Oncologic Issues in the Neonate

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Baby with bumps

You are asked to evaluate a baby in NICU 3 who does not seem right to the nurse in the unit. Baby’s tone is decreased and has brachcephaly. Baby also has hepatosplenomegaly. ...
Blood work

- WBC 55,000, HGB 7, Plt 117 with 80% blasts.
Questions?

1. What is the diagnosis?
2. What is the prognosis?
3. What are these patients at risk for in the future?
Transient Myeloproliferative Disorder of the Neonate

• Associated with Down Syndrome
• Some babies are mosaic’s with subtle phenotypes
• Morphologic features are consistent with congenital leukemia
• Spontaneous remission occurs
Complications

- Respiratory complications from massive hepatomegaly
- Hyperleukocytosis leading to poor tissue perfusion
- Hepatic fibrosis can lead to liver failure
- 20-30 % of patients go on to develop acute myeloid leukemia later in life
Pathophysiology

• Invariably due to mutations of the GATA1 gene.
• Lead to truncated GATA1 isoform that functions as dominant negative inhibiting GATA1’s effect on megakaryocyte differentiation
• GATA1 mutations are rarely found in patients who don’t have down syndrome
• Additional mutations necessary for patients with TMD to develop acute myeloid leukemia
Treatment

- We have an open biologic study here
- Most patients do not need treatment
- Chemotherapy given to patients with WBC >100,000 massive hepatosplenomegaly, hydrops, pleural effusions, pericardial effusions, ascites, or life threatening liver disease
- Chemotherapy is very mild and typically short course (cytarabine)
This baby has a big spleen!

You are called to assess a baby who has a webbed neck and as you assess the baby you note pectus excavatum. 4 extremity blood pressures suggest a coarctation of the aorta. Baby has an enormous spleen which is rock hard and palpable in the pelvis.
Peripheral blood counts

CBC  WBC 77,000, platelets 149,000, HGB 11
Smear: 10% monos, 60% polys, 8% metamyelocytes, 5% promyelocytes, 5% eosinophils
Juvenile Myelomonocytic Leukemia

- Associated with neurofibromatosis, Noonan’s syndrome
- Present with pallor, infection, bleeding, or symptoms from organomegaly
- Elevated WBC with absolute monocytosis usually present
- Maculopapular skin rash common
JMMML-Like Picture and Noonan’s Syndrome

- Seen in up to 10% of babies with Noonan’s syndrome
- Diagnosed during first few months of life (in contrast to patients with JMMML median age 1.8 years)
- Spontaneous regression usually occurs, but can progress to fatal disease
- Associated with PTEN and RAS mutations
A big honkin’ liver

- You are asked to evaluate a term newborn who has an enormous liver mass.
- Baby having difficulty breathing and is intubated
Neuroblastoma

- Can arise at any site along the sympathetic chain
- Most tumors arise in abdomen, often the adrenal
- Primary can’t be found in 1% of cases
- Massive involvement of liver causing respiratory compromise is common in infants with Stage IV-S disease
Diagnosis
NEUROBLASTOMA STAGING SYSTEM

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (nodes attached to and removed with the primary tumor may be positive).</td>
</tr>
<tr>
<td>Stage 2A</td>
<td>Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically.</td>
</tr>
<tr>
<td>Stage 2B</td>
<td>Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor. Enlarged contralateral lymph nodes must be negative microscopically.</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Unresectable unilateral tumor infiltrating across the midline, with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement.</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs (except as defined for stage 4S).</td>
</tr>
<tr>
<td>Stage 4S</td>
<td>Localized primary tumor (as defined for stage 1, 2A, or 2B), with dissemination limited to skin, liver, and/or bone marrow (limited to infants, 1 year of age).</td>
</tr>
</tbody>
</table>

Note: Multifocal primary tumors (e.g., bilateral adrenal primary tumors) should be staged according to the greatest extent of disease, as defined previously, followed by a subscript “M” (e.g., $3_M$).

The midline is defined as the vertebral column. Tumors originating on one side and “crossing the midline” must infiltrate to or beyond the opposite side of the vertebral column.

Marrow involvement in stage 4S should be minimal, that is, less than 10% of total nucleated cells identified as malignant on bone marrow biopsy or on marrow aspirate. More extensive marrow involvement would be considered to be stage 4. The MIBG scan (if done) should be negative in the marrow.

Prognosis

• Age less than 18 months—better prognosis

• Histology

• N Myc amplification Stage

• 4S disease has good prognosis, even without therapy
Stage IV S Neuroblastoma

• Symptomatic patients need emergent medical intervention
• Safe biopsy
• Myc status (N-Myc amplified get therapy)
• Patients who are asymptomatic can be observed closely—until 3 months
Our patient

- Received emergent radiation therapy
- Next morning patient is anuric
- Creatinine > 2.0

What do you think happened?
Tumor Lysis Syndrome

- Result of release of nuclear and cytoplasmic degradation products
- Potassium, principle intracellular cation, increases and can be worsened by renal insufficiency.
- Uric acid comes from breakdown of nucleic acids
- Crystals precipitate in collecting ducts of renal tubules
- Phosphate and calcium crystalize causing secondary hypocalcemia
Treatment of Tumor Lysis Syndrome

• Hydration (at least 1.5 X maintenance)
• Alkalinization no longer standard of care due to concern about calcium and phosphate precipitation.
• Allopurinol
• Rasburicase
Sacroccocygeal mass in newborn
Sacrococcygeal Teratoma in Newborn

- Most common germ cell tumor of childhood
- Most frequently recognized neoplasms in fetuses and neonates
- 75% of patients are females
- Most are exophytic and visible on exam
- 80% diagnosed within first month of life
- One in five have malignant component
Sacroccocygeal Teratoma Treatment

• If detected on Ultrasound, growth velocity should be observed
• If threatens fetal survival, premature delivery warranted
• Early and complete excision mainstay of management
• Half of recurrences associated with malignant yolk sac component
• Most important risk factor incomplete resection
Neonate with multiple congenital anomalies

Baby is born with anal atresia, VSD, a tracheo-esophageal fistula, a renal anomaly, and malformed thumbs.

1. What classic pediatric blood disorder might this patient have?
2. How do you work this up?
Fanconi’s Anemia

- First coined to describe familial aplastic anemia and physical anomalies
- Now known that patients who appear to be normal can have the disorder.
- For diagnosis, necessary to have chromosomal breaks with clastogenic stress
- Mean age of diagnosis 8 years
Fanconi Anemia Age Distribution
Fanconi’s Anemia: Physical Examination

- Classic Fanconi’s: short stature, thumb abnormalities, café au lait and hypopigmented spots, characteristic facial features
- In Thromocytopenia absent radii (TAR) syndrome, radii absent but thumbs present, whereas thumbs abnormal in FA
- The VACTERL-H association (Vertebral anomalies, anal atresia, cardiac defect, tracheoesophageal fistula, renal defects, limb anomalies, hydrocephalus) should make you think of Fanconi’s
- At least 25% of FA patients do not have physical anomalies
Fanconi Anemia Anomalies

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>All Patients</th>
<th>Male</th>
<th>Female</th>
<th>≤1 yr</th>
<th>≥16 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (%)</td>
<td>1206</td>
<td>631</td>
<td>534</td>
<td>43</td>
<td>104</td>
</tr>
<tr>
<td>Skin pigment and/or café au lait</td>
<td>55%</td>
<td>57%</td>
<td>55%</td>
<td>37%</td>
<td>61%</td>
</tr>
<tr>
<td>Short stature</td>
<td>51%</td>
<td>54%</td>
<td>53%</td>
<td>47%</td>
<td>57%</td>
</tr>
<tr>
<td>Upper limbs</td>
<td>43%</td>
<td>46%</td>
<td>43%</td>
<td>63%</td>
<td>39%</td>
</tr>
<tr>
<td>Abnormal gonads, male</td>
<td>—</td>
<td>32%</td>
<td>—</td>
<td>37%</td>
<td>44%</td>
</tr>
<tr>
<td>Abnormal gonads, female</td>
<td>—</td>
<td>3%</td>
<td>—</td>
<td>50%</td>
<td>6%</td>
</tr>
<tr>
<td>Head</td>
<td>26%</td>
<td>27%</td>
<td>28%</td>
<td>37%</td>
<td>18%</td>
</tr>
<tr>
<td>Eyes</td>
<td>23%</td>
<td>25%</td>
<td>23%</td>
<td>33%</td>
<td>24%</td>
</tr>
<tr>
<td>Renal</td>
<td>21%</td>
<td>24%</td>
<td>19%</td>
<td>42%</td>
<td>19%</td>
</tr>
<tr>
<td>Birth weight ≤ 2500 g</td>
<td>11%</td>
<td>11%</td>
<td>12%</td>
<td>47%</td>
<td>8%</td>
</tr>
<tr>
<td>Developmental disability</td>
<td>11%</td>
<td>12%</td>
<td>12%</td>
<td>5%</td>
<td>8%</td>
</tr>
<tr>
<td>Ears, hearing</td>
<td>9%</td>
<td>11%</td>
<td>8%</td>
<td>23%</td>
<td>11%</td>
</tr>
<tr>
<td>Legs</td>
<td>8%</td>
<td>9%</td>
<td>7%</td>
<td>16%</td>
<td>7%</td>
</tr>
<tr>
<td>Cardiopulmonary</td>
<td>6%</td>
<td>5%</td>
<td>8%</td>
<td>16%</td>
<td>5%</td>
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<tr>
<td>Gastrointestinal</td>
<td>5%</td>
<td>4%</td>
<td>5%</td>
<td>28%</td>
<td>6%</td>
</tr>
<tr>
<td>No anomalies</td>
<td>25%</td>
<td>21%</td>
<td>26%</td>
<td>16%</td>
<td>23%</td>
</tr>
<tr>
<td>Short stature and/or skin only</td>
<td>11%</td>
<td>13%</td>
<td>10%</td>
<td>5%</td>
<td>19%</td>
</tr>
</tbody>
</table>

*Data represent percentage of patients with the abnormality.*
Patients with FA have increased Sensitivity to clastogenic (cause DNA Breaks) agents such as mitomycin C and diepoxy butane (DEB)
Complementation Groups in Fanconi’s Anemia

Fusing cell lines from Individuals with FA rescued cells from clastogenic sensitivity
FA Genes are “Caretaker Genes”

Various FA genes encode proteins that form a complex. This Complex ubiquinates Fanc-D Which then interacts with BRCA1 in DNA damaged cells, Regulating DNA repair, apoptosis, And progression into cell cycle.
Result of Mutations

- Frequently develop aplastic anemia
- High rate of myelodysplasia
- High rate of AML
- High rate of liver tumors
- High rate of epithelial malignancies (head and neck cancers, cervical cancer, skin cancer)
Fanconi’s Anemia: Who to Evaluate

• Screening recommended for all children with aplastic anemia
• Any patient with unexplained macrocytosis and birth defect
• VACTERLH-like syndromes or structural defects of GU system
• Unusual sensitivity to chemotherapy