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Adult Langerhans Cell Histiocytosis with Caecal and Regional Lymph Node Involvement

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Abstract

Background: Langerhans cell histiocytosis (LCH) is a group of idiopathic disorders characterized by the proliferation of specialized bone marrow-derived Langerhans cells and mature eosinophils. Involvement of the gastrointestinal tract is very rare in LCH and has only been described in case reports and small series.

Case description: A 58-year-old woman who presented with recurrent and progressive right lower quadrant pain, bloating and change in bowel habits was submitted to surgical treatment. A computed tomography scan of the abdomen revealed circumferential caecal wall thickening as well as multiple mesenteric lymph nodes which were suspicious for involvement by a caecal tumour. A right hemicolectomy was performed.

Results: Upon opening the caecum, a soft, nodular, poorly circumscribed, grey-white to yellow mass measuring 4 cm in greatest dimension was observed close to the ileocaecal valve. Multiple lymph nodes were also identified in the surrounding mesenteric fat. Histology revealed a mucosal lesion of the caecum and terminal ileum characterized by proliferation of histiocytic cells and accompanied by a moderate number of eosinophils and lymphoid cells. Some of the regional mesenteric lymph nodes exhibited at least focal involvement with numerous histiocytes. Immunoperoxidase studies showed that the histiocytic cells were reactive to langerin, CD1a, S-100 and CD68 antigens.

Based on these findings, a diagnosis was reached of Langerhans cell histiocytosis with lymph node involvement.

Conclusions: LCH is rare in adults, and gastrointestinal tract involvement even rarer. Our case presented as a mass lesion located in the mucosa of the caecum and terminal ileum. With the increasing number of colonoscopies being performed, gastroenterologists and pathologists should be aware of this rare cause of colon polyps.

Key words: *Caecum; histiocytes; Langerhans cell histiocytosis; immunohistochemistry; diagnosis*

Introduction

Langerhans cell histiocytosis (LCH) is a rare disease characterized by abnormal proliferation of Langerhans cells derived from the bone marrow [1]. It is a challenging disease with a wide clinical spectrum ranging from solitary lesions of a single site (usually bone or skin) to multiple or disseminated lesions with multiple organ involvement leading to severe organ dysfunction [2]. Involvement of the gastrointestinal (GI) tract is extremely rare in adults. LCH can involve any portion of the (GI) tract from the oral mucosa to the anal canal and perianal skin, either as part of generalized disease or as a separate primary entity. Although it can occur at any age, it mostly affects children younger than two years of age [3]. GI tract LCH in adults can manifest as colon polyps [4-12]. We report a rare case of LCH involving the caecum and regional lymph nodes in an adult who presented with symptoms of intestinal obstruction. The histological features supported by immunohistochemistry helped the right diagnosis to be reached.

Case report

A 58- year-old woman presented with a 6-month history of intermittent right lower quadrant pain, bloating

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Abbreviations

LCH= Langerhans Cell Histiocytosis
GI= Gastro Intestinal
RDD= Rosai - Dorfman Disease

and change in bowel habits. The abdominal pain was dull and slightly aggregated by physical work and released after rest. The patient's medical history was unremarkable, and she denied any fever, haematochezia or weight loss. Her physical examination was negative for abdominal tenderness and rebound, and no abnormal mass or lymphadenopathy was noted. Laboratory tests demonstrated a normal complete blood count, metabolic profile, and tumour markers including cancer antigens 125 and 19-9. Subsequent imaging evaluation including chest/abdomen computed tomography revealed circumferential caecal wall thickening as well as multiple mesenteric lymph nodes which were suspicious for involvement by a caecal tumour. On the basis of a presumptive clinical diagnosis of a caecal mass, the patient underwent a right hemicolectomy. The patient recovered well from surgery and her postoperative course was uneventful.

Methods

The resection specimen was fixed in 10% buffered formalin, and then processed routinely. The sections were stained with haematoxylin and eosin. Using the avidin-biotin complex method, immunohistochemical staining was performed on paraffin sections. Primary antibodies were used: CK AE1/AE3, CD68, CD1a, S100 protein, CD21, CD35, CD117, Langerin (CD207), HMB-45, Melan-A, Ki-67 (MIB-1), CD3 and CD20.

Pathologic findings

The surgical specimen consisted of a 27.0 cm segment of ileum and caecum and a vermiform appendix measuring 7.0 cm. On cut surface, a soft, nodular, poorly circumscribed, grey-white to yellow mass measuring 4.0 cm in greatest dimension was observed in the caecum, close to the ileocaecal valve. A sessile smooth polyp measuring 1.2 cm was found at the other side of the mass. Multiple lymph nodes ranging in size from 0.3 cm to 1.0 cm were identified in the surrounding mesenteric fat. Otherwise, the rest of the large bowel and ileum appeared normal.

Histopathological examination revealed a mucosal lesion of the caecum and terminal ileum characterized by nodular proliferation and accumulation of sheets or islands of large cells with indistinct cell borders and abundant often granulous cytoplasm. The nuclei varied from reniform-to-oval shape with fine, vesicular chromatin, nuclear grooves, and a single inconspicuous nucleolus (Figure 1a). The lesional cells were permeated by a mixed inflammatory infiltrate of a variable number of eosinophils and small B lymphocytes with intermixed CD3-positive T cells. Additional microscopic features included areas of central necrosis and multinucleated giant cells. High-grade nuclear features were not seen. Mitotic figures were present (10 mitosis per 10 high power field). The overlying mucosa showed focal ulceration (Figure 1b). Some of the regional mesenteric lymph nodes exhibited at least partial architectural distortion and ectatic lymphatic sinuses filled with numerous histiocytes (Figure 2). The caecal polyp close to the mass lesion was a sessile, high grade tubular adenoma.

Several immunohistochemical stains that were applied to further characterize the cells in question in both the caecal lesion and lymph nodes revealed that cells of the histiocytic infiltrate were positive for Langerin (Figure 3a) and CD1a (Figure 3b). LCH cells also stained positive for S100 (Figure 3c), CD68 and negative for cytokeratins AE1/AE3, CD117, and "melanoma cocktail" that included HMB-45, Melan-A/MART1. MIB-1 labelling index was found to be as high as 10%. Electron microscopy was not performed to document the presence of Birbeck granules since staining for Langerin and CD1a was strongly positive. The overall morphological and immunohistochemical find-

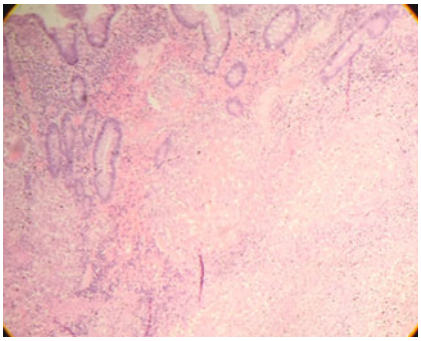

Figure 1a. Subepithelial focus showed replacement of the l-propria by a collection of histiocytic cellular infiltrate admixed with lymphocytes and eosinophils (H&E, magnification 100x).

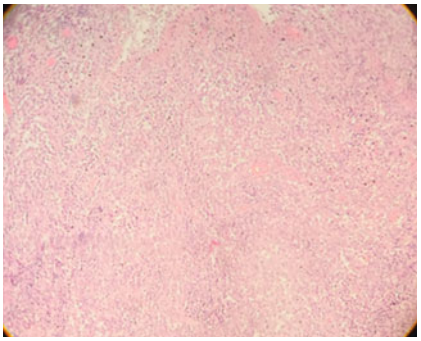

Figure 1b. Photomicrography of submucosal LCH nodule with central ulceration (H&E, magnification 100x).

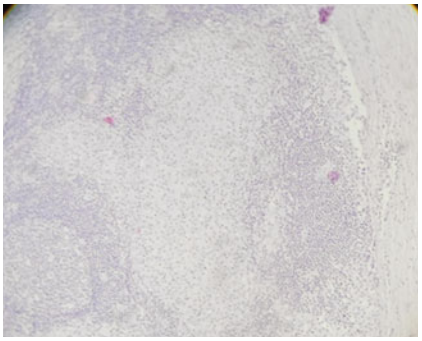

Figure 2. LCH involving the regional lymph node (H&E, magnification 100x).

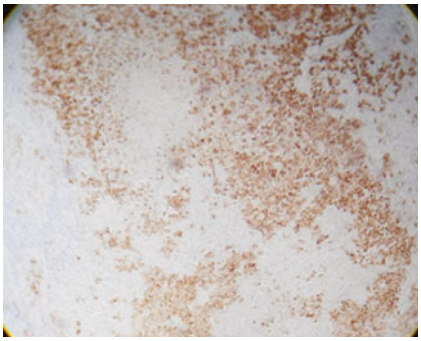

Figure 3a. Langerin immunostaining. Histiocytes show positive expression (100x).

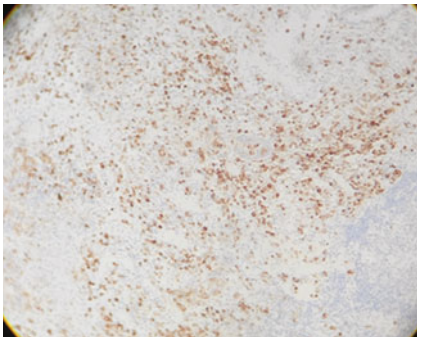

Figure 3b. Immunohistochemistry for CD1a. The histiocytic cells show positive staining for CD1a (100x).

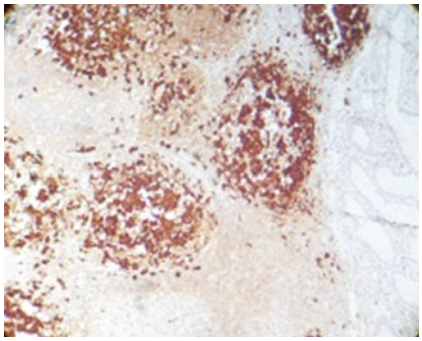

Figure 3c. Many of the Langerhans cells are strongly positive for S100 protein (100x).

ings supported the diagnosis of Langerhans cell histiocytosis (LCH) with lymph node involvement. The patient was subsequently referred for medical oncology evaluation of this pathologic finding with malignant potential. Systemic scans and bone marrow biopsy were recommended to rule out any metastasis through staging evaluation.

Discussion

Adult colonic LCH is an exceedingly rare disease identified in both children and adults. It is characterized by proliferation and accumulation of cells with characteristics of Langerhans cells. The aetiology and pathogenesis are unknown [1]. However, there is evidence that Langerhans cell proliferations represent a spectrum of disease that ranges from reactive to neoplastic phenomenon [13]. A literature review showed only a handful of previously reported cases of adult colonic LCH [4-12]. The exact incidence is at present unknown. Most adult cases involved patients who were asymptomatic on clinical presentation and predominantly female. The lesions were encountered on routine endoscopy and were described as a solitary lesion without systemic illness [4,5,7]. In children, colonic LCH has presented with protein-losing enteropathy and diarrhoea [3,7,12]. The largest series of adult colonic LCH published to date included a total of 10 cases. Only one patient progressed to extracolonic disease with involvement of the skin [7]. Endoscopically, seven of ten patients presented with a solitary colonic polyp and half were asymptomatic at presentation. Anatomic distribution was characterized by involvement of the caecum (n=2), ascending colon (n=1),transverse colon (n=1), sigmoid colon (n=2) and anus (n=1). Another published study included a total of eight cases. Two out of eight adult patients with colonic involvement by LCH presented with multiple lesions, one of whom developed cutaneous disease two years after the initial diagnosis [10]. One patient died of disseminated disease five years after the first symptom (right hip pain related to involvement of femoral head).

Tissue biopsy is necessary to make the correct diagnosis. Conventional histology shows lesions containing mononuclear cells with reniform-to-oval-shaped nuclei with nuclear grooves. A concomitant infiltration by lymphocytes and eosinophilic granulocytes forming pseudoabscesses is characteristic [14]. Given that LCH has a distinctive immunohistochemical profile, immunohistochemistry is essential to highlight these features and exclude other lookalike lesions. The most important markers are CD1a, langerin and S100. Definitive histological diagnosis of LCH requires the coexpression of CD1a on the surface of lesional cells and langerin. Recent studies demonstrated a crucial role for langerin in the biogenesis of Birbeck granules [15]. Langerin is as sensitive and specific as CD1a and more specific than S100 in the diagnosis of LCH and in distinguishing it from other histiocytic disorders [16,17].

We believe that our case illustrates three distinct clinicopathologic features not previously reported in this clinical setting: the size of the lesion, the focal involvement of lymph nodes and the coexistence of a colonic tubular adenoma. In addition, the presence of focal necrosis, the invasion of lymph nodes, the index of MIB-1 proliferation and mitotic figures suggest a more aggressive behaviour of LCH.

S100 positivity points to the differential diagnosis of malignant melanoma, which may present as a primary or metastatic lesion at the gastrointestinal tract [4]. However, melanoma lacks the reniform nucleus, and the degree of nuclear pleomorphism is frequently much more striking than in LCH. Melanoma is usually HMB-45 and Melan-A positive and CD1a negative.

The differential diagnosis should also include extranodal Rosai-Dorfman disease (RDD). Within the GI tract, it can present as either an isolated lesion or widespread extranodal disease [7,18]. However, RDD does not have the nuclear irregularities and grooves that are characteristic of LCH. In addition, RDD shows emperipolesis. CD1a expression

has been reported to be negative in RDD.

Histiocytic sarcoma is a rare malignant neoplasm with frequent extranodal presentation that includes the skin and the GI tract [7]. The tumour cells are markedly atypical and the MIB-1 fraction may be very high. Haemophagocytosis may be present. The tumour can be immunoreactive for S100 protein, but the expression is usually weak and focal. Immunostaining for CD1a is negative [7,14].

Systemic mastocytosis often shows GI tract involvement. Histologically, it is characterized by an abnormal proliferation of tissue mast cells within the mucosa. The mast cells can show a range of morphologic appearances and resemble histiocytes. Positive immunohistochemical staining for CD117 can help identify the mast cells and facilitate diagnosis [7]. In our case, CD117 was not expressed.

In summary, colonic involvement with LCH in adults is extremely rare and can be diagnostically problematic for both endoscopists and pathologists. To the best of our knowledge, this is the first Greek case to be reported. Most patients are asymptomatic; the condition is encountered incidentally as a solitary polyp. Our case presented with intermittent right lower abdominal pain. Morphology and detailed immunophenotype help to determine the type of dendritic cells as Langerhans cells. On the other hand, it is important to remember that without a clonality assay, morphological and immunohistochemical findings alone cannot discriminate which Langerhans cell proliferation represents a reactive or neoplastic process. Rare cases of LCH may progress to multifocal, multisystem disease. Clinical follow-up is recommended.

Ethical Approval - Informed Consent: *Written informed consent was obtained from the patient for publication of her personal clinical and lab data.*

Conflict of interest: *The authors declare that they have no conflict of interest.*

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