International Journal of Clinical Oncology (2020) 25:1945–1950
https://doi.org/10.1007/s10147-020-01739-1

ORIGINAL ARTICLE

# Gastrointestinal lesion in adult-onset Langerhans cell histiocytosis

Yasuo Matsubara[1] · Masayuki Kobayashi[2] · Yasuki Hijikata[1] · Yasunori Ota[3] · Yoshihiro Hirata[1] · Lay Ahyoung Lim[1] · Hiroshi Yotsuyanagi[1] · Arinobu Tojo[2]

Received: 3 May 2020 / Accepted: 25 June 2020 / Published online: 8 September 2020


## Abstract

**Background** Langerhans cell histiocytosis (LCH) is a rare disease primarily occurring in children, and commonly involves the bone and skin; gastrointestinal tract involvement is notably rare. The incidence and significance of gastrointestinal lesions in adult LCH are unclear; thus, we aimed to investigate adult Japanese cases of LCH and clarify the features of gastrointestinal involvement.

**Methods** We gathered clinical information on 43 Japanese cases of adult LCH and analyzed patient backgrounds, affected organs, features of the gastrointestinal lesions, and the clinical courses.

**Results** Thirteen patients underwent endoscopic examinations: an upper gastrointestinal endoscopy alone in 5, lower gastrointestinal endoscopy alone in 3, and both in 5 patients. A gastric lesion (one case), colonic lesion (one case), and both gastric and rectal lesions (one case) were detected. The three cases of gastrointestinal involvement also exhibited nongastrointestinal multisystem LCH lesions and showed no gastrointestinal symptoms or increased uptake on positron emission tomography. Endoscopy revealed small erosions without specific features; histological examinations were required for diagnosis. These three cases were treated with chemotherapy, comprising vinblastine/prednisolone, methotrexate, and daily 6-mercaptopurine, for 36 weeks; in two cases, the clinical condition remained stable for several years post-treatment. One case showed recurrence 1 year 7 months after treatment, and chemotherapy was re-administered. No case with single-system disease exhibited gastrointestinal involvement.

**Conclusions** Although gastrointestinal LCH lesions are rare, they were more common than expected in our cases of multisystem LCH. However, these lesions were relatively small and did not affect the patients' clinical courses.

**Keywords** Adults · Gastrointestinal tract · Langerhans cell histiocytosis

## Introduction

Langerhans cell histiocytosis (LCH) is a rare disease characterized by the clonal proliferative accumulation of monocyte/macrophage lineage cells, which are similar to Langerhans cells (LCs) both morphologically and immunohistochemically [1, 2]. Although LCH is generally defined by the proliferation of CD1a + /Langerin + LC-like cells, the specific origins of these cells are yet to be identified.

While LCH may occur at any age, the disease is mainly observed in children between the ages of 1 and 4 years; the incidence of LCH in adults is very rare (1–2 cases per million) [3]. Further, it is more prevalent in Caucasians in Northern European countries than in both Asians and Africans, as well as in men rather than women [4, 5]. LCH presents with a wide clinical spectrum, ranging from a single-organ disease that may remit spontaneously, to a multiorgan disease accompanied by severe organ dysfunction [6–8]. Clinical manifestations vary widely due to differences in the age of onset, LC proliferation rates, and the involved tissues and organs. Commonly affected sites include the bone, skin, and lungs; however, LCH may involve nearly any site

✉ Arinobu Tojo
a-tojo@ims.u-tokyo.ac.jp

1 Department of General Medicine, IMSUT Hospital, Institute of Medical Science, The University of Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo 108-8639, Japan

2 Department of Hematology/Oncology, IMSUT Hospital, Institute of Medical Science, The University of Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo 108-8639, Japan

3 Department of Diagnostic Pathology, IMSUT Hospital, Institute of Medical Science, The University of Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo 108-8639, Japan

or organ [1, 2]. LCH involving the gastrointestinal tract is therefore possible, though notably rare. Adult cases of gastrointestinal LCH have often been reported as solitary cases found incidentally [13–15], and studies including multiple cases [12] are rare. Reports regarding adult gastrointestinal LCH lesions from the viewpoint of overall adult LCH are lacking. Thus, the incidence and significance of gastrointestinal lesions in adult LCH therefore remain unclear; thus, our study aimed to investigate cases of adult LCH in Japanese subjects, as well as the features of any gastrointestinal involvement.

## Materials and methods

After receiving approval from the research ethics committee, we identified cases of adult-onset LCH treated in our hospital between 2010 and 2019. Clinical information on 43 cases were gathered, all with biopsy-confirmed evidence of LCH. LCH was diagnosed using the histopathology findings of biopsies from the affected organs; they showed infiltration of cells, which were ovoid or elliptic in shape, had grooved folded or indented nuclei, and tested positive for the CD1a and S100 or Langerin antigens. Systemic scanning with positron emission tomography (PET)–computed tomography (CT), computed tomography (CT), magnetic resonance imaging (MRI), and/or bone scintigrams were used to detect the site of involvement. We then analyzed patient backgrounds, affected organs, features of the gastrointestinal lesions, and clinical course.

## Results

The study group included 20 men and 23 women, with a median age of 42.5 years (range 17–77 years); the clinical features are summarized in Table 1. The bone was the most commonly affected site ($n=23$), followed by the skin ($n=13$), lungs ($n=11$), lymph nodes ($n=10$), hypothalamic–pituitary region ($n=8$), liver ($n=4$), and others ($n=7$). The disease was located in a single system in 22 cases, and was multisystemic in 21. Thirteen of the 43 patients underwent endoscopic examinations: an upper gastrointestinal endoscopy alone in 5, a lower gastrointestinal endoscopy alone in 3, and both modalities in 5 cases (Table 2). All upper gastrointestinal endoscopies were performed for screening, and no patient that underwent an upper gastrointestinal examination complained of abdominal symptoms.

Colonoscopies were performed for screening in five, PET accumulations in two, and diarrhea in one case. Gastrointestinal lesions were noted in three cases; a gastric lesion was detected in one case, a colonic lesion in one case, and both gastric and rectal lesions in one case. These three cases also exhibited nongastrointestinal multisystem LCH lesions; however, no case of single-system disease had gastrointestinal involvement, and PET accumulations were not revealed in the three gastrointestinal lesions. Endoscopically, one case of a gastric lesion showed a small erosion within the gastric antrum (Fig. 1a, b), whereas another showed small erosions within the gastric fornix and angle (Fig. 1c, d). One case of a colonic

**Table 1** Clinical features of patients with adult-onset LCH

| | Total | Upper GI endoscopy | Lower GI endoscopy |
|---|---|---|---|
| *n* | 43 | 10 | 8 |
| Age in years: median (range) | 42.5 (17–77) | 50.1 (23–77) | 44 (23–65) |
| Sex, *n* (%) | | | |
| Male | 20 (46.5%) | 5 (50%) | 5 (62.5%) |
| Female | 23 (53.5%) | 5 (50%) | 3 (37.5%) |
| Organs involved *n* (%) | | | |
| Bone | 23 (53.5%) | 6 (60%) | 3 (37.5%) |
| Skin | 13 (30.2%) | 5 (50%) | 4 (50%) |
| Lung | 11 (25.6%) | 4 (40%) | 4 (50%) |
| Lymph nodes | 10 (23.3%) | 2 (20%) | 2 (25%) |
| Hypothalamic-pituitary region | 8 (18.6%) | 1 (10%) | 1 (12.5%) |
| Liver | 4 (8.2%) | 2 (20%) | 2 (25%) |
| Others (thyroid, pleura, thymus, pancreas, gall bladder, etc.) | 7 (16.3%) | 3 (30%) | 1 (10%) |
| Classification *n* (%) | | | |
| Single-system | 22 (51.2%) | 3 (30%) | 4 (50%) |
| Multisystem | 21 (48.8%) | 7 (70%) | 4 (50%) |

*GI* gastrointestinal, *LCH* Langerhans cell histiocytosis

**Table 2** Characteristics of the 13 adult LCH patients that underwent endoscopic examination

| Case no | Age/sex | Diagnosed organ(s) with LCH other than the GI tract | Reason for upper/lower gastrointestinal endoscopy | Gastrointestinal lesion |
|---|---|---|---|---|
| 1 | 62/F | Bone, muscle | Upper examination for screening | None |
| 2 | 58/F | Bone, skin, lung, liver, lymph node | Upper/lower examination for screening | Colon |
| 3 | 40/F | Bone, skin, lymph node | Lower examination for PET accumulation | None |
| 4 | 29/M | Lung, liver, hypothalamus, thymus, pancreas | Upper/lower examination for screening | Stomach, rectum |
| 5 | 46/M | Bone | Upper/lower examination for screening | None |
| 6 | 41/F | Skin | Lower examination for diarrhea | None |
| 7 | 42/M | Bone, lung | Upper examination for screening | None |
| 8 | 23/M | Skin | Upper/lower examination for screening | None |
| 9 | 55/F | Bone, skin, oral cavity, anus, ear canal | Upper examination for screening | Stomach |
| 10 | 77/M | Skin | Upper examination for screening | None |
| 11 | 65/M | Lung | Lower examination for PET accumulation | None |
| 12 | 59/F | Bone, skin, lymph node, bone marrow | Upper examination for screening | None |
| 13 | 50/M | Lung, liver | Upper/lower examination for screening | None |

*GI* gastrointestinal, *LCH* Langerhans cell histiocytosis, *PET* positron emission tomography

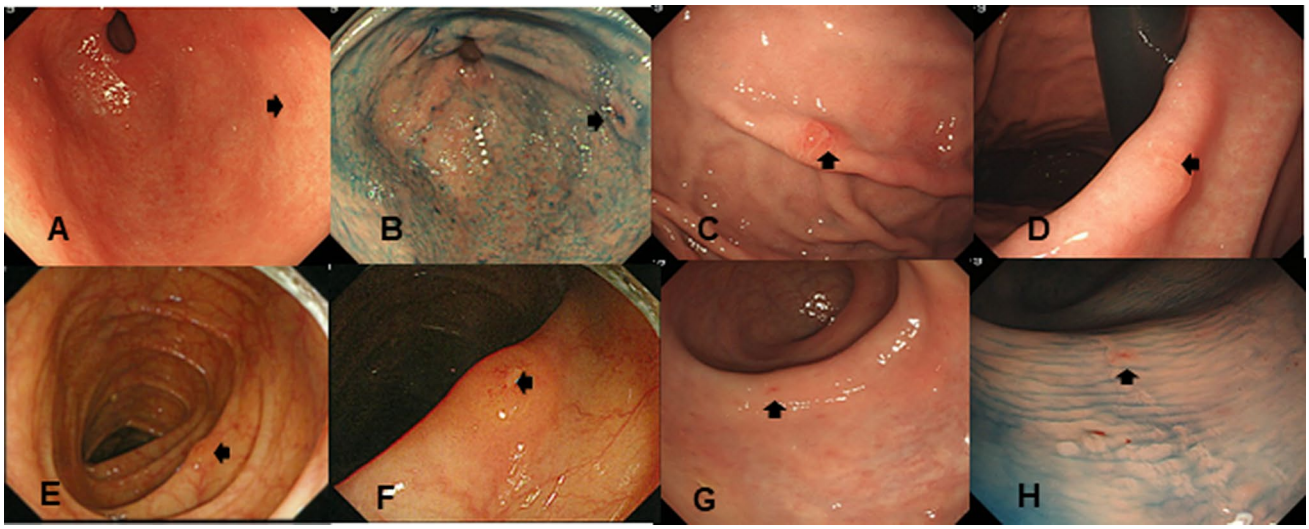


**Fig. 1** Endoscopic views of gastrointestinal lesions in cases of adult LCH. Tiny erosions were found in the stomach and large intestine. **a**, **b** Gastric antrum of case no. 9. White-light image (**a**) and indigo carmine contrast image (**b**). **c**, **d** Gastric fornix (**c**), and gastric angle (**d**) of case no. 4. **e**, **f** Transverse colon of case no. 2. Distant view (**e**) and close-up view (**f**). **g**, **h** Rectum (**g**, **h**) of case no. 4. White-light image (**g**) and indigo carmine contrast image (**h**). Black arrows indicate the lesions

lesion exhibited a small erosion within the transverse colon (Fig. 1e, f), while another showed a small erosion in the rectum (Fig. 1g, h). None of these lesions indicated specific endoscopic features differentiating them from other diseases; therefore, histological examinations were required for diagnosis. The biopsy specimens, which were positive for the CD1a antigen confirmed via immunostaining (Fig. 2, the representative figure), indicated LC infiltration. Atypical cells with abundant weakly eosinophilic cytoplasm and large grooved oval nuclei were observed; the majority of these expressed CD1a and weakly expressed S100.

These three cases were treated using the Special C regimen, which consisted of vinblastine/prednisolone and methotrexate along, with daily 6-mercaptopurine, for 36 weeks [9]. All three patients achieved complete response at the end of treatment. Two patients had no active disease (follow-up time: 4–5 years). A relapse had occurred in one patient at 1 year 7 months after treatment, and chemotherapy was taken again.

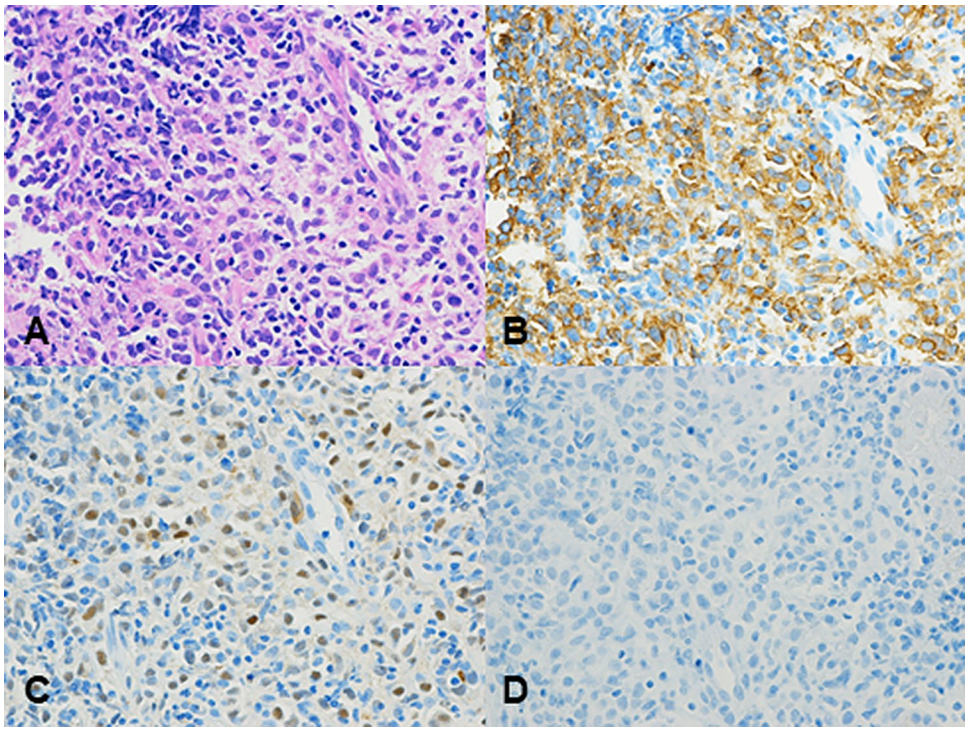


**Fig. 2** **a** Stomach biopsy of case no. 4 with histiocytic infiltrate in the lamina propria (×400). **b**, **c**, **d** CD1a, S100, and BRAF immunostain, respectively. Histiocytes were positive for CD1a (**b**) and S100 (**c**) and negative for BRAF (**d**)

## Discussion

Gastrointestinal tract involvement in LCH is rare (< 5%) and tends to be associated with severe systemic diseases and poor prognoses in children [10, 11]. In a retrospective study involving ten cases of gastrointestinal involvement in adult LCH, 50% of the cases were incidentally found during screening; the other 50% displayed unrelated symptoms [12]. Eight of the ten cases presented with a solitary polyp, and two presented with ulcers, primarily in the small and large intestines. Most patients who presented with single-system lesions had favorable clinical outcomes, while patients who presented with multifocal gastrointestinal involvement developed cutaneous diseases within several years.

Among all gastrointestinal LCH lesions, gastric LCH is notably rare. Two literature reviews reported that most patients with gastric LCH had a single-system gastric lesion with a benign clinical course, whereas some patients experienced a dissemination of the disease [13, 14]; the majority of the lesions were elevated gastric lesions or polyposis. Adult cases of gastrointestinal LCH were often reported as solitary cases found incidentally during cancer screening or investigation for gastrointestinal symptoms; thus, the exact frequency of gastrointestinal tract involvement in LCH is still unknown [13–15].

In this study, gastrointestinal lesions were found in 3 of the 13 patients with LCH who underwent endoscopies. Considering only those with multiorgan diseases, three out of the eight patients displayed gastrointestinal involvement, a frequency far more common than formerly acknowledged. These lesions exhibited tiny erosions with no specific endoscopic features under usual white-light observation. This morphological feature did not correspond with the features described in previously reported cases, which mainly reported a polypoid appearance (Table 3). These differences in both frequency and morphological findings may be attributed to the small size and nonspecific findings of the gastrointestinal lesions in this study.

In many cases of adult LCH, endoscopic examinations are not always performed without either evidence suggesting gastrointestinal involvement, or positive PET–CT results. Even via endoscopy, lesions such as those noted in this study may be easily missed; an accurate diagnosis would thus be difficult without a biopsy. Further, it may be possible that the prevalence of LCH differs globally due to differences among races [4, 5]; however, cases reported in Japan seemed to share no similarities with ours [14, 15]. As our study included no cases of single-organ gastrointestinal LCH, it was concluded that the prevalence of single-system gastrointestinal lesions was notably rare.

*BRAF-V600E* mutations have been described in more than half of all LCH cases [4]. B-raf is a serine/threonine kinase belonging to the RAF kinase family; its signaling cascade is involved in many cellular functions including cell growth, proliferation, differentiation, and apoptosis. The *BRAF-V600E* mutation is more common in multisystem LCH than in single-system LCH [16], and is associated with an increased risk of relapse [17]. We performed

**Table 3** LCH lesions and endoscopic findings of present cases (no. 1–3) and previous reported cases (no. 4–13) from the single center [12]

| Case no | Age/sex | Gastrointestinal lesion | Endoscopic findings | Diagnosed organ(s) with LCH other than the GI tract |
|---|---|---|---|---|
| 1 | 58/F | Colon | Erosion | Bone, skin, lung, liver, lymph node |
| 2 | 29/M | Stomach, rectum | Erosion | Lung, liver, hypothalamus, thymus, pancreas |
| 3 | 55/F | Stomach | Erosion | Bone, skin, oral cavity, anus, ear canal |
| 4 | 40/F | Colon | Polyp | None |
| 5 | 60/M | Colon | Polyp | None |
| 6 | 55/M | Colon | Polyp | None |
| 7 | 60/F | Colon | Polyp | None |
| 8 | 68/M | Stomach | Polyp | None |
| 9 | 51/F | Colon | Polyp | None |
| 10 | 77/F | Colon | Polyp | None |
| 11 | 56/F | Colon | Ulceration | Skin (2 years after the initial diagnosis) |
| 12 | 63/F | Colon | Not available | None |
| 13 | 54/F | Anus | Ulceration | Skin (2 months after the initial diagnosis) |

immunohistochemical examinations of the *BRAF-V600E* mutation in two of the three gastrointestinal cases with negative results. Data regarding the *BRAF-V600E* mutation in adult cases of LCH exhibiting gastrointestinal tract involvement is scarce, although a case of single-system colonic adult LCH with a *BRAF p.V600E* mutation has been reported [18]. The relationship between the *BRAF-V600* mutation and gastrointestinal LCH remains elusive.

The prognosis of LCH relates to the number of involved organs, risk-organ involvement, and age of onset [19]. LCH is clinically categorized as either unifocal or multifocal single-system LCH, or as multisystem LCH; the prognosis of single-system LCH is better than that of multisystem LCH. Patients with liver, spleen, and bone marrow damage are at a higher risk of unfavorable outcomes; however, adult cases of LCH generally have better prognoses than childhood cases.

Treatments for adult LCH are not standardized due to the rarity and heterogeneity of the disease, but are usually based on organ involvement with or without risk-organ involvement; to date, only a few trials have sought to establish a therapy for adults [20]. The Japan LCH Study Group has recently formulated the Special C regimen for multifocal LCH in adults, with good results having been reported [9]. Our latest report showed that 80% (20 of 25 cases) who received the special C regimen at least achieved a partial response. In terms of adverse events, those of grade three severity were seen in 32% (eight of 25) patients; decline in the white blood cell count was most commonly observed (four cases) [21].

All three cases of gastrointestinal LCH within our study demonstrated multisystem involvement and were treated with the Special C regimen. At the end of this therapeutic regimen, all patients showed a complete response. While a relapse had occurred in one patient at 1 year 7 months after treatment, and chemotherapy was re-administered, the post-treatment clinical conditions of the other two patients remained stable for several years.

Within the limits of the relatively small sample size and retrospective design of this study, the gastrointestinal lesions presented no gastrointestinal symptoms and did not affect the clinical course; the significance of these gastrointestinal lesions therefore remain unclear. As such, more cases need to be analyzed, and more follow-up assessments are required to elucidate the significance of gastrointestinal lesions in adult multisystem LCH.

In summary, although apparent gastrointestinal lesions are reported to be notably rare, gastrointestinal lesions in this study appeared to be more prevalent than expected. These lesions were relatively small, and biopsies were needed for diagnosis. Although they did not seem to affect the clinical course, more research is needed to elucidate the significance of these lesions.

**Acknowledgements** We would like to thank Tamami Denda and Yukihisa Tanaka for their technical support in pathological investigations.

**Author contributions** MK collected and summarized the clinical data. YM drafted the manuscript. LAL designed and generated all figures. MK, YH, YO, YH, LAL, HY, and AT reviewed the manuscript. All authors read and approved the final manuscript.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflicting interests to disclose.

## References

1. Egeler RM, D'Angio GJ (1995) Langerhans cell histiocytosis. J Pediatr 127(1):1–11. https://doi.org/10.1016/s0022-3476(95)70248-2

2. Beverley PC, Egeler RM, Arceci RJ et al (2005) The Nikolas symposia and histiocytosis. Nat Rev Cancer 5(6):488–494. https://doi.org/10.1038/nrc1632
3. Lian C, Lu Y, Shen S (2016) Langerhans cell histiocytosis in adults: a case report and review of the literature. Oncotarget 7(14):18678–18683. https://doi.org/10.18632/oncotarget.7892
4. Badalian-Very G, Vergilio JA, Degar BA et al (2012) Recent advances in the understanding of Langerhans cell histiocytosis. Br J Haematol 156(2):163–172. https://doi.org/10.1111/j.1365-2141.2011.08915.x
5. Swerdlow SH, Campo E, Harris NL et al (2017) WHO classification of tumours of haematopoietic and lymphoid tissues, vol 2. World Health Organization Classification of Tumours. International Agency for Research on Cancer (IARC). 69008 Lyon, France. https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/WHO-Classification-Of-Tumours-Of-Haematopoietic-And-Lymphoid-Tissues-2017
6. Chang KL, Snyder DS (2008) Langerhans cell histiocytosis. Cancer Treat Res 142:383–398. https://doi.org/10.1007/978-0-387-73744-7_17
7. Howarth DM, Gilchrist GS, Mullan BP et al (1999) Langerhans cell histiocytosis: diagnosis, natural history, management, and outcome. Cancer 85(10):2278–2290. https://doi.org/10.1002/(sici)1097-0142(19990515)85:10<2278:aid-cncr25>3.0.co;2-u
8. (1996) A multicentre retrospective survey of Langerhans' cell histiocytosis: 348 cases observed between 1983 and 1993. The French Langerhans' Cell Histiocytosis Study Group. Arch Dis Child 75(1):17–24. https://doi.org/10.1136/adc.75.1.17
9. Morimoto A, Shimazaki C, Takahashi S et al (2013) Therapeutic outcome of multifocal Langerhans cell histiocytosis in adults treated with the Special C regimen formulated by the Japan LCH Study Group. Int J Hematol 97(1):103–108. https://doi.org/10.1007/s12185-012-1245-0
10. Groisman GM, Rosh JR, Harpaz N (1994) Langerhans cell histiocytosis of the stomach. A cause of granulomatous gastritis and gastric polyposis. Arch Pathol Lab Med 118(12):1232–1235
11. Yadav SP, Kharya G, Mohan N et al (2010) Langerhans cell histiocytosis with digestive tract involvement. Pediatr Blood Cancer 55(4):748–753. https://doi.org/10.1002/pbc.22663
12. Singhi AD, Montgomery EA (2011) Gastrointestinal tract langerhans cell histiocytosis: a clinicopathologic study of 12 patients. Am J Surg Pathol 35(2):305–310. https://doi.org/10.1097/PAS.0b013e31820654e4
13. Terracciano L, Kocher T, Cathomas G et al (1999) Langerhans cell histiocytosis of the stomach with atypical morphological features. Pathol Int 49(6):553–556. https://doi.org/10.1046/j.1440-1827.1999.00909.x
14. Nozaki Y, Oshiro H, Nakajima A (2010) Image of the month. Langerhans cell histiocytosis of the stomach mimicking early gastric cancer. Clin Gastroenterol Hepatol 8(9):A18. https://doi.org/10.1016/j.cgh.2010.01.009
15. Wada R, Yagihashi S, Konta R et al (1992) Gastric polyposis caused by multifocal histiocytosis X. Gut 33(7):994–996. https://doi.org/10.1136/gut.33.7.994
16. Heritier S, Emile JF, Barkaoui MA et al (2016) BRAF mutation correlates with high-risk Langerhans cell histiocytosis and increased resistance to first-line therapy. J Clin Oncol 34(25):3023–3030. https://doi.org/10.1200/JCO.2015.65.9508
17. Berres ML, Lim KP, Peters T et al (2015) BRAF-V600E expression in precursor versus differentiated dendritic cells defines clinically distinct LCH risk groups. J Exp Med 212(2):281. https://doi.org/10.1084/jem.2013097701202015c
18. Cortazar JM, Kim AS (2017) Incidental Langerhans cell histiocytosis of the colon with BRAF p.V600E mutation. Blood 130(16):1870. https://doi.org/10.1182/blood-2017-07-796607
19. Gadner H, Grois N, Arico M et al (2001) A randomized trial of treatment for multisystem Langerhans' cell histiocytosis. J Pediatr 138(5):728–734. https://doi.org/10.1067/mpd.2001.111331
20. Kobayashi M, Tojo A (2018) Langerhans cell histiocytosis in adults: advances in pathophysiology and treatment. Cancer Sci 109(12):3707–3713. https://doi.org/10.1111/cas.13817
21. Kobayashi M, Ando S, Kawamata T et al (2020) Clinical features and outcomes of adult Langerhans cell histiocytosis: a single-center experience. Int J Hematol. https://doi.org/10.1007/s12185-020-02892-z