ARROCase: Neuroblastoma

Resident: Clayton B. Hess, MD (Radiation Oncology)
Staff: Ruben C. Fragoso, MD, PhD ( Radiation Oncology)
Jonathon M. Ducore, MD, MPH (Pediatric Oncology)
Regina F. Gandour-Edwards, MD (Pathology)
Cameron Foster, MD (Nuclear Medicine)

University of California Davis Comprehensive Cancer Center
Outline

• Case Presentation
• Overview
• Etiology
• Epidemiology/Presentation
• Work-up
• Risk Stratification
• General Management
  – Low Risk
  – Intermediate Risk
  – High Risk
• Radiation Treatment Planning
Case Presentation

• CC: left eye swelling x 1 week
• HPI: 2 year old girl; concerns for child abuse
• PMH: unremarkable
• SH: Foster care
• Physical Exam:
  – Palpable soft tissue mass in lateral aspect of left orbit with fullness of upper lid. Significant (6-8mm) proptosis/exophthalmos of left globe. Some restriction in upward gaze in left eye. Full motility in right eye. Fixes and follows with each eye. No pupillary defects.
Work up

• Head CT
  – Soft tissue mass in the left periorbital region with intracranial extension, adjacent small subdural hematomas in left frontal and temporal lobes.

• Bone Survey (due to concern for trauma/child abuse)
  – Indistinct irregular left orbital roof and frontal bone, concerning for focal bony lesion.
  – No other abnormalities
Work up

- MRI of brain and orbit
  - Enhancing lesion of the left sphenoid with intraorbital, left lateral extraorbital, transphenoidal, and intracranial components.
  - Findings concerning for neuroblatoma vs. rhabdomyosarcoma
Work up

CT of the chest, abdomen, and pelvis showed no evidence of metastatic disease.

MIBG* Scan: shown left, only minimal radiotracer activity is noted in the left orbit corresponding to the left orbital mass seen on MRI.

* MIBG = I-123 metaiodobenzylguanidine
Work up

- Bone Scan: Increased tracer activity in left sphenoid sinus and left lateral orbit
- No evidence for distant osseous metastases
Work up

• Urine catecholamines:
  – VMA-to-creatinine ratio: 28 mg/g (elevated)
  – HVA-to-creatinine ratio: 20 mg/g (within normal limit)

• Bone marrow biopsy (BMB)
  – 50% clusters of foreign cells
  – CONSISTENT WITH METASTATIC NEUROBLASTOMA
Work up

• Excisional biopsy with orbitotomy.

• Pathology:
  – Unfavorable histology
  – Poorly differentiated subtype
  – MYCN oncogene was not amplified by FISH
  – Mitotic-Karyorrhexis Index (MKI) < 100
  – Invading into adjacent skeletal muscle, no necrosis, no calcifications, no ganglion cells
  – 46XX
Treatment

• Induction Chemo (per COG ANBL00P1)
  C1: cisplatin/etoposide
  • Residual disease on BMB
  C2-5: Vin/cisplatin/doxo/mesna/cyclophos/carbo/ifos
  • Residual disease on BMB b/w cycles 4 and 5
• Orbitozygomatic craniotomy with resection of orbital roof, sphenoid bone, tumor involving orbit and temporalis muscle
  – Intra-operative: Extending through peri-orbita, frontal bone, orbit, zygoma, sphenoid bone, maxillary bone and temporalis muscle.
  – Gross Total Resection
  – Final Pathology: Residual neuroblastoma with bone invasion
• Post-op consolidative RT (next slide)
• Six cycles of Accutane (isotretinoin)
• Autologous stem cell transplant
  – Preparative regimen: Melphalan/etoposide/carbo (no TBI)
Post-op Consolidative RT

- 2160 cGy in 180s to primary site with 2cm margin
- Four-field, 3DCRT
- Mixed energies, 6 and 15 MV
- MLC and dynamic wedge to improve dose homogeneity
Post-op Consolidative RT

STRUCTURES (Right to left on 1.0 line)
- Left Optic Nerve
- Optic Chiasm
- Left Middle Ear
- Left Inner Ear
- Left Lens
- Left Eye
- Right Eye
- Brainstem
- Left Temporal Lobe
- Right Optic Nerve
- Right Lens
- Right Inner Ear
- Right Middle Ear
- Right Temporal Lobe
- Brain
- Cord
Case Summary

- 2 year old girl with IPSS high-risk, unfavorable histology, NMYC non-amplified, orbital neuroblastoma (versus unknown primary with orbital rim metastasis), stage 4 by virtue of extensive marrow involvement.
- Treated in 4 phases
  1. Intensive induction chemotherapy
  2. Local therapy: surgical resection of the primary followed by consolidative orbital radiation
  3. Adjuvant cis-RA
  4. Autologous stem cell transplant
- 3 years later she remains without evidence of disease
- Treatment side effects
  - Growth delay (requiring supplemental growth hormone)
  - Bilateral sensorineural hearing loss
  - Headaches of unclear etiology
Overview

- Neuroblastoma is an enigmatic pediatric malignancy
- Early stages can be cured with surgery alone; some cases spontaneously regress or even mature to a benign ganglioneuroma
- Advanced stage disease is more common and may be fatal
Etiology

• Fetal adrenergic neuroblasts of neural crest tissues
• May arise from any site in the sympathetic nervous system
• Most common sites of origin:
  – Adrenal medulla (30-40%)
  – Paraspinal ganglia in abdomen or pelvis (25%)
  – Thoracic (15%)
  – Head and neck (5%)
Epidemiology

• Most common extra-cranial solid pediatric tumor
• Most common malignancy of infancy
• Median age: 17 months
• 75% < 2 years; 90% < 5 years
Presentation

• 60% are metastatic at presentation with mets mostly to bone, liver, skin
• Pain is most common presenting symptom
• Symptoms depend on location; paraneoplastic syndromes not uncommon
  – Cord compression (so-called “dumbbell shaped tumor”)
  – Catecholamine-induced HTN or diarrhea (Kerner-Morrison syndrome)
  – Cervical sympathetic involvement with Horner’s syndrome (ptosis, miosis, anhidrosis)
  – Orbital rim mets (Racoon eyes)
  – Skin mets (Blueberry muffin sign)
  – Random eye muscle jerks due to anti-neural antibodies (Opsoclonus-myoclonus syndrome)
  – Hepatomegaly from liver mets (Pepper syndrome)
  – Limping due to bone metastases (Hutchinson syndrome)
Screening is not recommended

• Urinary catecholamine screening
  – Results in overdiagnosis and false positives
  – No improvement in overall survival
  – Screening only identifies tumors likely to spontaneously regress anyway.
Work up

• Labs
  – Urine catecholamines (VMA, HVA)

• Imaging
  – Abdominal ultrasound
  – CT/MRI (calcification on imaging is a favorable sign)
  – Bone Scan
  – MIBG scan

• Bilateral bone marrow biopsy
I-123 MIBG Scan

- MIBG (metaiodobenzylguanidine) is a derivative of norepinephrine and epinephrine that is concentrated in secretory granules of both normal and neoplastic neural crest.
- It is labeled with radioactive iodine (I-123 metaiodobenzylguanidine) and administered to assess for metastases.
- MIBG scan sensitivity and specificity are both ~ 90%. Cannot distinguish between cortical bone involvement and marrow involvement; bone scan is still recommended for standard workup.
- Normal activity in adrenal medulla.
- Activity in ectopic neuroendocrine tumors: Pheochromocytoma, Neuroblastoma, Carcinoid, Medullary thyroid carcinoma, Paraganglioma.
- Biodistribution: liver (diffuse homogeneous), spleen, kidney (primary route of elimination), heart, salivary glands, and to a lesser extent bowel and lung.
Histology

• A small round blue cell tumor
  – Other small round blue cell tumors: lymphoma, Ewings/PNET, rhabdomyosarcoma, medulloblastoma, and retinoblastoma
• Homer-Wright Pseudo-Rosettes
• Stains for NSE or synaptophysin
Prognostic Factors

• Age and stage at initial presentation remain two most important factors that influence outcome.

• Risk Groups
  – Two systems for determining Risk Group are available:
    • Children’s Oncology Group (COG) (most commonly used)
    • International Neuroblastoma Risk Group (INRG)
  – Both take into account the following prognostic factors:
    • Pathology
    • Biology
    • Stage
    • Age
Prognostic Factors

• **Pathology**
  – Shimada system (old)
  – International Neuroblastoma Pathology Committee (new, updated Shimada)

• **Biology**
  – MYCN gene (most prognostic)
  – 1p and 11q deletion
  – 17q gains
  – DNA ploidy

• **Staging**
  – Multiple older surgical staging systems have fallen out of favor
  – Current (1993) Post-op INSS: Stages 1, 2A, 2B, 3, 4, 4S
  – Pre-op INRG: Stages L1, L2, M, MS

• **Age**
  – <18 mo = favorable
  – > 5 years = unfavorable
Pathology

International Neuroblastoma Pathology Committee System (1999, i.e. revised Shimada)

• **NEUROBLASTOMA**
  - Favorable
    - < 1.5 years
      - intermediate differentiation OR
      - poor differentiation and low/intermediate MKI (mitosis-karyorrhexis index = # mitoses/5,000 cells)
    - 1.5 – 5 years
      - well differentiated with low MKI
  - Unfavorable
    - <1.5 years
      - poor differentiation and high MKI
    - 1.5 – 5 years
      - poor differentiation OR
      - intermediate or high MKI
    - > 5 years

• **GANGLIONEUROBLASTOMA** – favorable if no nodular component

• **GANGLIONEUROMA** – favorable if no nodular component
Biology

- **N-MYC (MYCN) amplification**
  - Occurs in 30-40% of advanced stage NB
  - Portends unfavorable outcome, even in disease settings that would otherwise be favorable

- **Chromosomal deletions 1p (23%) and 11q (35%)**
  - Both associated with worse prognosis

- **Chromosomal gains in 17q (around 50%)**
  - Most common genetic alteration in NB; occurs in 50% of cases
  - Associated with worse prognosis

- **DNA ploidy**
  - Hyperdiploid outcomes superior to diploid
  - Ploidy is an important discriminator of response to chemo
Neuroblastoma Staging Systems

• Most commonly used system is the International Neuroblastoma Staging System (INSS) based on clinical, radiographic, and surgical findings.

• Others staging systems include:
  – Evans and D’Angio (1971)
  – St. Jude/Pediatric Oncology Group (POG)
Current INSS Surgical Staging (1993)

Stage 1: Localized
   Complete resection +/- microscopic residual, LN negative

Stage 2A: Localized
   Incomplete gross resection, LN negative

Stage 2B:
   +/- complete resection, regional LN positive

Stage 3:
   Unresectable unilateral tumor, crosses midline +/- regional LN
   OR localized with contralateral LN positive
   OR midline tumor with bilateral extension or LN positive

Stage 4:
   Distant LN positive OR non-stage 4S distant mets

Stage 4S:
   Stage 1, 2A, 2B < 1 year of age with mets limited to skin, liver, marrow (cells <10% of total nucleated cells)
Pre-op Staging

• Used in INRG risk group definitions
  – L1: localized, not involving vital structures
  – L2: locoregional with one or more image-defined risk factors (e.g. encasement of vasculature)
  – M: distant mets (not stage MS)
  – MS: mets AND age < 18 months with mets to skin, liver, and bone marrow only (<10% involvement)
COG Risk Groups (uses INSS surgical staging)

- **Low Risk (12 yr OS > 90%)**
  - Any path, any bio, INSS stage 1, any age
  - Any path, non-amplified MYCN, INSS stage 2A/2B, any age
  - Favorable path, hyperdiploidy & non-amplified MYCN, INSS stage 4S, < 12 months
- **Intermediate Risk (12 yr OS > 80%)**
  - Any path, non-amplified MYCN, INSS stage 3, and < 18 mo
  - Favorable path, non-amplified MYCN, INSS stage 3, and > 18 mo
  - Any path, non-amplified MYCN, INSS stage 4, and < 18 mo
  - Favorable path, diploid AND non-amplified MYCN, INSS stage 4S, and < 12 mo
  - Unfavorable path, non-amplified MYCN, INSS stage 4S, and < 12 mo
- **High Risk (12 yr OS 30-40%)**
  - Unfavorable path, non-amplified MYCN, INSS stage 3, and > 18 mo
  - Any path, MYCN amplified, stage 2A-4S and any age.
General Management

• Low Risk (4 yr OS 99%)
  – Surgery alone; RT reserved for residual/recurrent disease

• Intermediate Risk (3 yr OS 75-98%)
  – Resectable: surgery +/- chemo
  – Unresectable: neoadjuvant chemo → surgery
  – Role of RT controversial in intermediate risk disease
General Management

• High risk (10 yr OS 59%)
  – Four phases
    • Induction chemotherapy
    • Maximal surgical resection and management of residual disease with consolidative RT to primary and metastatic sites of disease
      – Improvement in local control with RT: 21-81% vs. 10-52%
      – Typical doses: 12 – 37.5 Gy (21 Gy standard, higher for gross residual tumor may be beneficial)
    • Cis-retinoic acid (cis-RA)
    • Autologous bone marrow transplant
## General Management

### SUMMARY

<table>
<thead>
<tr>
<th>Risk group</th>
<th>management</th>
<th>5Yr EFS</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>surgery alone</td>
<td>&gt; 90%</td>
<td>Chemo: 6-12 weeks</td>
</tr>
<tr>
<td>1) resected +/- microscopic residual</td>
<td>surgery alone</td>
<td>&gt; 90%</td>
<td>Carbo VP 16 alternate with Carbo CP/Dox</td>
</tr>
<tr>
<td>2) unresectable or STR or Recurrence</td>
<td>chemo → surgery</td>
<td>60 – 90%</td>
<td>Carbo CP/Dox</td>
</tr>
<tr>
<td>3) symptomatic (Cord comp, resp distress)</td>
<td>immediate chemo → surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4) If no resp to Chemo</td>
<td>RT 21 Gy/1.5 Gy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>Resection/LND → chemo +/- RT</td>
<td>90% FH</td>
<td>Chemo: 12–24 weeks</td>
</tr>
<tr>
<td>1) Resectable</td>
<td>Chemo→2nd look surgery +/- RT</td>
<td>50 – 80% UH</td>
<td>Carbo VP 16 alternate with Carbo CP/Dox</td>
</tr>
<tr>
<td>2) Unresectable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Risk</td>
<td>Dose Intensive CT → surgery → +/- TBI+ABMT → RT 21.6/1.8 → cisRA for 6 m</td>
<td>30-50%</td>
<td>Chemo: Add Ifosfamide and CDDP</td>
</tr>
<tr>
<td>Stage 4S with respir distress</td>
<td>Supportive RT 4.5 Gy/1.5 Gy</td>
<td>75-90%</td>
<td></td>
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Contribution from Baoqing Li, MD, PhD
Weill Cornell Medical College, NY, NY
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Indications for RT in Neuroblastoma

• No role for RT in low risk disease
• RT is controversial in intermediate risk disease
• RT to primary site in high risk, residual, or recurrent NB
• RT for hepatomegaly in 4S disease or palliation of other mets
RT for Hepatomegaly

- Liver irradiation for symptomatic stage 4S disease
- Dose: 450-600cGy in 2-4 fractions (450cGy in 3 fractions)
- Volume: opposed lateral fields to avoid renal and ovarian exposure
- Borders
  - Anterior: 2 cm anterior to liver
  - Posterior: anterior vertebral body
  - Superior: 2 cm superior to liver
  - Inferior: superior iliac crest to avoid ovarian exposure
RT to primary site or residual MIBG-positive metastatic site

- Most abdominal and pelvic sites are best treated with AP fields
- Dose: 21.6 Gy in 1.8 Gy daily fractions
- If entire peritoneum needs to be irradiated, dose should be < 15 Gy
- If major portion of both lungs are irradiated, dose should be < 15 Gy
- GTV
  - primary tumor volume = pre-surgery CT/MIBG scans
  - Bone met site = volume positive on MIBG/bone scan after induction chemo
- PTV = GTV + 2cm
- Dose constraints:
  - Liver: < 50% to receive 9 Gy and < 25% to receive > 18 Gy
  - Contralateral kidney: < 50% to receive > 8 Gy and < 20% to receive > 12 Gy

2. Berthold, Lancet Oncology 2005 GERMAN NB97


4. Children’s Cancer Study Group (CCSG);1971 (Evans, 1971, PMID 5100400; Evans, 1980, PMID 7370930)


14. POG 8104 (Castleberry. JCO 10:1299. 1992). Infants with Neuroblastoma and regional lymph node metastases have a favorable outlook after limited postoperative chemotherapy: a Pediatric Oncology Group study

15. POG 8104 (Nitschke. JCO 6:1271. 1988)

16. POG 8104 (Strother et al, J Ped Hem Oncol 1995; 17: 254-259)

17. POG 8742/9244 (Strother. Euro J Cancer 12:2121. 1997) Event-free Survival of children with biologically favorable neuroblastoma based on the degree of initial tumor resection: Results from the Pediatric Oncology Group


