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Malignant histiocytosis of the intestine: the early histological lesion

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SUMMARY A histological study of peroral jejunal biopsies and resection specimens from patients with malignant histiocytosis of the intestine (MHI) has revealed characteristic lesions consisting of intramucosal histiocytic aggregations which invade surface and crypt epithelium. These lesions are found in 'uninvolved' jejunal mucosa in the presence of obvious tumour elsewhere and also in peroral jejunal biopsies many years earlier than the diagnosis of MHI. It is suggested that they represent the early lesion and their recognition in peroral jejunal biopsies could be important in improving the prognosis of the disease.

The increased incidence of intestinal lymphoma in patients with coeliac disease is well recognised,[1] and the nature of the lymphoma has recently been characterised as a form of malignant histiocytosis.[2 3] This disease, which has been termed malignant histiocytosis of the intestine (MHI) to distinguish it from classical malignant histiocytosis (also known as histiocytic medullary reticulosis), occurs either as a complication of long-standing coeliac disease or in patients without a history of malabsorption in whom villous atrophy and crypt hyperplasia can be demonstrated in uninvolved jejunal mucosa. In either case the clinical features are similar with a relatively short history of abdominal pain and weight loss preceding an acute abdominal emergency usually occasioned by perforation of the tumour. The diagnosis of MHI before the acute abdominal episode can be extremely difficult, even after a diagnostic laparotomy, while the prognosis after perforation of what often turns out to be multiple tumours is very poor. It has been suggested,[3] that the disease originates in the monocyte-macrophage cells in the lamina propria of the small intestine and that a prolonged latent phase with localisation of malignant cells to the small intestine might precede the florid manifestations, at which time the disease is usually disseminated. Recognition of the disease in its early localised stage may improve the prognosis. Accordingly, a critical examination of peroral jejunal biopsies and 'uninvolved' jejunal mucosa—that is, remote from sites of obvious tumour—from patients with MHI has been undertaken in an attempt to establish the histological features of the early stages of the disease which may be recognisable in peroral jejunal biopsies.

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Methods

Peroral jejunal biopsies were available from nine patients who, at varying intervals after the biopsy, were subsequently shown to have MHI by examination of surgical or postmortem tissues. The pathological features of the tumour in four of the patients have been described elsewhere[3 11] (Table 1). In some patients more than one biopsy had been performed at different times. In four patients the jejunal biopsies had been processed by the method described by Perera *et al.*[4] and 120 serial sections had been cut and stained after fixation in Bouin's fixative. In the remaining five patients a single strip of sections was available from formalin-fixed tissue.

Surgical specimens of jejunum from seven patients with MHI were selected on the basis of good fixation (in formalin) and preservation of histological detail equal to that seen in peroral jejunal biopsies. In three of these cases the peroral jejunal biopsies had also been examined as described above. The sections examined in detail were from areas well separated from tumour and in which no macroscopic abnormality was present. The tumours of four of these patients have been described elsewhere[3] (Table 2). All sections were stained with haematoxylin and eosin and in three cases selected sections of surgically removed jejunum were stained for lysozyme by the unlabelled antibody (PAP) immunoperoxidase technique after trypsin disgestion.[5] Sections from peroral

Table 1 *Jejunal biopsies from patients with MHI*

Patient	*Biopsy-diagnosis interval (yr)*	*Villous atrophy*	*Histiocytic aggregates*	*Crypt destruction*	*Ulceration*
FG	5	Severe	—	—	—
	4	Severe	—	—	—
	2	Severe	—	—	—
	1	Severe	±	+	—
	None	Severe	+	+	—
MvD	5	Severe	±	+	+
EW*	2	Severe	±	—	—
EC*	None	Severe	±	+	—
WL	None	Severe	+	—	+
EG*	1	Severe	—	—	—
	6 months	Severe	—	—	—
FN	7	Severe	—	—	—
DW*	3 months	Severe	—	—	—
RW	7	Severe	—	—	—
	None	Mild	—	—	—

*Patients previously reported: EW, EG, DW,[3] EC.[11]

jejunal biopsies from 30 patients with uncomplicated coeliac disease ranging in age from 2 to 60 years were examined as controls.

Results

These are summarised in Tables 1 and 2. All cases and controls showed the classical histological features of coeliac disease. These included variable degrees (usually severe) of villous atrophy, crypt hyperplasia, intraepithelial lymphocytic infiltration, irregularity of surface enterocytes, and a dense lamina propria infiltrate consisting almost solely of plasma cells with a variable number of eosinophils and occasional neutrophils.

Table 2 *Surgical resection specimens from patients with MHI*

Case	*Previous jejunal biopsy*	*Villous atrophy*	*Histiocytic aggregates*	*Crypt destruction*	*Ulceration*
EW*	+	Severe	±	+	+
FN	+	Severe	±	—	±
EG*	+	Severe	+	—	±
WM	—	Severe	±	+	±
QP	—	Severe	+	±	+
RM*	—	Severe	—	—	±
PD*	—	Severe	±	+	+

*Patients previously reported[3]

In five jejunal biopsies and all seven resection specimens distinctive histological features, not seen in control sections, were present. These took the form of small collections or sheets of histiocytes showing no, or minimal, atypia (Figs. 1, 2, 3). They were frequently sited below the surface epithelium.

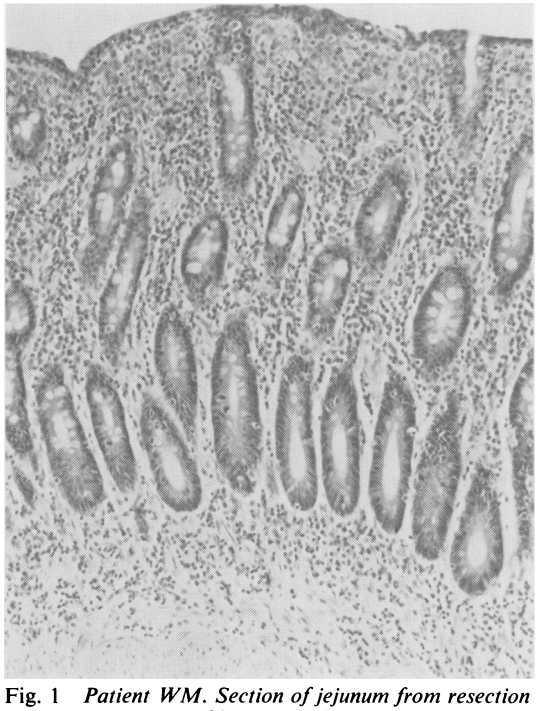

Fig. 1 *Patient WM. Section of jejunum from resection showing aggregates of histiocytes beneath the surface epithelium. Haematoxylin and eosin, × 100. (In this and the following figures original magnifications are given.)*

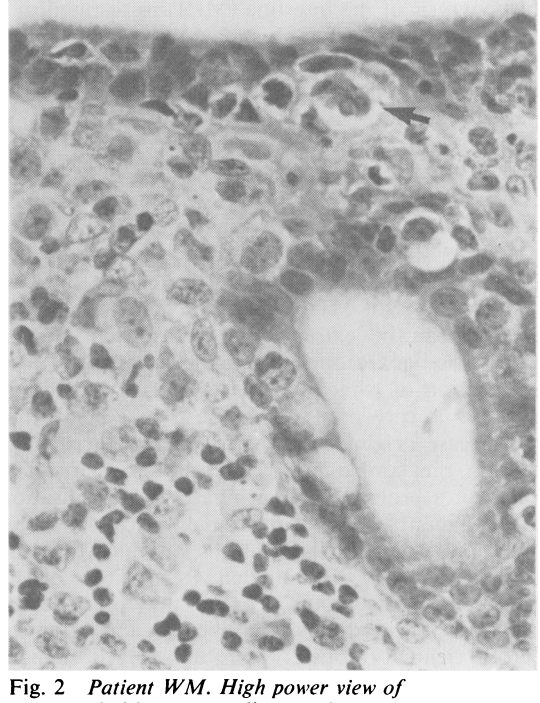

Fig. 2 *Patient WM. High power view of subepithelial histiocytes illustrated in Fig. 1 showing invasion of surface epithelium by single cells (arrow). Haematoxylin and eosin, × 400.*

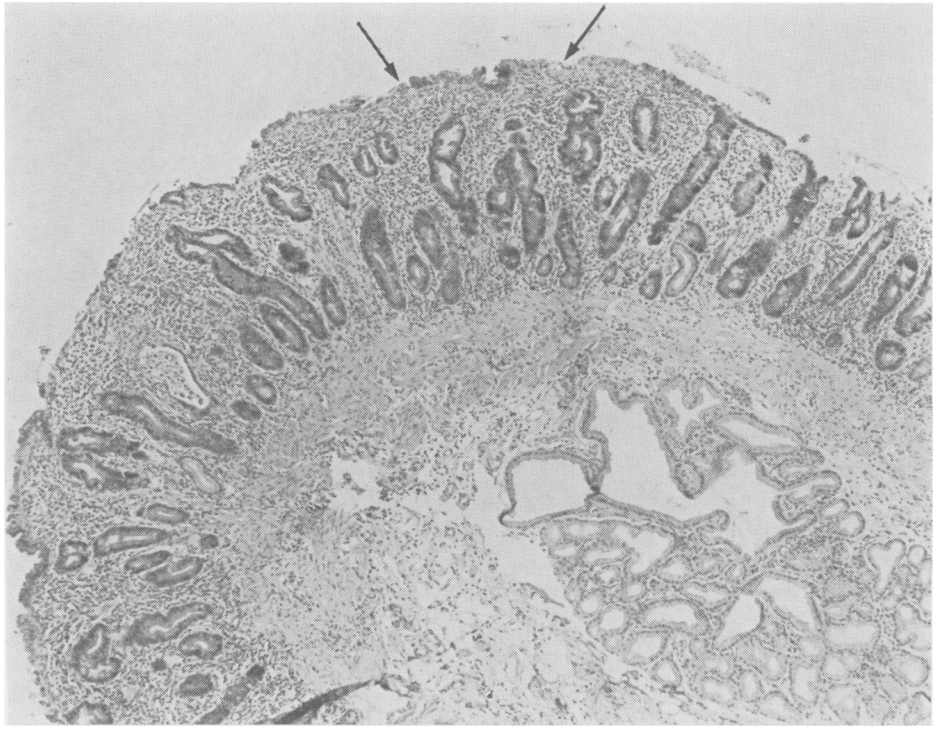

Fig. 3 *Patient MvD. Section of peroral biopsy showing collections of histiocytes around a partially destroyed crypt (left). Similar cells are present below the surface epithelium (arrows). Collection of Brunner's glands indicates that biopsy is from the duodenum. Haematoxylin and eosin, ×40).*

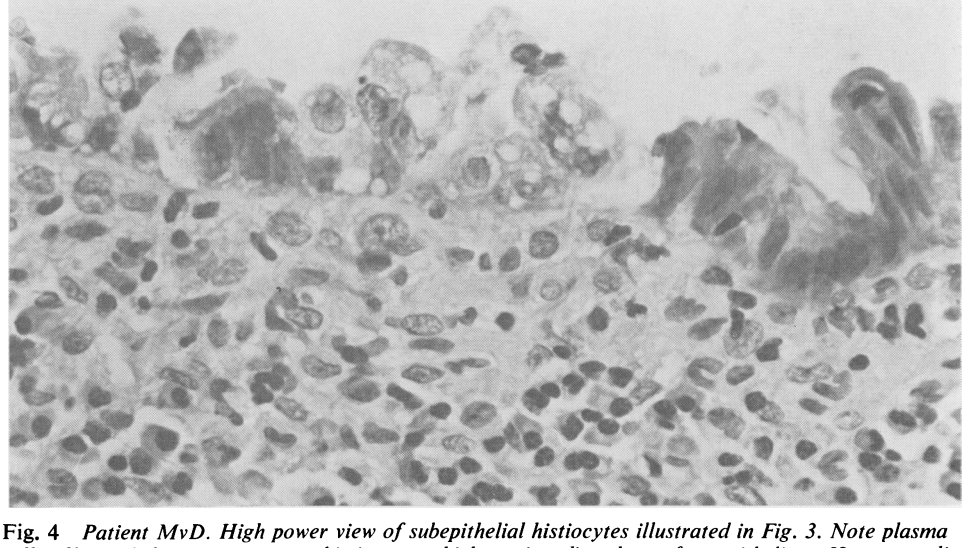

Fig. 4 *Patient MvD. High power view of subepithelial histiocytes illustrated in Fig. 3. Note plasma cell infiltrate below giving way to histiocytes which are invading the surface epithelium. Haematoxylin and eosin, ×400.*

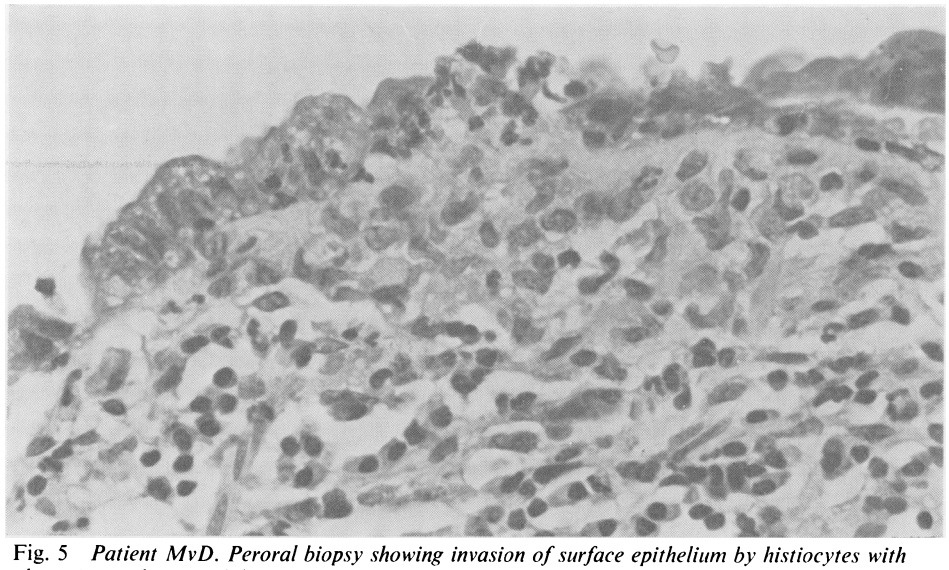

Fig. 5 *Patient MvD. Peroral biopsy showing invasion of surface epithelium by histiocytes with ulceration and neutrophil reaction. Haematoxylin and eosin, × 400.*

Invasion of epithelium by the histiocytes could often be discerned (Figs. 2, 4) and in its most advanced form resulted in small surface ulcerations (Fig. 5) or destruction of intestinal crypts (Figs. 3, 6, 7). In the latter case histiocytic crypt 'abscesses' were sometimes formed. Immunoperoxidase studies confirmed the histiocytic nature of these cells by the demonstration of lysozyme within them (Fig. 7).

Discussion

Histiocytic aggregates are not a normal finding in

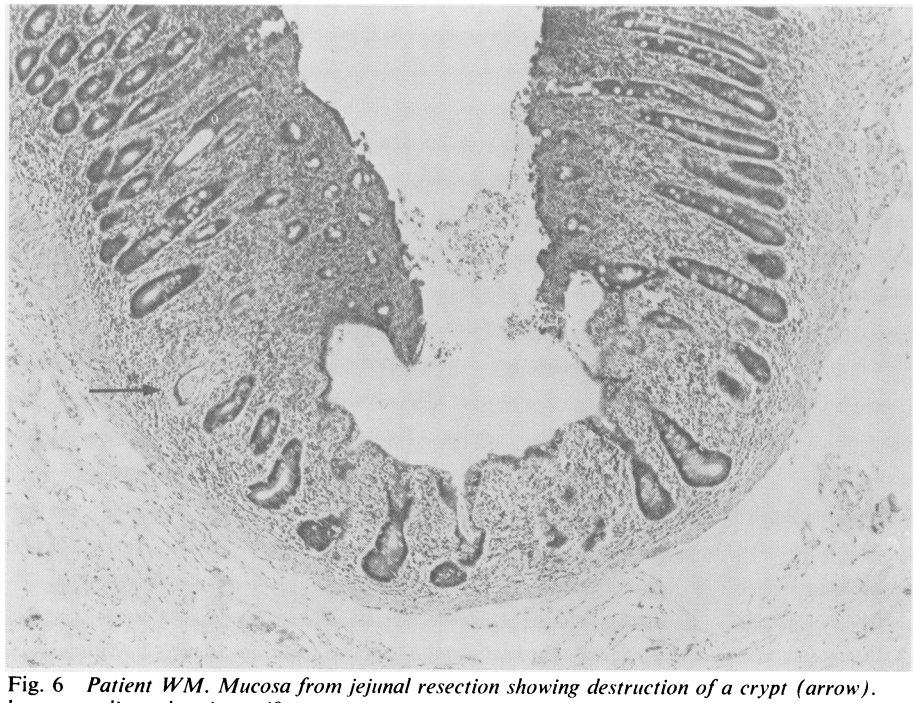

Fig. 6 *Patient WM. Mucosa from jejunal resection showing destruction of a crypt (arrow). haematoxylin and eosin, × 40.*

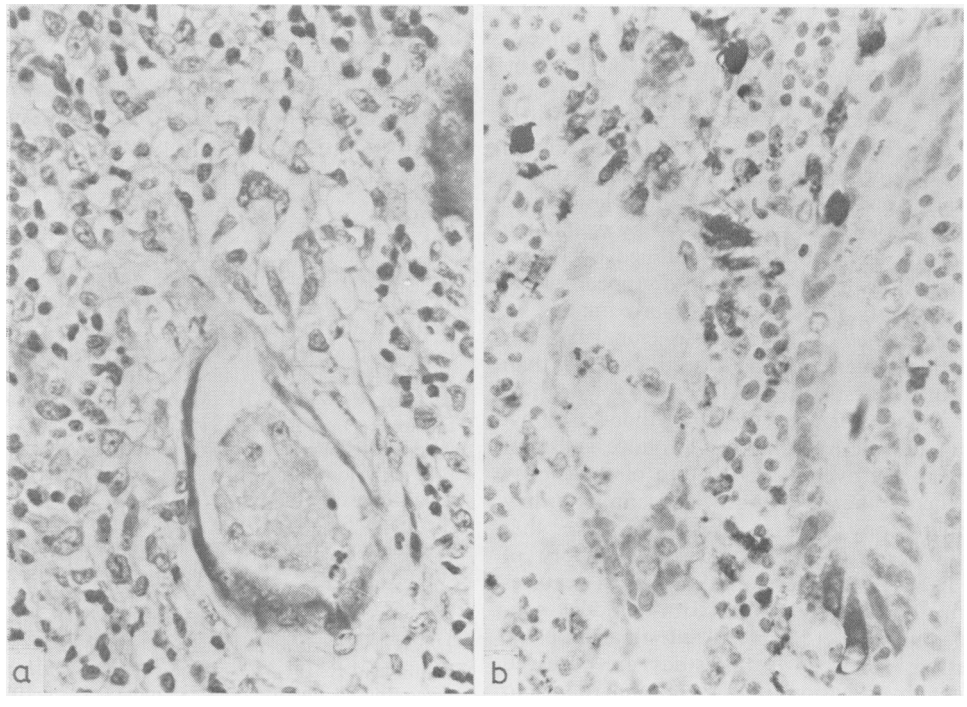

Fig. 7 *Patient WM. (a) High power detail of crypt illustrated in Fig. 6 showing surrounding histiocytes one of which is multinucleated. Some of the histiocytes show slight coarsening of nuclear chromatin with prominent nucleoli. Degenerate histiocytes are present within the crypt lumen. Haematoxylin and eosin, ×400. (b) Same area stained for lysozyme showing positive staining of the histiocytes and Paneth cells of adjacent crypt. Immunoperoxidase, ×400.*

the lamina propria of coeliac mucosa. The aggressive nature of these aggregates is borne out by the associated destruction of crypts and surface epithelium with subsequent ulceration. That the disease can progress from what appear to be collections of well-differentiated histiocytes to an obviously malignant—and often markedly pleomorphic—tumour is not surprising when other lymphoreticular tumours are considered. Follicular centre cell lymphoma, for example, in its early stages can be extremely difficult to distinguish from benign reactive lymphoid hyperplasia but can evolve into a markedly pleomorphic tumour.[6]

The characterisation of the lesions described in this study supports the suggestion that so-called 'non-granulomatous ulcerative jejunoileitis' is but a manifestation of MHI. Once ulceration occurs, exposing the lamina propria to intestinal contents, the resulting inflammatory reaction could totally obscure the neoplastic cells. Evidence of healing of these ulcers is commonly found in MHI consistent with a prolonged latent phase during which it is possible, though not established, that the malignant cells are confined to the lamina propria of the bowel. Thus, in one case (MvD) the early lesions were present in the peroral biopsy five years before overt tumour developed. Similarly long (eight year) latent intervals between ulceration and the development of obvious lymphoma have been described by Whitehead[7] and Thompson (personal communication). An analogy has already been drawn with mycosis fungoides[3 8] and an additional appropriate analogy is with the precancerous lesions of ulcerative colitis, which may both precede and accompany the development of invasive carcinoma.[9]

The nature of these microscopic lesions helps to explain reports of abdominal lymphoma complicating coeliac disease in which mesenteric nodes and other organs are involved without an intestinal lesion being identified.[10 11] To identify the lesions excellent fixation of surgical material is necessary and they would be unlikely to be found in necropsy specimens. The multifocal nature of these lesions may account for the high rate of recurrence, both immediate and remote, that characterises MHI after surgical resection of macroscopic tumour.

It has been suggested that the peroral jejunal biopsy has little to contribute in the diagnosis of

MHI except to confirm jejunal villous atrophy where there has been no previous biopsy unless, that is, a focus of obvious tumour is biopsied by chance.[11] This study suggests, however, that the early lesion can readily be demonstrated in peroral biopsies; the chance of finding these lesions should be greatly enhanced by the use of a multiple biopsy instrument. It must be stressed that these lesions are extremely focal and are best detected by examining serial sections of the biopsy as outlined by Perera *et al.*[4] The lesions may appear and disappear within a single strip of serial sections (approximately 12 sections) and when reviewing these jejunal biopsies it is advisable to scan over all 120 sections rather than seeking out the best orientated sections for detailed study as is done for assessment of villous atrophy. The small destructive infiltrates produce sufficient distortion in the overall architecture of the biopsy to allow them to be picked out with scanning or low power microscopy. It is suggested, therefore, that patients, with or without a previous history of coeliac disease, who develop the clinical features suggesting the possibility of MHI, should be subjected to multiple peroral small intestinal biopsies. If the lesions described in this study are observed subsequent investigations should be undertaken to confirm the diagnosis and exclude dissemination. These have been described in detail elsewhere,[11] and include serum lysozyme, bone marrow aspiration, liver biopsy and, if necessary, laparotomy.

In only one of the cases described in this report (FG) was the diagnosis of MHI actually made on the jejunal biopsy. It was confirmed by a marrow aspirate which showed numerous phagocytic malignant histiocytes and the patient is currently receiving chemotherapy. As experience with the early lesion accumulates it will become clearer whether a confident diagnosis of MHI can be made solely from the finding of these lesions in peroral biopsies without other confirmatory evidence. It is hoped that treatment of MHI in the early phase, when it is more likely to be localised to the intestine, will improve the prognosis of this highly lethal disease.

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