Malignant Histiocytosis of the Intestine Simulating Crohn's Disease

Report of a Case

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We report a case of malignant histiocytosis of the intestine (MHI) in which clinical and small bowel barium examination led to an initial diagnosis of Crohn's disease. The patient's symptoms and radiologic features improved dramatically with steroid therapy, and the patient remained free of severe symptoms for five years; at this stage, massive rectal bleeding occurred and segmental ileal resection was performed. Pathology findings of the resected specimen revealed nonspecific ulceration of the ileum. The correct diagnosis, MHI, became apparent six months after surgical intervention, on the appearance of multiple lymphadenopathy. [Key words: Malignant histiocytosis of the intestine; Crohn's disease]

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Malignant histiocytosis of the intestine (MHI) is a characteristic clinical syndrome first described by Isaacson and Wright[1] in 1978.

Frequent symptoms of the disease are weight loss, abdominal pain, and diarrhea, with small bowel barium examination showing narrowed areas with valvular thickening, alternating with areas of dilatation and stretched valvulae.[2]

Because MHI and Crohn's disease have similar clinical and radiologic features, diagnostic dilemmas occasionally present themselves.[3] In this paper, we report the clinical course and radiologic and histologic features of a patient with MHI. This patient was previously assumed to have Crohn's disease.

REPORT OF A CASE

We report the case of a 30-year-old Japanese man who was in good health until April 1979, when he developed nausea, vomiting, abdominal pain, bloody diarrhea, and low-grade fever. He then consulted his physician. There was no history of weight loss, hematochezia, or ingestion of enteric coated potassium tablets. Physical examination showed a febrile man in good general condition. Digital examination showed anal fissure. Results of laboratory tests were unremarkable, except for those results showing mild anemia and a high sedimentation rate. Examination of stool culture and investigation for parasites yielded negative results. The tuberculin skin test was negative. Upper gastrointestinal tract endoscopy disproved peptic ulcer disease, and colonoscopy yielded normal endoscopic findings. Small bowel barium examination showed a "cobblestone" appearance in the terminal ileum, no lumen narrowing, and normal appearance in the proximal small intestine (Fig. 1). Evaluation, including that by abdominal CT scan and bilateral iliac bone marrow biopsy specimens, showed no evidence of malignant lymphoma. A diagnosis of Crohn's disease was made, particularly in view of the regional involvement, *i.e.*, the cobblestoning in the small bowel barium examination and the complicating anal lesion. Colonoscopy was performed for a second time, and rectal biopsies showed no evidence of focal proctitis or "sarcoid-like" granuloma. The patient was treated with prednisolone, parenteral nutrition, and sulfasalazine. He was free of symptoms after one month and remained symptom free until October 1984, when he was hospitalized with acute exacerbation of his previous symptoms and massive rectal bleeding. He was brought to the Second Department of Surgery, Hyogo College of Medicine. Emergency colonoscopy and upper gastrointestinal tract endoscopy revealed that the bleeding did not originate

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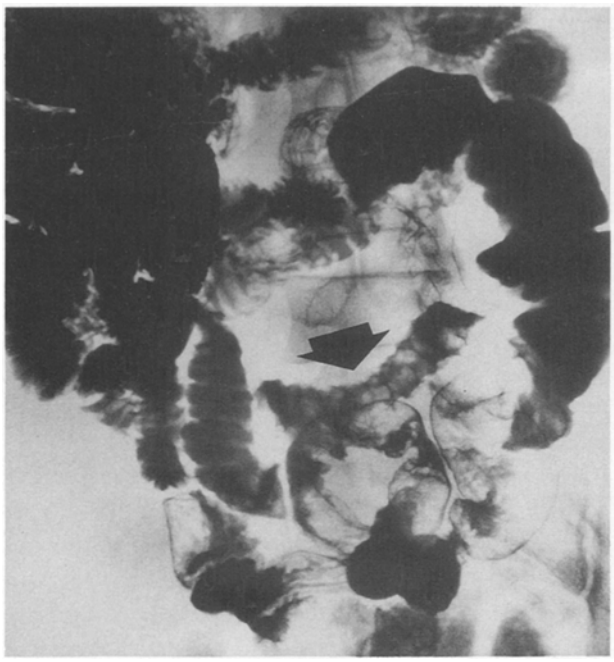

Figure 1. Film from a small bowel ileal x-ray examination, showing "cobblestoning" of the terminal ileal mucosa and indicating the presence of Crohn's disease.

in the colonic or gastroduodenal mucosa. Selective SMA angiography revealed extravasation of the terminal ileum, which was speculated to be the source of massive intestinal bleeding. Repeated bleeding occurred within one week, and an emergency operation was performed. At laparotomy, we found a circular stricture of 2 cm in the terminal ileum. Intraoperative endoscopy detected no other abnormal lesion either in the colon or in the small intestine. Only partial resection of the ileum was performed, and the resected segment specimen showed a solitary, nonspecific, annular ulcer (Fig. 2).

Microscopically, the ulcer crater was filled with a layer of necrotic granulation tissue. Many inflammatory lymphocytes and plasma cells were distributed without granulomas along the full thickness of the intestinal wall (Fig. 3). Pathology diagnosis was nonspecific ulcer of the small intestine. The patient's postoperative course was uneventful, and he was discharged one month later. Six months after discharge, he was found to have multiple subcutaneous tumors and abnormal shadows in both lungs. Histopathologic examination (hematoxylin and eosin) of the subcutaneous tumors and axillary lymph nodes showed sheets of large, pleomorphic, malignant histiocytes interspersed with small lymphocytes. Re-examination of the operated

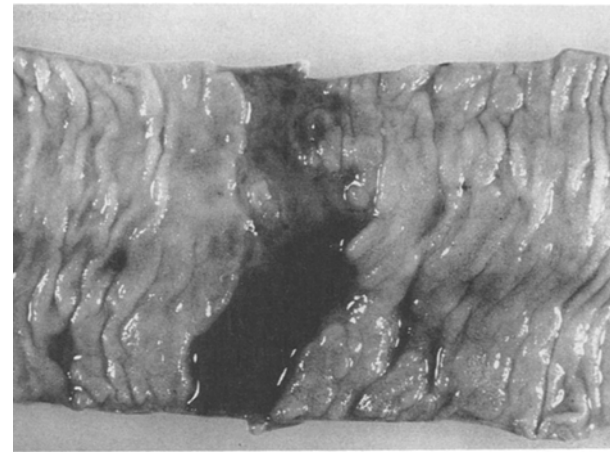

Figure 2. Photograph of resected ileal specimen, showing a "napkin-ring" ulcer.

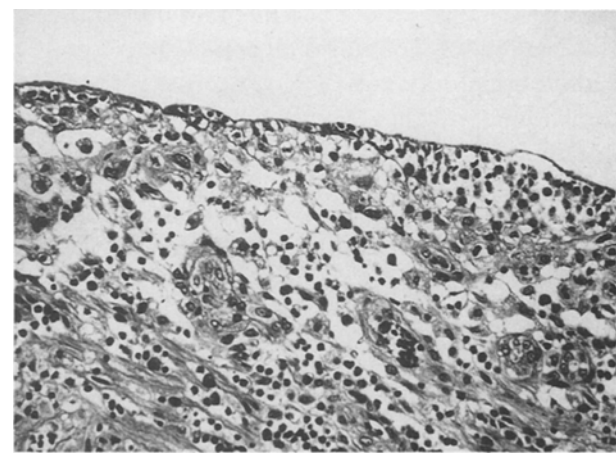

Figure 3. Photomicrograph showing many inflammatory lymphocytes and plasma cells distributed along the full thickness of the intestinal wall.

specimen revealed atypical large cells in the lymph nodes. We then diagnosed MHI and began combined chemotherapy. However, the disease was not responsive to chemotherapy, and the patient died after a hypotensive episode.

DISCUSSION

Diagnosis of MHI is rather difficult. MHI can be suspected in a patient who has relapsing clinical malabsorption with abdominal symptoms and/or alternating narrowed and thickened areas of the small intestine on radiologic examination. MHI may also be considered in patients not previously known to have celiac disease. Mead *et al.*[4] reported four of nine diagnosed cases of MHI without celiac disease. MHI has three main clinical entities: lymphoma complicating a long history of celiac dis-

ease, lymphoma complicating a short history of adult celiac disease, and presentation with a lymphoma.[5] Clinical findings do not differ significantly from those of Crohn's disease, and we failed to diagnose MHI in our case. On the first small bowel examination, the cobblestone appearance characteristic of Crohn's disease was found. The anal lesions and the successful therapeutic effects of prednisolone and sulfasalazine encouraged our diagnosis of Crohn's disease in this patient. Branton and Guyer[2] described Crohn's disease as one of the conditions which made a differential diagnosis in MHI. MHI should be suspected when radiologic examination of the small intestine shows areas of luminal narrowing associated with nodular valvular thickening alternating with more dilated areas with normal valvulae. There had been no previous documentation of cobblestone appearance being a radiologic property of MHI. The small bowel examination performed six months after the first onset showed remission, the cobblestoning having disappeared. We speculate that the cobblestone appearance mimicked conditions of mural thickening, mucosal, edema, or intraluminal hemorrhage. Therefore, we believe, from the radiographic point of view, that early changes of MHI could be confusing when dealing with widespread edema and thickened bowel wall. Hyams *et al.*[6] reported that rectal biopsies showing evidence of focal colitis and/or granulomas appear to be helpful in the differential diagnosis of lymphoma and Crohn's disease. In fact, in our case, the rectal biopsy showed no evidence of Crohn's disease.

At the time the massive bleeding began, angiography demonstrated the bleeding point to be located in the part which had previously shown the cobblestone lesion. On operation, we found a "napkin-ring" stenosis of the ileum, and the resected segment specimen showed a solitary annular ulcer. As far as differential diagnosis of small bowel ulceration is concerned, an extensive list should be considered, including such entities as Crohn's disease, tuberculous enteritis, typhoid fever, bacillary dysentery, staphylococcal septicemia, Zollinger-Ellison syndrome, and neoplastic processes. Histologic examination in this patient ruled out Crohn's disease, tuberculous peritonitis, and lymphoma. Isaacson *et al.*[7] reported multiple inflammatory benign ulcers in patients with MHI. Mead *et al.*[4] reported that the gross morphology of MHI consisted of multiple strictures and tumors and, occasionally, multiple ulcers in the small bowel. In this case, retrospective, immunohistochemical examination of the ileal ulcer showed evidence of MHI. We speculate that infiltration of the bowel wall was circumferential, forming a napkin-ring ulcer. These findings also informed us of a variation of MHI.

Prognosis of the MHI in this case was poor because of late diagnosis, the already widespread nature of the disease, and resistance to chemotherapy. In other cases, gastrointestinal perforation and/or hemorrhage were common treatment-related complications.[4] Earlier diagnosis prior to operation, if possible, will improve the now miserable results of complicated MHI. Isaacson[8] reported that villous atrophy of the small intestine was the putative lesion of MHI. Their diagnosis was confirmed by the demonstration of granular cytoplastic staining for α-1-antitrypsin in the tumor cells.[8] However, it is very difficult to obtain a sufficiently large biopsy specimen from the affected lesion of the small bowel. It is also difficult for the pathologist to detect early MHI lesions, as our case showed.

Doctors treating inflammatory bowel disease, especially Crohn's disease, have many chances to diagnose cases without representative clinical outcomes and/or pathologic entities. Our case unexpectedly indicated the difficulty of eliminating a possible diagnosis on the basis of a few positive results. Both MHI and Crohn's disease are very difficult to diagnose because of their wide clinical spectrum and great variation in both macroscopic and microscopic appearance. Only specific positive results can encourage doctors to eliminate most other putative possibilities. It is very difficult for us to show direct evidence of MHI beyond the cobblestone appearance, the affected anal lesion, and the effectiveness of sulfasalazine. To make the final diagnosis, we recognize the need for inquiring minds supported by wide knowledge, even in cases with adequate positive findings. It is to be hoped that the accumulation of precise documented analyses of the clinical courses of MHI patients will lead to more established examination procedures and clinical categorization, which will help in the diagnosis of MHI.

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