**INTRODUCTION**

Langerhans cell histiocytosis (LCH) is characterized by unifocal, multifocal single-system, or multi-system disease that brings heterogeneous clinical presentation. Though it primarily attacks children between 1 and 4 years old, the disease occurs in all age groups. According to the extent of involvement, LCH results in benign or life-threatening consequences. An indolent form of a single organ disease may remit spontaneously, while multiorgan disease presents with various conditions, including eosinophilic granuloma, characteristic papulosquamous granulomatous, diabetes insipidus, exophthalmos, radicular nerve pain, muscle weakness, bowel and bladder dysfunction, pituitary dysfunction, a range of thyroid, growth hormone, and gonadotropin disturbances. Meanwhile, it
may affect any system or organ of the body, but those more frequently affected are bone (80% of cases), skin (33%), pituitary gland (25%), liver (15%), lungs (15%), spleen (15%), the hematopoietic system (15%), lymph nodes (5%–10%), and the central nervous system excluding the pituitary (2%–4%).

Gastrointestinal (GI) LCH in adults is very rare, especially with unifocal, single-system involvement. Owing to the vague pathogenesis and limited data available to guide the treatment of GI LCH in adults, the management of patients is still obscure or controversial. In this present article, two cases of solitary GI LCH in adults were described and the features of this disease in the literature were summarized in order to provide a consistent body of data.

2 | CASE PRESENTATION

2.1 | Case 1

A 45-year-old female without symptom underwent upper-GI endoscopy for checkup. The endoscopy revealed a polypoid lesion with approximately 0.6 cm in size in her stomach, and there was a depression in the center of this lesion (Figure 1). Laboratory investigations, including complete blood cell count, biochemical analysis, and serum levels of carcinoembryonic antigen, were within normal ranges, and the biopsy specimen was sent for histopathology.

Microscopic examination showed that there were sheets of intermediate-sized cells with ovoid nuclei, and inconspicuous nucleoli were observed in the mucosa lamina propria (Figure 2A), accompanied by a certain number of lymphocytes and eosinophils (Figure 2B). Neoplastic diseases such as carcinoma, lymphoma, melanoma, and metastatic breast cancer were suspected. Immunohistochemical analysis revealed that these intermediate-sized cells strongly expressed S100 (Figure 2C), CD1a (Figure 2D), and moderately expressed langerin (Figure 2E), but they were negative for pan-cytokeratin, CAM5.2, CD20, CD79a, CD3, EBER, CD138, GATA-3, and melanoma marker (HMB45). The BRAF V600E mutation was detected based on the finding of the protein with weakly positive immunohistochemistry (Figure 2F). No helicobacter pylori (HP) was discovered in the gastric foveola. Combined with the morphological features, the diagnosis of LCH was confirmed.

Afterward, the patients underwent a complete removal of the lesion by endoscopic submucosal dissection (ESD). The ESD specimen revealed that no LCH lesion remnant was found.

The patient was advised to rule out multi-system involvement. According to the computed tomography (CT) scan of whole body, there was no evidence of multifocal diseases.

2.2 | Case 2

A 67-year-old male complained stool blood for 1 year. The colonoscopy demonstrated that his sigmoid colon was local incrassation with approximately 3.5 cm in diameter, and his tumor marker CA125 elevated (21.60 U/ml, normal range ≤15.00 U/ml). Considering the possibility of colon tumor, the clinician advised him to perform surgery. Subsequently, the patient underwent laparoscopic sigmoid resection. The surgical specimen was examined for histopathology, and a pedunculated polyp with 4.0 × 2.0 × 1.0 cm was observed.

Histopathological examination exposed that the lesion was a tubular adenoma with high-grade dysplasia, of which some areas evolved into a moderately differentiated adenocarcinoma with head invaded. Significantly, there were numbers of inflammatory cells, including neutrophils, eosinophils, and lymphocytes in the head and neck of the polyp (Figure 3A). These cells were admixed with coffee bean like cells with irregular nuclei and longitudinal nuclear grooves (Figure 3B). Immunohistochemical staining was performed to identify the distinctive cells that were diffusely positive for S100 (Figure 3C), strongly positive for CD1a (Figure 3D), but negative for CD68, CK7, CK20, and CDX-2. No deletion of mismatch repair (MMR) protein was identified, but the BRAF V600E mutation was observed. The Ki-67 index was approximately 20%. These findings supported the diagnosis of LCH.

Imaging investigation for systemic had no sign of multi-system involvement.

3 | DISCUSSION

Langerhans cell histiocytosis is monoclonal Langerhans cell proliferation, of which the clinical classification depends on whether the disease affects localized single-system or disseminated multisystem. In single-organ disease, bone involvement is present in more than 90% of cases,5 while the incidence of GI LCH in adults is rare. To the best of our knowledge, only about 21 cases have been reported in the English literature till date. Among the previous reported cases6–11 and our two cases (Table 1), the age range was 29–77 years.
According to reports in the literature, it was more popular in Caucasians in Northern European countries than in both Africans Asians. However, the Asians to Caucasians ratio in our study was 11:12 that was the same as male-to-female ratio. The results of gender distribution were different from the reports made by Singhi et al. that female occupied most of the GI LCH. Fourteen patients were asymptomatic, while nine patients presented with corresponding GI symptoms, such as abdominal pain (four patients), dysphagia (two patients), nausea/diarrhea (one patient), anemia (one patient), constipation (one patient), and stool blood (one patient). In our case 2, it is unclear if the stool blood was relevant to LCH, because the patient had malignant tumor at the same time. In upper-GI, most cases occurred in stomach body (seven cases); other locations contained stomach fundus (two cases), stomach angle (one case), stomach antrum (one case), lower esophagus (one case), and middle esophagus (one case). In lower GI, most cases occurred in sigmoid (three cases), cecum (two cases), ascending colon (two cases), rectum (two cases), transverse colon (one case), and descending colon (one case).
The lesion was described as an elevation or polyp (size: 0.2–4.0 cm) in seven cases of upper-GI LCH and all cases (11 cases) of the lower-GI LCH, while others involved erosion (two cases) and ulcer (two cases). There was nothing especially endoscopic finding in only one case. These results that LCH in adults is predominantly asymptomatic and usually presents a small solitary polyp with GI involving are similar to previous reports in the literature.\(^1,5\) Although the recent discovery has suggested that LCH is neoplastic nature, the pathogenesis of LCH is still unclear.\(^14\) A study proved that more than half LCH cases contained BRAF-V600E mutations.\(^15\) B-raf is a serine/threonine kinase that belongs to the RAF kinase family, which is involved in many cellular functions, such as cell growth, proliferation, differentiation, and apoptosis. The BRAF-V600E mutation is more common in multisystem than in single-system and is connect with an increased risk of relapse.\(^12\) Nevertheless, the data of BRAF-V600E mutation of GI LCH in adult cases is scarce up to now. In our study, the BRAF V600E mutation was present in 5 of 7 evaluable cases for a mutation frequency of

| Case | Race | Sex/age | Symptom | Site | Endoscopic finding (size) | Treatment | BRAF V600E | Follow-up (month) |
|------|------|---------|---------|------|---------------------------|-----------|-------------|------------------|
| 1    | Caucasian | F/59 | Dysphagia | Middle Esophagus | Ulcer (*) | Biopsy | P | NA |
| 2    | Asians | M/61 | Epigastric pain | Lower Esophagus | Solitary elevated lesion (0.4 cm) | Biopsy | N | 4/NED |
| 3    | Asians | F/56 | NO | Stomach body | Solitary submucosal elevation (0.5 cm) | Biopsy | P | 3/NED |
| 4    | Asians | M/48 | NO | Stomach body | Solitary elevation (<1 cm) | Biopsy | NA | 12/NP |
| 5    | Asians | M/51 | NO | Stomach body | Solitary elevation (0.5 cm) | Biopsy, ESD | NA | 12/NED |
| 6    | Caucasian | F/29 | NO | Stomach body | Normal | Biopsy | P | NA |
| 7    | Asians | M/37 | Stomach discomfort | Stomach body | Erosion (*) | Biopsy | N | 14/NS |
| 8    | Asians | F/47 | Abdominal pain, diarrhea, nausea | Stomach body, fundus | Large area with scattering Erosions (7 cm area) | Surgical resection | NA | 20/NED |
| 9    | Asians | M/64 | NO | Stomach fundus | Solitary elevation (1.0 cm) | Biopsy, ESD | NA | 6/NED |
| 10   | Caucasian | F/59 | Epigastric pain | Stomach angle | Ulcerated lesion (1.5 cm) | Surgical resection | NA | NA |
| 11   | Caucasian | M/68 | Dysphagia | Stomach antrum | Solitary Polyp (*) | Biopsy | NA | 22/NED |
| 12   | Caucasian | M/60 | NO | Cecum | Polyp (*) | Biopsy | NA | 7/NED |
| 13   | Caucasian | F/60 | NO | Cecum | Polyp (*) | Biopsy | NA | 12/NED |
| 14   | Asians | M/49 | NO | Ascending colon | Polyp (0.2 cm) | Biopsy | NA | NA |
| 15   | Caucasian | F/40 | Anemia | Ascending colon | Polyp (*) | Biopsy | NA | 21/NED |
| 16   | Caucasian | F/51 | NO | Transverse colon | Polyp (*) | Biopsy | NA | 5/NED |
| 17   | Caucasian | M/65 | NO | Descending colon | Polyp (0.6 cm) | snare diathermy | NA | 12/NED |
| 18   | Caucasian | F/55 | NO | Sigmoid | Polyp (*) | Biopsy | NA | 26/NED |
| 19   | Caucasian | F/77 | Constipation | Sigmoid | Polyp (*) | Biopsy | NA | 2/NED |
| 20   | Caucasian | F/53 | NO | Rectum | Sessile polyp (0.4 cm) | CSP | NA | 12/NED |
| 21   | Asians | M/51 | NO | Rectum | Polyp (0.6 cm) | EMR | NA | NA |

**Abbreviations:** CSP, cold snare polypectomy; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; F, female; M, male; N, Negative; NA, not available; NED, no evidence of disease; NP, no progression; NS, no symptom; P, positive.

*Size was not specified for the patient.*
and plasma cells. This inflammatory infiltration of background accompanied by a variable number of lymphocytes, eosinophils, and plasma cells. This inflammatory infiltration of background serving as a good clue for diagnosis can be quite significant, when Langerhans cells are atypical. The aggregated histiocytic cells were positive for CD1a, S100, and langerin (CD207), and they played an important role in identifying other common tumors of the GI tract, such as carcinoma, lymphoma, and malignant melanoma. Like LCH, other S100 immunoreactive lesions that have been reported in the GI tract, including granular cell tumor and Rosai–Dorfman, also express CD68 with different degrees. However, the expression of CD1a is negative in granular cell tumor, which has been reported with variant results in Rosai–Dorfman disease. Electron microscopy was formerly one of the criteria required for definitive diagnosis. Since it has been proved that the expression of langerin completely correlates with the existence on electron microscopy of Birbeck granules, it is no longer recommended.

Once the diagnosis of LCH is determined, on account of distinct treatment and prognosis for single-system or multisystem involvement, a careful clinical workup for each patient should be attentive to.

Individuals with unifocal, single-system involvement do not require systemic therapy, other than local excision or observation. Whereas, patients with multi-system LCH predominantly need chemotherapy. On the other hand, the prognosis of single-system LCH is better than multi-system LCH. The data of adult LCH is limited and standardized protocols are sparse, and thus most treatments are based on the pediatric experience. In unifocal bone lesion, therapy protocols depend on the size, location, and symptoms, which can provide a significant reference to the GI LCH patients with clinical symptoms. In all cases (Table 1), the treatments contained ESD (three cases), surgical resection (three cases), endoscopic mucosal resection (one case), snare diathermy (one case), and cold snare polypectomy (one case), and 14 patients did not undergo surgical resection after biopsy. All patients had a good prognosis during the follow-up period, except for six cases. Nevertheless, careful follow-up is still necessary to rule out systemic disease, because only one reported case had skin and bone involved during 2 years of follow-up. The patient was not unifocal, but multiple polyps in upper GI. Of note, due to the short follow-up time within our cases study, future studies will be required for the definitive assessment of disease progression.

4 CONCLUSIONS

In summary, GI LCH in adults with unifocal, single-system involvement is extremely rare and usually presents as an incidental finding. Most patients are asymptomatic, and a small solitary polyp in GI tract can be observed under routine endoscopy. Biopsy and immunohistochemistry are necessary for confirming and excluding malignant lesion. Clinical follow-up is essential to rule out systemic disease, even though the overall prognosis of single-system LCH is favorable.

CONFLICT OF INTEREST

All authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets used and analyzed during the current study are available from the corresponding author request.

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