Small round cell tumors of bone and soft tissue, part 2 (non-Ewing group)

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Where in the world is Carmen Sandiego (or the diagnosis!)
Other small round cell tumors to consider

- Undifferentiated neuroblastoma
  - Retroperitoneal, paraspinal location
- NUT translocation carcinoma
  - Midline head, neck, and upper thorax location
- Extrarenal rhabdoid tumor
  - Any location, favors “paraxial” sites
  - Age important
  - History of previous rhabdoid tumors
Other round cell sarcomas of bone

• Mesenchymal chondrosarcoma
  – Mostly Paraxial
• Small cell osteosarcoma
  – Mostly Extremities
Undifferentiated neuroblastoma

- Defined in the International Neuroblastoma Classification as:
  - Diagnosed only by supplementary techniques
  - Patients may have elevated serum catecholamine levels.
  - Contain undifferentiated cells with indiscernible-to-thin cytoplasm
  - Contain no neuropil.
  - Cells contain nuclei with salt-and-pepper chromatin.
  - The majority contain prominent nucleoli, a marker of bad prognosis
Undifferentiated Neuroblastoma
Undifferentiated Neuroblastoma
Gross and Microscopic Features
Poorly differentiated Neuroblastoma
Neuropil
Undifferentiated Neuroblastoma Prognosis and Clinical Outcome: Classification

- **Good prognosis**
- Poorly differentiated neuroblastomas with low or intermediate MKI, <1.5 years of age
- **Poor prognosis**
- Poorly differentiated neuroblastomas with high MKI, <1.5 years of age
- Poorly differentiated neuroblastomas, age 1.5-5 years, any MKI
- Neuroblastoma, any type, age >5 years
- Undifferentiated neuroblastoma
Undifferentiated Neuroblastoma Ancillary Diagnostic Techniques

- Tyrosine Hydroxylase
- N-myc IHC
- C-myc IHC
- PHOX2B: a novel marker
- Neural markers (often non-specific)
- N-myc FISH (does not exclude alveolar rhabdomyosarcoma)
Undifferentiated Neuroblastoma

**PHOX2B**

- PHOX2B: a transcription factor for peripheral autonomic nervous system.
- Mutated in Ondine’s curse
  - neuroblastoma, sleep apnea, and Hirschsprung’s disease
- Expressed by neuroblastoma, paraganglioma, and pheochromocytoma.
- Universally expressed in small series of undifferentiated neuroblastomas in one study (6/6) and in no “neuroblastoma-like undifferentiated sarcoma”
- Negative in panel of 109 other tumors (8 diagnoses).
Ondine, a water nymph with an unfaithful mortal lover

“Every waking breath will be a testament to my love”

The curse: stop breathing when asleep.
Undifferentiated NBL

• Nucleolar type, associated findings:
  – N-myc expression - associated with *MYCN* amplification
  – C-myc expression - associated with lack of amplification
  – May not show MYCN amplification
  – Outcome not affected by other factors (MKI, age, ploidy, etc), [caveat: usually high stage lesions]
**BRD4-NUT carcinoma**

- Predominately affects young patients, but wide age range
- Usually involves midline structures: upper respiratory tract, mediastinum
- Characterized by t(15;19)(q13;p13.1) translocation
- Almost invariably fatal course
**BRD4-NUT carcinoma**

- Resembles small cell carcinoma.
- May not show obvious epithelial differentiation on H and E stain, but should be cytokeratin-positive (as are 15% of Ewing sarcoma).
- Squamous differentiation is often abrupt.
Undifferentiated *BRD4-NUT* carcinoma

Courtesy of Sara Vargas, MD, Boston Children’s Hospital
Differentiating *BRD4-NUT* carcinoma

Courtesy of Sara Vargas, MD, Boston Children’s Hospital
BRD4-NUT carcinoma: cytokeratin
BRD4-NUT carcinoma NUT stain

Courtesy of Sara Vargas, MD, Boston Children’s Hospital
Pediatric epithelial/epithelioid malignancies to also consider:

- EBV-associated carcinoma (nasopharyngeal carcinoma)
- Mucoepidermoid carcinoma
- Keratin-positive sarcomas, such as rhabdoid tumor and epithelioid sarcoma
- Poorly differentiated germ cell tumor, e.g. embryonal carcinoma, yolk sac tumors
- Location, location, location!
Extrarenal rhabdoid tumor

- Wide variety of primary sites, including soft tissue and skin
- Primarily affects infants and younger children, with overlap with epithelioid sarcoma in older ones
- Diverse histologies, including “lymphomatoid” pattern described by Weeks and Beckwith.
Rhabdoid tumor - typical histology
Rhabdoid tumor, lymphomatoid
INI1 stain: lack of expression
Tumors lacking INI1 expression

- Rhabdoid tumor
- Epithelioid sarcoma
- Renal medullary carcinoma
- Extraskeletal myxoid chondrosarcoma
- Epithelioid MPNST

- Myoepithelial carcinoma
- Small cell hepatoblastoma
- Poorly differentiated chordoma
- Synovial sarcomas
Other Ewing-like tumors of bone

- Mesenchymal chondrosarcoma
- Small cell osteosarcoma
Mesenchymal chondrosarcoma: clinical

- Most common form of chondrosarcoma in children
- Occurs in unusual locations:
  - Craniofacial bones, chest wall, spine, sacrum
- Extraosseous locations:
  - Meninges included
- Highly malignant
  - Prolonged course with late metastases (survival 21-67%)
Mesenchymal chondrosarcoma: pathology

- Biphasic appearance
  - Undifferentiated small blue cells or spindle cells
  - Well-differentiated cartilage
- Other features:
  - Hemangiopericytoma appearance
  - Foci of chondroid ossification
  - Myxoid zones
Mesenchymal chondrosarcoma: small cell component
Mesenchymal chondrosarcoma: spindle cell component
Mesenchymal chondrosarcoma: HPC pattern
Mesenchymal chondrosarcoma: cartilage with ossification
Mesenchymal chondrosarcoma: myxoid focus
Mesenchymal chondrosarcoma: IHC

- **Sox9**: positive in round cells and chondrocytes
- β-catenin: negative in round cells, positive at cartilage interface
- Osteocalcin: negative in round cells, positive in bony matrix
- **S100**: positive in only occasional cases in round cells; usually positive in cartilage
- EMA (30%) and desmin (50%) can be positive
- FLI1 negative; CD99 can be positive
Sox9 (Nine Socks): the product of the SRY gene
SRY gene: androgen insensitivity

http://en.wikipedia.org/wiki/File:Orchids01.JPG
Mesenchymal chondrosarcoma genetics

- **HEY1-NCOA2** fusion gene
- Identified by genome wide screen using known cancer genes
- Results from submicroscopic 10 Mb interstitial deletion between 8q13 and 8q21.
- Detected in 15 of 16 cases by fusion FISH (not break-apart FISH).
Hay (Hey1) and Non Commissioned Officer (NCOA2)

1 bale of “hey”

NCO[A2]
Small cell osteosarcoma

- A rare form of osteosarcoma (<2%)
- Small blue cell tumors with osteoid production
- Usually in long bones, second decade
- May have worse prognosis than other osteosarcomas,
  - But too few cases to be sure.
Small cell osteosarcoma: imaging

- Intramedullary, permeative lesion
- Ill-defined margins
- Cortical destruction
- Aggressive periosteal reaction
- Soft tissue mass
Small cell osteosarcoma: histology

- Small blue cells with hyperchromatic nuclei
- Similar to Ewing sarcoma
- At least focal osteoid production
- Osteoid must be separated from non-osteoidal matrix
- Tumor spindling may be present (also seen in some Ewings)
- CD99 MAY be negative (but also positive)
Osteoid: think of bubble gum
The problem

- Minimal amounts of osteoid
- Overlap with sclerosing Ewing sarcoma (atypical Ewing).
Sclerosing Ewing sarcoma
Synovial sarcoma: a mimicker of Ewing sarcoma
Synovial sarcoma

- Peak incidence in young adults, but most common non-rhabdomyosarcoma of soft tissue.
- Mainly in extremities, but has propensity to occur in odd locations (including nerve).
- Ranges from intermediate to high grade (mitoses, necrosis are key factors).
- Monophasic variants often confused with Ewing sarcoma.
Monophasic variant of synovial sarcoma
Synovial sarcoma IHC

- Epithelial markers (cytokeratin, EMA): usually but not always positive
- CD99: usually positive, furthering confusion
- BCL2: sensitive but non-specific
- TLE1: a “surrogate” fusion marker: typically positive
  - Specificity has been questioned.
- Reduced INI1 expression (not mutation)
Genetics of synovial sarcoma: SSX-SS18 fusion
t(X;18): Freshman co-ed
SSX genes

- SSX1
- SSX2
- SSX4
- Not predictive of outcome
- Have been linked to histology
Colorado Street Bridge, Pasadena, CA
SSX-SS18 fusion protein: a molecular bridge to badness

- SS18-SSX serves as a bridge between activating transcription factor 2 (ATF2) and transducin-like enhancer of split 1 (TLE1).
- TLE1 attaches to histone deacetylase complex (HDAC), resulting in altered epigenetics.
- Results in repression of ATF2 target genes.
- HDAC inhibitors rescues target gene expression, leading to growth sup
Deconstruction of the SS18-SSX Fusion Oncoprotein Complex: Insights into Disease Etiology and Therapeutics


http://dx.doi.org/10.1016/j.ccr.2012.01.010
An Illustrative case of Synovial sarcoma treachery
Courtesy of Zhongxin Yu, MD
University of Oklahoma

- 14 years old with left hip pathological fracture
CD99: negative
INI-1: negative (occasional positive)
Vimentin: negative
Other IHC

- Lymphoma markers: negative
  - (CD3, CD5, CD20, CD43, CD79a, PAX5, TdT, CD117, CD34)
- Myeloperoxidase: weakly positive, focal
- Myogenin and desmin: negative
- S-100: negative
- NSE and synaptophysin: negative
- CD68, CD163: negative
- EMA and pan-cytokeratin: negative
Preliminary Diagnosis

• Small round blue cell tumor of the bone
  – ? Ewing’s sarcoma
    • Pending EWS FISH result
  – ? Ewing’s - like small cell osteosarcoma
    • Pending FISH to rule out Ewing’s sarcoma
    • ?rebiopsy to get more tissue with osteoid
Final diagnosis

- FISH is negative for *EWSR1* rearrangement
- FISH is positive for *SYT(SS18)* rearrangement
- Final diagnosis—Synovial sarcoma
Post-therapy