Surveillance of Isolated Colonic Langerhans Cell Histiocytosis in an Adult: A Case Report

Sandhya Kolagatla, MD1*, Joshua K. Jenkins, MS2*, Joseph Elsoueidi, MD3, and Nagabhishek Moka, MD4

Abstract
Langerhans cell histiocytosis (LCH) is a rare disorder involving the proliferation of myeloid-derived dendritic cells. It most commonly affects children aged less than 1 to 2 years old. Langerhans cell histiocytosis in adults is more uncommon with an estimated incidence of 1 to 2 cases per 1 million. Langerhans cell histiocytosis can present as a multisystem or single-system disease involving bone, skin, lymph nodes, and various other organ systems. The spectrum of symptoms can range from asymptomatic disease, localized skeletal or dermatologic manifestations, or systemic symptoms of weight loss, fever, and other organ-specific manifestations. Langerhans cell histiocytosis with isolated involvement of the gastrointestinal tract is exceedingly rare with only approximately 14 cases reported in the English medical literature. Here, we report an additional case of LCH presenting as an isolated colonic polyp. This patient was also followed for a 3-year period after initial diagnosis to provide valuable follow-up data. With this case, we aim to contribute to the literature by further characterizing the presentation, treatment, and disease course of this rare phenomenon and provide valuable data to guide future screening guidelines for isolated LCH polyps in the colon.

Keywords
hematology oncology, histiocytosis, Langerhans cell, pathology, polyp

Introduction
Langerhans cells (LCs) are the major antigen-presenting cells of the epidermis.1 Langerhans cell histiocytosis (LCH) is a neoplasm of these cells, which is characterized by the accumulation of CD1a+/CD207+ dendritic cells within granulomatosis lesions. These cells are functionally immature and have the ability to infiltrate most organ systems within the human body.1,2 Langerhans cell histiocytosis has both multisystem and single-system variants.1 The multisystem variant (formerly termed Letterer-Siwe disease) may have skin, lung, liver, bone, bone marrow, and lymph node involvement. This form is classically seen in children 2 years old or younger.1 Another form of LCH with multisystem involvement manifests as a triad (formerly known as Hand-Schuller-Christian disease) which consists of diabetes insipidus, exophthalmos, and osteolytic bone lesions. This form is most commonly reported in children between the ages of 2 and 6 years old. The single-system variant manifests as either a localized bony lesion in a child between the ages of 7 and 12 or an isolated, spontaneously resolving skin lesion (formerly known as Hashimoto Pritzker syndrome) presenting in a neonate.1 Langerhans cell histiocytosis involvement of the gastrointestinal (GI) tract, however, is extremely rare.

Langerhans cell histiocytosis is much more common in children than adults. The estimated incidence of LCH in children younger than 15 years old is approximately 4.6 cases per 1 million1 compared with an estimated adult incidence of approximately 1 to 2 cases per 1 million.4 The clinical presentation of LCH is also highly variable across pediatric and adult cases. In cases of GI involvement, pediatric patients

1Appalachian Regional Healthcare, Whitesburg, KY, USA
2Lincoln Memorial University–DeBusk College of Osteopathic Medicine, Harrogate, TN, USA
3University of Kentucky, Lexington, USA
4Appalachian Regional Healthcare, Hazard, KY, USA
5Sandhya Kolagatla and Joshua K. Jenkins are co-first authors.

Received August 20, 2022. Revised October 18, 2022. Accepted November 8, 2022.

Corresponding Author:
Joshua K. Jenkins, MS, Research, Lincoln Memorial University–DeBusk College of Osteopathic Medicine, 6965 Cumberland Gap Parkway, Harrogate, TN 37752, USA.
Email: josh.jenkins@lmunet.edu

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).
have displayed symptoms, such as failure to thrive, bloody diarrhea, anemia, and hypoalbuminemia. In adult cases of GI involvement, however, many patients have been found to be asymptomatic with LCH lesions being discovered on routine colorectal cancer screening. When symptoms are present in these adult cases, signs and symptoms of constipation, dysphagia, anemia, and cecal volvulus have been reported.

Diagnosis is typically made via histologic examination of a biopsied lesion. Histologically, LCH cells present as large oval cells with abundant cytoplasm and bean-shaped nuclei on hematoxylin and eosin (H&E) staining. These pathologic cells stain positively with antibodies to S100, CD1a, and anti-Langerin (CD207). Positive staining with CD1a or CD207 confirms the diagnosis of LCH. Electron microscopy can also yield a diagnosis, which demonstrates intracytoplasmic rod-shaped organelles with a terminal vesicular dilation giving the classic appearance of tennis racket (Birbeck) granules. Langerhans cell histiocytosis cells also have the ability to activate other immunologic cells; therefore, light microscopy of LCH lesions will typically reveal a background containing other histiocytes, lymphocytes, macrophages, neutrophils, eosinophils, and fibroblasts. Studies in recent years have also shown B-raf (BRAF) V600E mutations in 35% to 69% of LCH cases.

In a recent literature search by Yilmaz et al, 35 studies reporting adult cases of LCH involving the GI system were found. Only 14 of those cases involved isolated cases of colonic polyps. We report an additional case of LCH involving an isolated colonic polyp in an adult male patient. This case is unique in that extensive follow-up data were collected over a period of 3 years after the initial diagnosis. Currently, no national or organizational guidelines exist for monitoring isolated LCH manifesting as colon polyps in adults after resection.

**Case Description**

A 42-year-old Caucasian man presented to the outpatient gastroenterology clinic with chronic watery diarrhea over a 2-year time period. He noted associated cramping abdominal pain, but denied association with food consumption, unexplained weight loss, melena, hematochezia, fever, nausea, and vomiting. His past medical history was significant for anxiety, hypertension, gastroesophageal reflux disease (GERD), and stroke. His medication list consisted of antacids, ranitidine, and aspirin. His family history was significant for Crohn’s disease in both his father and grandfather. His social history was significant for a 50-pack-year smoking history. Physical examination was unremarkable with the exception of morbid obesity. Laboratory values, including a complete blood count (CBC), comprehensive metabolic panel (CMP), and lactate dehydrogenase (LDH) were all within normal limits. The patient was scheduled for outpatient esophagogastroduodenoscopy (EGD) and colonoscopy for further evaluation. Esophagogastroduodenoscopy revealed chronic active gastritis of the antrum. Biopsies from the antrum revealed *Helicobacter pylori*. Colonoscopy revealed an isolated 1-cm polyp in the ascending colon (Figure 1). The polyp was resected and sent for histopathologic evaluation, and the patient was started on a 14-day regimen of pantoprazole 40-mg twice daily, amoxicillin 1-g twice daily, and metronidazole 500-mg 3 times daily.

Hematoxylin and eosin staining of the colon polyp (Figure 2) demonstrated gastrointestinal mucosa with proliferation of Langerhans cells, characterized by abundant pale eosinophilic cytoplasm, irregular and elongated nuclei with prominent nuclear grooves and folds, fine chromatin, and indistinct nucleoli with conspicuous eosinophils in the background.
revealed scattered positivity for CD68 (Figure 3A) and strong positivity for S100 (Figure 3B) and CD1a (Figure 3C). Immunohistochemical staining demonstrated negativity for CD117, SMA, CMV, and HSV-2. The histopathological findings were found to be consistent with a diagnosis of colonic LCH. Mutation detection testing was performed, consisting of BRAF V600E Exon 15 (1799 T>A) via polymerase chain reaction (PCR) and SNaPShot multiplex primer extension, which both resulted negative.

The patient followed up approximately 2 months after endoscopy. He reported completing the H pylori treatment regimen and noted significant improvement in his chronic diarrhea symptoms. Positron emission tomography (PET) and a bone marrow biopsy were performed to rule out systemic involvement of LCH. Both testing modalities revealed no evidence of disease. Two-years after initial diagnosis, the patient underwent repeat colonoscopy and PET scan. Each modality continued to demonstrate no evidence of residual or recurrent disease. Three years after initial diagnosis, the patient was evaluated in the outpatient clinic during an additional follow-up visit. The patient continued to remain asymptomatic.

**Discussion**

Adult colonic LCH is exceptionally rare. Gastrointestinal tract LCH is most often found in male children with high-risk multisystem disease and a multitude of symptoms. In contrast, adult cases are predominantly female with isolated findings in the GI tract and more often present asymptotically.5 In adults with GI tract involvement, incidental polyps in the colon and small intestine tend to be the most common presentation.5

The cause and pathogenesis of LCH remain unclear. The suspected pathogenesis has evolved since initial reports of the disease in the early 1900s. After the invention of the electron microscope in the 1930s, the Birbeck granule ultrastructure was discovered in the pathologic histiocytes of LCH lesions. At the time, only epidermal LCs were known to contain Birbeck granules, thus leading to the initial assumption that the pathologic histiocytes in LCH originated from the epidermal dendritic cells themselves.2 Contrasting this theory is the belief that these histiocytes derive from a common myeloid progenitor cell—the macrophage-dendritic cell progenitor (MDP)—which is the stage of commitment to the mononuclear phagocyte system.2,10

It is known that 30% to 60% of LCH cases harbor BRAF V600E proto-oncogene mutations.8,11,12 This mutation results in constitutive, RAS-independent activation of the downstream kinases extracellular signal-regulated kinase (ERK) and mitogen-activated kinase (MAPK)/ERK kinase (MEK).13 Most BRAF mutations are found on exons 11 and 15 with the T1799A mutation having valine substituted for glutamic acid.11 Berres et al2 proposes that the misguided myeloid differentiation model of LCH pathogenesis may account for the broad spectrum of clinical presentations, extent of disease severity, and dissemination based on the stage at which the molecular mutation occurs in the MAPK molecular pathway. The patient in the present case was tested for BRAF mutation on exon 15 along with another method for mutation detection which both resulted negative. We suspect the absence of severe multisystem disease may correlate with this absence of genetic mutation.

Treatment of LCH especially in adults is not clear due to the rarity of disease. Treatment is generally defined by factors such as age, extent of disease, and risk factors. Therapy usually focuses on the status of BRAF mutation as treatment against BRAF has demonstrated a favorable prognosis. One study revealed a favorable response to vinblastine, a BRAF inhibitor, in combination with steroids in children; however, due to the risk of neurotoxicity in adults, cytarabine is preferred.14 Another study revealed a favorable response to cytarabine, prednisone, and cladribine in multisystem LCH involving the colon, rectum, and biliary tract.12 In the present case, the patient received no chemotherapy or systemic therapy given the isolated presentation involving a single ascending colon polyp and the absence of BRAF mutation. Currently, systemic chemotherapy is indicated only for multisystem disease and cases of unresponsive single-system disease.15

![Figure 3](image-url)
Due to the uncommon occurrence of these lesions, no current standard of care exists regarding follow-up and surveillance. Depending on the location and extent of the initial occurrence, clinicians have offered annual systemic imaging and endoscopic workup if GI tract involvement is found. This case provides unique follow-up data 3 years after the initial diagnosis of colonic LCH in an adult patient. Future efforts should be aimed toward the creation of screening guidelines after complete resection of colonic polyps with pathologic findings of LCH to improve the quality and cost of care.

Conclusion

To summarize, we describe a case of an asymptomatic adult male patient with single system, unifocal LCH of the colon presenting as a polyp found incidentally during colonoscopy. Gastrointestinal tract involvement with LCH in adults is very rare. Langerhans cell histiocytosis should be considered in the differential when polyps demonstrating strong positivity for S100 and CD1a on IHC staining are resected from the colon. On discovery, it should be remembered that treatment is based on the extent of dissemination and the presence of BRAF mutation. Systemic imaging and bone marrow biopsy may be performed to establish a diagnosis of multisystem versus single-system disease. Given the rarity of diagnosis and lack of universally accepted chemotherapy protocol, a multidisciplinary approach for management is vital. National organizations should work toward creating guidelines regarding colonic polyps with LCH features on histology to guide clinicians in providing appropriate and effective care.

Acknowledgments

No acknowledgments are necessary.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Written informed consent was obtained from the patient for their anonymized information to be published in this article.

Prior Presentation of Abstract Statement

This case was presented as an abstract at the Southern Regional Meeting in New Orleans on February 13, 2020.

ORCID iDs

Sandhya Kolagatla https://orcid.org/0000-0002-9749-3723
Joshua K. Jenkins https://orcid.org/0000-0002-9875-4286
Nagabhishek Moka https://orcid.org/0000-0002-4906-0106

References

1. Bologna JL, Schaffer JV, Duncan KO, Cerroni L. Histiocytoses. In: Dermatology essentials. 2nd ed. Amsterdam, The Netherlands: Elsevier; 2022:789-794.
2. Berres ML, Merad M, Allen CE. Progress in understanding the pathogenesis of Langerhans cell histiocytosis: back to Histiocytosis X. Br J Haematol. 2015;169(1):3-13.
3. PDQ Pediatric Treatment Editorial Board. Langerhans cell histiocytosis treatment (PDQ®): health professional version. In: PDQ Cancer Information Summaries [Internet]. Bethesda, MD: National Cancer Institute (US); 2002. http://www.ncbi.nlm.nih.gov/books/NBK65799/.
4. Baumgartner I, von Hochstetter A, Baumert B, Luetolf F, Follath F. Langerhans’-cell histiocytosis in adults. Med Pediatr Oncol. 1997;28(1):9-14.
5. Singh AD, Montgomery EA. Gastrointestinal tract Langerhans cell histiocytosis: a clinicopathologic study of 12 patients. Am J Surg Pathol. 2011;35(2):305-310.
6. Chikwava K, Jaffe R. Langerin (CD207) staining in normal pediatric tissues, reactive lymph nodes, and childhood histiocytic disorders. Pediatr Dev Pathol. 2004;7(6):607-614.
7. Favara BE, Feller AC, Pauli M, et al. Contemporary classification of histiocytic disorders. The WHO committee on histiocytic/reticulum cell proliferations. Reclassification working group of the histiocyte society. Med Pediatr Oncol. 1997;29(3):157-166.
8. Badalian-Very G, Vergilio JA, Degar BA, et al. Recurrent BRAF mutations in Langerhans cell histiocytosis. Blood. 2010;116(11):1919-1923.
9. Yilmaz N. Langerhans cell histiocytosis mimicking Crohn’s disease: a case report and review of the literature. Ann Clin Case Rep. 2020;5:1817.
10. Merad M, Sathe P, Helft J, Miller J, Mortha A. The dendritic cell lineage: ontogeny and function of dendritic cells and their subsets in the steady state and the inflamed setting. Annu Rev Immunol. 2013;31:563-604.
11. Alayed K, Medeiros LJ, Patel KP, et al. BRAF and MAP2K1 mutations in Langerhans cell histiocytosis: a study of 50 cases. Hum Pathol. 2016;52:61-67.
12. Therrien A, El Haffaf Z, Vartielle-Bladou C, Côté-Daigneault J, Nguyen BN. Langerhans cell histiocytosis presenting as Crohn’s disease: a case report. Int J Colorectal Dis. 2018;33(10):1501-1504.
13. Maurer G, Tarkowski B, Baccarini M. Raf kinases in cancer roles and therapeutic opportunities. Oncogene. 2011;30(32):3477-3488.
14. Abla O, Weitzman S. Treatment of Langerhans cell histiocytosis: role of BRAF/MAPK inhibition. Hematology Am Soc Hematol Educ Program. 2015;2015:565-570.
15. Arici M, Girschikofsky M, Généreau T, et al. Langerhans cell histiocytosis in adults. Report from the International Registry of the Histiocyte Society. Ear J Cancer. 2003;39(16):2341-2348.