Langerhans cell histiocytosis of the gastrointestinal tract

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Abstract

We report a case of a 28 year-old lady who presented with a history of perianal pain and discharge per rectum over several months. Biopsies of ulcers observed endoscopically at 50 cm and at 30 cm from the anal verge, showed colonic mucosa containing mononuclear cells, with reniform nuclei, fine vesicular chromatin, nuclear grooves, indistinct cell borders and abundant eosinophilic cytoplasm. An accompanying mixed inflammatory infiltrate, with prominent numbers of eosinophils, was also present. Immunohistochemically, the mononuclear cells were positive for S100, CD68 and CD1a. The morphological and immunohistochemical features were of Langerhans cell histiocytosis (LCH) involving the colon.

Gastrointestinal tract (GIT) involvement by LCH is quite rare, especially in adults. It is important for pathologists to be aware of the occurrence of this entity in the GIT, to enable correct diagnosis and appropriate management of effected patients.

Keywords CD1a; gastrointestinal tract; Langerhans cells; ulcer

Case report

A 28-year-old female presented with perianal pain and discharge per rectum, which she had experienced over a period of approximately 6 months. Sigmoidoscopy showed two ulcers at 50 cm and at 30 cm from the anal verge. Multiple biopsies were taken.

Histologically, the biopsies comprised colonic mucosa with a dense inflammatory infiltrate in the lamina propria composed of conspicuous numbers of eosinophils, as well as lymphocytes and plasma cells (Figure 1a and b). Admixed were many mononuclear cells with indistinct cell borders and abundant eosinophilic cytoplasm. The nuclei were reniform in shape and contained fine, vesicular chromatin, nuclear grooves, and a single, inconspicuous nucleolus (Figure 1c).

Immunohistochemistry showed that the mononuclear cells were histiocytes that were S100 and CD68 positive but also expressed CD1a (Figure 1d). The overall features were of Langerhans cell histiocytosis (LCH) of the gastrointestinal tract.

The electronic patient record disclosed that this patient had a known history of LCH. She initially presented 5 years previously with a single lesion in her left knee joint, which was surgically excised and diagnosed as a localized histiocytoma. Subsequent bone marrow aspirate disclosed normal trilinear haematopoiesis, and cytogenetic evaluation showed a normal karyotype.

Three years later, she presented to her clinician with mild haematochezia of 4 months' duration, in addition to chronic diarrhoea and abdominal pain. Colonoscopy showed pancolitis, with occasional normal intervening mucosa, and multiple deep serpiginous ulcers, including a large 10 cm ulcer in the rectum. Multiple biopsies confirmed gastrointestinal involvement by LCH.

A staging positron emission tomography (PET) scan revealed multi-systemic involvement, with the thyroid, bone and colon affected. The patient underwent induction therapy with vinblastine (6 mg/m^2 intravenous bolus weekly for 12 weeks) and prednisolone (40 mg/m^2/day orally for 6 weeks and then same dose thrice weekly for 6 more weeks). Maintenance therapy consisted of vinblastine (6 mg/m^2 intravenous bolus every 3 weeks), prednisolone (40 mg/m^2/day, 5 days every 3 weeks), and 6-mercaptopurine (50 mg/m^2/day orally) for 1 year.

The patient achieved complete remission as confirmed by a repeat colonoscopy after 6 weeks and repeat PET scan after 12 weeks. The symptoms prompting the current biopsy commenced 3 months after treatment was discontinued.

Following the most recent biopsy confirming colonic involvement by LCH, the patient is currently on weekly methotrexate, and has no significant side effects from the treatment.

Discussion

Clinical features

According to the World Health Organization (WHO) classification, Langerhans cell histiocytosis (LCH), previously histiocytosis-X, is classified as a histiocytic disorder with variable clinical course, characterized by the abnormal proliferation and dissemination of Langerhans cells derived from the bone marrow.[1]

The aetiology and pathogenesis of LCH remain poorly defined. It has variably been considered as a neoplastic disorder, an immune-dysregulatory disorder, and a reactive disorder with characteristics of both.[2,3] Infection with Epstein–Barr virus (EBV) has been described as a triggering event in selected cases,[4] while smoking has been identified as the main risk factor for isolated pulmonary LCH.[5]

LCH is a rare disease in adults, with an incidence in the order of 1–2 cases per million,[6] and a mean age at diagnosis of 35 ± 14 years.[7]

Presenting symptoms in adult LCH patients depend on the pattern of organ involvement. Weight loss, fever and local pain,

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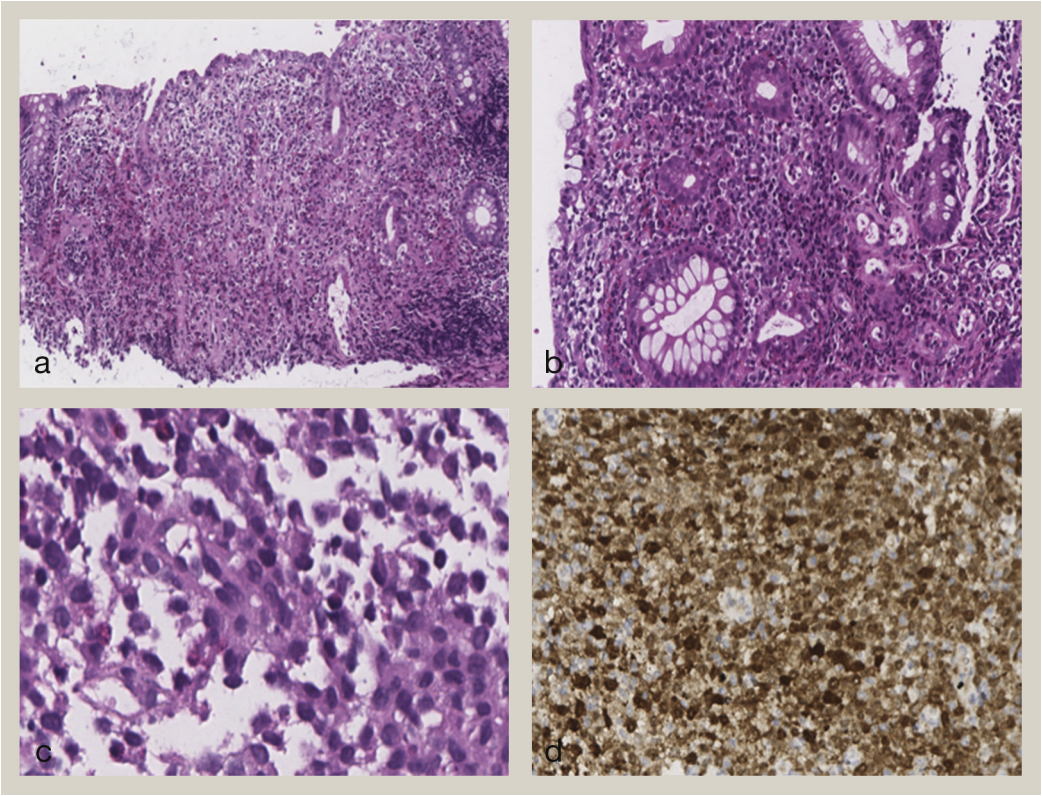

Figure 1 Langerhans cell histiocytosis of colon: colonic mucosa with a dense inflammatory infiltrate in the lamina propria composed of conspicuous numbers of eosinophils (**a**), as well as lymphocytes and plasma cells (**b**). Admixed are many mononuclear cells with reniform nuclei, nuclear grooves, fine, vesicular chromatin, indistinct cell borders and abundant eosinophilic cytoplasm (**c**). The mononuclear cells are positive for CD1a (**d**), as well as CD68 and S100.

particularly due to bone involvement, are the most common symptoms at presentation.[6] Bone lesions are most commonly localized to the skull, particularly to the jaw, which might lead to loosening, and/or loss, of teeth. Long tubular bones, vertebrae, ribs and pelvis are less frequently involved. Diabetes insipidus, due to pituitary gland involvement, is one of the most characteristic manifestations of LCH, with affected patients presenting with polyuria and polydipsia. Other symptoms include skin rash, lymphadenopathy, gingival hypertrophy, disturbed balance and memory problems.[7,8] Pulmonary involvement is frequently observed in adults, and it may occur as occurs as part of 'multi-system disease' or as isolated pulmonary LCH, a distinct disease entity accounting for approximately 20% of adult LCH patients.[6,9]

Gastrointestinal tract (GIT) involvement by LCH is exceedingly rare, and although it can occur at any age, the peak incidence is in children under the age of 2 years, with a male-to-female ratio of 2:1.[10,11] GIT LCH in adults is rather infrequent, being described in a small number of case reports.[12–15] In 2011, Singhi and Montgomery reported a series of 10 adult patients with GIT LCH, with an age range of 40–77 years (mean, 58.4 years).[16] Involvement of the GIT in LCH may present a major clinical problem. Children present with symptoms of failure to thrive, bloody diarrhoea, anaemia, hypoalbuminaemia, severe malabsorption, and/or protein-losing enteropathy.[16,17] It has classically been associated with systemic illness and poor prognosis.[10] In the series of GIT LCH by Singhi and Montgomery, 50% of adult patients were asymptomatic and were undergoing routine colorectal cancer screening, whereas the remaining presented with symptoms considered to be unrelated, namely constipation, dysphagia, anaemia, and caecal volvulus.[16]

Endoscopically, GIT LCH lesions can appear as ulcerations or polyps.[16] LCH can be a solitary lesion in the GIT, or, less commonly, there may be multi-focal GIT involvement.[16] GIT LCH can involve the stomach,[15,18,19] small bowel,[20] large bowel[12–14] and/or anus.[21,22]

Pathology

Microscopically, LCH is characterized by destructive granulomatous lesions, or by histiocytic infiltrates arranged in sheets, nests, or clusters, containing mononuclear cells with indented nuclei sharing the morphology of dendritic antigen presenting Langerhans cells. A concomitant infiltration by lymphocytes and eosinophilic granulocytes forming pseudoabscesses is characteristic.[23]

In the GIT, biopsies show predominantly intra-mucosal disease. LCH of the GIT is typically composed of sheets or islands of large cells, with indistinct cell borders and abundant lightly eosinophilic-to-eosinophilic cytoplasm. The nuclei vary from reniform-to-oval in shape, and contain fine, vesicular chromatin, nuclear grooves, and a single, inconspicuous nucleolus.[16] The lesional cells are usually permeated by a mixed inflammatory infiltrate of a variable number of eosinophils, lymphocytes,

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