Clinical Presentation

- 4 year old male infant
- 6 weeks of early morning vomiting and bilateral horizontal gaze palsy
- Birth history: born to 23 year old G1P0 mother @ 40 weeks by emergent C-section, no NICU stay
- Family history:
  - patient is one of two children; sister, healthy at 6 months of age
  - mother died of cancer at age 27 years (stomach, possibly other organs) 5 months prior to this presentation

Multifocal Tumor

Clinical Summary

- No resection attempted
- Diagnosis (clinical): infiltrative low grade glioma
- Treatment:
  - COG A9952 (Carboplatin and vincristine)
- 1 month:
  - Worsening nausea, vomiting and dizziness
  - MRI demonstrated increase in tumor size in both locations
  - Biopsy and shunt placement
Clinical Summary

- Revised Diagnosis (pathology): high grade astrocytoma
- Treatment modified:
  - Focal irradiation with temozolomide
  - MRI 1 month after completing treatment showed diffuse leptomeningeal enhancement and lumbar puncture positive for tumor
  - Treatment modified:
    - Head Start 1 (cisplatin, cyclophosphamide, etoposide and vincristine)
- Additional testing performed on tumor

Integrated Diagnosis @ CHLA Center for Personalized Medicine

Chromosomal Microarray

Chromosomal Microarray

Sanger Sequencing
**Chromosomal Microarray Report**

**RESULT**
Chromosomal microarray (CMA) analysis demonstrated an extensively complex pattern of chromosomal gains, as well as several single-copy regions of loss of heterozygosity, and three regions of chromosomal amplification. The key findings include:

- **Gains**:
  - Chromosome 5: gains on 5q33-q35 and 5q14-q13, indicating potential involvement in cancer-related processes.

- **Losses**:
  - Chromosome 17: losses on 17p13.1-p13.3 and 17q21-q22, consistent with tumor suppressor genes like TP53.

- **Amplifications**:

**INTERPRETATION**
The results support the diagnosis of a complex chromosomal rearrangement, consistent with a recent tumor sample.

**Clinical Summary**

- **Sequencing confirmed the presence of TP53 c.884C>T (p.R282W) mutation in blood**
- **Tumor progressed and DOD 8 months from initial diagnosis**
- **Autopsy was performed**

**Autopsy Pathology**

- **Tumor suppressor gene, maintenance of genomic stability "guardian of the genome"**
  - Cell cycle arrest (p21) to repair DNA
  - Activation of apoptosis

**Clinical Summary Family Members**

- **Sister**:
  - Sequencing confirmed the presence of the same TP53 c.884C>T (p.R282W) mutation
  - No evidence of disease (wbMRI)

- **Mother**:
  - 4 months after giving birth to patient’s younger sister presented with HA, nausea and vomiting
  - CT scan demonstrated lesions in brain, stomach, liver and lung
  - Gastric mass biopsy: moderate to poorly differentiated adenocarcinoma (initial diagnosis)
  - Lung mass biopsy and subsequent gastric mass resection

**Mother’s Pathology**
Mother’s Pathology

Clinical Summary Family Members

- Mother:
  - Final Dx: Metastatic gestational trophoblastic neoplasm, choriocarcinoma
  - Died of cardiopulmonary arrest while receiving cranial radiation
- Diagnosis?

TP53 Testing on Mother’s Tumor

Transmission of TP53 Germline Mutation From Male Carrier to Female Partner

Transmission of TP53 Germline Mutation From Male Carrier to Female Partner

- How often?
  - Gestational CC in 1/50,000 deliveries
  - French LFS cohort (415 TP53 mutation carriers)
    - 78 fathers w/ 213 pregnancies
    - 2 additional cases of gestational CC
  - Gestational CC occurs in ~1/100 of the deliveries in female partners of TP53 mutation carriers
  - 500-fold increased risk

This is the 4th case of CC in female partner of a TP53 mutation carrier.
Li Fraumeni Syndrome

Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study

88.8% in surveillance gr.
59.6% in non-surveillance gr.

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