31st European Congress of Pathology
Congenital Tumours and Pseudo-tumours
Case 7

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Liverpool, UK
Case 7

• Intrauterine death diagnosed at 26 gw.

• Perinatal autopsy
Blueberry Muffin Syndrome

**Descriptive term**
An infant is born with multiple blue/purple marks or nodules in the skin.

**Pathogenesis:**
(i) Extramedullary erythropoiesis
(ii) Bleeding into the skin (purpura)
(iii) Disseminated malignancy
Blueberry muffin syndrome – Differential Diagnosis

**Haematological disorders such as:**
- Haemolytic disease of the new-born (rhesus or ABO incompatibility)
- Hereditary spherocytosis
- Twin-twin transfusion syndrome

**Vascular lesions**
- Multiple hemangiomas of infancy,
- Multifocal lymphangioendotheliomatosis
- Blue rubber bleb nevus syndrome
- Multiple Glomangiomas

**Congenital infections such as:**
- Rubella
- Cytomegalovirus
- Herpes simplex
- Coxsackie virus
- Parvovirus
- Epstein Barr virus
- Syphilis

**Tumours such as:**
- Congenital leukaemia cutis
- Langerhans cell histiocytosis
- Neuroblastoma
- Congenital rhabdomyosarcoma
- Ewing's
- BCOR rearranged Sarcoma
Lt Clavicular lesion

Expanded ribs
Skull (parietal bone) lesion

Dural lesion
Tumour morphology similar at all sites
Monotonous sheets of undifferentiated round blue cells
No evidence of Rhabdomyoblastic, Ganglionic, Schwannian, Epithelial differentiation
No Neuropil, chondroid, osteoid or significant myxoid or collagenous matrix
WIDESPREAD METASTASIS
Cancer cell traits like proliferation, survival, self-renewal and migration - the normal developmental programme.

Adult cancers require multitude of genetic and epigenetic changes to acquire these cancer characteristics.

Congenital and infantile tumours have low mutation burden.
PHOX2b - negative
Syneptophysin - negative
Tyrosine hydroxylase – negative
NB84- Negative

SNP array
NO evidence of MYCN amplification
NO segmental chromosome abnormalities (NO evidence of 1p loss, 11q loss or 17q gain)

Variant analysis of Alk
No known somatic activating variants identified.

No Phox 2b mutation
### IMMUNOHISTOCHEMISTRY

<table>
<thead>
<tr>
<th>Marker</th>
<th>Result</th>
<th>cf.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD99, NKX2.2,</td>
<td>Negative</td>
<td>Ewing's</td>
</tr>
<tr>
<td>MyoD1, Myogenin, Desmin</td>
<td>Negative</td>
<td>Rhabdomyosarcoma</td>
</tr>
<tr>
<td>TLE1, Bcl2, keratin</td>
<td>Negative</td>
<td>Synovial Sarcoma</td>
</tr>
<tr>
<td>CD45, CD20, CD3, MPO</td>
<td>Negative</td>
<td>Lymphoma /Leukaemia</td>
</tr>
<tr>
<td>SATB2</td>
<td>Negative</td>
<td>Small cell osteosarcoma</td>
</tr>
<tr>
<td>BCOR , Bcl6</td>
<td>Negative</td>
<td>BCOR rearranged sarcoma</td>
</tr>
<tr>
<td>WT1, (ETV4 Not done)</td>
<td>Negative</td>
<td>CIC-DUX sarcoma</td>
</tr>
<tr>
<td>WT1 and others</td>
<td>Negative</td>
<td>DSRCT</td>
</tr>
<tr>
<td>INI1</td>
<td>Positive (retained)</td>
<td>Rhabdoid tumour</td>
</tr>
<tr>
<td>ERG, CD34</td>
<td>Negative</td>
<td>vascular tumour</td>
</tr>
<tr>
<td>SOX10</td>
<td>Negative</td>
<td>Melanocytic tumours</td>
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<tr>
<td>Synaptophysin, NFP,CD56, Tyrosine hydroxylase , NB84</td>
<td>Negative</td>
<td></td>
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Undifferentiated Sarcoma

Vs

Undifferentiated Neuroblastoma
Neuroblastoma is made up of two population of cells:

- Adrenergic Type (ADRN)
- Mesenchymal type (MES)
Neuroblastoma is biphasic

<table>
<thead>
<tr>
<th>MES (Mesenchymal cells)</th>
<th>ADRN (Adrenergic cells)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recapitulate</td>
<td>more differentiated</td>
</tr>
<tr>
<td>migrating neural crest cells</td>
<td></td>
</tr>
<tr>
<td>Properties</td>
<td></td>
</tr>
<tr>
<td>Huge metastatic potential</td>
<td>No</td>
</tr>
<tr>
<td>Chemoresistant</td>
<td></td>
</tr>
<tr>
<td>Tumour progenitor /stem cell properties</td>
<td>No</td>
</tr>
<tr>
<td>IHC</td>
<td></td>
</tr>
<tr>
<td>PHOX2b, GATA3, HAND2 TH (Tyrosine hydroxylase) and DBH (Dopamine beta hydroxylase) NEGATIVE</td>
<td>PHOX2b, GATA3, HAND2 TH (Tyrosine hydroxylase) and DBH (Dopamine beta hydroxylase) POSITIVE</td>
</tr>
</tbody>
</table>
Adrenergic

Mesenchymal
Mesenchymal

Adrenergic

Mesenchymal
Mesenchymal

Adrenergic

Mesenchymal
Mesenchymal Adrenergic

Adrenergic
Mesenchymal
Mesenchymal

Adrenergic

Mesenchymal
Mesenchymal

Adrenergic

Mesenchymal
6/8 sections - Negative

2/8 sections – Focal positive
Placenta – Variable PHOX2b positivity
Diagnosis – **Undifferentiated Neuroblastoma**

Unusual predominance of MES type cells possibly due to early gestational age of the fetus.

Widespread metastasis could be explained by (i) MES phenotype and (ii) immunodeficient state at this early gestation.

No adverse molecular markers (myc amplification / segmental chromosomal abnormalities) ; Non tumour tissue microarray - normal

Not typical , but similar to 4s Neuroblastoma
Learning points- conceptual

• Congenital tumours are kind of developmental disorder.

• There is intra-tumoral heterogeneity within undifferentiated Neuroblastoma with variable composition of mesenchymal (MES) and adrenergic (ADRN)cells.
Learning points- possible practical implications

• Occasional Neuroblastoma may be negative for PHOX2b and other conventional Neuroblastoma markers particularly on a needle core biopsy.

• MES cells can survive classical therapy and over time seed relapse. Current bone marrow assessment for residual disease using PHOX2b and other adrenergic markers may underestimate minimal residual disease.
Sorry for taking a circuitous route to the diagnosis!

THANK YOU.