Journal of Clinical and Translational Pathology **2024** vol. 4(4) | 172–177
DOI: 10.14218/JCTP.2024.00038

Case Report

Unique Morphologic Features of a Case of Hermansky-Pudlak Syndrome in the Colon: Extensive Mucosal Lipofuscin Pigmented Histiocytes and Crohn's-like Mucosal Granulomatous Colitis

Amanda Meindl[1], M. Sambasiva Rao[1] and Guang-Yu Yang[2]

[1]*Department of Pathology, Northwestern Memorial Hospital, Chicago, IL, USA;* [2]*Department of Pathology, Virginia Commonwealth University School of Medicine, Richmond, VA, USA*

Received: November 07, 2024 | **Revised:** December 10, 2024 | **Accepted:** December 17, 2024 | **Published online:** December 31, 2024

Abstract

Hermansky-Pudlak syndrome (HPS) is a rare, autosomal recessive disorder predominantly affecting individuals of Puerto Rican descent. It is characterized by oculocutaneous albinism, platelet storage pool deficiency, and lysosomal ceroid accumulation in tissues. Lysosomal dysfunction has been shown to be associated with pulmonary fibrosis and granulomatous colitis in HPS patients, accounting for a significant portion of morbidity and mortality in this population. Clinical and endoscopic gastrointestinal manifestations in HPS patients are similar to those of active Crohn's disease, including abdominal pain, bleeding, fissures, fistulas, and perianal involvement. Histology reveals granulomatous colitis that can be difficult to distinguish from Crohn's disease. Identifying distinct morphologic features from Crohn's disease is crucial for the diagnosis of HPS. Here, we present a case of a 27-year-old male with a history of HPS and refractory granulomatous colitis with severe perianal disease, who underwent total proctocolectomy and perianal excision. The unique, distinguishing morphologic features from Crohn's disease in this case are: 1) grossly diffuse ulceration in the ano-rectum and cecum, 2) ulcerative and granulomatous inflammation predominantly involving the mucosa and submucosa of the colon, and 3) accumulation of ceroid pigment in the histiocytes of the lamina propria throughout the entire gastrointestinal tract. Immunohistochemical stains for CD3 and FoxP3-positive T cells in the granulomatous colitis were further analyzed. Thus, we fully document the extent of disease involvement and morphologic features in this patient and extensively discuss the similarities and differences between HPS and Crohn's disease.

Citation of this article: Meindl A, Rao MS, Yang G-Y. Unique Morphologic Features of a Case of Hermansky-Pudlak Syndrome in the Colon: Extensive Mucosal Lipofuscin Pigmented Histiocytes and Crohn's-like Mucosal Granulomatous Colitis. J Clin Transl Pathol 2024;4(4):172–177. doi: 10.14218/JCTP.2024.00038.

Keywords: Hermansky-Pudlak syndrome; Granulomatous colitis; Crohn's-like colitis.

*__Correspondence to:__ Guang-Yu Yang, Department of Pathology, Virginia Commonwealth University School of Medicine, 1101 E Marshall St, 4th Floor, Suite 4002, Box 980662, Richmond, VA 23298, USA. ORCID: https://orcid.org/0000-0002-5987-7750. Tel: +1-804-828-0183, Fax: +1-312-503-0647, E-mail: guangyu.yang@vcuhealth.org

Introduction

Hermansky-Pudlak syndrome (HPS) is a rare autosomal recessive disorder characterized by a triad of associated complications: oculocutaneous albinism, bleeding diathesis due to platelet storage pool deficiency, and granulomatous colitis. Excessive lysosomal ceroid accumulation in tissues has been linked not only to the development of granulomatous colitis in these patients but also to pulmonary fibrosis. Granulomatous colitis in HPS patients shares clinical and histopathologic features with Crohn's disease; however, differences have been documented, most notably a lack of response to conventional Crohn's therapies.[1–5] It has been postulated that these two disease processes may even exist on a colitis spectrum; however, no definitive direct links (molecular, immunologic, serologic) have been established. At least eleven genes (*HPS1–8*) have been identified in association with this disease, variably involved in the biogenesis of lysosome-related organelles such as melanosomes, platelet delta granules, and others.[6,7] It is hypothesized that accumulation of ceroid pigment in histiocytes due to dysfunctional vesicles eventually leads to rupture of histiocytes, activation of cytokine cascades, and the formation of granulomas.[1] Patients with HPS and granulomatous colitis present with clinical features similar to those of Crohn's disease, including abdominal pain, bloody diarrhea, and fever. Fistulas and abscesses are often observed, and occasionally patients present with "metastatic" cutaneous involvement or contiguous extension from the diseased bowel at the stoma site. Additional cutaneous involvement may include vulvar, perineal, and perianal disease.[1,2]

Granulomatous colitis has been observed in 15–20% of HPS patients, although the actual prevalence is thought to be significantly higher.[2,8,9] In general, the diagnosis of granulomatous colitis in these patients is based on biopsy results and endoscopic findings. These patients typically do not respond well to traditional therapies used for Crohn's disease

and often require surgical intervention. To the best of our knowledge, there have been only a few cases of patients with HPS-associated granulomatous colitis who underwent total proctocolectomy as a first-line surgical approach. Total proctocolectomy is rarely performed as the first surgical tactic, as general surgical management typically includes initial subtotal colectomy, followed by completion proctectomy.[10,11]

Endoscopic findings in HPS-associated granulomatous colitis include patchy involvement of the colonic mucosa with superficial and deep ulcers, pseudopolyps, and occasional fistula formation. The ileum may occasionally be involved, but isolated small bowel disease has not been definitively documented.[2,12] Histologically, HPS-associated colitis shows areas of broad ulcer formation, chronic inflammation (either superficial or full-thickness), numerous non-caseating granulomas, and deposition of brown ceroid pigment in histiocytes within the lamina propria of the mucosa.[9,10] Here, we present a case of a 27-year-old male with a history of HPS and refractory granulomatous colitis with severe perianal disease who underwent total proctocolectomy and perianal excision. The unique morphologic and immunohistochemical features were extensively characterized, and the similarities and differences between HPS and Crohn's disease are further discussed.

Case

Clinical presentation

The patient initially presented in 2006 with bloody diarrhea and was diagnosed with granulomatous colitis with distal colonic involvement. The patient was treated with immunomodulatory therapy, initially with minimal response (sulfasalazine, 6-mercaptopurine, prednisone). He was then started on infliximab, with a good response, but quickly required dose escalation in 2007. The patient did well, with minimal progression of the disease, until 2013, when he developed antibodies to infliximab, resulting in the worsening of the disease and the development of *Clostridium difficile* colitis. At that time, he was switched to HUMIRA; however, he continued to progress, requiring weekly dose increases. Additional therapies were initiated, but he developed perianal pain, rectal discomfort, and subsequent perianal and rectal abscesses. The patient underwent a diverting loop ileostomy in 2016, followed by incision and drainage of perianal and perirectal abscesses. Despite these interventions, the patient experienced persistent perianal and rectal disease and subsequently underwent total proctocolectomy with anal resection in July 2017.

Pathology and immunohistochemistry findings

Gross findings in proctocolectomy specimen: Gross examination of the total proctocolectomy specimen revealed prominent mucosal ulceration and multiple small pseudopolyps ranging in size from 0.2 cm to 1.0 cm in greatest dimension, involving the cecum (Fig. 1a, black arrow) and ano-rectum (Fig. 1a, blue arrow; high magnification in Fig. 1b). Pericolonic fat was abundant without definitive streaking or stranding. No areas of definitive fistula formation were identified.

Histologic and histochemical features: Histologically, in the ano-rectum (Fig. 1c) and cecum (Fig. 1d), diffuse ulcerative inflammation with numerous non-caseating granulomas was identified, predominantly involving the mucosa and submucosa. The granulomatous inflammation extended superficially into the muscularis propria, but no muscular or neural hypertrophy was seen (Fig. 1e). Well-formed non-caseating granulomas were mainly located in the deep portion of ulcers, surrounded by intense lymphocyte infiltration (Fig. 1f).

In the morphologically or grossly unremarkable colon and small bowel, numerous pigment-laden histiocytes were identified, predominantly in the lamina propria of the deep mucosa (Fig. 2a). The pigment-laden histiocytes were analyzed histochemically, revealing that the pigmented material was positive for periodic acid–Schiff-diastase stain (Fig. 2b) and acid fast bacilli (AFB) stain (Fig. 2c), but negative for iron stain (Fig. 2d), confirming that the pigment was ceroid lipofuscin. No pigment was detected in the granulomas. Numerous pigment-laden histiocytes were also identified in the pericolonic lymph nodes (Fig. 2e and f). These findings, together with the clinical information, supported the diagnosis of Hermansky-Pudlak syndrome-associated granulomatous colitis.

Histochemical and immunohistochemical findings in granulomas: Granulomatous inflammation was analyzed by histochemistry, revealing no microorganisms by AFB and Grocott's methenamine silver staining. The non-caseating granulomas were further highlighted by CD68 immunostaining (Fig. 3a and b). Numerous CD3-positive T cells (Fig. 3c and d) and FoxP3-positive T regulatory cells (Fig. 3e and f) were found surrounding and infiltrating the granulomas. CD20-labeled B lymphocytes were mainly located at the surface of the ulcer and were rarely seen within the granulomas (Fig. 3g and h). In the morphologically or grossly unremarkable colon and small bowel, the pigmented histiocytes were further labeled by CD68 immunostaining (Fig. 3i and j) but were negative for S100, confirming their histiocytic origin.

Discussion

Hermansky-Pudlak syndrome is a rare, still largely poorly understood disease process. The clinical and pathologic features of granulomatous colitis present in these patients resemble Crohn's disease but can have a complicated and protracted clinical course, often refractory to traditional therapies. The morphologically or grossly unremarkable colon and terminal ileum, as well as the extent of disease in the patient presented here, were thoroughly documented, as the resection specimen extended from the terminal ileum to the perianal tissues and skin. One to two sections per 10 centimeters of bowel were submitted for histologic examination. The first unique morphologic finding was numerous ceroid-laden cells in the lamina propria of the mucosa throughout the entire length of the morphologically or grossly unremarkable colon, as well as in pericolonic lymph nodes. These pigmented cells were confirmed to be histiocytes by CD68-positive staining. Intracytoplasmic ceroid pigment accumulations were confirmed with positive AFB and periodic acid–Schiff-diastase stains and negative iron stains. These results indicate that the identification of ceroid-laden histiocytes in the colonic mucosa, particularly in biopsy specimens, would be a significant approach to distinguishing Hermansky-Pudlak syndrome from Crohn's disease. To the best of our knowledge, the involvement of lymph nodes by ceroid-laden histiocytes in patients with HPS has been documented only once previously, during the autopsy of a patient with HPS and pulmonary fibrosis.[13]

While HPS-associated colitis and Crohn's disease do appear to share similarities, there are notable differences between the two entities. There have been no documented cases of HPS showing granulomatous involvement of the upper gastrointestinal tract or oral cavity, as seen in Crohn's disease. Both entities can show cutaneous involvement,

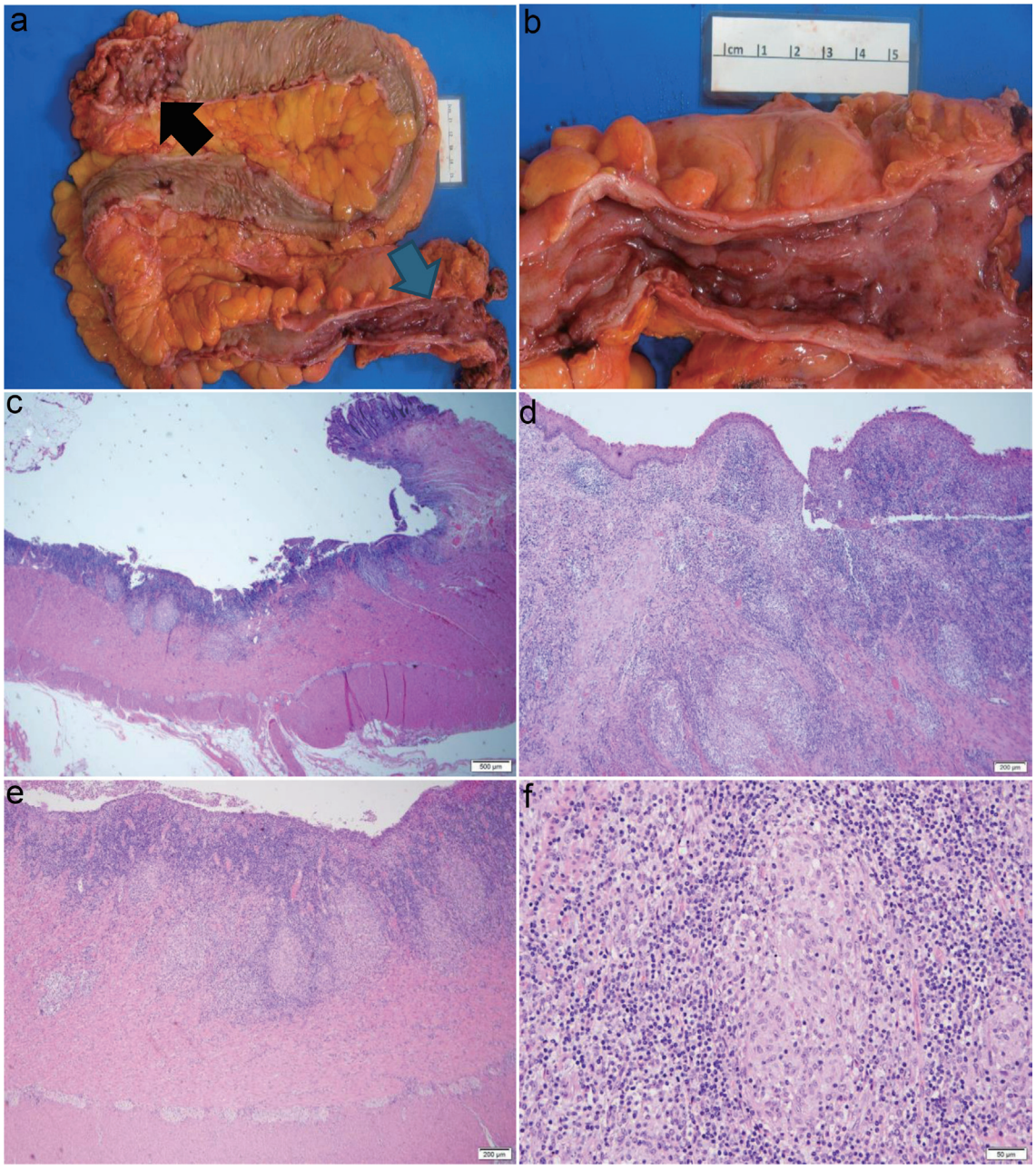

Fig. 1. Gross and histopathologic features in Hermansky-Pudlak syndrome (HPS) proctocolectomy specimen. Total proctocolectomy with mucosal ulceration and pseudopolyps in the cecum (a, black arrow) and ano-rectum (a, blue arrow), with higher magnification of the ano-rectum (b). Ano-rectum (c) and cecum (d) show diffuse ulcerative inflammation and numerous non-caseating granulomas involving the mucosa and submucosa. Granulomas superficially extend into the muscularis propria (e). Well-formed granulomas are mainly located deep to ulcers and surrounded by intense lymphocyte infiltration (f). Magnification: a, 1×; b, 2×; c, 20×; d, 40×; e, 40×; f, 100×.

termed metastatic Crohn's; however, cutaneous involvement appears to be much more common in Crohn's disease patients.[2,10,14] In the ulcerative areas of the cecum and ano-rectum, the unique morphologic features that differentiated this case from Crohn's disease were ulcerative and granulomatous inflammation with extensive lymphocyte and plasma cell infiltrates, predominantly limited to the mucosa and submucosa, and superficially extending into the muscularis propria. No transmural inflammation or transmural granulomas were identified.

T lymphocytes and FoxP3-labeled T regulatory cells play a crucial role in granuloma formation. It has been well documented that T lymphocytes and T regulatory cells accumulate and proliferate in the granulomas of sarcoidosis and Mycobacterium tuberculosis, playing a crucial role in granuloma formation, persistence, and resolution.[15] In the present case, CD3-labeled T lymphocytes and FoxP3-labeled T regulatory cells were well identified in or surrounding the granulomas, with only a few CD20-labeled B cells present. These results support the role of T lymphocytes and T regulatory cells in

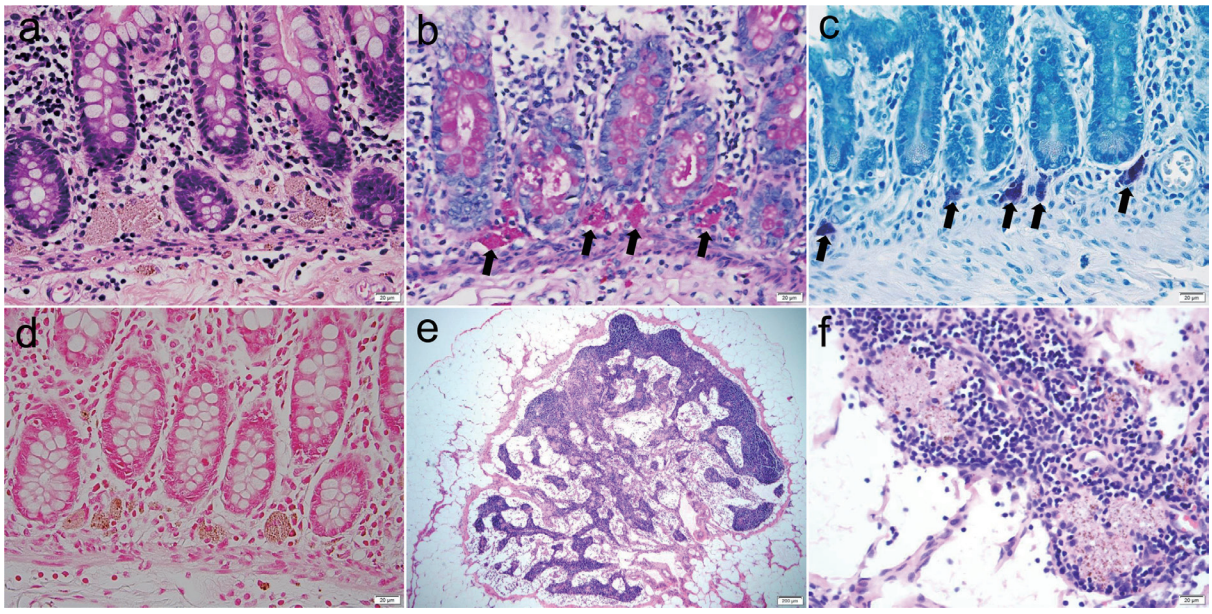

Fig. 2. Pigment-laden histiocytes in proctocolectomy specimen. Numerous pigment-laden histiocytes are identified in the lamina propria of the deep mucosa in the normal colon (a). Pigmented material is periodic acid–Schiff-diastase (PAS-D) (arrows pointing to pink color-stained cells in the lamina propria, b) and acid-fast bacilli (AFB) (arrows pointing to purple color-stained cells in the lamina propria, c) positive and negative for iron stain (d). Numerous pigment-laden histiocytes are present in pericolonic lymph nodes (e, f). Magnification: a-f, 200×.

the formation of non-caseating granulomas.

Hermansky and Pudlak, Czechoslovakian physicians, first described two patients with oculocutaneous albinism, prolonged bleeding, and pigmented macrophages in the bone marrow; thus, this disease was named HPS. The clinical diagnosis of HPS can be established in a proband with hypo-

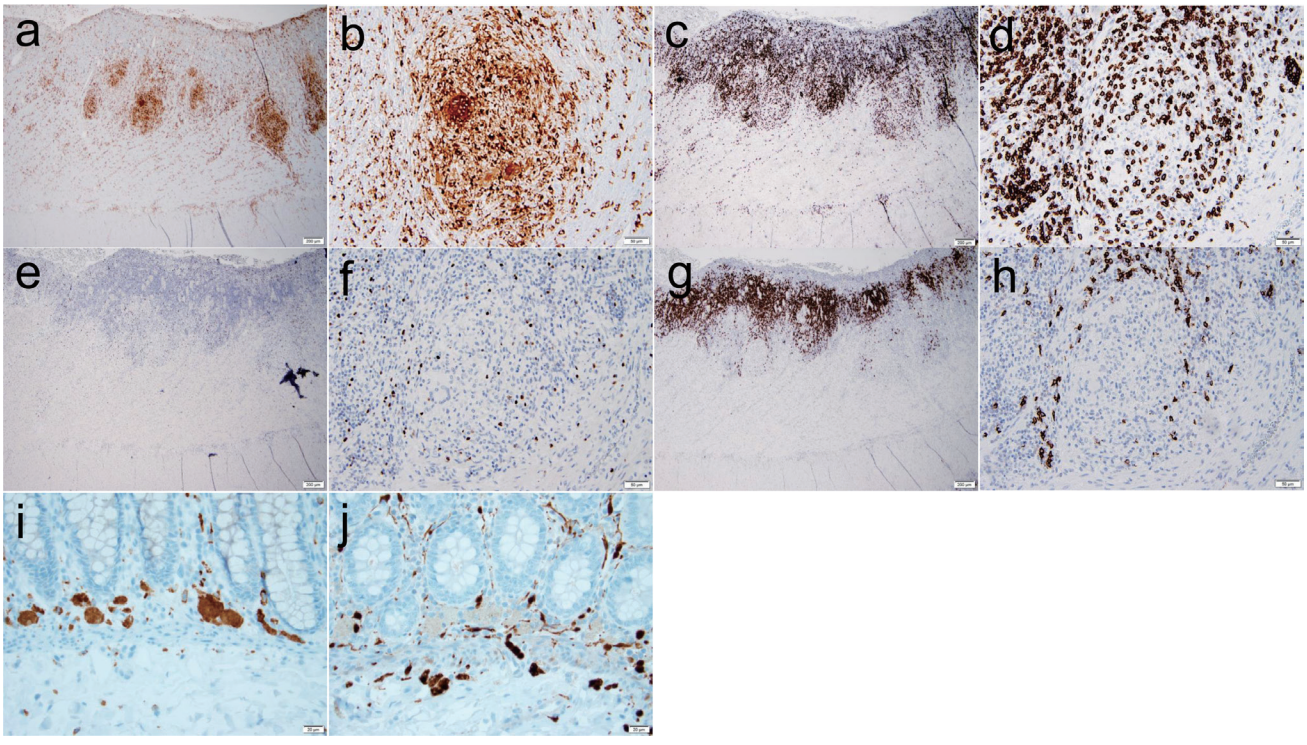

Fig. 3. Histochemical and Immunohistochemical Features in Hermansky-Pudlak syndrome (HPS). Granulomas highlighted by CD68 (a, b). Numerous CD3-positive T cells (c, d) and FoxP3-positive T regulatory cells (e, f) surround and infiltrate the granulomas. CD20-positive B cells at the surface of the ulcer (g) and at the periphery of the granuloma (h). Pigmented histiocytes in normal colon labeled by CD68 (i, j). Magnification: a, 40×; b, 100×; c, 40×; d, 100×; e, 40×; f, 100×; g, 40×; h, 100×; i, 200×; j, 200×.

pigmentation of the skin and hair, characteristic eye findings, and the demonstration of the absence of platelet delta granules (dense bodies) on electron microscopy. Identification of biallelic pathogenic variants in eleven genes (*AP3B1*, *AP3D1*, *BLOC1S3*, *BLOC1S5*, *BLOC1S6*, *DTNBP1*, *HPS1*, *HPS3*, *HPS4*, *HPS5*, or *HPS6*) confirms the diagnosis of HPS if clinical features are inconclusive. So far, eight different subtypes of HPS have been reported in the literature (HPS-1 to HPS-8).[16] It has been reported that at least eleven genes coding for proteins in the BLOC-1, BLOC-2, BLOC-3, and AP-3 complexes are implicated in the process of HPS.[7] Genotyping shows that patients with biallelic variants in HPS1, HPS3, HPS4, HPS6, or HPS7 are associated with colitis or inflammatory bowel disease.[17,18] Clear clinical presentation—particularly hypopigmentation of the skin and hair, colitis, and platelet dysfunction—facilitated the diagnosis in our case, and no further subtyping was performed.

Clinically, the patient presented here had extensive perianal and perineal disease but did not exhibit other definitive cutaneous involvement by granulomatous inflammation. Importantly, these patients tend not to respond to traditional therapies for Crohn's disease and often require extensive surgical management. This may point to a difference between the two diseases at a molecular and biological level. However, there have been documented cases of some patients—though not all—responding well to infliximab, an immunomodulatory drug used in the treatment of Crohn's disease. This suggests that the tumor necrosis factor-alpha pathway may play a key or partial role in the pathogenesis of both HPS and Crohn's disease.[12,19] Further research into the biological mechanisms of this disease process and the functional genes linked to HPS is necessary to better understand this entity. Much of our understanding of HPS is based on murine models due to the lack of available human tissue for studies.[20] If we can better understand the pathogenesis of this process, perhaps more targeted therapies can be developed for these unique patients.

Conclusions

Our case clearly indicates that the identification of 1) ceroid-laden histiocytes in the colonic mucosa and 2) a chronic, active granulomatous inflammatory process limited to the mucosa and submucosa are key morphologic features of HPS that distinguish it from active Crohn's colitis. Further study of T cell-associated immune mechanisms and tumor necrosis factor-alpha pathway involvement in HPS will be crucial for understanding the pathogenesis of HPS and providing the foundation for biologic or immune-targeted therapies.

Acknowledgments

We thank the Department of Pathology for supporting faculty research initiatives and the Pathology Network Shared Resource of Roswell Park Comprehensive Cancer Center for their technical assistance.

Funding

This study was partially supported by an NIH R01 Award to GYY (R01DK137885).

Conflict of interest

One of the authors, GYY, has been an editorial board member of *Journal of Clinical and Translational Pathology* since May 2021. Other authors declared no potential conflicts of interest regarding the research, authorship, and/or publication of this article.

Author contributions

Conceptualization, methodology, final analysis, writing, review, and editing (AM, MSR, GY), methodology, data curation and analysis, original draft, and editing (AM). All authors have approved the final manuscript.

Ethical statement

The protocol was approved by the Institutional Review Board of Northwestern Memorial Hospital (Chicago, IL). Individual consent for this retrospective analysis was waived. Written informed consent was obtained from the patient for the publication of this case report.

Data sharing statement

All data used to support the findings of this study are included in the article.

References

[1] Felipez LM, Gokhale R, Guandalini S. Hermansky-Pudlak syndrome: severe colitis and good response to infliximab. J Pediatr Gastroenterol Nutr 2010;51(5):665–667. doi:10.1097/MPG.0b013e3181d2dcbb, PMID:20543722.
[2] Weitz N, Patel V, Tlougan B, Mencin A, Kadenhe-Chiweshe A, Morel KD, *et al*. Metastatic cutaneous involvement of granulomatous colitis in Hermansky-Pudlak syndrome. Pediatr Dermatol 2013;30(6):e278–e280. doi:10.1111/j.1525-1470.2012.01728.x, PMID:22471786.
[3] Koulali H, Azzmouri S, Tajir M, Zerrouki K, Haloui A, Elmqaddem O, *et al*. Granulomatous Colitis Due to Hermansky-Pudlak Syndrome. ACG Case Rep J 2024;11(11):e01477. doi:10.14309/crj.0000000000001477, PMID:39493955.
[4] Li W, Hao CJ, Hao ZH, Ma J, Wang QC, Yuan YF, *et al*. New insights into the pathogenesis of Hermansky-Pudlak syndrome. Pigment Cell Melanoma Res 2022;35(3):290–302. doi:10.1111/pcmr.13030, PMID:35129281.
[5] Ambur AB, Nyckowski TA. Hermansky-Pudlak syndrome. J Osteopath Med 2022;122(11):601–602. doi:10.1515/jom-2022-0068, PMID:35670551.
[6] Carmona-Rivera C, Golas G, Hess RA, Cardillo ND, Martin EH, O'Brien K, *et al*. Clinical, molecular, and cellular features of non-Puerto Rican Hermansky-Pudlak syndrome patients of Hispanic descent. J Invest Dermatol 2011;131(12):2394–2400. doi:10.1038/jid.2011.228, PMID:21833017.
[7] Pennamen P, Le L, Tingaud-Sequeira A, Fiore M, Bauters A, Van Duong Béatrice N, *et al*. BLOC1S5 pathogenic variants cause a new type of Hermansky-Pudlak syndrome. Genet Med 2020;22(10):1613–1622. doi:10.1038/s41436-020-0867-5, PMID:32565547.
[8] Mora AJ, Wolfsohn DM. The management of gastrointestinal disease in Hermansky-Pudlak syndrome. J Clin Gastroenterol 2011;45(8):700–702. doi:10.1097/MCG.0b013e3181fd2742, PMID:21085008.
[9] Grucela AL, Patel P, Goldstein E, Palmon R, Sachar DB, Steinhagen RM. Granulomatous enterocolitis associated with Hermansky-Pudlak syndrome. Am J Gastroenterol 2006;101(9):2090–2095. doi:10.1111/j.1572-0241.2006.00733.x, PMID:16848805.
[10] Hazzan D, Seward S, Stock H, Zisman S, Gabriel K, Harpaz N, *et al*. Crohn's-like colitis, enterocolitis and perianal disease in Hermansky-Pudlak syndrome. Colorectal Dis 2006;8(7):539–543. doi:10.1111/j.1463-1318.2006.01046.x, PMID:16919103.
[11] Schinella RA, Greco MA, Cobert BL, Denmark LW, Cox RP. Hermansky-Pudlak syndrome with granulomatous colitis. Ann Intern Med 1980;92(1):20–23. doi:10.7326/0003-4819-92-1-20, PMID:7350869.
[12] Seward SL Jr, Gahl WA. Hermansky-Pudlak syndrome: health care throughout life. Pediatrics 2013;132(1):153–160. doi:10.1542/peds.2012-4003, PMID:23753089.
[13] Ohbayashi C, Kanomata N, Imai Y, Ito H, Shimasaki H. Hermansky-Pudlak syndrome; a case report with analysis of auto-fluorescent ceroid-like pigments. Gerontology 1995;41(Suppl 2):297–303. doi:10.1159/000213751, PMID:8821340.
[14] Salvaggio HL, Graeber KE, Clarke LE, Schlosser BJ, Orlow SJ, Clarke JT. Mucocutaneous granulomatous disease in a patient with Hermansky-Pudlak syndrome. JAMA Dermatol 2014;150(10):1083–1087. doi:10.1001/jamadermatol.2014.147, PMID:24989352.
[15] Taflin C, Miyara M, Nochy D, Valeyre D, Naccache JM, Altare F, *et al*. FoxP3+ regulatory T cells suppress early stages of granuloma formation but have little impact on sarcoidosis lesions. Am J Pathol 2009;174(2):497–508. doi:10.2353/ajpath.2009.080580, PMID:19147826.
[16] Thielen N, Huizing M, Krabbe JG, White JG, Jansen TJ, Merle PA, *et al*.

Hermansky-Pudlak syndrome: the importance of molecular subtyping. J Thromb Haemost 2010;8(7):1643–1645. doi:10.1111/j.1538-7836.2010.03898.x, PMID:20456745.
[17] O'Brien KJ, Parisi X, Shelman NR, Merideth MA, Introne WJ, Heller T, *et al*. Inflammatory bowel disease in Hermansky-Pudlak syndrome: a retrospective single-centre cohort study. J Intern Med 2021;290(1):129–140. doi:10.1111/joim.13224, PMID:33423334.
[18] Bhattad S, Libre M, Choi JM, Mohite RS, Singh N, Markle JG. Hermansky-Pudlak syndrome with early onset inflammatory bowel disease due to loss of dysbindin expression. Eur J Med Genet 2023;66(7):104786. doi:10.1016/j.ejmg.2023.104786, PMID:37172778.
[19] Kouklakis G, Efremidou EI, Papageorgiou MS, Pavlidou E, Manolas KJ, Liratzopoulos N. Complicated Crohn's-like colitis, associated with Hermansky-Pudlak syndrome, treated with Infliximab: a case report and brief review of the literature. J Med Case Rep 2007;1:176. doi:10.1186/1752-1947-1-176, PMID:18067668.
[20] El-Chemaly S, Young LR. Hermansky-Pudlak Syndrome. Clin Chest Med 2016;37(3):505–511. doi:10.1016/j.ccm.2016.04.012, PMID:27514596.