CASE REPORTS

Langerhan’s cell histiocytosis complicating small bowel Crohn’s disease

C Lee-Elliott, J Alexander, A Gould, R Talbot, J A Snook

Abstract
Langerhan’s cell histiocytosis is a rare infiltrative disorder of unknown aetiology. A variety of tissues may be affected, but clinically evident intestinal involvement is unusual. An adult patient is described with Crohn’s disease of the terminal ileum who subsequently developed Langerhan’s cell histiocytosis with extensive infiltration of the small bowel.

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Langerhan’s cell histiocytosis (LCH), previously known as histiocytosis X, is a disorder resulting from tissue infiltration with characteristic cells of monocyte/macrophage lineage. These cells have immunohistochemical and morphological similarities to Langerhan’s cells, specialised histiocytes normally found in the skin and squamous mucosae, which have surface membrane expression of CD1a and characteristic cytoplasmic organelles of unknown function (Birbeck granules) on electron microscopy. The definitive diagnosis of LCH requires the finding of CD1a expression or Birbeck granules in lesional cells.

LCH may present at any age, though most cases occur in childhood. The manifestations are protean, though overt intestinal involvement is rare. The aetiology of LCH remains to be established: the capacity of less aggressive variants of LCH to remit spontaneously might imply a reactive process, though the finding of monoclonality suggests that LCH may result from neoplastic proliferation. An intriguing link relates more aggressive forms of LCH to various haematological malignancies.

Case report
A 76 year old woman presented in November 1993 with a six month history of low grade watery diarrhoea, right iliac fossa discomfort, weight loss, and malaise. She had a history of recurrent unexplained iron deficiency during the 1980s, and of erythema nodosum in 1987.

Physical examination including sigmoidoscopy was unremarkable. Basic blood tests showed a low serum albumin concentration (32 g/l) and modestly raised inflammatory markers (erythrocyte sedimentation rate, 61 mm in first hour; C reactive protein, 14 mg/l). A small bowel barium study showed narrowing of the terminal ileum, with disorganisation of the mucosal pattern. At colonoscopy the colon looked normal, but examination of the terminal ileum showed patchy hyperaemia.

Figure 1: Histological appearances of ileal biopsy specimens at presentation (haematoxylin and eosin ×250).

Figure 2: The cutaneous eruption of Langerhan’s cell histiocytosis.

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with shallow aphthoid ulceration. Examination of ileal biopsy specimens showed granulomatous inflammation of the lamina propria with scattered crypt abscesses (Fig 1), entirely consistent with the clinical diagnosis of Crohn's disease.

She initially responded well to the treatment with the combination of oral corticosteroids and slow release mesalazine. She remained corticosteroid dependent, however, and during the summer of 1994 she developed recurrent symptoms that proved refractory to treatment with intravenous corticosteroids, metronidazole, and an elemental diet. She therefore underwent an extended right hemicolectomy. At laparotomy, gross thickening of the ileal wall was noted, along with modest mesenteric and para-aortic lymphadenopathy. After a transient improvement she developed worsening diarrhoea and abdominal pain with vomiting and further weight loss. A purplish maculopapular eruption was noted over the lower ribs bilaterally (Fig 2). Her chest x ray was normal, but barium follow through showed changes of extensive mucosal infiltration of the small bowel wall (Fig 3). Gastroscopy showed areas of nodular mucosa in the post-bulbar duodenum.

A progressive leucocytosis developed, composed of cells of myelomonocytic lineage (peak leucocyte count 97 × 10⁹/l). Bone marrow aspiration showed gross myeloid hyperplasia with trilineage dysplasia, and the appearances were considered to be those of chronic myelomonocytic leukaemia in an accelerated phase. Cytogenetic analysis showed a Robertsonian translocation between the long arms of chromosomes 13 and 14, presumed to be constitutional.

Histological examination of biopsy specimens from duodenum and skin, and of the resection material, showed an unusually destructive infiltrate composed largely of histiocytes exhibiting mitotic activity and expressing CD1a and S100 (Fig 4). Electron microscopy of material from the skin biopsy specimen showed Birbeck granules (Fig 5). In the resected small bowel, infiltrates in the lamina propria had the appearance of loose granulomata, and were associated with loss of villous architecture. In contrast with the original ileal mucosal biopsy specimens, however, there were sub-epithelial clusters of atypical macrophages in the resection specimen, which were CD1a positive (Fig 6).

Parenteral nutritional support was started, and she was given a single intravenous dose of etoposide. This resulted in a substantial fall in her leucocyte count, but her clinical condition failed to improve. She went on to develop bone marrow failure, and ultimately died from an overwhelming fungal septicaemia.

Discussion
LCH is an uncommon disorder. Most cases occur in children, with an incidence in the paediatric population of less than five cases per million per year.1,2 There is a remarkably wide spectrum of disease behaviour in LCH, from localised tissue involvement with a tendency to spontaneous remission at one extreme, to progressive systemic disease with a poor prognosis at the other.3,4 Involvement of lung, bones, liver, spleen, skin, and the posterior pituitary are commonly described.1,4,5 Clinically apparent intestinal involvement is rare in LCH,1,4,5 and only a handful of case reports (all in children) record this. Typically, intestinal LCH presents as a diffuse enteropathy associated with widespread disease and a poor prognosis.1,5,6 Cases more closely
resembling Crohn's disease on clinical or radiological grounds, or both have been described, and the histological similarities have been highlighted. For example, Surphen and Fechner have reported a child with segmental ileal narrowing, while Grapin et al have described a case with complex anal fistulae. There is no evidence in these cases, however, that LCH developed as a complication of pre-existing Crohn's disease.

Did our patient have low grade Crohn's disease subsequently complicated by LCH, or could she have had LCH all along? We favour the first explanation for two reasons. Firstly, it fits better with her history of recurrent iron deficiency anaemia and erythema nodosum. Secondly, her ileal tissue macrophages were CD1a negative at initial presentation but strikingly positive later, implying that LCH infiltration occurred after the initial samples were taken. Although LCH has not to our knowledge been previously described as a complication of Crohn's disease, there is a well recognised increased incidence of (other) myeloproliferative and lymphoproliferative disorders in patients with inflammatory bowel disease.

Active inflammatory bowel disease is known to enhance mucosal recruitment of circulating cells of monocyte/macrophage lineage. Overt intestinal involvement with LCH does not normally occur without evidence of major tissue infiltration elsewhere, so the predominance of intestinal involvement in our patient might perhaps be accounted for by pre-existing (Crohn's) disease facilitating the accumulation of LCH cells. An alternative explanation for this distribution of disease, however, may lie in the aberrant expression of cellular adhesion molecules, which has recently been shown in LCH, resulting in abnormal homing properties of the affected cells.

The attractive explanation for the development of chronic myelomonocytic leukaemia in our patient is that the leukaemic cells are precursors of the infiltrating Langerhan's cells. There may, however, be a more complex explanation, because a wide range of (other) myeloproliferative and lymphoproliferative disorders have been reported in association with LCH. While the treatment given for LCH may be the cause in some instances, the malignancy pre-dates treatment in a substantial proportion of cases and so presumably reflects an as yet undefined oncogenic factor associated with LCH.

In conclusion this case illustrates the development of intestinal LCH as a complication of ileal Crohn's disease. LCH should be considered in the differential diagnosis of Crohn's disease that becomes refractory to medical treatment, particularly if there is evidence of an accompanying multisystem disorder.

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