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Original Article

Isolated Langerhans cell histiocytosis of the stomach: a case report and literature review

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Abstract: Langerhans cell histiocytosis (LCH) is a rare disorder characterized by an abnormal proliferation of pathologic Langerhans cells. The clinical presentation of LCH is highly variable, ranging from a single-system limited disease, to severe, multi-organ diseases with high mortality. LCH usually affects children but very rarely involves adults. The most frequent sites for LCH are the bones, skin, lungs, pituitary gland, and lymph nodes. Gastrointestinal tract involvement by LCH is extremely rare, and only a few cases have been reported. We herein present anIsolated LCH of the stomach in adult. We have reviewed the histologic features and implications of this diagnosis.

Keywords: BRAF V600E, gastrointestinal tract, immunohistochemistry, Langerhans cell histiocytosis, stomach discomfort

Introduction

Langerhans cell histiocytosis is a rare disease with a variable clinical presentation, caused by monoclonal Langerhans cell proliferation. Its prognosis and treatment depend on the extent and severity of disease. Recent evidence suggests that it is a neoplastic proliferation potentially derived from amyeloid-lineage precursor. Involvement of the gastrointestinal tract in Langerhans cell histiocytosis is exceedingly rare and is most often encountered in the pediatric population, in the setting of systemic disease. We present a very rare case of an isolated LCH of the stomach in an adult, incidentally identified by stomach discomfort.

Materials and methods

Clinical data

A 37-year-old man was admitted to our department with a 10-month history of stomach discomfort, which became serious prior to the ingestion of food. There was no additional past medical or surgical history. Laboratory values, including urine analysis, complete blood cells count, erythrocyte sedimentation rate, and serum biochemistry (electrolytes, alkaline phosphatase, and liver function), were within the normal ranges. The chest radiograph was normal. Under the clinical diagnosis as gastritis, he was referred to a gastroenterologist for further evaluation. Because of this persistent and refractory stomach discomfort, an upper gastrointestinal endoscopy was recommended. Then gastroscopy examination revealed a less common inflammatory lesion, presenting as a mild erosion in the corpora ventriculi (**Figure 1**). A biopsy was performed, and the specimens were examined for histopathology.

Methods

All specimens were fixed in 10% buffered neutral formalin. The 4-μm thick continuous slices were made. Immunohistochemical staining was performed on all tissues, 4-μm sections of the paraffin-embedded tissue were deparaffinized, rehydrated in a graded series of alcohol and microwave-treated for 10 min in a citrate buffer (pH 6.0). Endogenous peroxidase activity was blocked using 0.3% hydrogen peroxide. The tissues were processed in an automatic immunohistochemical staining machine with the standard protocols (California, BIOCARE MEDICAL,

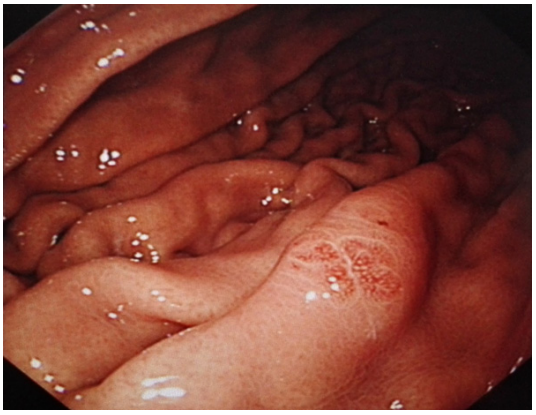

Figure 1. The gastroscopy examination revealed less common inflammationand a mild erosion in the corpora ventriculi.

LLC, Automatic immunohistochemistry, intelliPATH™ FLX) and DAKO Real™ EnVision™ Detection System (K5007, DAKO). We used the the following primary antibodies: Vimentin (clone V9, OriGene), S100 (clone poly, OriGene), CD1a (clone 010, OriGene), langerin (clone343828, OriGene), Pan-cytokeratin (clone AE1, OriGene), CD68 (clone PG-M1, OriGene), CD163 (clone 10D6, OriGene), CD21 (clone 2G9, OriGene), CD35 (clone E11, OriGene), CD117 (clone poly, OriGene), CD34 (clone QBEnd-10, OriGene), DOG-1 (clone SP31, OriGene), cyclinD1 (clone DCS-6, OriGene), MLH1 (clone ES05, OriGene), MSH2 (clone 25D12, OriGene), MSH6 (clone EP49, OriGene), PMS2 (clone EP51, OriGene), HP, P53 (clone DO7, OriGene), Ki-67 (clone UMAB107, OriGene). All antibodies were incubated for 1 h at room temperature. The sections were visualized with 3-3'-diaminobenzidine and tissues were counterstained with Mayer's hematoxylin. The negative and the positive controls were performed, respectively. The BRAF mutation was detected by an allele-specific polymerase chain reaction on the same paraffin-embedded block.

Results

Microscopically, several pieces of reactive gastritis-like lesions were observed; one piece of which exhibited dense intra-mucousin filtration of monotonous, intermediate-sized, mononuclear ovoid cells (**Figure 2A**). In addition, eosinophils and lymphocytes were scattered among these cells. It was a partially circumscribed mass with an ill-defined border. Based on this finding, an inflammatory process was considered less likely. Neoplastic diseases such as carcinoma, lymphoma, melanoma, stromal tumor, and follicular dendritic cell tumor, or normal lymphoid follicles weresuspected. The cells within the lesions exhibited abundant cytoplasms and convoluted nuclei, often with linear grooves. Mitosis was scarce and no necrosis was observed. We performed immunohistochemical staining to characterize the lesions. The aggregated histiocytic cells were positive for vimentin, S100 (**Figure 3A**), CD1a (**Figure 3B**), and langerin (CD207) (**Figure 3C**), but negative for Pan-cytokeratin, CD68, CD163, CD21 (**Figure 3D**), CD35, CD117, CD34, DOG-1, cyclinD1, and p53. The Ki-67 index was approximately 30%. In combination with the morphological features, these findings confirmed the diagnosis of Langerhans cell histiocytosis (LCH). MMR (mismatch repair) was tested in this lesion; no deletion of MMR protein was identified. No *Helicobacter pylori* (HP) was identified in the gastric foveola with immunohistochemical labeling. No BRAF V600E mutation was detected based on negative immunohistochemical staining (**Figure 3E**). The BRAF mutation was tested using an allele-specific polymerase chain reaction on the same paraffin-embedded block, which documented the absence of the BRAF V600E mutation.

The patient was investigated to rule out multisystem involvement. No obvious lesion was detected with enteroscopy. A whole-body bone scan, an abdominal ultrasonography, and a thoracic computed tomography (CT) scan were performed, all of which revealed no evidence of multifocal diseases. At present, the patient had not received any chemotherapy and remained free of symptoms for 14 months after diagnosis.

Discussion

Langerhans cells are immunoreactive, derived from bone marrow, and belong to the dendritic cell population. They are an important type of antigen presenting cell and mononuclear phagocyte in the immune response. Langerhans cell histiocytosis is a rare heterogeneous disorder characterized by abnormal proliferation and accumulation of pathologic Langerhans cells. LCH has several synonyms, including his-

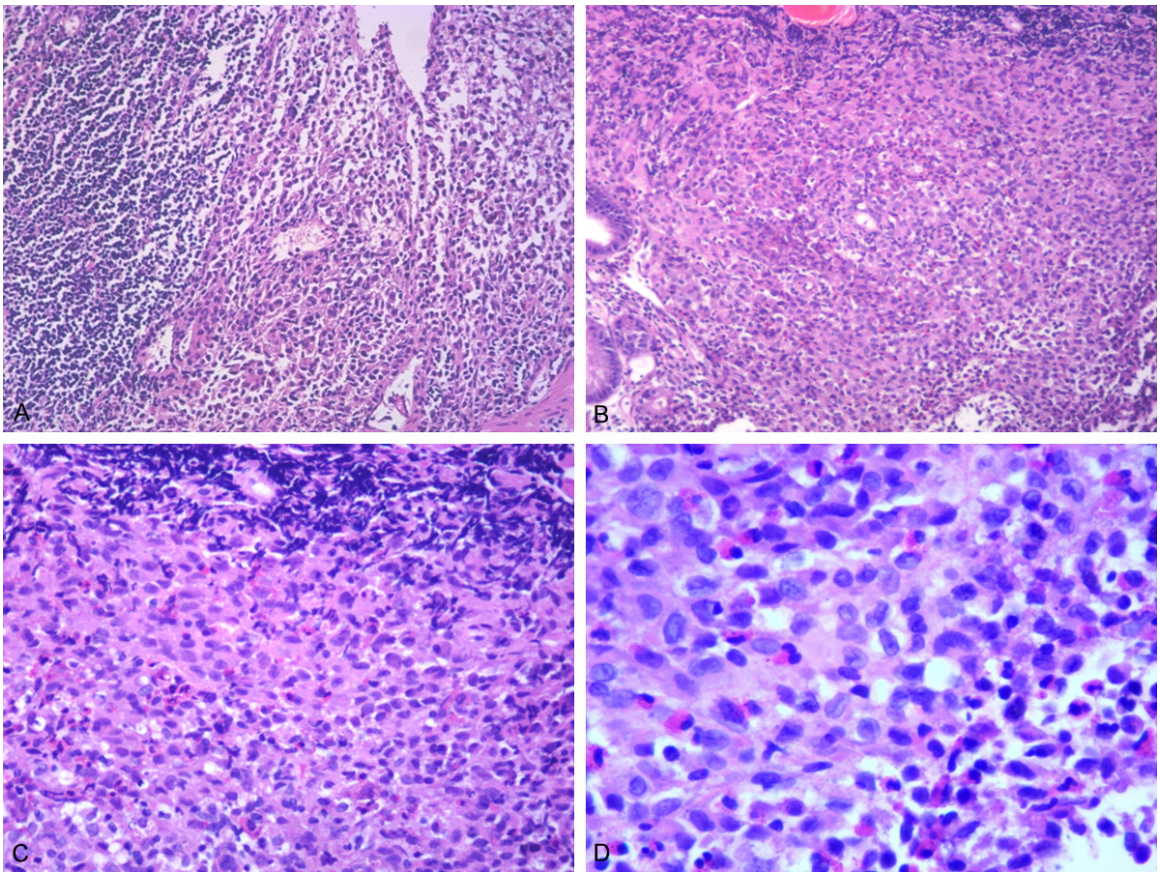

Figure 2. Morphological features of LCH. A. Microscopically, accumulating LCH cells were demonstrated under low power (hematoxylin and eosin × 100). B. Eosinophils and lymphocytes were scattered among these cells (hematoxylin and eosin × 100); C. Eosinophils and lymphocytes were scattered among these cells (hematoxylin and eosin × 200); D. Histiocytoid cells with abundant cytoplasms and convoluted nuclei were identified under high power, some of which exhibited nuclear grooves (hematoxylin and eosin × 400).

tiocytosis X, eosinophilic granuloma, and others [1, 2]. LCH involving the gastrointestinal tract is extremely rare. The majority of reported cases with gastrointestinal involvement occur in children who present with severe systemic diseases.

The age of onset for LCH in adults varies between 21 and 77 years [3, 4]. LCH occurs more commonly in males [1-3, 5], yet some studies reported a female gender predominance, especially for those lesions involved in the GI tract [6], or a relatively even gender distribution [7]. The current clinical classification of LCH describes a broad spectrum ranging from localized single-system involvement to disseminated multisystem disease. In unifocal disease, bone involvement is present in more than 90% of cases. Extra-skeletal involvement includes a variety of organs: skin, lymph nodes, lungs, liver, spleen, bone marrow, or central nervous system, leading to multiple clinical presentations [1, 2, 5]. One Germany-based registry reported LCH in adult patients affecting, in decreasing order of frequency, bone, skin, pituitary gland, liver/spleen, brain, and the GI tract, the latter accounting for only 2% of cases.

LCH presents various clinical forms, involving different systems and different sites in the same system with variable outcomes. For example, in pulmonary LCH, patients often complain of non-productive cough and dyspnea, constitutional symptoms such as fever and weight loss, or eventually chest pain from spontaneous pneumothorax. In bones LCH, patients often have pain in single or multiple bones, depending on the distribution of the diseases. In the GI tract, usually the colorectum and small intestine are involved; only several

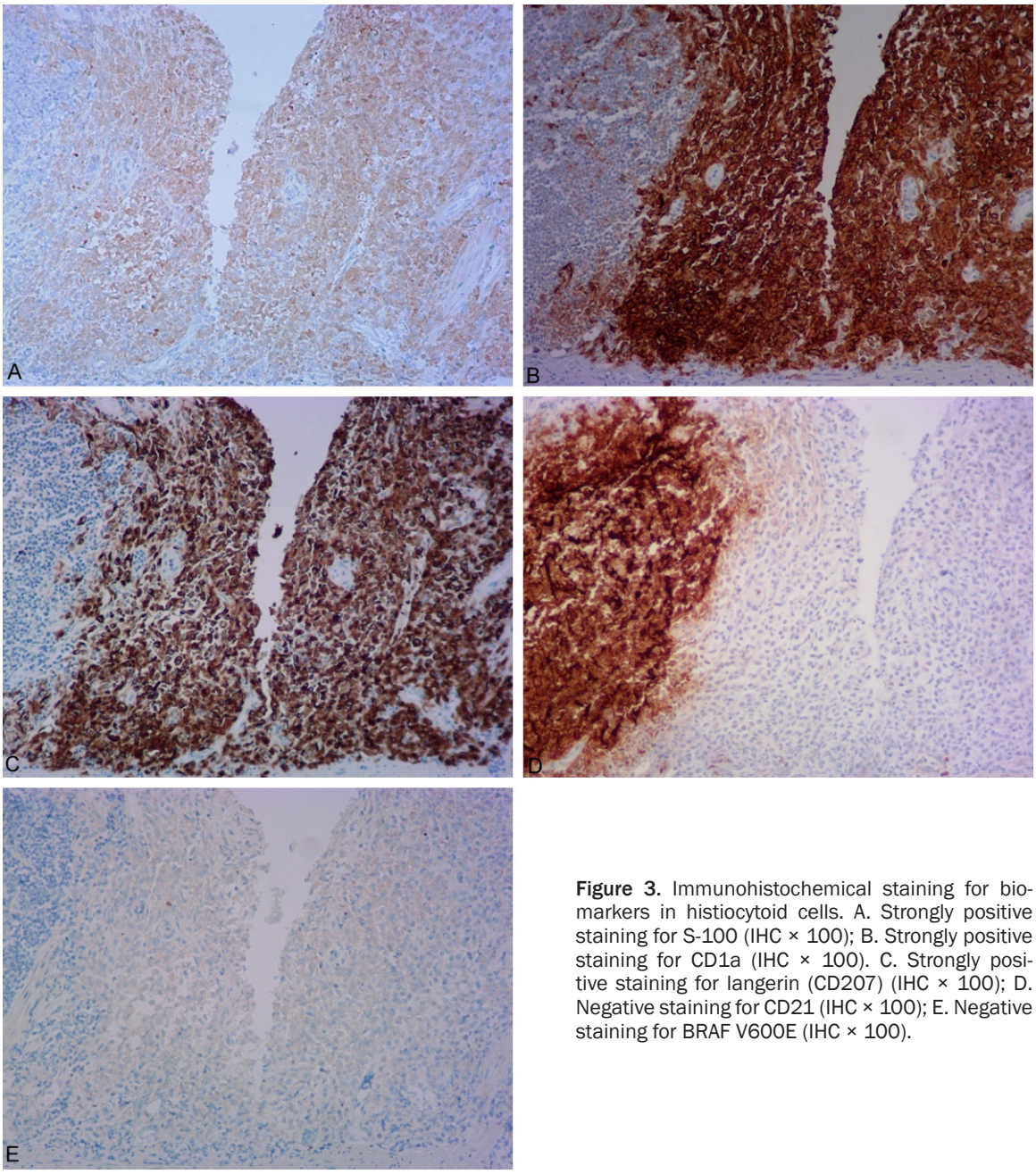

Figure 3. Immunohistochemical staining for biomarkers in histiocytoid cells. A. Strongly positive staining for S-100 (IHC × 100); B. Strongly positive staining for CD1a (IHC × 100). C. Strongly positive staining for langerin (CD207) (IHC × 100); D. Negative staining for CD21 (IHC × 100); E. Negative staining for BRAF V600E (IHC × 100).

cases have been reported in the stomach [6, 8-10] (**Table 1**).

In the majority of adults, LCH is typically encountered as an isolated polyp. Up to 50% of patients were asymptomatic, and usually without multisystem involvement [6, 11, 12]. To the best of our knowledge, adult LCH involving the GI tract as asolitary erosion in the stomach has not been previously described. The only clinical presentation is slight stomach discomfort, and gastroscopy examination reveals a mild erosion in the corpora ventriculi.

Clinical monitoring includes respiratory functional tests and imaging such as CT, MRI, and positron emission tomography (PET-CT). PET-CT is able to detect the foci of metabolically active LCH (especially in lung, skull, extremities), to instruct therapy and to predict prognosis.

LCH lacks pathognomonic, clinical or radiographic characteristics. A definitive diagnosis should be based on a histological and immunohistochemical examination of biopsy specimens. Histologically, LCH is composed of Lan-

Table 1. Reported cases of adult LCH

Ref.	Gender/age (yr)	Organ	Clinical manifestation	Treatment	IHC and molecular test	Follow up (month)	Status
Shaodong Yangl *et al.*	Female/40	Sublingual gland	A painless mass in the right floor of the mouth	Surgery	S100, CD1a	17 months	ANED
Mohamad Jihad Mansour *et al.*	Male/32	Lungs and the colo-recto-anal part	Non-productive cough and exertional dyespnea	Biopsy specimen chemotherapy	S100, CD1a	6 months	ANED
Amir Behdad *et al.*	Female/59	Esophageal	Dysphagia	Biopsy	S100, CD1a, CD207, Braf mutation	Undescribed	ANED
Edith Simona Ianosi *et al.*	Female/26	Lungs	Progressive worse dry cough and dyspnea	Biopsy	CD1a, Braf mutation	6 months	ANED
Mohammad M. Karimzada*et al.*	Female/20	Appendix, colon	Acute appendicitis	Biopsy	S100, CD1a, CD207	12 months	ANED
Uday Shankar	Female/53	Colon, rectum	Asymptomatic	Biopsy	S100, CD1a	2 months	DOD

NA: Not available; +: Positive; -: Negative; ANED: Alive with no evidence of disease; DOD: Died of disease.

gerhans-type cells with ovoid nuclei and a longitudinal nuclear groove (imparting a "coffee-bean" appearance), fine chromatin with delicate nuclear membrane, and inconspicuous nucleoli. These cells are admixed with a variable number of inflammatory cells including eosinophils, lymphocytes, and conventional histiocytes. Eosinophils can be quite prominent, serving as a good clue for diagnosis, when the eosinophilic granules are washed out in frozen sections. However, their presence is not required to achieve a correct diagnosis. Mitotic figures and necrosis are features of LCH. In lymphnodes, the cells are often distributed in a sinus pattern, and overlooked as conventional, non-neoplastic sinus histiocytosis. The histological diagnosis of LCH can be confirmed by dendritic cell markers, such as CD1a and langerin (CD207), as well as S100, vimentin, P53, cyclinD1 and Bcl-2. Nonetheless, LCH is a clonal process with activated BRAF V600E mutations, suggesting that LCH is a neoplastic lesion [1, 2, 5]. The recent discovery of somatic BRAF V600E mutations in more than half of the LCH lesions confirms the neoplastic nature of this disease and is considered an indicator of severity, and it provides a potential target for treatment [13]. The use of the BRAF inhibitor vemurafenib in LCH patients have shown promising results and should be considered for severe or refractory cases. Ultrastructurally, LCH is characterized by the presence of distinctive Birbeck granules in the cytoplasms, structures with a zipper-like morphology that may be dilated at one end, imparting a tennis racket-like shape [1, 2, 8].

In our case, histologically, LCH is admixed with a variable number lymphocytic infiltration, which is easily misdiagnosed as lymphoid follicles. For example, eosinophil infiltration can be seen only in the focal area. The association of S-100, CD1a, langerin, as well as p53 and cyclinD1, confirmed the histopathological diagnosis. Other antibodies (CD21, CD35, CD68, CK, CD117) can be used to identify similar tumors or inflammatory reactions. MMR was tested in this lesion; no detection of a mismatch repair protein was observed. Immunohistochemical labeling HP was not observed in the gastric foveola. No BRAF V600E mutation was detected. Neoplastic diseases such as poorly differentiated carcinoma, lymphoma, melanoma, stromal tumor, and follicular dendritic cell tumor should be excluded.

The prognosis of LCH depends on the pathologic type and anatomic distribution of the disease. The treatment for LCH is variable, depending on age, the extent of the disease and risk factors [1, 2]. Therapeutic modalities include surgical excision, radiation therapy, topical therapy, and systemic chemotherapy. The clinical course of LCH varies from lesions that are spontaneously resolved, to a chronic disease, or a disseminated and life-threatening disease. In our case, the patient received no chemotherapy or systematic therapy. Long-term follow-up to exclude progression of the disease and systemic involvement is necessary. The overall prognosis in LCH is favorable. A retrospective analysis of 35 patients aged 14 years and older with multisystem involvement who received combination chemotherapy demonstrated a 3-year overall survival rate of 81% ± 10%. Theoverall survival of patients with GI tract involvement has not been specifically studied. The majority of reported cases with gastrointestinal involvement occurs in children and presents with severe systemic disease.

Conclusion

Isolated LCH of the stomach is quite rare and should be considered in the differential diagnosis. Its diagnosis can be challenging for a clinician. A definitive diagnosis of LCH is made upon biopsy, yielding cells that are morphologically and immunohistochemically compatible with Langerhans cells. Due to its rarity and varied presentation, the multidisciplinary treatment is very important. Local excision is the treatment of choice and long-term follow up is necessary.

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Disclosure of conflict of interest

None.

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