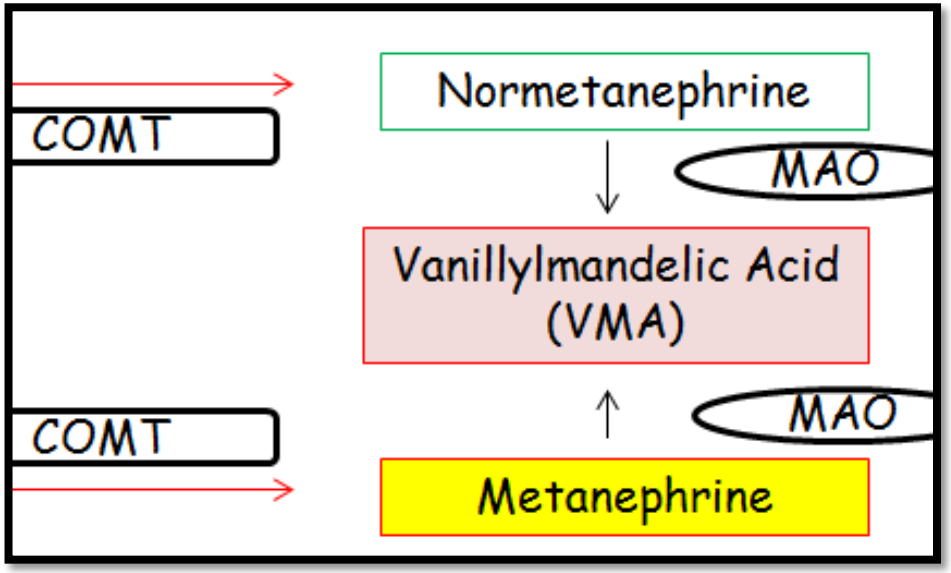
- Background
- Pathology
- Clinical
  - Classic: (paroxysmal) HTN plus HA, Sweats, Palpitations
  - Reality: incidental (imaging), screening familial syndrome
    - Tend to be bilateral if familial

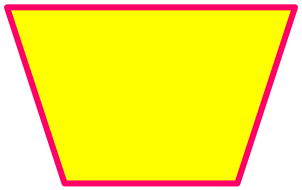
Pheochromocytoma/MEN 2

- Data
  - Plasma metanephrines; Urine catecholamines (fractionated)
  - Imaging: CT/MRI, Nuclear: (MIBG/PET)



Plasma
Sensitive
Not Specific





24 hr Urine
VMA
Metanephrines

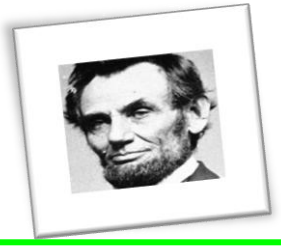
Pheochromocytoma/MEN 2

- Background
- Pathology
- Clinical
- Data
- Treatment
  - Adrenalectomy
    - Medical pretreatment with α-1-antagonist (phenoxybenzamine) $\rightarrow$ β-blocker (HR control)
- Special Notes

Pheochromocytoma/MEN 2

- Background
- Pathology
- Clinical
- Data
- Treatment
- Special Notes
  - Complication: Catecholamine-induced CM
    - Takotsubo-like syndrome
  - Extra-adrenal: 10% (referred to as paraganglionomas)
    - 95% within abdomen (para-aortic location)
  - VHL: loss of function of a tumor suppressor gene
    - VHL – ubiquitin ligase induces degradation of HIF
    - Components include Pheo, Renal cell, Hemangioblastoma

Pheochromocytoma
MEN 2 Syndromes

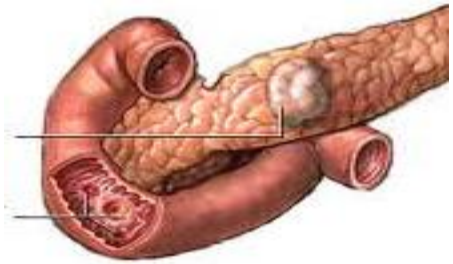


Ca+2

MEN 1

Ca+2

RET



MTC

Pheo

MTC

Pheo

MEN 1
Pituitary
Parathyroid
Pancreas (neuroendocrine)

RET

MEN 2a

MTC
Pheo

PTH

MEN 2b

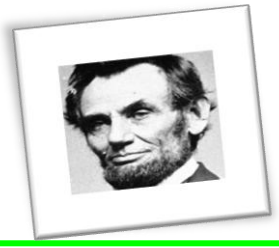
Marfanoid

Gain of function

The most challenging part of the MEN syndromes is knowing you are in the middle of one.

If a question seems convoluted with disparate features, think MEN

Pheochromocytoma
MEN 2 Syndromes



Ca+2

RET

MTC

Pheo

MTC

Pheo

MEN 2a

RET

MEN 2b

MTC
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PTH

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Reality Check:
100% - MTC
50% - Pheo

Pheochromocytoma
MEN 2 Syndromes

Ca+2

RET

MTC

Pheo

MTC

Pheo

MEN 2a — RET — **MEN 2b**

MTC
Pheo

PTH — Gain of function — Marfanoid

The most challenging part of the MEN syndromes is knowing you are in the middle of one.

If a question seems convoluted with disparate features, think MEN

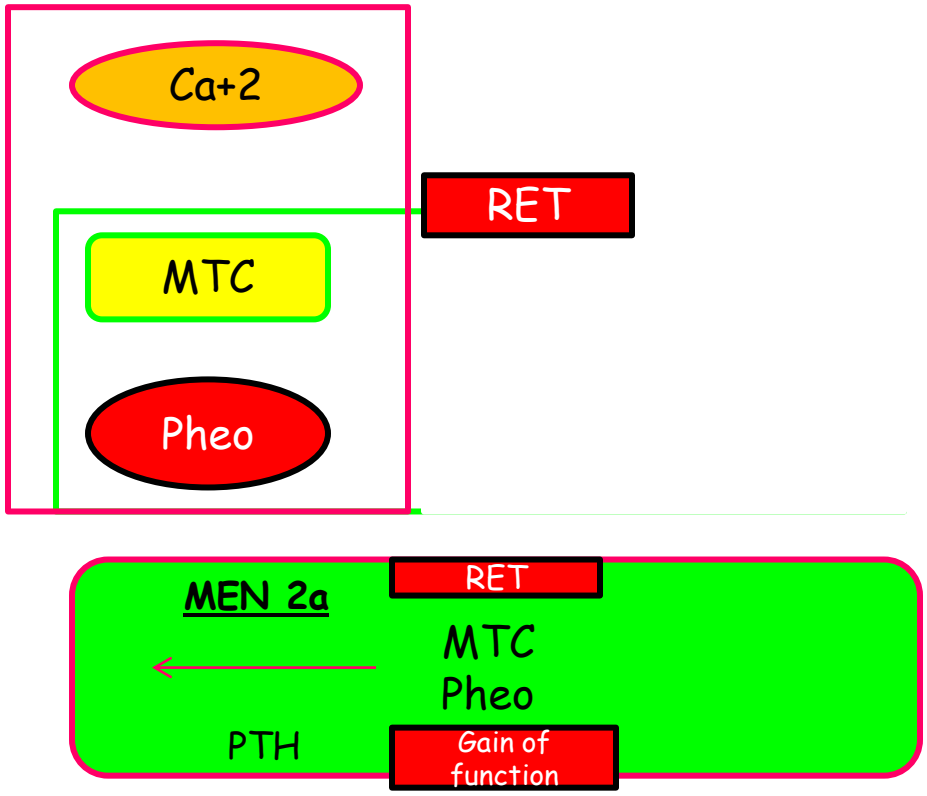
Reality Check:
100% - MTC
50% - Pheo

2a
20% - PTH hyperplasia

PTH:
Hypercalcemia
Stones

Pheo:
HTN, palpitation,
HA, sweats

Pheochromocytoma
MEN 2 Syndromes



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2b
Marfanoid Features
Mucosal Neuromas

Pheochromocytoma
MEN 2 Syndromes

RET

MTC

Pheo

RET

MEN 2b

MTC
Pheo

Gain of function

Marfanoid

Pheochromocytoma
MEN 2 Syndromes

Reality Check:
100% - MTC
50% - Pheo

2b
Marfanoid Features
MSK
(no aorta, lens)

Mucosal Neuromas
Tongue, Lips

Flesh colored nodules
Neuromas
(not lipomas or angiofibromas)

RET

MTC

Pheo

RET

MEN 2b

MTC
Pheo

Gain of function

Marfanoid

MEN 2/ Medullary Thyroid Carcinoma

- Background
  - AD genetic syndromes with high penetrance and RET mutations characterized by Medullary Thyroid Carcinoma (100%), Pheochromocytoma (50%) plus:
    - 2A: Parathyroid hyperplasia (20%).
    - 2B: Mucocutaneous (neuromas) and MSK (Marfan-like MSK features; aorta/lens not involved).
  - Aggressive tumor with majority having metastases at time of dx.
- Pathogenesis/Pathology
- Clinical
- Data/Diagnostics
- Treatment

MEN 2/ Medullary Thyroid Carcinoma

- Pathogenesis
  - RET gene: codes for a protein that is a receptor tyrosine kinase. It induces growth and differentiation signals .
  - Gain of function mutation with constitutively active.
- Pathology

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  - Precursor
  - Carcinoma racellular amyloid de

Calcitonin

ngo red stain with apple-green birefrigence under polarized light

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  - Precursor: early finding of parafollicular (C-cell) hyperplasia
  - Carcinoma: uniform cells that stain (+) for calcitonin with extracellular amyloid deposits that stain (+) for Congo red.

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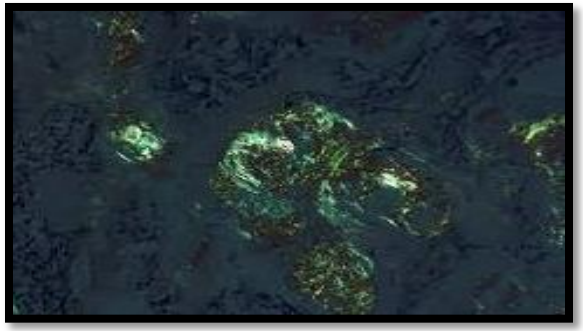

Congo red stain with apple-green birefrigence under polarized light

MEN 2/ Medullary Thyroid Carcinoma

- Clinical: initial presentation in MEN 2 Syndromes
  - Solitary nodule +/- cervical adenopathy
    - 2A: HyperPTH/Pheo symptoms
    - 2B: Mucocutaneous neuromas (lips/tongue)/Pheo symptoms


Neck Mass

MEN 2/ Medullary Thyroid Carcinoma

- Background
- Pathogenesis/Pathology
- Clinical
- Data/Diagnostics
  - FNA with immunohistochemical stain for calcitonin
  - Serum Calcitonin: serial assessment (known cancer) or screening (in familial syndromes)
    - IV pentagastrin or calcium stimulation
    - Level correlates with size of mass
  - May express CEA – monitoring, not diagnostic
- Treatment

MEN 2/ Medullary Thyroid Carcinoma

- Background
- Pathogenesis/Pathology
- Clinical
- Data/Diagnostics
- Treatment
  - Thyroidectomy – MTC is an aggressive tumor; found early (or in setting of familial syndrome), excision is definitive rx.
  - Most have metastasized at time of dx.

MEN 2
Pheochromocytoma & Medullary Thyroid Carcinoma

- Patient with HTN/palpitations, blah, blah → MTC derivative
  - RET mutation
  - Calcitonin
  - Amyloid deposits: Congo Red stain
  - Treatment → Thyroidectomy

MEN 2
Pheochromocytoma & Medullary Thyroid Carcinoma

- Patient with HTN/palpitations, blah, blah → MTC derivative
  - RET mutation
  - Calcitonin
  - Amyloid deposits: Congo Red stain
  - Treatment → Thyroidectomy

- Patient with neck mass stains (+) with Congo Red (or calcitonin), what other signs/symptoms might they have? → Pheo derivative
  - Symptoms (HTN, palpitations, HA, sweats)
  - Metabolites: VMA/Metanephrines
  - Unilateral v Bilateral tumor of the medulla

MEN 2
Pheochromocytoma & Medullary Thyroid Carcinoma

- Patient with HTN/palpitations, blah, blah → MTC derivative
  - RET mutation
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- Distinguish:
  - 2a (HyperPTH) from 2b (Marfanoid/Neuromas)
  - MEN 1 (Pituitary, Parathyroid, Pancreas) v MEN 2
  - MEN 2 from VHL (Renal Cell, loss of suppressor)

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