Malignant histiocytosis (histiocytic medullary reticulosis) with spindle cell differentiation and tumour formation

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SUMMARY Malignant histiocytosis (histiocytic medullary reticulosis) in a 45-year-old white man is described. Unusual features were presentation as a surgical emergency with signs of obstruction and peritonitis due to an ileal tumour and extensive spindle cell differentiation. Problems in the differential diagnosis of malignant histiocytosis are briefly discussed.

Malignant histiocytosis has been defined by Rappaport (1966) as a systemic, progressive, invasive proliferation of morphologically atypical histiocytes and of their precursors. The disease, which is also known as histiocytic medullary reticulosis, was first recognised by Scott and Robb-Smith (1939). Since then reports of single cases and series of cases have included those by Marshall (1956), Greenberg et al. (1962), Serck-Hanssen and Purchit (1968), Abele and Griffin (1972), Byrne and Rappaport (1973), and Warnke et al. (1975).

Greenberg et al. (1962), who reviewed 47 previously reported cases, stressed the repetitious clinical features of the disease which usually runs a rapid course and occurs over a wide age range and in both sexes. Fever, malaise, and weight loss are common presenting symptoms. Lymphadenopathy has been a common initial finding in some series (Byrne and Rappaport, 1973; Warnke et al., 1975). Others have noted only minimal to moderate lymphadenopathy in about half of their cases (Greenberg et al., 1962; Abele and Griffin, 1972). Additional features which may be noted at the time of presentation or during the course of the illness include hepatosplenomegaly, jaundice, anaemia, thrombocytopenia, and purpura. Tumour formation is uncommon but has occasionally been found in the soft tissues during life (Warnke et al., 1975) or in various organs at necropsy (Marshall, 1956; Clark and Dawson, 1969).

This case is reported because of the rare clinical presentation as a surgical emergency with signs of obstruction and peritonitis due to a large tumour in the ileum and because the pathology was atypical due to the prominent spindle cell differentiation in the ileal tumour, lymph nodes, and bone marrow.

Case report

A 45-year-old white man was admitted as a surgical emergency complaining of severe abdominal pain. For the previous two weeks he had had several attacks of mild abdominal pain accompanied by vomiting and he had passed melaena stools. He had recently lost about 6 kg in weight, but previously had been in good health and had no relevant past medical history. Physical examination revealed a pale adult male (haemoglobin 8 g/dl) with generalised abdominal tenderness and rebound tenderness. A diagnosis of peritonitis was made and at laparotomy a tumour was found in the wall of the ileum extending through to the serosa. Radical small bowel resection with removal of enlarged mesenteric nodes and end-to-end anastomosis was performed. Postoperatively he remained anaemic in spite of repeated blood transfusions and he developed a chest infection and pyrexia. On the sixth postoperative day his abdomen had become distended and tense and a second laparotomy was performed. A large amount of blood was found in the peritoneal cavity. There was a generalised oozing from the operation site, but no bleeding point was found. The findings suggested a disturbance of haemostasis and the following investigations were carried out: Hb 11.7 g/dl; Hct 0.38; MCHC 31 g/dl; WBC 15.2 x 10⁹/l with a polymorphonuclear leucocytosis; Coombs' test negative; platelets less than 50 x 10⁹/l; prothrombin time,

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test 15 s, control 10 s; fibrinogen titre, test 1/128 no lysis, control 1/128 no lysis; kaolin cephalin time, test 40 s, control 33 s; thrombin time (saline), test 10 s, control 13 s; thrombin time (protamine), test 7 s, control 9 s; fibrinogen degeneration products latex (FDP) test, less than 5 μg/ml; ethanol gel test, positive. These results suggested incipient disseminated intravascular coagulation. There was no evidence of further intra-abdominal bleeding, but the patient became increasingly jaundiced, the direct reaction bilirubin rising to 308 μmol/l, and he died 10 days after admission to hospital. Immediately before death the FDP latex titre was greater than 160 μg/ml.

GROSS PATHOLOGY

Surgical specimen The resected ileum was 70 cm long; 30 cm from one end there was a tumour in the bowel wall about 5 cm long. On the cut surface the tumour formed a uniform white mass, 2.5 cm thick at its maximum, almost encircling the bowel wall and extending from the ulcerated mucosal surface to the serosa (Fig. 1). The muscle coat had been destroyed and adhesions in the region of the tumour had caused marked kinking of the bowel. The adjacent mesentery contained numerous lymph nodes up to 1.5 cm long.

Necropsy The body was deeply jaundiced and there was a small amount of yellow fluid in the peritoneal cavity. The anastomosis in the small bowel was intact and there was no evidence of leakage, but the small and large bowel were dilated and covered with abundant greenish-yellow exudate. The liver was enlarged and weighed 3500 g and was of a greenish-yellow colour. The spleen weighed 275 g and showed no gross abnormality. There were numerous small lymph nodes in the mesentery but no evidence of generalised lymphadenopathy. The kidneys were enlarged and together weighed 425 g. Abundant red marrow was present in the shaft of the humerus. There were no other relevant findings.

Histology The following special stains were used as required: Elastic von Gieson, Perl's Prussian blue, phosphotungstic acid haematoxylin, Slidder's reticulin, periodic acid-Schiff reagent with and without diastase, Lendrum's Martius scarlet blue (MSB), methyl green pyronin, Sudan black. Frozen sections were also stained with Sudan 4.

The tumour in the ileum was very pleomorphic. In places the cells were round or oval and measured about 15 μm in diameter and had abundant eosinophilic cytoplasm which was not pyroninophilic. They did not contain any intracellular mucin and the nuclei were large and vesicular, irregular in size and shape, and often multiple or multilobed. There were frequent mitoses, some of which were bizarre, and some of the cells had prominent pink staining nucleoli, but these were generally inconspicuous. Bizarre giant cells up to 35 μm diameter were also present (Fig. 2). A striking feature throughout most

Fig. 1 Cut surface of the ileal tumour showing infiltration of the full thickness of the bowel wall.

Fig. 2 Ileal tumour. Pleomorphic histiocytes, some of which are multinucleated, infiltrating the ileal mucosa. The mucosal epithelium is at the top right (arrow). Haematoxylin and eosin × 250.
Fig. 3  Ileal tumour. Area showing spindle cell differentiation. H and E × 400.

Fig. 4  Ileal tumour. Malignant histiocytes near the ulcerated surface containing large amounts of haemosiderin. Perl’s Prussian blue × 400.

Fig. 5  Ileal tumour. Malignant histiocytes in this field mainly round or oval containing phagocytosed red blood cells (arrows). H and E × 400.
of the tumour was the transition from round or oval cells to those with a spindle appearance, which were either pleomorphic or better differentiated resembling that of immature fibroblasts (Fig. 3). In areas showing spindle cell differentiation, there was also a dense reticulin network and evidence of collagen formation.

Towards the ulcerated surface there was clear evidence of the histiocytic nature of the tumour cells which showed marked phagocytic activity and contained large amounts of haemosiderin and numerous phagocytosed red blood cells (Figs. 4 and 5).

The larger mesenteric nodes were extensively infiltrated by tumour, which, in places, had destroyed the normal architecture, but elsewhere had distended and filled the sinusoids. Many of the cells were pleomorphic and obviously malignant and resembled those in the ileal lesion, while others were better differentiated and had the appearance of mature histiocytes.

In the necropsy material the most significant finding was the presence of numerous histiocytes showing marked erythrophagocytosis in the sinusoids of the mesenteric nodes, red pulp of the spleen, hepatic sinusoids, and diffusely infiltrating the bone marrow. As in the surgical specimen, some of the histiocytes were well differentiated and about 10 µm in diameter, while others were bizarre and up to 60 µm in diameter. The larger cells had a vacuolated cytoplasm, but stains for lipid were negative and these spaces probably marked the site of lysed red blood cells. In addition to red blood cells, the histiocytes also contained abundant haemosiderin and smaller numbers of phagocytosed lymphocytes and polymorphonuclear leucocytes (Fig. 6). Foci of spindle cell differentiation were present in a number of the lymph nodes, and a small nodule, about 1-5 mm diameter, with a similar appearance was found in the marrow of the humerus, which also showed marked erythroid hyperplasia (Fig. 7). The spleen contained foci of extramedullary haemopoiesis, and the

![Fig. 6](image1.jpg)

**Fig. 6** Mesenteric lymph node removed at necropsy showing infiltration of the subcapsular sinusoid by vacuolated histiocytes containing phagocytosed red blood cells. One of the histiocytes is very large and bizarre. H and E × 400.

![Fig. 7](image2.jpg)

**Fig. 7** Marrow of the humerus. At the top left the infiltrating histiocytes are round (arrow). Towards the bottom right they become spindle shaped, forming a small nodule. H and E × 175.
presence of numerous bile thrombi in the bile canaliculi in the liver indicated a severe degree of cholestasis. Fibrin thrombi were not identified in sections of lung, liver, kidney, and adrenal stained by the MSB method.

Discussion

Byrne and Rappaport (1973), in a clinicopathological study of 24 cases of malignant histiocytosis, listed various synonyms used to describe the disease which, in addition to histiocytic medullary reticulosis, have included malignant reticulohistiocytosis, histiocytic reticulosis, and leukaemic reticuloendotheliosis and is a source of considerable confusion.

They also defined diagnostic criteria, of which the most important are cytological atypia and evidence of phagocytosis.

In our case the presence of phagocytosed red blood cells and haemosiderin within the tumour cells in the ileal lesion leaves no doubt that they were malignant histiocytes.

It could be suggested that the histiocytic proliferation in other organs and tissues was unrelated to the neoplastic process and was secondary to a haemolytic process (Rappaport and Crosby, 1957), but the bizarre appearance of the histiocytes and their similarity to those in the ileal lesion indicate that they were part of a systemic neoplastic process.

Another possibility which has to be considered is that the ileal lesion was a malignant fibrous histiocytoma (Soule and Enriquez, 1972; Kempson and Kyriakos, 1972). While the histological appearance of the ileal tumour might be acceptable, the diffuse involvement of other organs does not suggest metastatic spread from a malignant fibrous histiocytoma which behaves like other soft tissue sarcomas. The diagnosis of malignant histiocytosis in our case thus seems to be established beyond any reasonable doubt.

Infiltration of the mucosa of the gastrointestinal tract has been present in a number of cases of malignant histiocytosis, and has occasionally been associated with severe haemorrhage due to mucosal ulceration (Marshall, 1956; Clark and Dawson, 1969; Imamura et al., 1971; Abele and Griffin, 1972; Warnke et al., 1975). We are not, however, aware of any other case in which the initial manifestation of the disease was a small bowel tumour which required surgical resection.

The other unusual pathological finding in our case was the prominent spindle cell differentiation in the ileal tumour which was also present but to a lesser extent in the lymph nodes and bone marrow. Imamura et al. (1971) refer briefly to a spindle cell sarcomatous pattern in tumour nodules in the liver in their case of malignant histiocytosis, but this is the only report we have found where this feature is mentioned.

Spindle cell differentiation is a common finding in tumours falling into the category of fibrous histiocytoma (Soule and Enriquez, 1972; Kempson and Kyriakos, 1972).

Following tissue culture studies, Ozzello et al. (1963) suggested that tissue histiocytes can assume the structure and function of fibroblasts. More recently, however, Ozzello and Hamels (1976) have carried out tissue culture and electron microscopic studies on examples of dermatofibrosarcoma protuberans and have concluded that although neoplastic histiocytes can acquire fibroblastic features it is unlikely that they can transform into true fibroblasts.

Whatever the precise histogenesis, the striking feature in this group of lesions is the intimate mixture of histiocytes and fibroblast-like cells in varying proportions, and it would not be surprising if this pattern was found, from time to time, in other lesions of histiocytic origin.

Problems in the differential diagnosis of malignant histiocytosis have been discussed in detail elsewhere (Byrne and Rappaport, 1973; Burke et al. 1974; Warnke et al., 1975). Among the conditions which have to be distinguished from malignant histiocytosis are Hodgkin's disease, histiocytic lymphoma (reticulum cell sarcoma), sinus histiocytosis with massive lymphadenopathy, hairy cell leukaemia (leukaemic reticuloendotheliosis), and histiocytosis X.

The differentiation of malignant histiocytosis from histiocytosis X, especially Letterer Siwe disease, can be difficult, the most important distinguishing feature being the presence of cytologically atypical histiocytes in malignant histiocytosis. The histiocytes in histiocytosis X have also been found to contain Langerhans' cell granules on electron microscopy (de Man, 1968; Imamura and Muroya, 1971). Langerhans' cell granules have, however, been found in some cases which the authors have considered to be examples of malignant histiocytosis (Imamura et al., 1971; Henderson and Sage, 1973) and Henderson and Sage (1973) have suggested that some cases of malignant histiocytosis may represent a proliferation of the same cell type as histiocytosis X. Their case also had marked eosinophilia. Liao et al. (1972) have also reported four similar cases of malignant histiocytosis with cutaneous involvement and eosinophilia. They did not find any Langerhans' cell granules but commented that their cases shared certain features with leukaemic reticuloendotheliosis and histiocytosis X.

It is clear from the foregoing that there are cases of systemic histiocytic proliferation which defy precise
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categorisation. This is not surprising considering the widespread distribution and versatility of the histiocyte.

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References


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