Incidental Gastric Langerhans Cell Histiocytosis and Synchronous Adenocarcinoma of the Colon: An Interesting Case Report and Literature Review

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Abstract. Background/Aim: Langerhans cell histiocytosis (LCH) is an uncommon disorder characterized by an abnormal monoclonal proliferation of pathologic Langerhans cells. The clinical presentation of LCH is very unpredictable, ranging from single-system limited disease to severe multi-organ disease with a high mortality rate. LCH usually affects children and very rarely adults. The most common body parts affected by LCH are the bones, skin, lungs, pituitary glands, and lymph nodes. Gastrointestinal tract involvement by LCH is exceptionally rare, and only a few cases have been reported. Case Report: We present the case of a 50-year-old woman who was referred to our clinic by her primary care physician for an upper endoscopy and colonoscopy and was diagnosed with H. pylori–related gastritis and a synchronous gastric LCH and primary colonic adenocarcinoma. We describe the histologic characteristics and clinical implications of the LCH diagnosis. A review of the published literature revealed that LCH presenting as a gastric solitary lesion is rare. Conclusion: This case highlights the importance of recognizing this rare condition to ensure proper patient follow-up.

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Langerhans cell histiocytosis (LCH) is a clonal proliferation of epidermal dendritic cells (i.e., Langerhans cells) that is usually seen in children between 1 and 3 years old. However, very rarely, the disease can also occur in adults. Though LCH is more common in male children (male:female ratio of 2:1), among adults, it has a female predominance (1, 2). Gastrointestinal (GI) tract involvement by LCH can manifest in both children and adults, with female predominance. The estimated annual incidence of LCH is 4 to 8 cases per million children and 1 to 2 cases per million adults (3). The clinical presentation of LCH is highly variable, ranging from mild single-system disease to severe multi-organ disease with high mortality (4).

Langerhans cells within the lesion are characterized by immunohistochemical positivity for S100 and CD1a. Ultrastructurally, Birbeck granules are the hallmark of the disease (5). In adults, LCH may affect the skin, with vesicles, papules, and nodules that can become ulcerated, or may affect the lungs and bones (6, 7).

Here, we present a case of gastric LCH from a patient with Helicobacter pylori–related gastritis and a synchronous adenocarcinoma of the colon.

Case Report

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

An obese 50-year-old woman with a clinical history of Helicobacter-positive gastritis, gastro-esophageal reflux disease (GERD) without esophagitis, and iron-deficiency anemia was referred by her primary care physician for an esophagogastroduodenoscopy and colonoscopy to exclude occult gastrointestinal bleeding. Esophagogastroduodenoscopy revealed patchy mild inflammation characterized by erythema in the gastric body and antrum. Cold representative biopsies of the antrum and gastric body mucosa were obtained (Figure 1A). On colonoscopy, a single sessile mass measuring 40 mm
in greater dimensions was found in the sigmoid colon. Cold biopsies were taken. Microscopic examination of the colonic lesion revealed a moderately differentiated invasive adenocarcinoma arising from an adenoma. Immunostaining for DNA mismatch repair proteins (MMRs) showed no loss in expression of MLH1, MSH2, MSH6, or PMS2 proteins, indicating a low probability of microsatellite instability.

The patient was evaluated to rule out multisystem involvement by LHC and to determine the clinical stage of the adenocarcinoma. A whole-body bone scan, abdominal ultrasonography, and thoracic computed tomography (CT) scan were performed, all of which revealed no evidence of multifocal LCH or metastatic colon cancer. The patient was referred to a surgeon and oncologist for clinical and therapeutic evaluation of the colon adenocarcinoma and LCH.

The colon cancer was surgically resected. The patient underwent a left subtotal colectomy demonstrating a 3×2×1 cm adenocarcinoma involving the muscularis propria and pericolonic soft tissue, with metastatic adenocarcinoma in 1 of 15 regional lymph nodes. The colonic cancer was staged as pT3N1M0. The abdomen and pelvis CT scan revealed no evidence of metastatic colon cancer. The patient received adjuvant chemotherapy with 12 cycles of FOLFOX-6 [leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin]. The *H. pylori*–related gastritis was treated with triple antibiotic therapy.

Methods. The gastric biopsy was composed of 3 fragments of tan tissue measuring up to 3×2×2 mm. A 4 μm tissue section was used for the conventional hematoxylin and eosin (H&E) stain. Additional 4 μm tissue sections were submitted for immunohistochemical (IHC) review. The slides were stained using a Ventana Discovery XT automated system (Ventana Medical Systems, Tucson, AZ, USA) as per the manufacturer’s protocol with proprietary reagents. The slides were deparaffinized on the automated system with EZ Prep solution (Ventana). A heat-induced antigen retrieval method was used in Cell Conditioning 1 (Ventana). The slides were counterstained with hematoxylin. Finally, the slides were dehydrated and cover-slipped as per normal laboratory protocols. Each stain contained appropriate positive and negative controls.

Results

Microscopic examination of the gastric mucosa revealed a monotonous proliferation of atypical histiocytic-like cells with abundant pink granular cytoplasm. The nuclei within these cells were lobulated, with frequent grooves and inconspicuous nucleoli (Figure 1A and 1B). The atypical cells were immunohistochemically positive for CD-1a,
Langerin, S100, and Cyclin D1 (Figure 1C, D, E, and F, respectively) and negative for cytokeratin (AE1/AE3), CD117, CD68, CD20, and CD3. These morphological, immunohistochemical, and molecular results supported the diagnosis of LCH. The strong cyclin D1 expression suggested a neoplastic LCH lesion, which was supported by the BRAF immunohistochemical analysis showing weak positivity (Figure 1G); the BRAF molecular analysis also revealed a BRAF V600E mutation. In addition, the biopsy showed a background of H pylori–positive chronic active gastritis. The immunohistochemical stain for H pylori was diffusely positive (Figure 1H).

**Discussion**

LCH is a complex and poorly understood disorder characterized by abnormal monoclonal neoplastic proliferation of myeloid stem cells and an accompanying immune-inflammatory component (1-3).

Advances in diagnostic techniques have allowed for an improved understanding of histiocytic disorders, therefore in 2016, a group of experts reclassified histiocytic disorders into five groups based on clinical, histologic, and molecular aspects (16). According to these new guidelines, LCH is classified within the L Group (Langerhans-related group). As a result, the previously used terms (eosinophilic granuloma, Hashimoto-Pritzker syndrome, Hand- Schüller-Christian disease, and Letterer–Siwe disease) were replaced by a classification system that divided LCH into four different subgroups depending on the number of organs or systems involved. The disease outcomes are monitored using a disease activity score differentiating between a high-risk multisystemic condition, a low-risk multisystemic condition, and a single-organ (or system) condition (17). This classification focuses on the prognosis of the disease and provides guidelines for the most appropriate therapy.

In adult patients, LCH most frequently affects the lungs, bones, and skin, and the involvement of the GI tract is uncommon. In 2011, Singh et al. published a large series of 12 patients with GI tract–involved LCH (8). The author concluded that, in adults, LCH usually presents incidentally as a solitary colorectal polyp and that, in rare cases, LCH can later evolve into a systemic disease, requiring close patient follow-up (8). Presentation of LCH as a gastric lesion is a rare event and only a few cases have been reported (8-15). In most patients with gastric LCH, the gastric lesion was solitary, as it was in our case, and polyoid or elevated.

Interestingly, in the case reported here, LCH was associated with a concomitant H pylori–related chronic active gastritis. Only a few similar cases have been previously published (18). H pylori infection has been related to gastric carcinogenesis. This association is based on epidemiological data; pathological changes observed in the gastric mucosa; and chemical products from bacteria, including CagA and VacA, that may induce DNA damage (19, 20). Though the role of these toxins in the insurgence of gastric lymphomas has been extensively studied, their role in the pathogenesis of LCH is unknown and requires further investigation.

Follow-up molecular studies for our case showed that the patient’s LCH tumor cells carried a BRAF V600 mutation. The presence of BRAF mutations in LCH have been previously reported. Badalian-Very et al., using a 115–cancer gene subset of the OncoMap panel, reported the presence of oncogenic BRAF V600E mutations in 57% of cases of LCH (21). BRAF V600E mutations have also been reported in some cases of pulmonary LCH, which was historically considered to be a purely reactive disease, linked to cigarette smoking in adults (22). The BRAF protein is part of the MAPK pathway (via mitogen-activated kinase proteins), which is responsible for the activation (phosphorylation) of proteins involved in the regulation of the cell cycle, proliferation, and differentiation (23). Oncogenic BRAF mutations have been identified in approximately 45% to 57% of patients with LCH (24-26). The presence of a BRAF mutation is a favorable finding, as it provides the opportunity for BRAF-inhibitor therapy for a patient (27).

Finally, the presence of a synchronous colonic adenocarcinoma in this patient was also interesting. A prior analysis showed that 32% (n=42/132) of patients with LCH had an additional malignancy (28). Of the malignancies, 74% were solid tumors, 17% were lymphomas, and 9% were other hematologic malignancies. Of the solid tumors, 10% were colorectal. In this analysis, it was noted that most malignancies were diagnosed before LCH, suggesting that LCH may represent a specific dendritic cell reaction to the malignancy (28). In our case, the LCH diagnosis was made concurrently with the colon cancer diagnosis. It is possible that the systemic increase in cytokines, activation of growth factors, and random DNA replicative errors may contribute to the insurgence of both neoplastic processes (29).

In summary, we reported the presence of gastric LCH in a patient with concomitant H pylori–related chronic active gastritis and a colorectal invasive adenocarcinoma.

**Conflicts of Interest**

The Authors have no relationship that could reasonably be perceived by a reader as potential conflicts of interest at the time of submission.

**Authors’ Contributions**

Linda B. Mora and Morgan Hough collected the data and drafted the manuscript; Lynn Moscinski critically reviewed the final version of the manuscript and provided some of the histologic pictures; Justin Gomez critically reviewed the final version of the manuscript.
and provided the clinical and endoscopic history; Dr. Domenico Coppola designed the study, evaluated the data and reviewed the final version of the manuscript.

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References

13 Wada R, Yagihashi S, Konta R, Ueda T and Izumiyama T: Gastric polyposis caused by multifocal histiocytosis X. Gut 33(7): 994-996, 1992. PMID: 1644344. DOI: 10.1136/gut.33.7.994


29 Tomasetti C, Li L and Vogelstein B: Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention. Science 355(6331): 1330-1334, 2017. PMID: 28336671. DOI: 10.1126/science.aaf9011

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