Multiple Endocrine Neoplasia, Type 2B: Dermal and Mucosal Manifestations May Herald Diagnosis

Peter M. Sadow, M.D., Ph.D.
Associate Director, Head and Neck Pathology
Massachusetts General Hospital
Massachusetts Eye and Ear Infirmary

Associate Professor of Pathology,
Harvard Medical School
Twitter: @PathDocBoston #USCAP2016

Multiple Choice Question
Multiple Endocrine Neoplasia

Which of the following statements is correct?:
A. I remember the Rule of 10s vaguely
B. I have diagnosed medullary thyroid carcinoma
C. I have diagnosed a pheochromocytoma
D. I have diagnosed a mucosal neuroma.
E. I have suggested a syndrome in my report
F. At least 2 of the above

Agenda

- Multiple Endocrine Neoplasia Syndromes
  - Cases
- Subtyping of MEN Syndromes
  - MEN2A, classical type and subtypes
  - MEN2B
- MEN2B
  - Unique disease
  - Dermal and mucosal manifestations
  - Implications for diagnosis and the role of the pathologist

ACCME/Disclosure

Dr. Sadow has nothing to disclose
Take Home Points

- Pathologists need to recognize the major findings heralding syndromes
- If you have never made a diagnosis of an entity before, do a quick search before signing out
- Any unusual finding in a baby/kid, especially neoplasia, should be assessed
- Know testing options, tissue or sera

Case Presentation

The patient is an ~3300 yo male who was in his usual state of health until his late teens/early 20s when he began to experience dramatic changes in body habitus.

Physical Presentation

- Dolichocephaly (elongated head relative to width)
- Prognathism (projected lower jaw)
- Kyphosis (curvature of the spine with pronounced hump)
- Narrow shoulders
- Dolichostenomelia (long, thin limbs)
- Widened pelvic girdle (iliac crest distance)
- Arachnodactyly (long, spindly digits)

Family History

- Parents
  - Amenhotep III, Queen Tiye – phenotypically normal
- Offspring:
  - Tutankhamun – normal head structure (contrary to some reports), with evidence of a palate abnormality and lower limb abnormality
  - No known genetic abnormality
Differential Diagnosis

- Marfan Syndrome
- Froehlich Syndrome (pituitarism)
  - Growth hormone secreting pituitary abnormality (acromegaly)
- Artistic Differences
Case Presentation

- 9-year-old boy presents 6 year history of:
  - Asymptomatic tongue papules
  - Chronic constipation
- Physical Exam:
  - marfanoid habitus
  - coarse facies
  - tooth malposition
  - multiple soft, yellow papules measuring 3 to 12 mm on the tip of his tongue
Multiple Mucosal Neuromas

Unencapsulated Mucosal Neuromas

courtesy of W. Faquin, MGH

Palisaded Encapsulated Neuroma
(diagnostic pitfall)

courtesy of G.P. Nielsen, MGH

Palisaded Encapsulated Neuroma

S100

courtesy of G.P. Nielsen, MGH

Neurofilament
**Palisaded Encapsulated Neuroma**
- Typically occur on the face, neck and oral mucosa
  - Generally solitary
  - May appear in clusters
- May have RET exon 13 mutation, but rarely associated with MEN2B or PTHS
  - Not exon 15 and predominantly 16 of MEN2B

**Final Pathological Diagnosis**
- Mucosal neuromas
- Note: The morphological features, combined with the clinical picture are suggestive of Multiple Endocrine Neoplasia type 2B; clinical follow up needed

**Additional Work Up**
- Thyroid U/S – 2 hyperechoic nodules.
- CT abdomen showed large colon distention.
- Calcitonin 277 pg/mL (nl value, <10)
- Normal metanephrines.
- De novo mutation in the gene encoding ret proto-oncogene (RET M918T) was found.

**Additional Info**
- Total Thyroidectomy & bilateral neck dissection
  - medullary thyroid carcinoma with multiple metastatic lymph nodes.
- Rectal bx: intestinal ganglioneuromatosis.
- Life expectancy up to 21 years
- Any finding of lingual neuromas in a child should prompt work up
16 yo girl

Additional Findings

- Both eyes w thickened upper and lower lids & neuroma @ left upper conjunctival lid margin.
- PEx: 3.0 x 2.0 cm thyroid nodule
  - Medullary thyroid carcinoma by FNA and TTX
- Abdominal CT: Pheochromocytoma (4.5 cm) of the right adrenal gland, which was removed surgically.

SOS1 frameshift mutations cause pure mucosal neuroma syndrome, a clinical phenotype distinct from multiple endocrine neoplasia type 2B

RET Gene

- REarranged During Transfection
  - Chromosome 10q11.2
- 21 exons encoding a transmembrane tyrosine kinase
- Mutations occurring in Familial Medullary Thyroid Cancer and Multiple Endocrine Neoplasia Type 2A occur in the extracellular domain (exons 10 and 11)
**FMTC and MEN2A**

- Mutated extracellular domain leads to variable manifestations of these syndromes due to which mutation is present
- Variable degree of modulation of ligand-bound receptor complex
- However, since there is such a wide variability in both degree and course of these syndromes, this solitary germline mutation cannot be solely responsible

---

**The Details**

- “Another consequence of this process is the binding of adaptor proteins, which are able to bind phosphotyrosines such as … and connect the RET receptor to several intracellular signalling pathways, in particular the MAPK and the PI3K pathways that usually control intracellular activities such as proliferation, survival and migration”
MEN Type 2B

- Spectrum of clinical manifestations
- 75% de novo germline mutations
- 95% of mutations result in M918T
  - Exon 16
- <5% of mutations A883F
  - Exon 15 – less well known

Clinical Manifestations

- All individuals w MEN2B develop medullary thyroid carcinoma
- Approximately 50% develop pheochromocytoma
- Generalized ganglioneuromatosis, throughout the aerodigestive tract, manifesting in intestinal dysfunction in infants (Hirschsprung-like)
  - Bloating, intermittent constipation, diarrhea

Clinical Manifestations

- Skeletal malformations
  - Marfanoid body habitus
  - Narrow long facies
  - Pes cavus
  - Pectus excavatum
  - High-arched palate
  - Scoliosis
  - Slipped capital femoral epiphyses
Medullary Thyroid Carcinoma

Range of Morphology

Cut surface

Organoid nests - “Zellballen”

FromCourtesy V. Nosé, MGH

©PathDocBoston

73 yo woman with solitary upper lobe thyroid mass, spontaneous 400X magnification

Calcitonin

CEA

Congo Red

Congo Red Polarized
Summary I

• Mutations: Primarily RET M918T
  – Intracellular tyrosine kinase domain, constitutively active
  – Targetable with TKIs
• Outward manifestations of MEN2B
  – Mucosal neuromas, largely of the oral cavity & sclera with prominent corneal nerves
  – Marfanoid body habitus with associated Marfanoid features
    • High riding palate
    • Elongated facies
Summary II
- 75% sporadic germline mutations
- 25% familial
- Heralded by early onset advanced thyroid carcinoma (medullary)
- Head & Neck clinical manifestations are non-specific but appear earlier than other features
  - Mucosal neuromas – tongue and oral cavity
  - Combine this with musculoskeletal and GI anomalies to be highly suspicious

Summary III
- Pathologists rarely examine patients
  - Exception of cytologists and medical examiners
- Pathologists fundamentally examine the patient’s medical record
- Interesting clinical histories in children are red flags for syndromes
  - MAKE SURE YOU READ THEM!!

Thanks for your kind attention!

@PathDocBoston
#USCAP2016
#InSituPathologists