A Problematic Peripheral Nerve Sheath Tumor

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Clinical History

• A 64 year old woman
• Presented with progressive enlargement of a painful mass in the left foot

On examination:
• Skin fold freckling in the right torso (front and back), stops at midline
• No dermal lesions
History:

- A previous surgery for resection of a mass from the left leg diagnosed as a schwannoma (2013)
- 2 raised dermal lesions were biopsied and diagnosed as dermal nevi
- There is no family history of any type of neurofibromatosis
- The current biopsy was seen in an outside hospital and diagnosed as Schwannoma.
- She was referred to the MGH NF clinic for evaluation
Imaging

• MRI showed a multinodular lesion in the lateral foot
So - what’s the problem?

Clinical considerations

• This patient has multiple peripheral nerve sheath tumors and therefore has an underlying syndrome: NF1, NF2 or schwannomatosis

• Her clinical and pathological findings do not fit any of the NF syndromes

• Skin fold freckling are s/o NF1, multiple schwannomas are c/w schwannomatosis or maybe NF2
Multiple PNSTs - What type of NF?

- Neurofibromatosis 1
  - neurofibromas
- Neurofibromatosis 2
  - schwannomas
- Schwannomatosis
  - schwannomas
NF1

• NF1 most common 1 in 3,000 individuals.
• Autosomal dominant
• Germline mutations in the NF1 gene
• Half of the patients are founders - have a sporadic mutation and negative family history

• The hallmark of NF1 is the plexiform neurofibroma
  – often present in childhood.
  – carry a risk (9%) of malignant transformation to malignant peripheral nerve sheath tumor (MPNST).
– Other types of neurofibromas (dermal, diffuse, subcutaneous)

– Other types of malignancies including pheochromocytoma, leukemia, gliomas, breast cancer and others.
Non tumor manifestations

• Short stature
• Macrocephaly
• Learning disabilities – the most common clinical feature, low IQ, attention deficit disorder
• Cutaneous manifestations (café au lait, freckling)
  • Café au lait patches are very early manifestation (birth)
  • Freckling – age 3 years
• Bone/Skeletal abnormalities
  • Abnormality of maintaining bone structure (osteopenia, scoliosis, pseudoarthrosis of tibia)
• Eyes - Lisch nodules
• Cardio-Vascular: fibromuscular dysplasia of renal artery
Diagnostic Criteria for NF1

• 2 or more have to be present:
  – at least 6 café au lait spots (>5 mm in prepubertal; >15 mm after puberty
  – 2 neurofibromas OR 1 plexiform neurofibroma
  – Freckling
  – Tumor of the optic pathway
  – NF1 associated skeletal abnormality
  – A first degree relative with NF1
NF2

• NF2 affects 1 : 25,000 individuals
• Germline mutation in the *NF2* gene
• Autosomal dominant disorder
• 50% of patients have sporadic (de novo) mutations with no family history
• Vestibular schwannomas usually present (with clinical symptoms or on MRI) by age 30
• In addition: multiple schwannomas, meningiomas, ependymomas.
Clinical criteria for diagnosis

- Bilateral VS

OR

- First degree family with NF2 AND
  - unilateral VS <30 yrs OR
  - 2 NF2 associated lesions
Somatic Mosaics

- Mosaic forms of NF1 and NF2 are common (30%)
- Somatic mutation, later in development- only some of the cells have the mutation
- Manifestations are segmental, some of the clinical criteria may be late in developing or absent
- Clinical distinction between the different forms of NF becomes difficult
- Germline mutation may be not be detected - normal genetic testing
- Genetic risk to offsprings is undefined. If affected offspring often has more severe disease
Schwannomatosis

• 1:25,000.
• Most cases (85%) sporadic
• 15% are familial; SMARCB1, LZTR1
• Many cases are segmental (30%)
• Characterized by multiple schwannomas and meningiomas in the absence of vestibular schwannomas.
• Severe disabling pain
• Malignancies?
• Genetic risk is low
Neurofibroma or Schwannoma?

• When multiple - different forms of NF:
  • Neurofibroma : NF1
  • Schwannomas : Schwannomatosis OR NF2

• Different risks for malignant transformation

• Different criteria for diagnosis of malignancy (cellular schwannoma vs MPNST)

• Different risk for offsprings
Diagnosis?

- A) Hybrid tumor
- B) Schwannoma
- C) Neurofibroma
- D) Two of the above....
Immunostains

S100
In summary

- A benign peripheral nerve sheath tumor with areas of solid Schwann cell proliferation
- Mixed cell population (Schwann cells, myofibroblasts, perineurial like cells)
- Diagnosis: Peripheral nerve tumor with hybrid features; most consistent with Schwann cell rich neurofibroma
What are hybrid tumors and why should we report them?
Nerve sheath tumors with hybrid features of neurofibroma and schwannoma: a conceptual challenge

Feany et al, 2001
Hybrid Tumors

Difficult to classify – have mixed features

- Schwannoma/neurofibroma
- Perineurioma/schwannoma
- Neurofibroma/perineurioma
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<th>1st author, year</th>
<th>SC-NF</th>
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<td>Feany, 1998</td>
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<td>Park, 2012</td>
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<td>Harder, 2012</td>
<td>60</td>
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<td>2 NF1, 6 NF2, 18 schwannomatosis</td>
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<td>Lang, 2012</td>
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<td>Negative genetic testing for NF1 No signs of NF2 or schwannomatosis</td>
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Hybrid schwannoma/neurofibroma

- Myxoid schwannoma
- May be difficult to classify; some will remain unresolved - true hybrids
- Original series of schwannomatosis patients; 10% were misdiagnosed as neurofibromas or not classified (PNST)

*Maccolin, 2003*
S100
How does that affect clinical practice?

• In the case of a tumor without history of NF:
  The tumor should be diagnosed as “Hybrid tumor” or if immunohistochemical analysis led to a diagnosis of Neurofibroma or schwannoma —”schwannoma (or neurofibroma) with hybrid features (see note)”

• In cases where NF is suspected: correct pathological diagnosis

• Workup: S100, Sox10, Neurofilament, Glut1, EMA, SMA
Selected References

Thank You!