Clinical History

Diagnosed with ileocolonic Crohn Disease
Discontinued infliximab due to lack of insurance
Admitted for new onset severe abdominal pain and weight loss
Imaging shows significant colonic distention due to a sigmoid stricture
Readmitted with bleeding and pain
Readmitted with Hgb 4.4

11 yo 1998
17 yo 2004
27 yo 3/2015
Sigmoidoscopy shows ulcerations in the colon & mild melanosis
IV steroids started

IV steroids started
Diverting ileostomy 4/2015
Starts infliximab 4/2015
Total abdominal colectomy 6/2015

ACCME/ Disclosure

Dr. Hart has nothing to disclose
Diagnosis: Crohn-like colitis in Hermansky Pudlak Syndrome
Puerto Rico

<table>
<thead>
<tr>
<th>Region</th>
<th>NN</th>
<th>NM</th>
<th>MM</th>
<th>Total</th>
<th>P</th>
<th>q</th>
<th>Estimated Population</th>
<th>Corr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western</td>
<td>7</td>
<td>7</td>
<td>0</td>
<td>11</td>
<td>0.068</td>
<td>0.002</td>
<td>1.23046000</td>
<td>0.281</td>
</tr>
<tr>
<td>Central</td>
<td>825 (1943)</td>
<td>21 (54.1)</td>
<td>2 (0.52)</td>
<td>1098</td>
<td>0.931</td>
<td>0.009</td>
<td>1.12343100</td>
<td>1.38</td>
</tr>
<tr>
<td>Expresso(1)</td>
<td>12</td>
<td>16</td>
<td>0</td>
<td>26</td>
<td>0.074*</td>
<td>0.024*</td>
<td>1.10154100</td>
<td>1.38</td>
</tr>
<tr>
<td>Eastern</td>
<td>15</td>
<td>16</td>
<td>0</td>
<td>31</td>
<td>0.055</td>
<td>0.005</td>
<td>1.06046000</td>
<td>0.67</td>
</tr>
<tr>
<td>Total</td>
<td>285</td>
<td>73</td>
<td>0</td>
<td>361</td>
<td>0.094</td>
<td>0.000</td>
<td>1.27177100</td>
<td>0.67</td>
</tr>
</tbody>
</table>

*Fruit values were calculated using a minor allele frequency calculated from: \( \sqrt{\frac{P}{2q^2}} = 0.0281 \)

**Based on population for the island of Puerto Rico reported by the USA Census Bureau for the year 2000.**

**HPS includes Hermansky-Pudlak syndrome: q, minor allele frequency.

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**Albinism Associated with Hemorrhagic Diathesis and Unusual Pigmented Reticular Cells in the Bone Marrow: Report of Two Cases with Histochemical Studies**

*By F. Hermansky and P. Pudlak*  

The combination of the above described congenital abnormalities (albinism, pseudohemophilia and unusual pigmented macrophages in the bone marrow) in two unrelated patients suggests that a common syndrome is present.

Frantisek Hermansky (1916–1980)

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**Genes Associated with Hermansky Pudlak Syndrome**

<table>
<thead>
<tr>
<th>HPS subtype</th>
<th>Human locus</th>
<th>Mouse mutant</th>
<th>Protein function</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPS-1</td>
<td>HPS1</td>
<td>pale-eye (pe)</td>
<td>BLOC-3 subunit</td>
</tr>
<tr>
<td>HPS-2</td>
<td>HPS2/AR3BI</td>
<td>pearl (p)</td>
<td>AP-3 subunit</td>
</tr>
<tr>
<td>HPS-3</td>
<td>HPS3</td>
<td>cocoon (co)</td>
<td>BLOC-2 subunit</td>
</tr>
<tr>
<td>HPS-4</td>
<td>HPS14</td>
<td>light-beer (lb)</td>
<td>BLOC-3 subunit</td>
</tr>
<tr>
<td>HPS-6</td>
<td>HPS46</td>
<td>ruby-eye 2 (re2)</td>
<td>BLOC-2 subunit</td>
</tr>
<tr>
<td>HPS-7</td>
<td>HPS/DTNBP1</td>
<td>ruby-eye (re)</td>
<td>BLOC-2 subunit</td>
</tr>
<tr>
<td>HPS-8</td>
<td>HPS8/BLOC1S3</td>
<td>sand (sa)</td>
<td>BLOC-1 subunit</td>
</tr>
<tr>
<td>HPS-9</td>
<td>HPS9/FDN</td>
<td>palin (pa)</td>
<td>BLOC-1 subunit</td>
</tr>
</tbody>
</table>

Pigment Cell Melanoma Res. 26: 176–192

Hermansky Pudlak Syndrome Type 1

- **HPS1 germline mutation:**
  - Located on chromosome 10q23.1-q23.3
  - Encoded protein plays role in organelle biogenesis
  - Affected organelles include: melanosomes, platelet dense granules, lamellar bodies & lysosomes
  - Protein is a component of “Biogenesis of Lysosome-related Organelles Complex” [BLOC-3]

- **Clinical phenotype:**
  - Oculocutaneous albinism
  - Bleeding diathesis
  - Pulmonary fibrosis with ceroid (50-70%)
  - Granulomatous colitis with ceroid (10-20%)


HPS Protein Associated Complexes

Pigment Cell Melanoma Res. 26: 176–192
**HPS1 16 bp duplication**

- Clinical phenotype:
  - Visual impairment in 90%
  - Restrictive lung disease in 68%
  - Bleeding diathesis in 17%
  - Granulomatous colitis in 15%
- Most common mutation in Puerto Rico

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“Nor did wild rumors of all sorts fail to exaggerate, and still the more horrify the true histories of these deadly encounters. For unlike his brethren, the White Whale spurned the black ocean depths, and instead coursed the surface, reaping the harpoon boats that dared to approach him...”  

H. Melville; Moby Dick, or the Whale
**Gastrointestinal Disease in HPS 1 & 4**

- Clinical and histologic features:
  - Patchy chronic colitis with granulomas & ceroid
  - Ileal disease with stricture formation
  - Perianal disease
  - No reports of upper GI tract involvement
- Clinical management:
  - Poor response to steroids, mesalamine, azathioprine, antibiotics
  - Surgery often required
  - Several reports of good response with Infliximab
  - Active investigation of gene transfer

*Mor&M& Wolfson, J Clin Gastroenterol 2011
Hussain N et al, Clin Gastroenterol Hepatol 2006*

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**Intestinal Disease in Hermansky-Pudlak Syndrome: Occurrence of Colitis and Relation to Genotype**

- Elevated serum ASCA IgA titer
- Elevated anti-OmpC IgA titer
- 1 month s/p proctocolectomy developed a pelvic hematoma/abscess, drained via CT guidance
- Over the next year admitted several times for enterocutaneous fistula & partial small bowel obstruction due to intraabdominal adhesions
- Ultimately underwent exploratory laparotomy with lysis of adhesions, excision of the fistula, and revision of the ileostomy
Did Moby Dick have HPS?

- Born in the waters off N.W. Puerto Rico
- Oculocutaneous albinism
- Evidence of bleeding diathesis
- Evidence for pulmonary fibrosis

Histologic Mimics of Inflammatory Bowel Disease

<table>
<thead>
<tr>
<th>Heewon Aimee Kwak, MD</th>
<th>Lei Zhao, MD, PhD</th>
</tr>
</thead>
</table>

- Infectious agents
  - Infectious colitis: Salmonella, E. coli, Yersinia, C. jejuni, Shigella, E. histolytica, Tuberculosis
  - STD associated proctitis: Syphilis, N. gonorrhoea, C. trachomatis (LGV)
- Drug induced colitis:
  - NSAIDs
  - Mycophenolate
  - Biologics: Ipilimumab, Rituximab, Bevacizumab
- Diverticular colitis:
  - Crohn-like colitis
  - Ulcerative colitis-like

52 yo M with outside diagnosis of Crohn disease
Initial improvement on steroids
Ileocecectomy for episodic bleeding from a large cecal ulcer

[Crohn-like diseases highlighted in yellow]
Repeat Colonoscopy

Behçet’s disease

“Sigmoiditis” with Diverticular Disease
Etiologies
- Diverticular colitis
- Mucosal prolapse
- Ischemic colitis
- NSAID colitis
- Infectious colitis
- Crohn colitis-like
- Ulcerative colitis-like

Normal crypt architecture
PCR for Mycobacterial species negative
Courtesy Dr. Laura Lamps, Univ. of Arkansas
Segmental Colitis
Crohn’s-like Colitis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>Pathological features</th>
<th>Natural history of Crohn’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gelb &amp; Finkelstein (1974)</td>
<td>1</td>
<td>A, B, C</td>
<td>Surgery curative</td>
</tr>
<tr>
<td>McCune et al (1997)</td>
<td>4</td>
<td>A, B, C</td>
<td>Surgery curative</td>
</tr>
</tbody>
</table>

Pathological Features: A, non-caseating epithelial granulomas; B, mucosal inflammation; C, aphthous ulcers; D, transmural inflammation in the form of lymphoid aggregates; E, fissuring ulceration.


Gastrointestinal Tract Pathology in Patients With Common Variable Immunodeficiency (CVID)
A Clinicopathologic Study and Review

Jason A. Daniels, MD,* Howard M. Lederman, MD, PhD,† Anish Maitra, MBBS,* and Elizabeth A. Montgomery, MD*

<table>
<thead>
<tr>
<th>Antigen Site</th>
<th>No. of Samples Studied</th>
<th>Key Findings Likely to Result in Diagnostic Problems</th>
<th>Conditions Mentioned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagus</td>
<td>29</td>
<td>Goblet cell hyperplasia</td>
<td>None</td>
</tr>
<tr>
<td>Stomach</td>
<td>36</td>
<td>Prominent lymphocytes and apoptosis</td>
<td>CVID, Crohn’s disease, sarcoidosis</td>
</tr>
<tr>
<td>Small bowel</td>
<td>39</td>
<td>Villous thinning and intraepithelial lymphocytes</td>
<td>Crohn’s disease</td>
</tr>
<tr>
<td>Colon</td>
<td>34 &quot;auto&quot; of biopsies, 1 adenoma</td>
<td>Prominent crypt epithelial disorganization</td>
<td>Goblet cell dysfunction, Crohn’s disease</td>
</tr>
</tbody>
</table>

*Am J Surg Pathol • Volume 31, Number 12, December 2007

Clinical History

- 84 y.o. F presents with recurrent hematochezia, fatigue, and dizziness
- PMHx of osteoarthritis
- Prior colonoscopies: cecal ulcers with a normal terminal ileum
- Current colonoscopy: multiple ulcers throughout the entire colon with intervening normal mucosa – r/o Crohn disease

TABLE 1. Clinical and Endoscopic Findings of 12 Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Clinical Presentation</th>
<th>Endoscopic Findings</th>
<th>Location</th>
<th>No.</th>
<th>Specimen</th>
<th>Other Findings</th>
<th>Follow-up (mo)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>93</td>
<td>M</td>
<td>FTT, BD, anemia, and Hx</td>
<td>Ulcerative</td>
<td>Duodenum and ileum</td>
<td>Multiple</td>
<td>Biopsy</td>
<td>Skin and hematochezia</td>
<td>DD (12)</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>F</td>
<td>FTT, BD, anemia, and Hx</td>
<td>Ulcerative</td>
<td>Duodenum and ileum</td>
<td>Multiple</td>
<td>Biopsy</td>
<td>None</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>F</td>
<td>Arthritis</td>
<td>Peyer's</td>
<td>Ac</td>
<td></td>
<td></td>
<td></td>
<td>ANED (24)</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>M</td>
<td>Reye's</td>
<td>Peyer's</td>
<td>Cordon</td>
<td></td>
<td></td>
<td></td>
<td>ANED (27)</td>
</tr>
<tr>
<td>5</td>
<td>55</td>
<td>F</td>
<td>Reye's</td>
<td>Peyer's</td>
<td>Squared</td>
<td></td>
<td></td>
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<td>ANED (26)</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>F</td>
<td>Reye's</td>
<td>Peyer's</td>
<td>Cordon</td>
<td></td>
<td></td>
<td></td>
<td>ANED (12)</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>M</td>
<td>Reye's</td>
<td>Peyer's</td>
<td>Stomach and duodenum</td>
<td></td>
<td></td>
<td></td>
<td>ANED (27)</td>
</tr>
<tr>
<td>8</td>
<td>51</td>
<td>F</td>
<td>Reye's</td>
<td>Peyer's</td>
<td>TE</td>
<td></td>
<td></td>
<td></td>
<td>ANED (23)</td>
</tr>
<tr>
<td>9</td>
<td>77</td>
<td>F</td>
<td>Reye's</td>
<td>Peyer's</td>
<td>Stomach and ileum</td>
<td></td>
<td></td>
<td></td>
<td>ANED (62)</td>
</tr>
<tr>
<td>10</td>
<td>46</td>
<td>F</td>
<td>Reye's</td>
<td>Peyer's</td>
<td>Stomach and ileum</td>
<td></td>
<td></td>
<td></td>
<td>ANED (24)</td>
</tr>
<tr>
<td>11</td>
<td>63</td>
<td>F</td>
<td>Cecal submucosa</td>
<td>NA</td>
<td>Cordon and AC</td>
<td>Multiple</td>
<td>Right hematochezia</td>
<td>None</td>
<td>ANED (24)</td>
</tr>
<tr>
<td>12</td>
<td>54</td>
<td>F</td>
<td>Constipation</td>
<td>Ulcerative</td>
<td>Ac</td>
<td></td>
<td></td>
<td></td>
<td>None</td>
</tr>
</tbody>
</table>

AC indicates early relapse; ANED, after no evidence of disease; BD, bloody diarrhea; DC, duodenal cecum; FTT, fluid to thin; Hx, history; IA, intraabdominal; M, male; NA, not available; TE, terminal ileum.
Entamoeba histolytica
Crohn-like disease occurs in about 20% of Hermansky-Pudlak syndrome type 1 & 4 patients
Ceroid laden macrophages can be a diagnostic clue
Clinical correlation is necessary:
- Oculocutaneous albinism
- Bleeding diathesis
- Pulmonary interstitial fibrosis
GI symptoms may respond to Infliximab, but surgery is often necessary
Gene transfer therapy is under active investigation

27 year old male diagnosed with Crohn’s disease at age 11 after presenting with bloody diarrhea & abdominal pain
Lost his medical insurance at age 17 and received no medical care for the next 10 years
In March, 2015 he presented to the ER with symptoms consistent with a bowel obstruction
CT scan documented a stricture in the descending colon
Underwent a diverting loop ileostomy for decompression
Post-op he was treated with IV steroids and taper
After discharge he was switched to Infliximab & azathioprine

He presented back to the ER in June, 2015 with profuse rectal bleeding
He underwent an urgent abdominal proctocolectomy with creation of a short Hartmann pouch.
The small bowel was noted to be grossly normal at the time of surgery
Segmental Colitis
“Crohn-like colitis”

- Segmental colitis
- Fissuring ulceration
- Transmural inflammation with lymphoid aggregates
- Granulomas in some cases
- No evidence of Crohn elsewhere
- Never develops into classic Crohn