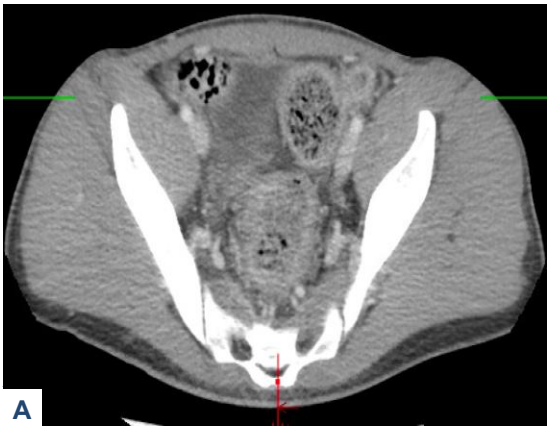
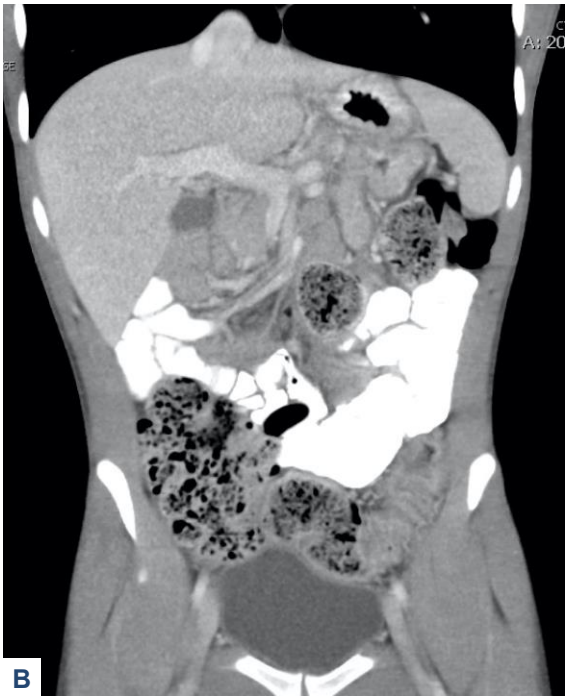
A 19-year-old girl presented with fatigue, fever and protracted bloody diarrhea for 3 weeks. She reported recurrent episodes of non-bloody diarrhea with abdominal cramps of lower intensity for the past couple months which resolved spontaneously. Her past medical history was significant for menorrhagia. She did not report any medication use except for an herbal supplement which she started 10 days ago. This supplement was provided by her grandma during a recent visit to San Juan. On physical examination, the patient was ill-looking, febrile and grey-haired, with reduced visual acuity and tender abdomen. Her lab workup was significant for leukocytosis, normocytic anemia and calprotectin 7400 ug/g (normal < 50). Microbiology workup (blood/urine/stool) was negative.

CT-abdomen:

Colonic wall thickening and surrounding mesenteric congestion of rectosigmoid, splenic flexure colon, mid transverse colon and hepatic flexure. The overall findings are consistent with chronic colitis (favoring Crohn's disease)





Endoscopy (colonoscopy):

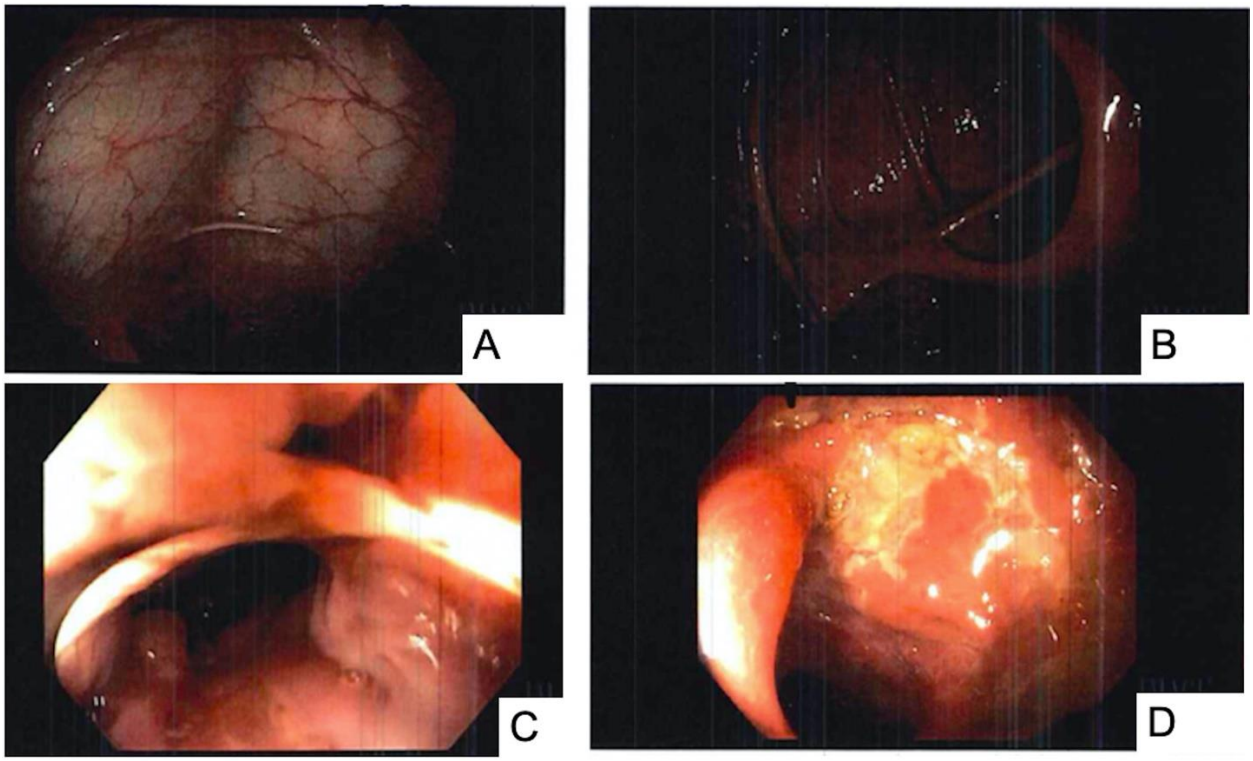


Fig1. A: Normal cecum; B: Normal ICV; C: Rectal stricture; D: Proctitis

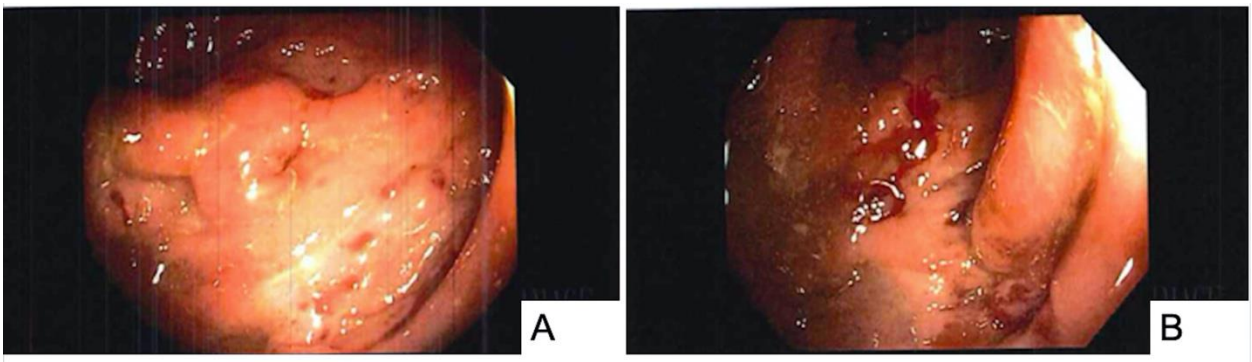


Fig2. A: Sigmoid ulcer; B: Rectosigmoid erosions

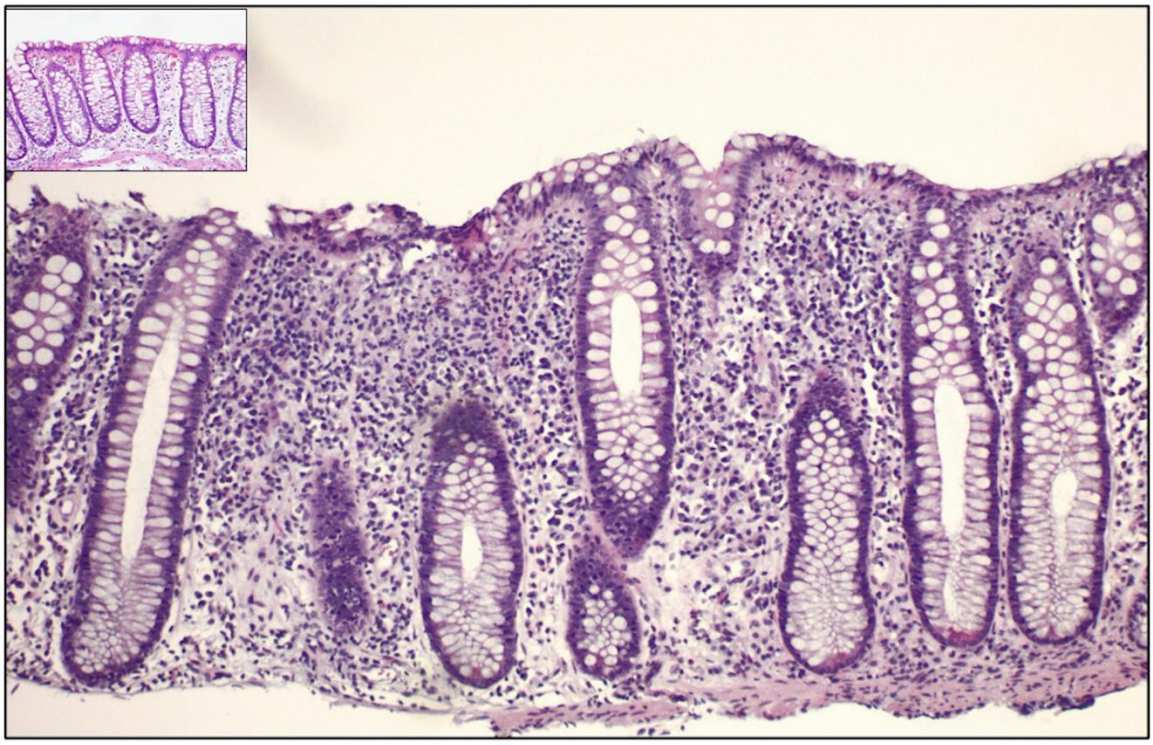


Fig3. Lamina propria inflammation with surface epithelial injury and Paneth cell metaplasia of sigmoid colon; Inset: Normal colon

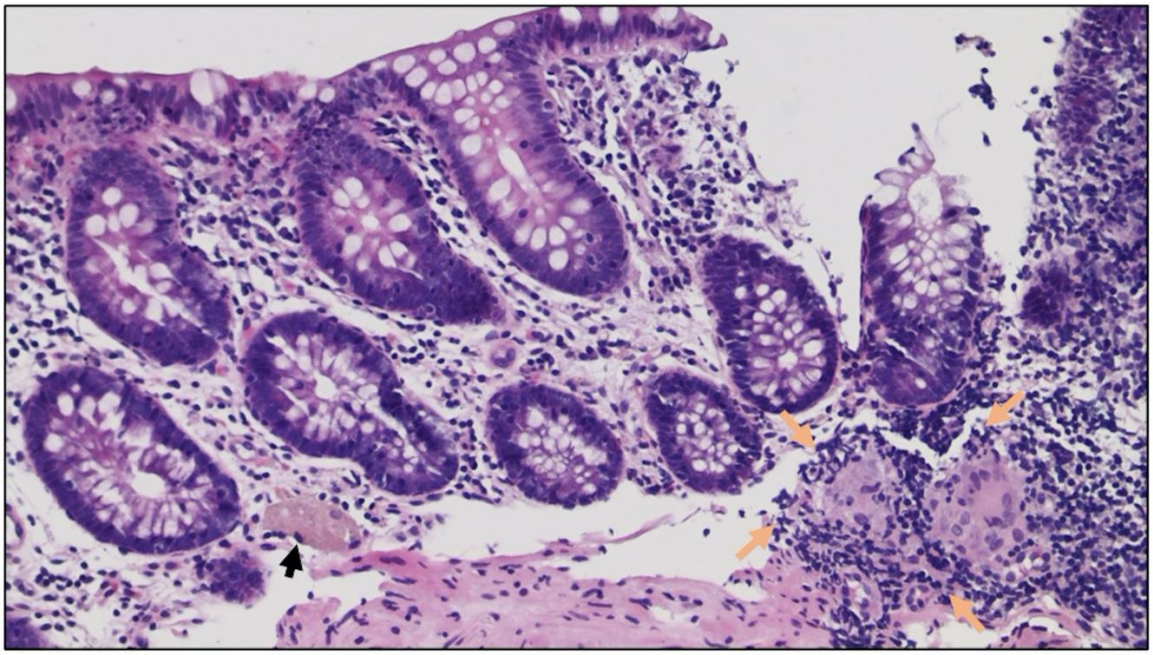


Fig4. Crypts with modest outline irregularity, non-necrotizing granuloma (orange arrows) and ceroid-laden macrophage (black arrow)

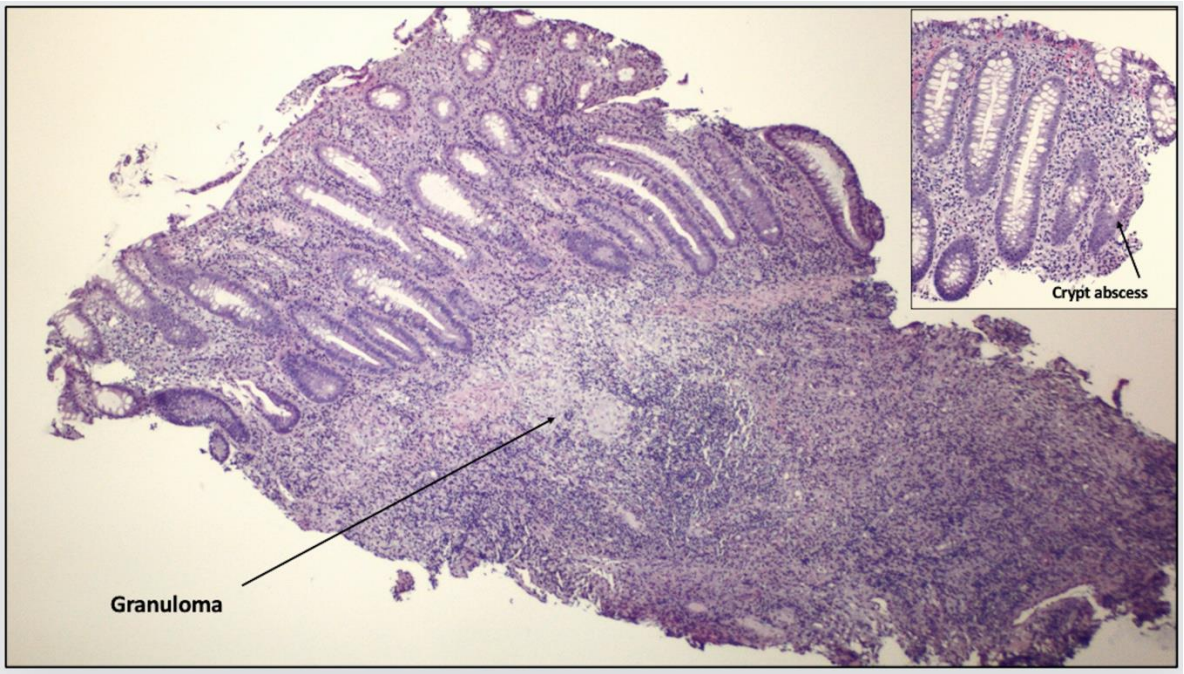


Fig5. Crypt injury with prominent inflammation extending to deep submucosa and non-necrotizing granuloma (long arrow); Inset: Crypt abscess (short arrow)

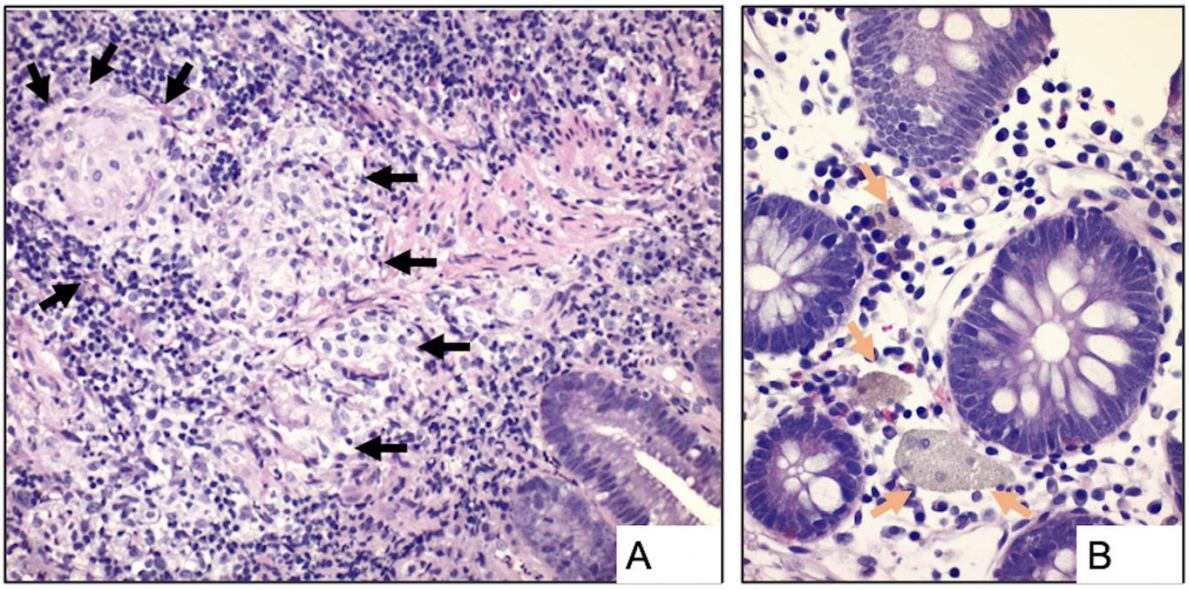


Fig6. A: Non-necrotizing granuloma (black arrows); B: Pigmented (ceroid-laden) macrophage (orange arrows)

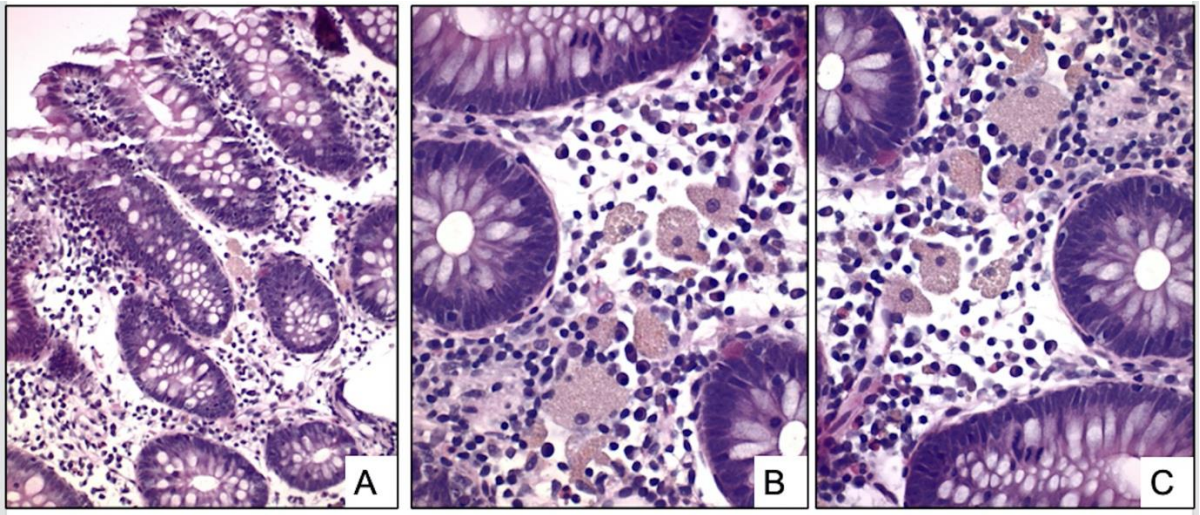


Fig7. A, B and C: Pigmented (ceroid-laden) macrophages within lamina propria

What is the most likely diagnosis?

1. Crohn's disease (CD)
2. Hermansky-Pudlak syndrome-associated colitis
3. Melanosis coli
4. Glycogen Storage Disease (GSD)-Ib associated colitis
5. Chronic Granulomatous Disorder (CGD)

The correct answer is (2) Hermansky-Pudlak syndrome-associated colitis

Discussion:

The patient was of Puerto Rican origin, had family history of albinism (4 family members) and carried the diagnosis of Hermansky-Pudlak syndrome (HPS). In addition to colitis with typical features, the patient presented with albinism and history of menorrhagia. A diagnosis of HPS-associated colitis was rendered, which was confirmed clinically.

HPS is a rare autosomal recessive disorder with eleven reported subtypes, which reflect genetic heterogeneity of the disease. The disease is most common among people who originate from Puerto Rico with an estimated prevalence of 1:1800, but has also been reported in other ethnic groups.[1,2] The syndrome is characterized by oculocutaneous albinism, a platelet-related bleeding diathesis and lysosomal accumulation of ceroid lipofuscin. This multisystemic disorder can present with myriad of clinical conditions.

HPS is caused by a mutation in one of the several *HPS* genes (*HPS1-HPS8*). Except for HPS1, the exact function of these gene products is unknown but they interact with each other in the biogenesis of lysosome-related organelle complex (BLOC). For example, BLOC-3 is formed by interacting of HPS1 with HPS4. Affected lysosome-related organelles are melanosomes in melanocytes, lamellar bodies in type-II pneumocytes, T-cells secretory granules and platelet delta granules. HPS subtypes 1 and 4 (BLOC-3) are associated with pulmonary fibrosis and gastrointestinal complications which clinically and pathologically overlap with Crohn's disease. Recently, HPS subtype 3 has also been reported to be associated with a mild form of Crohn's like colitis.[3] A mutation in the NOD2 gene, the first gene associated with Crohn's disease, has also been reported in some patients with HPS but the significance of this association has not been clarified yet.[4]

HPS subtype	GC	PF	Albinism	Bleeding Diathesis
I	Y	Y	Y	Y
II	?	Y	Y	Y
III	?	N	Y	Y
IV	Y	Y	Y	Y
IX	?	?	Y	Y
V	?	N	Y	Y
VI	Y	N	Y	Y
VII	?	?	Y	Y
VIII	?	?	Y	Y

TABLE1 Features of HPS subtypes. Y, present; N, not present; ?, unknown; GC, Granulomatous colitis; PF, Pulmonary fibrosis.

HPS-associated colitis has been reported with subtypes HPS1, 4 and 6 (Table 1).[1] Colitis mostly starts in adolescence but may occur at any age including childhood. The presenting symptoms include fever, watery diarrhea with malabsorption, cramping abdominal pain, fatigue and weight loss. Extra-intestinal manifestations, like hypoxia and diffuse chest rales, bleeding diathesis (bruising of lower legs), anxiety and horizontal nystagmus, may coexist.[1] On colonoscopy, the findings are indistinguishable from Crohn's disease. These findings include mucosal ulcerations, pseudo-polyps, granular mucosa with altered vascularity variably involving large bowel, and perianal fistulas and abscess. On microscopic examination, the predominant picture is granulomatous colitis with increased lamina propria chronic inflammation [Figs. 3-6A] and some crypt architectural distortion [Figs. 3 and 5], features that are very similar to Crohn's disease. The hallmark of this type of colitis is the presence of golden-colored lipofuscin laden macrophages in the lamina propria and submucosa [Figs. 6B and 7]. These macrophages tend to accumulate in small aggregates towards the deeper aspect of the lamina propria and have a somewhat "golden" or "yellowish" color. Although the colon is the most commonly involved site, the inflammatory changes may involve other parts of the gastrointestinal system.

It is recommended that any patient with oculo-cutaneous albinism who reports Puerto Rican ancestry and/or an abnormal bleeding history be formally evaluated for HPS. The work-up includes platelet aggregation study, electron microscopy (more sensitive), tissue biopsy and molecular subtyping with mutational analysis. There is no specific treatment for HPS and patients respond well to treatment modalities used for treatment of CD, especially anti-TGFβ drugs, but also corticosteroids and mercaptopurines. In view of the bleeding diathesis, the role of aminosalicylates remains questionable. These patients are advised to withhold any salicylates medications (ASA) or NSAIDs, and they receive prophylactic desmopressin prior to any intervention. Surgical intervention (total/subtotal/partial colectomy) is reserved for complicated or refractory cases. Currently, pulmonary fibrosis is the main cause of the poor prognosis in HPS patients.[3,5]

1. Crohn's Disease: Can affect any part of the GI tract, from mouth to anus. There is no definitive consensus on the exact cause, but it probably involves a complex interaction of genetic predispositions, environmental factors and abnormalities in immune regulation. CD is slightly more common in women and has a bimodal age presentation. The majority of patients present between 2nd and 4th decade of life. A second minor peak occurs between 5th and 7th decade of life. Although it has been reported in all ethnic groups, CD is more prevalent in Northern Americans, northern Europeans, the Welch, Ashkenazi Jews and Scandinavians. Its incidence is very low in south Americans and Asians. Among extra-intestinal manifestations, patients with CD have a prothrombotic tendency and are more susceptible to venous thromboembolism, versus the bleeding tendency associated in HPS.[6] Colonoscopy may show mucosal edema, longitudinal ulcerations with cobblestoning, and segmental luminal narrowing. The histologic features include crypt architectural distortion, transmural lymphoid aggregate, basal cell plasmacytosis, lamina propria expansion by lymphoplasmacytic infiltrate, Paneth cell or pyloric metaplasia and epithelioid granulomata. Neutrophilic inflammation manifests as cryptitis, crypt abscess or areas of aphthous ulcers. The histologic features can be almost indistinguishable from HPS-associated colitis. While lipofuscin containing macrophages can be seen in CD or any other form of chronic

inflammatory process, the color of the cytoplasmic pigment tends to be darker or more brown compared to that seen in HPS. Perianal complications (fistula/sinus tracts/abscess) and segmental strictures are common indications for surgical intervention in CD. Otherwise the goal of therapy is to induce and maintain clinical remission.[7,8]

3. Melanosis coli: This is characterized by accumulation of extensive pigment laden lamina propria macrophages. The pigment tends to be black to brown (melanin-like), but it is not melanin and hence sometimes is referred to as "pseudo-melanosis". Melanosis in the large bowel has been linked to use of laxatives, especially anthraquinone laxatives, but in many cases a definite association is difficult to find and the etiology remains unclear. Similar deposition of pigment laden macrophages in the lamina propria may occur at other sites in the gastrointestinal tract (esophagus, stomach, duodenum and appendix); however, these are associated with different etiologies. On colonoscopy, the involved mucosa reveals variably normal to striking dark-brown pigmentation. On microscopic exam, pigment laden macrophages are scattered in the lamina propria. The autofluorescent pigment is a polymer of melanin, glycoprotein and glycolipids (melanized ceroid). The pigmented cells will stain positive for CD68, and the pigments are PAS and acid-fast positive.[9] Despite some reducing properties similar to those of melanin, now it is clear that this pigment is different from true melanin. True melanin pigment deposition in the mucosa can occur in rare conditions including metastatic melanoma involving the GI tract, or rarely with increased melanocytes/ nevi formation in the esophagus or anal region.

IV. Glycogen Storage Disease (GSD)-Ib-associated colitis: Glycogen storage disease type Ib is an autosomal recessive disorder and results from mutation in SLC37A4 gene that encodes the G-6-P transporter (G6PT) protein of the endoplasmic reticulum membrane. This results in an interruption in the terminal step of gluconeogenesis or glycogenolysis leading to release of free glucose. The GSPT enzyme has also been found in high concentration in hematopoietic progenitor stem cells and in enteric/colonic epithelial cells. In addition to hepatosplenomegaly, hypoglycemia and neutrophil dysfunction, glycogen storage disease type-Ib is also associated with inflammatory bowel disease-like colitis which is clinically indistinguishable from Crohn's disease. The colitis occurs in the absence of the HLA loci that are known to be associated with Crohn's disease, ulcerative colitis or Bechet's disease.[10] The affected patients suffer from recurrent infections, chronic abdominal pain and diarrhea and persistent perianal complications (abscess/fistulas) since early childhood. Colonoscopy shows colonic segmental narrowing, altered mucosal vascularity, mucosal cobblestoning, circumferential ulcers and mucosal flattening. Microscopic examination reveals chronic inflammatory expansion of the lamina propria, granulomatous inflammation and ulceration/erosion. These patients respond well to treatment with G-CSF/GM-CSF. In refractory cases surgical intervention may also be needed.[10-12]

V. Chronic Granulomatous Disorder (CGD): This rare immunodeficiency disorder was first recognized in 1950. It can have X-linked inheritance (more common) or autosomal recessive inheritance. The underlying defect involves the NADPH-oxidase enzyme subunits leading to ineffective killing of phagocytosed microorganisms. CGD usually presents in early childhood with recurrent infections at multiple sites. It can involve any portion of the GI tract, from the mouth to anus, with the colon reported to be the most affected site and the esophagus the least

involved site. The spectrum of changes in the GI tract includes oral ulcers, delayed gastric emptying, colitis, abscesses, intestinal obstruction, dysmotility, strictures and fissures. On microscopic examination, GI involvement by CGD may mimic inflammatory bowel disease, sarcoidosis and mycobacterial infections. Changes of chronic colitis include architectural distortion, basal cell plasmacytosis, lamina propria expansion by lymphoplasmacytic infiltrate, Paneth cell metaplasia, prominent eosinophilic infiltrate (>30 per hpf), and microgranulomas. Single or clustered pigmented macrophages are easily identified in any layer of the bowel wall, and this helps to differentiate it from melanosis coli, which is restricted to the superficial lamina propria. This pigment is believed to result from ineffective digestion of microorganisms, membranes and lipids.[13] Specific tests for CGD include neutrophil function tests such as nitrogen blue test to assess phagocytic activity and mutational analysis. The treatment includes control of infections with appropriate antimicrobials. The colitis is managed with immunomodulators with good response in some cases, but the response is variable.[5,7]

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