Case # 56
Peripheral blood smear from a dog

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Signalment and history

• 7 month old, male, intact, Afghan hound
• Prolonged lethargy and failure to gain weight since acquired from a breeder in Germany at 8 weeks old
• Diagnosed and treated at referring DVM:
  – Small intestinal bacterial overgrowth (↓B12, ↑folate)
  – Giardia and Coccidia
• 4 littermates
  – 1 euthanized due to failure of passive transfer
  – 1 diagnosed with megaesophagus and died
  – 1 in Korea with failure to gain weight
  – 1 in West Virginia with joint problems & failure to gain weight
On physical exam:

- T 100.6° F, P 140 bpm, R 132 brpm, CRT <2sec, no murmurs
- BCS 2/9
- Plantigrade stance in the hindlimbs
- Minor carpal and tarsal valgus deformities in all limbs

On radiograph

- No anatomical abnormality of hindlimbs

On chemistry

- No significant abnormalities
- Normal pre- and postprandial bile acid concentrations
- Endocrine tests are within normal limits
  - Insulin-like growth factor I/Thyroid panel/ACTH test
# CBC

<table>
<thead>
<tr>
<th>CBC</th>
<th>Patient’s values</th>
<th>Reference interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hct (%)</td>
<td>40.9</td>
<td>38.7 – 59.2</td>
</tr>
<tr>
<td>MCV (fL)</td>
<td>69.2</td>
<td>60.5 – 73.8</td>
</tr>
<tr>
<td>MCHC (g/dL)</td>
<td>33.1</td>
<td>32 – 37.2</td>
</tr>
<tr>
<td>Platelets (/μL)</td>
<td>208,000</td>
<td>152,000-518,000</td>
</tr>
<tr>
<td>MPV (fL)</td>
<td>15,0</td>
<td>8 – 14.6</td>
</tr>
<tr>
<td>WBC (/μL)</td>
<td>20,300 ↑</td>
<td>5,090 – 17,410</td>
</tr>
<tr>
<td>Neutrophils (/μL)</td>
<td>16,240 ↑</td>
<td>2,600 – 10,400</td>
</tr>
<tr>
<td>Lymphocytes (/μL)</td>
<td>2,842</td>
<td>390 – 6,730</td>
</tr>
<tr>
<td>Monocytes (/μL)</td>
<td>1,218</td>
<td>150 – 1,350</td>
</tr>
</tbody>
</table>
Blood smear

Differential for cytoplasmic granulation in leukocytes

- Mucopolysaccharidosis
- Chediak-Higashi syndrome
- May-Hegglin anomaly
- Toxic granulation
• Clinical presentation
  – Prolonged history
  – Musculoskeletal problems
  – Neurologic signs

• Cytoplasmic granulation in leukocytes
  – The patient and one littermate from West Virginia

Suspected diagnosis
Mucopolysaccharidosis (MPS)
4 diagnostic steps for MPS

1. Berry Spot test
   - Detect increased urinary GAG excretion

2. Electrophoresis
   - Determine the pattern of urinary GAG excretion

3. Enzymatic assay
   - Identify the deficient enzyme
   - Determine the types of MPS

4. Genetic test
   - Identify the mutation in the gene encoding enzymes
MPS

• Diverse group of lysosomal storage diseases (LSDs)
  – Deficiency of enzymes within lysosomes

• Lysosomes
  – Membrane-bound organelles
  – > 40 acid hydrolases

• MPS
  – Deficiency of one of 11 enzymes within lysosomes
  – Impaired degradation of glycosaminoglycans (GAGs) in lysosomes
  – Excretion of excess GAGs in urine
Glycosaminoglycans (GAGs)

- Chemical structure: Linear polysaccharides
  - Amino sugar
    - N-acetylglucosamine
    - N-acetylgalactosamine
  - Uronic acid or galactose
    - Iduronic acid
    - Glucuronic acid

- GAGs
  - Dermatan sulfate, keratan sulfate, heparan sulfate, chondroitin sulfate, hyaluronan
  - Types of urinary excreted GAGs vary depending on the deficient enzymes
Pathologic cascade of MPS

• Enzyme deficiency causes lysosomal GAG accumulation
• Lysosomal function for autophagocytic and endocytic transport pathway will be impaired
• Compromised lysosomal membrane integrity
  – Leakage of hydrolases and H⁺ into cytosol
• Undegraded GAG in extracellular matrix
  – Release of cytokines
  – Inflammation
Alder-Reilly granules

- Basophilic granules in leukocytes
- Accumulation of undegraded GAGs
- More frequently seen in bone marrow
- Special stains
  - Toluidine blue (+)
  - Alcian blue (+)
- Does not correlate with severity of diseases
## MPS types in people and animals

<table>
<thead>
<tr>
<th>Number</th>
<th>Eponym</th>
<th>Enzyme deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Hurler/Scheie</td>
<td>α-L-iduronidase</td>
</tr>
<tr>
<td>II</td>
<td>Hunter</td>
<td>Iduronate-2-sulfatase</td>
</tr>
<tr>
<td>IIIA</td>
<td>Sanfilippo type A</td>
<td>Heparan-N-sulfatase</td>
</tr>
<tr>
<td>IIIB</td>
<td>Sanfilippo type B</td>
<td>α-N-acetylglucosaminidase</td>
</tr>
<tr>
<td>IIIC</td>
<td>Sanfilippo type C</td>
<td>α-glucosaminide-N-acetyltransferase</td>
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<tr>
<td>IIID</td>
<td>Sanfilippo type D</td>
<td>N-acetylglucosamine-6-sulfatase</td>
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<tr>
<td>IVA</td>
<td>Morquio type A</td>
<td>N-acetylgalactosamine-6-sulfatase</td>
</tr>
<tr>
<td>IVB</td>
<td>Morquio type B</td>
<td>β-galactosidase</td>
</tr>
<tr>
<td>VI</td>
<td>Maroteaux-Lamy</td>
<td>N-acetylgalactosamine 4-sulfatase</td>
</tr>
<tr>
<td>VII</td>
<td>Sly</td>
<td>β-glucuronidase</td>
</tr>
<tr>
<td>IX</td>
<td></td>
<td>Hyaluronidase</td>
</tr>
</tbody>
</table>

MPS V and VIII no longer used
Treatment in people

- **Bone marrow transplantation (BMT)**
  - Deliver self-renewing population of cells
  - Capable of producing deficient enzymes

- **Enzyme replacement therapy (ERT)**
  - Effective in improving some clinical manifestations
  - Not effective in CNS lesions
    - Difficult in crossing blood-brain barrier

- **Gene therapy**
  - Viral vectors
Case summary

• Inherited disorder
  – Most consistent with MPS

• Management of MPS for vet animals
  – Supportive care
  – No commercially available treatment

• Do not use affected animals for reproduction
References

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• Dr. Urs Giger
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Questions?