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CASE REPORT

Intestinal Langerhans Cell Histiocytosis-like Lesion in an Adult Presented with Diverticulitis: A Reactive or Neoplastic Condition?

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Abstract The involvement of the gut by Langerhans cell histiocytosis (LCH) is very rare in adults; however this is usually observed with a disseminated disease in children. We report a 75-year-old male patient who underwent right hemicolectomy for a complicated intestinal diverticular disease. The surgical specimen revealed LCH-like proliferative lesion associated with diverticulitis. The overall morphological and immunohistochemical findings are indistinguishable from LCH. Systemic scans and subsequently performed bone marrow biopsies were free of disease. Although the HUMARA clonality assay cannot be assessed, the lack of evidence of LCH progression or disease elsewhere in the whole body strongly supported the possibility of an atypical reactive phenomenon probably due to the underlying intestinal diverticular disease. Therefore, it is important to avoid diagnosing such a unifocal Langerhans cell proliferation as LCH in patients with underlying pathologies in the absence of systemic involvement. Therefore, without knowledge of clonal status of a unifocal Langerhans cell proliferation, we recommend using the terminology of LCH-like lesion.

Keywords Langerhans cell histiocytosis · Langerhans cell hyperplasia · Langerhans cell histiocytosis-like lesion · Gastrointestinal tract · Diverticulitis

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Introduction

Symptomatic GI tract involvement by Langerhans cell histiocytosis (LCH) is unusual in adults. In most cases, such condition has been regarded as an indicator of a disseminated disease [1, 2]. Protein-losing enteropathy and diarrhea (sometimes bloody) are reported to be the main clinical findings of intestinal LCH [2–5]. When systemic disease is present skin, bones, liver, spleen, lungs and lymph nodes are usually affected.

World Health Organization (WHO) defined LCH as a clonal neoplastic proliferation of Langerhans cells, with expression of CD1a, S-100 protein, langerin and also the presence of Birbeck granules by ultrastructural examination [6]. The identification of Birbeck granules by electron microscopy has become dispensable today, since specific antiboides such as CD1a and langerin (CD207) are available for immunohistochemistry on paraffin sections in order to differentiate Langerhans cell lesions from other histocytoses.

We discuss herein the clinical and histological features of a case of intestinal LCH-like lesion presented with diverticulitis and intestinal obstruction in order to highlight current problems in unifocal Langerhans cell proliferative lesions.

Case Report

A 75-year-old man presented with severe acute abdominal pain, intermittent fever, nausea and vomits to emergency room. Clinical workup revealed diverticulitis and findings suggestive of intestinal obstruction and subsequently right hemicolectomy was undertaken. Past medical history revealed hypertension, essential tremor for more than

10 years and he was suffering from recurrent and progressive abdominal pain and intermittent fever for the last 6 months.

The histopathological examination of the large intestine revealed diverticulitis and also nodular and interstitial cellular proliferation at site of the diverticulae (Fig. 1a). Histopathologically, these cells were recognized as Langerhans cells with their characteristic folded, grooved, lobulated and indented nuclei showing thin nuclear membrane and inconspicuous nucleoli (Fig. 1b). Their cytoplasms were slightly eosinophilic. There was no frank eosinophilia associated with the cellular infiltrate. These cells were negative for anti-Langerin and were positive for anti-CD1a, HLA-DR, S100 protein, lysozyme and CD68 (Fig. 2). MIB-1 labeling index was found as high as 5%. The overall morphological and immunohistochemical findings were indistinguishable from LCH.

Systemic scans (Computerized Tomography, Magnetic Resonance Imaging and Ultrasonography) and upper gastrointestinal endoscopy did not reveal any pathological findings except grade I hepatosteatosis. The blood work revealed very mild anemia and mild leukocytosis. Subsequently, bone marrow trephine biopsy was performed and was found to be free of CD1a (+), Langerin (+) and S100 protein (+) cellular infiltrate. Following surgery, he required internalization due to postoperative gastroparesia and low blood potassium level. Supportive and symptomatic treatment helped to improve the overall health situation. The patient is still alive after 6 years and did not show any evidence of LCH progression or disease elsewhere in the whole body.

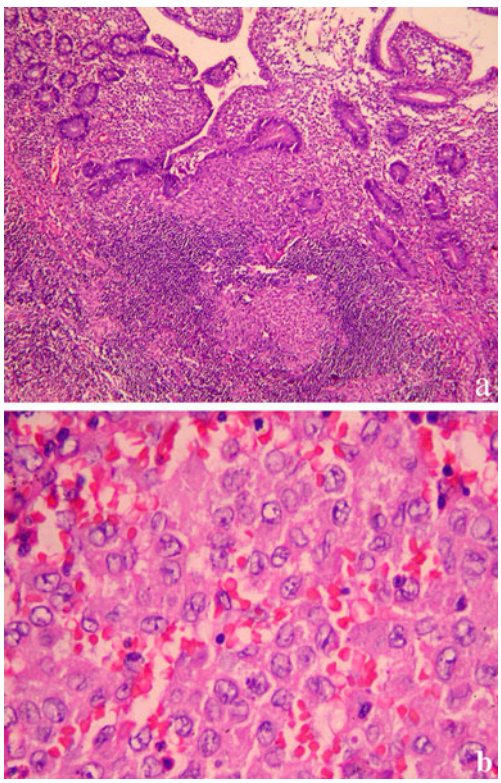

Fig. 1 **a**. Nodular and interstitial Langerhans cell proliferation in the lamina propria, **b**. Langerhans cells with their characteristic folded, grooved, lobulated and indented nuclei showing thin nuclear membrane and inconspicuous nucleoli (Original magnification, Haematoxylin and Eosin)

Discussion

GI tract involvement in LCH is rarely described in adults. However, this is most often described in children with multiorgan or disseminated disease [1–5]. Furthermore, the association of LCH-like lesion with diverticulitis has not been reported so far in the English literature. In most cases, LCH of the gut has been presented with protein-losing enteropathy and diarrhea [2–5]. However, when systemic disease is present; several sites such as skin, bones, liver, spleen, lungs and lymph nodes are usually affected [6]. In this context, the presented case is an example of GI tract LCH-like lesion with adult onset presenting with diverticulitis.

Langerhans cells, which are considered as immature dendritic cells (DC) present in the epidermis and mucosal epithelium and they contain unique cytoplasmic organelles, called Birbeck granules [6–8]. Recent studies demonstrated a crucial role for the langerin, in the biogenesis of these granules [7, 8]. In addition to anti-CD1a expression, langerin (CD207) is used on paraffin sections in order to discriminate Langerhans cell lesions from other histiocytic disorders [6–9]. Apart from skin localization, little is known for the prevalence of anti-Langerin expression in CD1a positive dendritic cells.

The presented case revealed a cellular infiltrate indistinguishable morphologically from Langerhans cell histiocytosis which was negative for anti-Langerin and was positive for anti-S100, CD1a, CD68, HLA-DR and lysozyme. Recent studies highlighted that Langerin is in fact not necessary for the establishment of the Langerhans cell system in the epidermis [7, 8, 10, 11]. Interestingly, a somatic missense mutation in the carbohydrate recognition domain of Langerin gene was also defined in a healthy white man whose Langerhans cells completely lack typical Birbeck granules and anti-Langerin expression [10]. In fact, little is known regarding the frequency of these mutations and the negativity for anti-Langerin in Langerhans cells. To complicate this controversial situation, it is of note that Langerin, which is regarded a highly specific marker of Langerhans cell and the lesional cells of Langerhans cell histiocytosis, is linked with the biogenesis of Birbeck granules [7, 8]. Interestingly, Langerin expressing non-

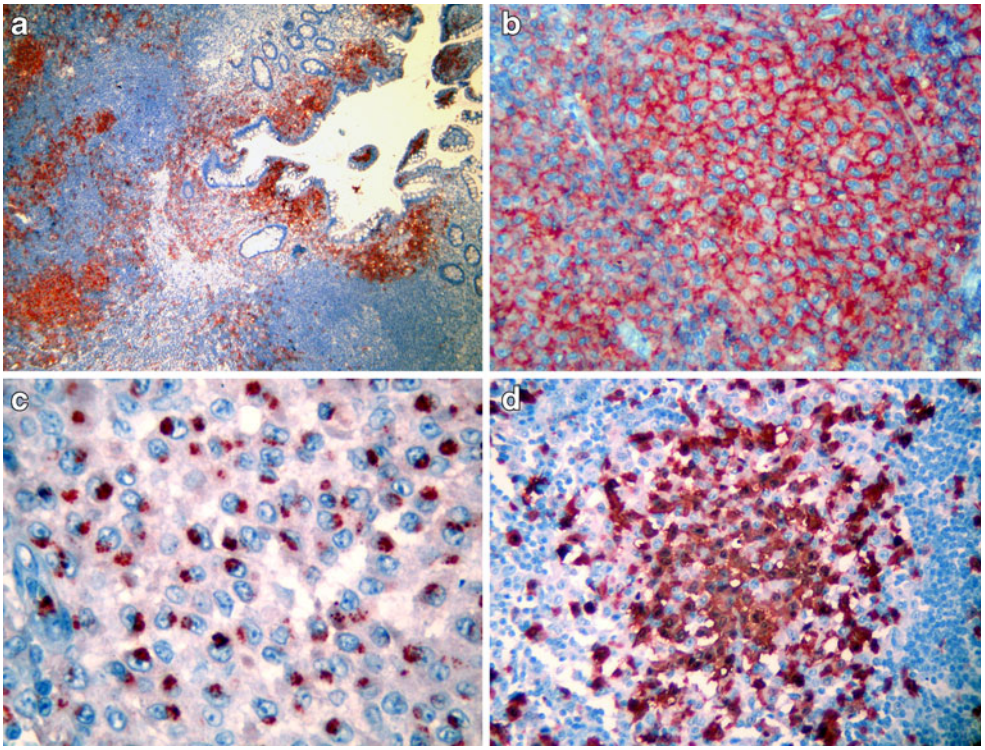

Fig. 2 **a**–**b** Membranous anti-CD1a positivity in nodular and interstitial cellular infiltration, **c**. Paranuclear anti-lysozyme expression in cellular infiltrate, **d**. Anti-S100 protein expression in the cellular infiltrate (Original magnification, anti-CD1a, anti-lysozyme, anti-S100 protein, respectively)

Langerhans dendritic cells, which are free of Birbeck granules, are also defined in the dermis [7, 8]. Recently, while focal Langerin immunoreactivity was also observed in histiocytic sarcomas, all non-Langerhans cell histiocytic disorders showed no expression of CD1a [9].

Although Langerin protein expression in Langerhans cell histiocytosis has been previously documented, the specificity of anti-Langerin expression as determined by immunohistochemistry in the context of other DC disorders has not been widely investigated in mucosal tissues. Therefore, the negativity or positivity for anti-Langerin alone appears to have a questionable role in the discrimination of Langerhans cells from other dendritic cells.

Langerhans cells, in fact are DC of bone marrow origin, and are responsible for processing and presenting antigens to T lymphocytes. As Langerhans cells physiologically belong to the immune system, it is not surprising that proliferation of these cells may also be a part of a secondary reactive phenomenon in the absence of systemic involvement. The cause of LCH is still unknown [6], although there are some theories which have grown from the research conducted over the past few years. However, there is evidence that Langerhans cell proliferations represent a spectrum of disease that ranges from reactive to neoplastic phenomenon [12–15].

Interestingly, adults with isolated LCH of the lung usually regress spontaneously or stabilize upon cessation of smoking [12]. This may indicate hypothetically that LCH arises in some conditions in a background of Langerhans cell hyperplasia or some of them are not even LCH. Similarly, some scabies infestations are demonstrated to be associated with Langerhans cell hyperplasia, which is totally cleared following the treatment of underlying pathology that is believed to cause an antigenic stimulus for epidermal Langerhans cells [14, 15].

It is of note that Singaram et al. [16] found increased number of calcitonin gene related peptide producing intraepithelial Langerhans cells in esophagitis. Schneider et al. [17] who investigated the histiocytic subpopulations in the GI tract, CD1a positive cells were seen exclusively within anal and esophageal squamous mucosa. In contrast Niess et al. [18] who investigated the lamina propria dendritic cells in the physiology and pathology of the GI tract found that the DC are not a rare cell type in the intestine but populate the entire lamina propria of the GI tract as an extensive network**.** However, little is known about Langerhans cell hyperplasia in the GI tract; as such proliferative lesions in the gut are very rare and are usually asymptomatic in adults. Moreover, Langerhans cell hyperplasia is a relatively new and developing concept in the field of surgical pathology and as well in the clinical medicine [13–15].

Generally, the clinical outcome of LCH is related to the number of organs affected at the time of presentation. The overall survival of patients with unifocal disease is usually higher than 95% [6]. Age of the patient is a less important prognostic factor in LCH than the number of involved organs [6]. Previous studies results showed that single-system LCH is a disease that can be treated alone by

surgery and adjuvant radiotherapy and/or chemotherapy is considered only in severe and multifocal disease [19–22]. On the other hand, some authors regard GI tract involvement of LCH as an indication of aggressive systemic treatment, irrespective of the patient clinical status [22]. However, all these considerations are made mostly by taking into consideration previous concepts where clonality assay are not assessed.

Langerhans cell lesions including hyperplasia and neoplasms in the GI tract are underestimated both clinically and histologically. In fact, the biological significance of unifocal LCH-like lesions is not well-known in males; however, there is evidence of polyclonality in similar lesions tested for HUMARA assay in females [6, 12, 13]. Moreover, the lack of LCH progression or disease elsewhere in the whole body and spontaneous regression in situations such pulmonary cases associated with smoking or in the case of scabies support strongly the possibility of a reactive phenomenon [6, 12–15].

It is clear that the clinical spectrum of Langerhans cell proliferations should be considered to be broad and includes from self-resolving involvement of a single organ to a potentially fatal multisystem disease. We believe that further molecular biological investigations in larger series are needed to define underlying pathogenesis of predisposing factors that lead unifocal LCH-like lesion and LCH, and therefore to define clearly the spectrum of Langerhans cell hyperplasia (LCH-like lesion), LCH and as well Langerhans cell sarcoma. It is clear that this discrimination is of clinical significance since polyclonal LCH-like lesions may be regressed spontaneously if the underlying stimulant pathological condition is cleared and this discrimination will avoid unnecessary adjuvant therapy in such patients. In summary, the presented case is an unusual example of LCH-like lesion in the gut of an adult presenting mainly with symptoms related to diverticulitis.

In summary, anatomical localization, morphology and detailed immunophenotype help to determine the type of DC as Langerhans cell. However, the origin of different DC subsets is still controversial. Further investigations with larger series will help to clarify these issues and will give us a better explanation in the correct classification of CD1a positive and Langerin negative dendritic cells in the gastrointestinal tract and other mucosal parts. On the other hand, it is important to remember that morphological and immunohistochemical findings are not useful alone to discriminate which Langerhans cell proliferation represents a reactive or a neoplastic phenomenon without assessing the clonality assay. Similar to the original proposal of Christie et al. [13], we recommend using the terminology of 'LCH-like lesion' without knowledge of clonal status of a unifocal Langerhans cell proliferation.

References

1. Levy J, Khaskelberg A, Garvin J (2001) Langerhans cell histiocytosis (LCH) involving the gastrointestinal tract: a clinical-electrogastrographic correlation. J Pediatr Gastroenterol Nutr 33:511–514
2. Santos-Machado TM, Cristofani LM, Almedia MT, Maluf PT, Costa PA, Pereira MA et al (1999) Disseminated Langerhans cell histiocytosis and massive protein-losing enteropathy. Braz J of Med and Biol Res 32:1095–1099
3. Egeler RM, Schipper ME, Heymans HS (1990) Gastrointestinal involvement in Langerhans cell histiocytosis (Histiocytosis X): a clinical report of three cases. Eur J Pediatr 149:325–329
4. Patel BJ, Chippindale AJ, Gupta SC (1991) Case report: small bowel histiocytosis-X. Clin Radiol 44:62–63
5. Terracciano L, Kocher T, Cathomas G, Bubendorf L, Lehmann FS (1999) Langerhans cell histiocytosis of the stomach with atypical morphological features. Pathol 49:553–556
6. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW (eds) (2008) WHO classification of tumours of haematopoietic and lymphoid tissues. IARC, Lyon
7. Merad M, Ginhoux F, Collin M (2008) Origin, homeostasis and function of Langerhans cells and other langerin expressing dendritic cells. Nat Rev Immunol 8:935–947
8. Chang SY, Kweon MN (2010) Langerin-expressing dendritic cells in gut-associated lymphoid tissues. Immunol Rev 234:233–346
9. Lau SK, Chu PG, Weiss LM (2008) Immunohistochemical expression of Langerin in Langerhans cell histiocytosis and non-Langerhans cell histiocytic disorders. Am J Surg Pathol 32:615–619
10. Verdijk P, Dijkman R, Plasmeijer EI, Mulder AA, Zoutman WH, Mieke Mommaas A et al (2005) A lack of Birbeck granules in Langerhans cells is associated with a naturally occurring point mutation in the human langerin gene. J Invest Dermatol 124:714–717
11. Kissenpfennig A, Aït-Yahia S, Clair-Moninot V, Stössel H, Badell E, Bordat Y et al (2005) Disruption of the langerin / CD207 gene abolishes Birbeck granules without a marked loss of Langerhans cell function. Mol Cell Biol 25:88–99
12. Negrin-Dastis S, Butenda D, Dorzee J, Fastrez J, D'Odémont JP (2007) Complete disappearance of lung abnormalities on high-resolution computed tomography: a case of histiocytosis X. Can Respir J 14:235–237
13. Christie LJ, Evans AT, Bray SE, Smith ME, Kernohan NM, Levison DA et al (2006) Lesions resembling Langerhans cell histiocytosis in association with other lymphoproliferative disorders: a reactive or neoplastic phenomenon? Hum Pathol 37:32–39
14. Bhattacharjee P, Glusac EJ (2007) Langerhans cell hyperplasia in scabies: a mimic of Langerhans cell histiocytosis. J Cutan Pathol 34:716–720
15. Burch JM, Krol A, Weston WL (2004) Sarcoptes scabiei infestation misdiagnosed and treated as Langerhans cell histiocytosis. Pediatr Dermatol 21:58–62
16. Singaram C, Sengupta A, Stevens C, Spechler SJ, Goyal RK (1991) Localization of calcitonin gene-related peptide in human esophageal Langerhans cells. Gastroenterology 100:560–563
17. Schneider EN, Smoller BR, Lamps LW (2004) Histiocytic subpopulations in the gastrointestinal tract: distribution and possible relationship to function. Appl Immunohistochem Mol Morphol 12:356–359
18. Niess JH, Reinecker HC (2005) Lamina propria dendritic cells in the physiology of the gastrointestinal tract. Curr Opin Gastroenterol 21:687–691

19. Selim MA, Shea CR. Langerhans cell histiocytosis. *eMedicine Specialities*, available at http://www.emedicine.com/derm/topic216.htm (last updated 07.02.2007).
20. Giona F, Caruso R, Testi AM, Moleti ML, Malagnino F, Martelli M et al (1997) Langerhans cell histiocytosis in adults: a clinical and therapeutic analysis of 11 patients from a single institution. Cancer 80:1786–1791
21. Choi SW, Bangaru BS, Wu CD, Finlay JL (2003) Gastrointestinal involvement in disseminated Langerhans cell histiocytosis (LCH) with durable complete response to 2-chlorodeoxyadenosine and high-dose cytarabine. J Pediatr Hematol Oncol 25:503–506
22. Hait E, Liang M, Degar B, Glickman J, Fox VL (2006) Gastrointestinal tract involvement in Langerhans cell histiocytosis: case report and literature review. Pediatrics 118:e1593–e1599