**ROSAH Syndrome**

- **Recurrent nonbloody fever**
- **Splenomegaly**
- **Anhidrosis**
- **Mental retardation**
- **Diabetes mellitus**

**Clinical Findings**

- **Ocular:** Nearly all patients develop vision impairment
  - Earliest feature: decreased vision and optic nerve edema
  - Onset: 4-12 years
- **Episodic fevers and polyarthralgia**
- **Increased susceptibility to viral illnesses** especially URIs
- **Hematologic:** Chronic pancytopenia
- **Exacerbated by infections**

**Pathophysiology**

- **Same de novo variant in all families**
- **Locus evolutionarily conserved in most species**
- **ALPK1 encodes an alpha kinase protein** in all cells, preferentially expressed in:
  - Retinal pigment epithelium
  - Optic nerve tissue
  - Myoepithelial cells of sweat glands

**ALPK1 involved in:**

- Establishing cell polarity
- Mechanism of anhidrosis
- Centrosome and ciliary function
- Mechanism in other retinal dystrophies
- NF-kB inflammatory pathway
- Other ALPK1 variants linked to inflammatory bowel disease
- RBC cytoskeleton formation

**Differential Diagnosis**

- **Unifying diagnoses**
  - Mitochondrial disease
  - Inborn Error of Metabolism: Isolated methylmalonic acidemia
  - Fabry disease
  - Gaucher Disease Type I
  - Inflammatory process ex: Hemophagocytic lymphohistiocytosis

- **Organ System Based Diagnosis**
  - Ocular: Retinitis pigmentosa/Sorsby fundus dystrophy
  - Pancreatic: Splenic sequestration, dyskeratosis congenita, MDS, hemolytic anemia
  - Endocrine: Mature onset diabetes mellitus of the young
  - Renal: Secondary to DMII

**Whole Exome Sequence**

- **Spleen/Immune System:**
  - Splenomegaly, onset childhood to 2nd decade
  - Low-grade ocular inflammation resistant to steroid or immunosuppression
  - Initially abnormal cone function followed by loss of rod function
  - Severe visual dysfunction by third decade
  - 4/5 families had cataract development

**Splenic/Musculoskeletal:**

- Spleenomegaly

**Renal:**

- Mild renal dysfunction

**Skin/Musculoskeletal:**

- Anhidrosis and nail dystrophy

**Dental:** Peg shaped teeth, enamel defects and predisposition to dental caries

**Diabetes mellitus type I testing:**

- Unregulated insulin antibodies
- Negative islet cell antibodies
- Negative Glucotic acid deacetylase antibodies

**Phenocurator (not used as an aid to form the differential diagnosis)**

**Case Report**

**We report a case of a 58 year old man with disparate findings in multiple organ systems notably: anhidrosis, pancreatectomy, splenomegaly, renal impairment, juvenile onset blindness, periodic episodes of fever/malaise, numerous dental caries and diabetes mellitus type II (DMII). This patient had substantial workup without a definitive diagnosis over the course of his life including repeated bone marrow biopsies and CT scans.**

**Pathology:**

- First presented at 10 yoa with painless, bilateral vision loss that started in central visual fields. Initially attributed to uveitis 2/2 scarlet fever. S/P bilateral cataract removal.
- Fx: Thin brother with DMII
- **Esophageal:** Thin non dysorphic blind man BMI: 21.7 Height: 181 cm
- **Abdominal:** Splenomegaly
- **Ocular:** Neovascular fibrotic disease in macula and chronic swelling/compression of optic nerve

**Workup:**

- **Pancytopenia Testing:**
  - WBC: 1.7-2.8 (x10E12/L)
  - ANC: 900 to 2000 (cells/µL)
  - Hemoglobin: 15 g/dL
  - Platelets: 60-80 (x10E9/L)
  - Hemolytic anemia labs/peripheral smear:
    - Normal
    - Neutrophils: 20%
  - Bone Marrow Biopsy
    - Hypercellular with maturing trilineage hematopoiesis,
    - No evidence of dysplasia

**Previous Genetic Testing:**

- From Bone Marrow:
  - JAK2(V617F): negative
  - FISH negative for deletion 5q, monosomy 7, deletion 7q, trisomy 8, deletion 17p and deletion 20q
  - Karyotype: Normal 46 XY
  - MDS Gene Panel: Normal

**From Blood:**

- Inherited Histocompatibility Anemia Panel: Normal

**Diagnosis and Phenotypic Characterization of ROSAH Syndrome through Whole Exome Sequence and Segregation Analysis**

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**References**

