Congenital Melanocytic Nevi, Cafe au lait Macules and Everything in Between

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Disclosure of Relationships with Industry

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Disclosures
I have no relevant relationships with industry
Objectives

Patterned Pigmentations/Somatic Mosaicisms-
Checklist for when to evaluate for associated systemic findings and what to evaluate for

- Congenital Melanocytic Nevi
- Epidermal and Sebaceous Nevi
- Becker’s Nevi
- Segmental Pigmentation Disorder
- Linear and Whorled Nevoid Hyper/Hypo-melanosis
- Broad blaschko-linear patterned pigmentation as a marker for McCune Albright Syndrome
- Pigmentation of the genitals
- Dermal Melanocytosis and when to worry


LCMN is a mosaic mutation of NRAS

Initial Visit Checklist

• Does this child have neurocutaneous melanosis?
• Is there a melanoma?
• What are these weird lumps?
Neurocutaneous melanosis?

• 50% who develop symptoms do so prior to 1 year
  – most by 2 years of age
  – another small peak at time of puberty
  – Seizures, hydrocephalus, cranial nerve deficits, mass effects

• Number of satellites most predictive
  – >20 satellites 5 fold increase in risk of NCM
  – 3 or more small or medium congenital nevi with no “mother ship”

• Size
  – > 20cm increases risk
  – Infant → about 6 cm on head and 9 cm on body

• Location of LCMN
  – Posterior midline

Large mothership with multiple satellites

Multiple small/medium congenital nevus phenotype
Imaging for NCM

• **Image if:**
  – LCMN with (10 or more?) satellites
  – 3 or more small or medium congenital nevi
  – LCMN with posterior midline (+ spine)

• **MRI of the brain**
  – Ideally before 6 months of age (3-6 months old)
  – Try feed and swaddle or sedate to avoid general anesthesia
  – Non contrast, heavily T1 and T2, volumetric sequences
  – Spine if possible, particularly if lumbosacral involvement

• **If positive**
  – Close follow up with Pediatric Neurology
  – Increases risk for melanoma

• **Follow up Imaging**
  – only if develop symptoms
Is there a melanoma?

- **Risk is around 5% lifetime for LCMN**
  - Half occur before 5 years old and almost all before puberty
  - Larger size → higher risk (75% assoc w > 40 cm)
  - Truncal location and multiple satellites → increase risk
  - Risk much higher for melanomas including cutaneous and extra-cutaneous if NCM

- Cutaneous MM present as **deep, fast growing or ulcerated nodules in the mothership**
  - Palpate
  - Pictures

- **CNS melanoma** actually may be more common
  - Especially if there is NCM with a LCMN
What are these weird lumps?

• **Proliferative nodules**
  – Don’t increase risk of melanoma
  – Ulcerate less often and less extensively than melanoma
  – Atypical histologic feature common on biopsy
    • Cytologic atypia, architectural disorder, pagetoid spread, high mitotic index
    • IH, FISH seem to have limited value
    • Some evidence for reduced methylation in melanomas
  – **Get expert and second opinions**

**First Follow up Checklist**

• Will it fade?
• Should we go straight to the surgeon?
• Support groups
Will it fade?

Should we go to the surgeon?

- Get to know your family
- Join the support group before discuss
- Complex discussion - experienced surgeon
  - Has not shown to decrease melanoma risk
  - Early surgery carries increased anesthesia risk and may not be advantageous
  - Surgical intervention adverse effects?
    • Darkening, peripheral lesions, new lesions
  - Scars vs nevi - function and form
  - Wait 1 year with photos to assess lightening


Support Groups - parents immediately, child before school age

Nevus Outreach - www.nevus.org

Nevus Network - www.nevusnetwork.org

The Congenital Nevus Support Group
2018 - Our 35th Year!
Follow up Checklist LCMN

• Serial exam with palpation every 3 months first 2 years then q6 months until age 5 then annually
  – Total body photography to assess for lightening and new lesions

• Counsel regarding xerotic skin, pruritus, and hypohidrosis
  – Ondansetron

• Counsel not to limit activity due to fear

• Low threshold for neurodevelopmental assessment

• The hope:
  – RAF and MEK inhibitors for tx of LCMN and NCM

Small and Medium CMN
MM in small/intermediate CMN

- Most were superficial
- Age range 18 to 79 years.

Illig L, et al. Congenital nevi less than or equal to 10 cm as precursors to melanoma. 52 cases a review, and a new conception. Arch Dermatol. 1985;121:1274-81.

Checklist Small and Medium CMN

- **Risk of Melanoma low**
  - <1% over a lifetime
  - Occur after puberty
- **Periodic evaluation after puberty with photos**
- **Discussion of removal**
  - Functional concerns
  - Psychosocial/Cosmetic concerns
  - Usually wait till after 3 yo
The exception to the rule

- 8 year-old Report of MM arising in CMN
- Change over months
- No regular medical monitoring done prior to visit for nodule
- PET scan and sentinel node neg
- NED 12 months later


Favorite References


Nevus Sebaceous is mosaic HRAS or KRAS Mutation

Epidermal (Keratinocyte) Nevus is mosaic of HRAS, KRAS, NRAS, PIK3CA, FGFR3, FGFR2, Keratin 1/10 mutations


Checklist for EN and NS

- **Detailed Physical Exam** to determine
  - Extent
  - Multifocality (*mouth, genitals, scalp*)
  - Musculoskeletal abnormalities

- **Detailed History** to ask about
  - Developmental milestones
  - Seizures
  - Issues with vision
Localized NS Checklist

• Tumor growth
  — Benign:
    • trichoblastomas, syringocystadenoma papilliferum
  — Malignant:
    • Basal cell cancer most common
    • < 1% in 651 excised NS in children (Rosen et al 2009)

• Excise? When?
  — Psychosocial, risk of general anesthesia, family ethic/culture
  — There is no rush \( \rightarrow \) after 3 yo due to anesthesia issues
  — Check in around puberty when thickening
**Localized EN Checklist**

- Less risk of tumors
- No medical reason to excise, based on disfigurement
- Rule out associated overgrowth syndromes like CLOVES, SOLAMEN, Proteus
Extensive/Multifocal NS Checklist

• **Neurology Consult**
  – 7% in recent cohort of 196 patients with neurologic issues
  – More common with centrofacial involvement
  – Intellectual disability and seizures most common
  – Screening imaging not helpful unless symptoms
    • 75% will have normal imaging

• **Ophthalmology Consult**
  – 2% in recent cohort of 196 patients
  – More common with neurologic abnormalities
  – Choristomas, colobomas, strabismus most common

• **Skeletal exam and look for scoliosis**
  – Scoliosis, gait, limb length, shoe wear patterns
  – Check calcium and phosphate hypophosphatemic vitamin D-resistant rickets
    • Bone pain, impaired mobility, bony deformities (birth to puberty)
**Extensive/Multifocal EN Checklist**

- Neurology Consult
- Ophthalmology Consult
- Skeletal Exam
- Consider hypophosphatemic vitamin D-resistant rickets
  - Bone scans, calcium, phosphorous

- **Is it epidermolytic keratinocytic nevus?**
Epidermolytic keratinocyte EN

- Consider biopsy at some point
- Important for genetic counseling
  - Keratin 1, 10 mutations
  - Risk of offspring with epidermolytic ichthyosis
  - Especially if nevus is over gonads or extensive
- Gonadal mosaicism highly variable

Phakomatosis Pigmentokeratotica

• Linear epidermal nevus + speckled lentiginous nevus

• HRAS or KRAS somatic mosaicism in a multipotent progenitor cell

• More likely to have systemic involvement than either alone
  – neurologic, ocular, musculoskeletal, urologic, renal or vascular

• Increase in non-dermatologic malignancy
  – Urologic and nephrologic tumors
  – Rhabdomyosarcomas


❖ Same HRAS mutation found in both the PPK and the rhabdomyosarcoma
Favorite References


Becker’s Nevus
(post zygotic beta-actin mutation)
Becker’s Nevus Checklist

• Is it in a female over the breast?
  – Watch breast development
  – Consider spironolactone 50-100 qd during thelarche

• If extensive rare skeletal or muscular abnormalities (like epidermal nevus syndrome)
  – Scoliosis most common

• Increased sebum production
  – Tinea versicolor, acne, pityrosporum folliculitis
    • Selenium sulfide wash
A funny café au lait spot: Could this be NF1?

Checklist for patterned pigmentation

• What is the pattern here?
  – Checkerboard, blaschkonian, round
  – Jagged coast or smooth
  – Café au lait or just café
  – Midline cutoff?

• Detailed physical exam
  – Are there other birth marks, CALM, skin findings, macrocephaly, or stigmata of NF1 or other diseases
  – JXG and nevus anemicus- NF1

• Detailed History
  – Developmental milestones
  – Issues with vision, musculoskeletal
  – Endocrine or precocious puberty

- **Double hit of Lynch Syndrome genes**: Can have multiple CALM, axillary freckling and hyperpigmented “mini macules” and other features of NF1
- **CMMRD**: more hematologic (NHL), colorectal cancer, high grade gliomas, medulloblastomas
- **Any patient with diagnosis of “sporadic NF1” who develops a malignancy other than malignant peripheral nerve sheath tumor, JMML or optic glioma at an early age should be evaluated for CMMRD**
**Segmental Pigmentation Disorder**

- Blocky, segmental, hyper/hypo-pigmented, patches with midline cutoffs
- Smooth borders
- Café au lait, not just café

**Generally good prognosis**

(Hogeling M, Frieden IJ. Br J Dermatolog 2010)
- Ask about developmental milestones
- Talk about CNS and eyes but no routine referrals
- Sun protection, self tanners

**If the pigmentary mosaicism is more blaschkonian**
“Linear and Whorled”
Nevoid Hyper/Hypo-melanosis

• Useful term for pigmentary change in more swirly whorly, blaschkonian pattern

• Perhaps more systemic findings then segmental pigmentation disorder (30% in this study) - >if hypo+hyper
    • 54 patients with nevoid hyper and hypo pigmentation
    • 15/54 had neurologic abnormalities, usually developmental delay and seizures
    • 3/54 hemihypertrophy
    • 2/54 cardiac: PDA, VSD
    • 1 with conical teeth, 1 with scoliosis

• Detailed exam and history

Mosaic partial trisomy 13

- *Phyllion*= leaf “phyllloid hypopigmentation”
- Hypopigmented round or oval asymmetric patches, reminiscent of the leaves of a begonia
- CNS defects, neurodevelopmental issues, absence corpus callosum, conductive hearing loss, choroidal and retinal coloboma, craniofacial defects, digital and other skeletal anomalies


Is this McCune Albright?

- CALM is most common presenting sign
  - Usually present at birth
  - Unilateral with sharp midline cutoff
  - “Broad blaschko-linear pattern”
  - Usually darker- just café, with no milk
  - Jagged “coast of Maine” border

- Look for oral pigmentation
  - Vermillion and mucosal pigmentation

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<th>Inheritance/ Gene</th>
<th>Cutaneous Pigmentation</th>
<th>Tubular Tumors</th>
<th>Gastrointestinal Involvement</th>
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<th>Thyroid Alarminomas</th>
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Abbreviations: AD, autosomal dominant; CALM, café-au-lait macule; CAMP, cyclic adenosine monophosphate; GH, growth hormone; GNAS, complex loci; guanine nucleotide-activating; IPMN, intraductal papillary mucinous neoplasm of the pancreas; PPMAD, primary pigmented nodular adrenocortical disease; PHAHR1, protein kinase; CAMP-dependent regulatory, type 1, α, STR12, \*.
If worry for McCune Albright:

- Bone survey for **polyostotic fibrous dysplasia** (not always near pigment)
  - Craniofacial 90% by 3.5 yrs old
    - Painless lump
  - Extremities 90% by 14 yrs old
    - Limp, pain, pathologic fracture
- **Endocrine abnormalities** (hyperfunctioning)
  - Hyperparathyroid, pituitary adenomas (GH), adrenal adenomas (Cushing, aldosteronism), thyroid cysts, testicular Leydig/Sertoli cell hyperplasia
- **Precocious puberty**
  - Menstrual spotting
  - Scrotal thickening and enlargement
- Gene requires affected tissue- mosaic
CALM looking macule of the genitals

PTEN Hamartoma Syndrome
(Bannayan Riley Ruvalcaba)
If lentigines of penis or vulva:

• Look for
  – Macrocephaly
  – Lipomas
  – Vascular malformations
  – Oral papillomas, acral keratoses, acanthosis nigricans
  – Joint hyperextensibility, scoliosis

• Ask about
  – Hypotonia, developmental delay, autism
  – Hamartomatous intestinal polyps (PHx, FHx)

Favorite References


Checklist Dermal Melanocytosis

• Location
  – Periocular location is more concerning for associated malignancy or glaucoma

• Associated birthmarks
  – Capillary malformations might think of phakomatoses
  – Café au laits, might think about constitutional mismatch repair deficiency

• Progressive rather than regressive
  – More appear and after birth, get darker, get more extensive, more defined borders or ragged borders
  – Might think about metabolic disorder
• Whether you see conjunctival involvement or not - **Eye exam if periocular**

• **Glaucoma**

• **Uveal melanoma**
  - Reported with Nevus of Ota (1/400)
  - Reported with phakomatosis pigmentovascularis
  - Usually associated with other mutations in concert with GNAQ- like BAP1

• **Yearly ocular exam before puberty, bi-annual after puberty**

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**Nevus of Ito and other locations**

• Risk of melanoma in this and other (non-periocular) locations vanishingly low

• No real worrisome associations unless extensive all over the body
Dermal Melanocytosis with Capillary Malformation

Phakomatosis Pigmentovascularis

- Used to think PPV was due to non-allelic twin spotting
- Post-zygotic mosaic activating mutations in GNA11 and GNAQ
  - Same genes as Sturge Weber
  - G-protein alpha subunit gene mosaic condition, like McCune Albright
- Identical mutation in both capillary malformation areas and dermal melanocytosis areas to pluripotent progenitor cell
- Other factors such as location and background ethnic skin color factors control expression
Sturge Weber?

- If High risk
  - Argument MRI is not 100% sensitive
    - Requires contrast
    - Requires GA
    - Perhaps just refer to Pediatric Neuro to be educated
  - Evidence for ASA preventing Sz is not clear


Phakomatosis Pigmentovascularis (and extensive dermal melanocytosis)

- About 50% have extracutaneous involvement in some series
  - Neurologic conditions include
    - psychomotor retardation, seizures, and cerebral atrophy;
    - symptoms typically present within the first months of life
  - Ophthalmologic associations include
    - conjunctival melanocytosis, episcleral vascular malformations, and glaucoma
    - Melanoma choroid and conjunctiva
  - Overgrowth of soft tissues or limbs

- Referral to ophthalmology, neurology, and close neurodevelopmental monitoring recommended.
Dermal melanocytosis as a clue to constitutional mismatch repair deficiency repair syndrome


Favorite References


• Large congenital melanocytic nevi are different from small and medium
• Extensive epidermal and sebaceous nevi more worrisome then localized
  — Phakomatosis pigmentokeratotica higher risk for badness
• Becker’s and breast hypoplasia
• Constitutional mismatch repair deficiency can look like NF1
• Some patterned pigmentation to not worry about
  — Segmental pigmentary disorder not so much
• Some patterned pigmentary pigmentation to worry about
  — Swirly whorly nevoid hyper or hypopigmentation if extensive
  — Phylloid → Trisomy 13 mosaicism
  — broad blaschko-linear → McCune Albright can take till puberty to fully manifest
• Macrocephaly and genital melanotic macule → think PTEN
• Dermal melanocytosis- annual eye exams for periocular. Should we evaluate forehead involvement like you would a PWS?
• Phakomatosis pigmentovascularis- check eyes and neurodevelopmental