Disclosures

• No relevant financial disclosures.
Clinical History

- 14 yo M with a h/o MDS s/p bone marrow transplant
- Significant family history for carcinoma and lymphoma
- Developmental delay
- Immunocompromised w/ recurrent infections
- GVHD
Radiology

T2 Coronal MRI

T2 Sagittal MRI
Gross & Microscopic
Differential Diagnosis & Discussion
Additional Autopsy Findings

• Full autopsy performed
  – Reticulated hyperpigmentation of the skin, absent nail beds, alopecia, testicular atrophy
  – Organizing and interstitial fibrosis, lung
  – L ventricular papillary muscle infarct
  – Mineralization, neocortex, basal ganglia, thalami, and leptomeningeal vessels

• Genetic Testing
  – Significantly shortened telomere lengths in blood
Dyskeratosis Congenita Hoyeraal-Hreidarsson Variant
Discussion

• Dyskeratosis Congenita is a disease characterized by shortened telomeres.
  - Clinical triad
    • Reticulated pigmentation of skin (poikiloderma)
    • Finger/toe nail dystrophy
    • Oral leukoplakia
  - Propensity to develop neoplastic disease particularly SCC and hematopoietic neoplasms.
  - Most patients experience severe immunodeficiency.

• Hoyeraal-Hreidarsson syndrome is a severe variant of DC characterized by cerebellar hypoplasia.

• Revesz syndrome shows exudative retinopathy and intracranial calcifications.

(Bakar et al., 2015)
Dyskeratosis Congenita - Telomeres

- Normally increased telomere activity is observed in tissues with rapid turnover (e.g., mucosa, nails, skin, hematopoietic stem cells)
- All known causative mutations affect function of telomerase activity/assembly, or in telomere integrity
- Maintenance of telomeres generally a neoplastic feature
  - Shortened telomeres may result in p53 involved cell arrest
  - Rarely, additional mutations result in chromosome instability
  - Cycles of chromosomal fusion/breakage -> tumorigenesis
• Most commonly due to X-linked recessive mutations in \textit{DKC1} gene resulting in single amino-acid substitution of dyskerin
  – Less common autosomal dominant and recessive forms
• Our patient found to have telomere lengths $<1^{\text{st}}$ percentile, but no specific identifiable mutation
• Variable age of onset
Key Points - Pathology

• DC is a clinical, radiological, pathological, and genetic diagnosis

• Cerebellar hypoplasia characteristic of HH
  – Hypoplasia of the granular layer *without* loss of Purkinje cells
    • Different from Ataxia-Telangiectasia and Myelocerebellar disorder
  – Additional NP findings
    • Reported cerebral calcifications, delayed myelination, hypoplasia of corpus callosum
References