Immunophenotype analysis of malignant histiocytosis of the intestine

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SUMMARY Five cases of malignant histiocytosis of the intestine and one case of true histiocytic lymphoma were studied using immunohistological techniques. In paraffin sections tumour cells in all cases were shown to contain α -1-antitrypsin and to express the leucocyte common antigen. Four of the five cases of malignant histiocytosis of the intestine and the case of histiocytic lymphoma expressed the epithelial membrane antigen. Cryostat sections in four cases of malignant histiocytosis of the intestine showed that most tumour cells reacted with anti-T cell monoclonal antibodies. Only a minority expressed a typical monocyte macrophage phenotype.

Malignant histiocytosis of the intestine has only recently been recognised¹⁻³ and is being increasingly diagnosed with the aid of immunohistochemical techniques, especially in association with coeliac disease.⁴ As fresh tissue for immunological studies is rarely available diagnosis of this disease has relied on the recognition of variable morphological patterns and the confirmation of the presence of α -1-anti-trypsin (α 1AT), a marker of histiocytic tumour cells in paraffin sections.⁵ The histogenesis of malignant histiocytosis of the intestine has been sparsely documented. A study of the immunological, immunohistochemical, and cytochemical properties of the cells of malignant histiocytosis of the intestine³ included only three cases, with a limited frozen section immunohistochemical analysis on only one case. A recent study of histiocytic lymphoma showed phenotypic heterogeneity within true histiocytic malignancies, with results in some cases, suggesting differentiation of the malignant histiocytes towards specialised subsets.⁶ This last study did not include cases of malignant histiocytosis of the intestine. The pronounced morphological heterogeneity within the neoplastic cells of cases of malignant histiocytosis of the intestine suggests that a similar immunophenotypic variation may be present. In our study we used immunoperoxidase techniques, and a large number of antisera (both monoclonal and polyclonal) were tested on cryostat and formalin fixed paraffin embedded sections from cases of malignant histiocytosis of the intestine. The results were compared with those of a case of true histiocytic lymphoma.

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Material and methods

Six patients were studied, five diagnosed cases of malignant histiocytosis of the intestine and one case of histiocytic lymphoma: all were positive for α 1AT.

CASE HISTORIES

Case 1 A 71 year old woman presented as an acute abdominal emergency following a three month history of diarrhoea, vomiting, weight loss, and general malaise. She had no noteworthy medical history. At operation, extensive tumours were seen throughout the jejunum and ileum. Histology showed the presence of multiple, often superficially ulcerated tumours composed of large malignant histiocytes with irregular nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm admixed with scattered lymphocytes. The non-ulcerated lengths of small intestine showed partial to subtotal villous atrophy. Malignant histiocytosis of the intestine was diagnosed. She died within three months: necropsy was not performed.

Case 2 A 62 year old man presented with a six month history of weight loss, anorexia, diarrhoea, and pain of the lower back. Laparotomy showed thickening of the terminal half of the ileum and enlarged mesenteric lymph nodes. Histology showed multiple nodules of tumour within the ileum and local lymph nodes composed of malignant histiocytes with irregular nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm. Multinucleate forms were present. The ileum unaffected by tumour nodules showed villous atrophy. Malignant histiocytosis of the intestine was diagnosed. He died one day after the operation. At necropsy further tumour nodules

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within the unresected small intestine were seen. Liver and spleen were normal.

Case 3 A 59 year old man presented with a three month history of weight loss, general malaise, and anorexia. He had no notable medical history. A barium meal showed a defect in the jejunum, which at laparotomy was found to be an ulcerated tumour (4.5 cm). Further tumour deposits were found within the jejunum, local lymph nodes, and liver. Histology of laparotomy specimens showed that the tumours were composed of large cells with irregular, often multi-lobed nuclei, showing considerable pleomorphism. Large multinucleated giant cells were prominent. The intestinal mucosa showed mild villous irregularity but no true villous atrophy. Malignant histiocytosis of the intestine was diagnosed. He died four days post-operatively: necropsy was not performed.

Case 4 A 61 year old man presented as an acute abdominal emergency with no notable medical history. Laparotomy showed a large tumour within the ileum with thickening of the adjacent intestinal wall

and spread to the local lymph nodes. The excised 280 cm of small intestine contained an ulcer 8 cm in depth that occupied most the mesenteric mass with walls and base composed of tumour up to 4 cm deep. The adjacent ileum was thickened, but no further areas of ulceration were noted. Histologically, the tumour consisted of a rather monomorphic infiltrate of medium to large cells with irregular, slightly indented nuclei, small nucleoli, and small amounts of eosinophilic cytoplasm. The intestinal origin of the tumour was seen over a short segment of the adjacent ileum. Villous atrophy was not evident, and the ileal mucosa had minimally shortened villi, which were distended by a non-specific chronic inflammatory cell infiltrate with increased numbers of intraepithelial lymphocytes. Centrocyclic lymphoma was diagnosed initially, but immunohistochemistry showed strong granular paranuclear staining for $\alpha 1$ AT. Malignant histiocytosis of the intestine was diagnosed. He died three months postoperatively: necropsy was not performed.

Table 1 Monoclonal antibodies used in this study

Monoclonal antibody	Specificity	Reference	Source
F10-89-4	Leucocyte common antigen	7	J Fabre
Dako LC	Leucocyte common antigen	8	Dakopatts
F8-11-13	Leucocyte common antigen	9	J Fabre
<i>Associated with HLA</i>			
DA6 147	†MHC Class II, DR (α chain)	10	K Guy
DA6 231	†MHC Class II, DP and DR (β chain)	11	K Guy
Leu10	†MHC Class II, DQ	12	Becton Dickinson
<i>Associated with monocyte or macrophages</i>			
*anti lysosyme	Lysosyme		Dakopatts
*anti $\alpha 1$ AT	$\alpha 1$ -antitrypsin		Dakopatts
FMC17	Monocytes	13	H Zola
FMC32	Monocytes	13	H Zola
OKM1	Monocytes, macrophages, granulocytes	14	Ortho Diagnostics
Leu M2	Human monocyte antigen	15	Becton Dickinson
MO2	Monocytes	16	Coulter Electronics Ltd
Dako-C3b	C3b receptor	17	Dakopatts
Dako-DRC1	Dendritic reticulum cells	18	Dakopatts
FMC8	Monocytes, Dendritic Reticulum cells	19, 20	H Zola
	Immature B cells, some B-CLL		
<i>Associated with T lymphocyte</i>			
OKT3	Pan T lymphocyte (T3 complex)	21	Ortho Diagnostics
UCHT1	Pan T lymphocyte (T3 complex)	22	Seward Laboratories Ltd
Leu4	Pan T lymphocyte (T3 complex)	23	Becton Dickinson
Dako T2	All immature, majority of mature T lymphocytes	24	Dakopatts
OKT4	Helper T lymphocytes, monocytes	21, 25	Ortho Diagnostics
Leu3a	Helper T lymphocytes, monocytes	23, 25	Becton Dickinson
OKT8	Suppressor or cytotoxic T lymphocytes	26	Ortho Diagnostics
Leu2a	Suppressor or cytotoxic T lymphocytes	23	Becton Dickinson
OKT11	Sheep erythrocyte receptor	27	Ortho Diagnostics
OKT6	Cortical thymocytes, interdigitating reticulum cells	23, 28	Ortho Diagnostics
Leu7	Natural killer cells	29	Becton Dickinson
<i>Associated with B lymphocyte</i>			
anti Kappa	κ light chain		Seward Laboratories
anti Lambda	λ light chain		Seward Laboratories
DA6 127	IgM heavy chain		K Guy
B1	B lymphocytes	30	Coulter Electronics Ltd
Dako Pan B	B lymphocytes	31	Dakopatts
Dako-EMA	Human milk fat globulin protein	32	Dakopatts
Leu M1	Granulocytes	33	Becton Dickinson

*Polyclonal antiserum.

†MHC = Major histocompatibility complex.

Fig. 1 Malignant histiocytosis of the intestine (case 3) showing diffuse infiltrate of large pleomorphic cells with irregular nuclei and prominent nucleoli. Multinucleated cells are present. Paraffin section, haematoxylin and eosin. $\times 250$.

Fig. 2 Malignant histiocytosis of the intestine (case 4). Tumour consists of slightly irregular medium sized cells showing mild nuclear pleomorphism, prominent nucleoli, and mild to moderate amounts of cytoplasm. Paraffin section, haematoxylin and eosin. $\times 250$; inset $\times 1000$.

Case 5 A 45 year old woman with a long history of coeliac disease presented as an acute abdominal emergency. Laparotomy showed a perforated ileum with multiple sites of stricture and ulceration. Histology showed the presence of multiple deposits of

tumour consisting of large pleomorphic histiocytes, often with multilobed nuclei and multinucleated forms. The jejunal mucosa showed severe, partial, and subtotal villous atrophy. Malignant histiocytosis of the intestine was diagnosed.

She died six weeks postoperatively. At necropsy no evidence of further intestinal tumour, or spread to the spleen, liver, or bone marrow was found.

Case 6 A 19 year old man presented with a four week history of a swelling in the left axilla. Histology showed the presence of a highly cellular neoplasm composed of large cells with moderate cytoplasm, large vesicular nuclei, and a high mitotic rate. True histiocytic lymphoma was diagnosed after immunohistochemical studies. He was alive one month postoperatively.

TISSUE SAMPLES AND IMMUNOHISTOCHEMICAL STAINING

A panel of antibodies (Table 1) were used on both cryostat and paraffin sections by a previously described immunoperoxidase technique.³⁴ Cryostat sections were incubated with primary monoclonal antibody at room temperature for 30 minutes; paraffin sections were incubated for 30 minutes at room temperature and stained for α 1AT and lysozyme and with other antisera overnight. Sections were trypsinised before staining for α 1AT and lysozyme.

Results

HISTOLOGY AND TUMOUR CLASSIFICATION

All five cases of intestinal neoplasm in this study were diagnosed as cases of malignant histiocytosis of the intestine based on morphological appearances after examination of paraffin sections stained with haematoxylin and eosin.^{1 35} All tissues showed characteristic granular paranuclear staining for α 1AT.

In cases 1, 2, and 5 there was either a history of coeliac disease, or villous atrophy was seen histologically. Case 3 showed only mild villous atrophy. Multiple deposits of tumour were present in cases 1, 2, 3, and 5. The histological appearances in each of these cases were similar, the tumours consisting of large pleomorphic cells with irregular nuclei and prominent nucleoli (Fig. 1). Multinucleated forms were often present. In contrast, in case 4 only one tumour deposit was noted within the small intestine, and true villous atrophy was not a feature. Histology showed a rather monomorphic population of medium to large cells with irregular indented nuclei, small nucleoli, and small to moderate amounts of cytoplasm (Fig. 2). Although this case was initially diagnosed as a centrocytic lymphoma, the subsequent strong paranuclear staining with α 1AT and the similarity with the less differentiated or blastic form of histiocytic lym-

Table 2 Immunohistochemical staining of paraffin sections

Case No	Diagnosis	Antibody					
		α 1AT	Lysozyme	F8-11-13	Dako LC	Dako-EMA	Leu M1
1	MHI	+	+	+	+++	++	—
2	MHI	+	+	+	+++	+	—
3	MHI	++	—	+++	+++	+	—
4	MHI	++	—	+++	+++	—	—
5	MHI	++	—	++	+++	+	—
6	HL	+++	—	—	++	+++	—

Negative (—) = <10%; mildly positive (+) = 10–30%; strongly positive (++) = 30–60%; very strongly positive (+++) = >60% positively reacting tumour cells.

MHI = Malignant histiocytosis of the intestine; HL = histiocytic lymphoma.

phoma, recognised by Isaacson and Wright,³⁶ resulted in a review diagnosis of malignant histiocytosis of the intestine.

True histiocytic lymphoma was definitively diagnosed in case 6 but only with the aid of immunohistochemical studies.

IMMUNOHISTOCHEMICAL STAINING OF PARAFFIN SECTIONS

All the paraffin sections were stained with various antisera that react with tissue fixed in formalin. Table 2 shows the results.

In all five cases of malignant histiocytosis of the intestine and in the one case of histiocytic lymphoma tumour cells reacted with α 1AT, although the intensity of the staining reaction between individual cells and the number of malignant cells staining within the specimens varied.

Only two of our cases showed staining for lysozyme in tumour cells (cases 1 and 2), and this is consistent with a previous report in which only a few cases of malignant histiocytosis of the intestine stained for lysozyme.⁵

The haemopoietic origin of the malignant cells was shown by reactivity with the leucocyte common antibodies. All six cases reacted strongly with Dako leucocyte common, a mixture of two monoclonal antibodies against different determinants on the leucocyte common antigen.⁹ F8-11-13, which recognises the high molecular weight form of the leucocyte common antigen,⁷ reacted strongly with three cases of malignant histiocytosis of the intestine (cases 3, 4, and 5) and reacted weakly with the two other cases. F8-11-13 did not react with the histiocytic lymphoma.

Five of the six cases reacted with epithelial membrane antigen (Dako), producing both a strong membrane and a focal cytoplasmic reaction. These findings are consistent with the observation of other workers who have shown reactivity of monoclonal antibodies against the human milk fat globule protein with histiocytic neoplasms and a proportion of cases of non-Hodgkin's lymphoma.³⁷ None of the cases reacted with Leu M1, which primarily detects granu-

locytes but which has recently been shown to react with Reed Sternberg and Hodgkin's cells.^{37 38}

IMMUNOHISTOCHEMICAL STAINING OF CRYOSTAT SECTIONS

Fresh frozen tissue was available from four of the cases of malignant histiocytosis of the intestine and from the case of histiocytic lymphoma. Table 3 gives the results of staining with a panel of monoclonal antibodies.

Reactivity with the leucocyte common antibodies F10-89-4 and Dako leucocyte common show that the tumour cells are of haemopoietic origin. Results with Dako leucocyte common and F8-11-13 were comparable with those seen with paraffin sections.

Expression of monocyte markers by tumour cells was variable. In each of the cases of malignant histiocytosis of the intestine studied a proportion of tumour cells showed reactivity with three of the panel

Fig. 3 Malignant histiocytosis of the intestine (case 3) stained with FMC 17. Proportion of tumour cells show strong membrane immunoreactivity. Cryostat section. $\times 400$.

Table 3 Immunohistochemical staining on frozen section

Monoclonal antibody	Case No and diagnosis				
	(1) MHI	(2) MHI	(3) MHI	(4) MHI	(6) HL
F10-89-4	+++	+++	+++	+++	+++
DAKO Lc	+++	+++	+++	+++	+++
F8-11-13	+	+	+++	+++	—
DA6 147	++	+	—	++	+
DA6 231	+++	+++	++	++	+++
Leu10	++	++	—	—	+++
FMC17	++	++	++	++	++
FMC32	++	++	++	++	+
OKM1	+++	+++	++	++	+++
Leu M2	—	—	—	—	+++
MO2	—	—	—	—	—
Dako C3b	—	—	—	—	—
Dako DRC1	—	—	—	—	—
FMC8	—	+	+++	+++	++
OKT3	—	+	—	+	NT
UCHT1	++	+++	+++	+++	—
Leu4	++	+++	+++	+++	—
Dako T2	++	++	+++	+++	—
OKT4/Leu3a	++	++	++	++	++
OKT8/Leu2a	—	—	—	—	—
OKT11	++	+	+	—	—
OKT6	—	—	—	—	—
Leu7	NT	NT	—	—	NT
κ or λ	—	—	—	—	—
DA6 147	—	—	—	—	—
BI/Dako-pan B	—	—	—	—	—

Negative (—) = <10%; mildly positive (+) = 10–30%; strongly positive (++) = 30–60%; very strongly positive (+++) = >60% positively reacting tumour cells; NT = not tested.
MHI = Malignant histiocytosis of the intestine; HL = histiocytic lymphoma.

of the monocyte macrophage monoclonal antibodies. All tissue sections contained a proportion of tumour cells that stained with the monoclonal antibodies

Fig. 4 Malignant histiocytosis of the intestine (case 3) stained with Leu4. Most of the large infiltrating tumour cells show strong immunoreactivity. Cryostat section, $\times 400$.

FMC17, FMC32, and OKM1 (Fig. 3) but that did not react with the antimacrophage monoclonal antibodies MO2 and Leu M2, or with monoclonal antibodies reacting with dendritic cell populations (Dako-C3b, Dako-DRC1, and OKT6). FMC8 stained most tumour cells in cases 3 and 4 and a few cells in case 2. Although FMC8 stains follicle centre dendritic reticulum cells in normal tissue (personal observation), this antibody cannot be thought of as lineage specific as it also stains immature B cells in some cases of B-chronic lymphatic leukaemia, as well as platelets, granulocytes, and monocytes.^{19 20} The histiocytic lymphoma showed reactivity with FMC17, FMC32, OKM1, Leu M2, and FMC8.

The staining of malignant histiocytosis of the intestine with T cell monoclonal antibodies again showed variable reactivity. All tissue sections reacted with the anti T4 monoclonal antibodies Leu 3a and OKT4 as did the histiocytic lymphoma. Both of these monoclonal antibodies react with cells of monocyte macrophage lineage.²⁵ Morphologically abnormal tumour cells, however, also reacted with other T cell monoclonal antibodies. A large proportion of tumour cells in all cases reacted with monoclonal antibodies detecting epitopes on the T3 complex (UCHT1 and Leu 4) (Figs. 4 and 5), and they also stained with Dako T2, which reacts with a T cell associated antigen.²⁴ Only two cases (2 and 4) showed reactivity

Fig. 5 Malignant histiocytosis of the intestine (case 4) stained with Leu4. Leu4 is reacting strongly with most of the tumour cells. Cryostat section. $\times 400$.

with OKT3. A few tumour cells in cases 1, 2, and 3 reacted weakly with OKT11. None of the cases reacted with the anti T8 monoclonal antibodies. Neither of the two cases tested reacted with Leu 7, an antibody which recognises natural killer cells. In serial sections a proportion of tumour cells reacting with T cell monoclonal antibodies also seemed to react with OKM1. The histiocytic lymphoma reacted with the anti T4 monoclonal antibodies but did not react with any of the other T cell monoclonal antibodies used.

There was variable expression of Class II major histocompatibility complex antigens. In cases 1 and 2 DR (α and β) and DQ antigens were detectable (DA6 231, DA6 147, and Leu 10, respectively). In cases 3 and 4 a few tumour cells expressing DR antigens could be detected, but tumour cells expressing DQ were not seen. The histiocytic lymphoma expressed DR (α and β) and DQ antigens. None of the cases reacted with the pan B lymphocyte markers Dako B, B1, or with the monoclonal antibodies to immunoglobulin light or IgM heavy chains.

Discussion

Each of the five cases of intestinal malignancy in this study exhibited clinical features and histological appearances, including strong paranuclear staining for α 1AT, which led to the clinicopathological diagnosis of malignant histiocytosis of the intestine based on the criteria described by Isaacson and Wright.^{1 35} In case 4 some features differed from the other cases but this case was similar morphologically to the

blastic or poorly differentiated form of histiocytic lymphoma recognised by Isaacson and Wright.³⁶

Reactivity of all five cases with leucocyte common antibodies confirms the haemopoietic lineage of the tumour cells. Both Dako leucocyte common and F10-89-4 react with cells of monocyte or macrophage lineage.^{7 8} F8-11-13, however, which reacts with the high molecular weight form of the leucocyte common antigen expressed by B cells and only a proportion of T cells⁹ and which does not react with cells of histiocytic lineage,⁴⁰ showed reactivity within our cases. This raises questions as to the histogenesis of these tumours.

Further questions as to the histogenesis of the tumours are raised by the observations that all the tumours strongly expressed some T cell markers. The finding that a proportion of tumour cells in all four cases of malignant histiocytosis of the intestine and the histiocytic lymphoma reacted with the monoclonal antibodies OKT4 and Leu3a is not unexpected as these antibodies have been shown previously to react with cells of monocyte or macrophage lineage.²⁵ Morphologically abnormal cells, however, also expressed antigens of the T3 complex (OKT3⁺, UCHT1⁺, Leu4⁺) and the T cell associated antigen recognised by Dako T2, as well as reacting with OKM1.

Although clinical history, morphological criteria, and staining for α 1AT showed that all cases were similar and could be diagnosed as malignant histiocytosis of the intestine, the results of immunohistochemical staining showed that the tumour cells of malignant histiocytosis of the intestine did not express a characteristic monocyte or macrophage phenotype. The immunophenotype of most cells in our cases would be the same as those of a T cell neoplasm with a background population of cells of macrophage lineage. It could be argued that cells with a monocyte or macrophage phenotype were the "true" malignant population with T cells a reactive component. Obvious abnormal cells did stain for α 1AT in paraffin sections; similar large multilobulated and multinucleated forms which could be identified in cryostat sections, however, reacted with T cell monoclonal antibodies.

Alpha 1AT is believed to be a reliable marker of malignant histiocytes.⁵ Recently, however, Stein *et al* reported a group of large cell lymphomas, positive for α 1AT and Ki 1, a proportion of which also expressed T cell markers.²⁴ These tumours bear immunophenotypic similarities to the present cases. Ki 1 also reacts with Hodgkin's and Reed-Sternberg cells,^{24 41} and α 1AT has also been reported to stain these cells.⁴¹ This raises the possibility that there may be a relation between malignant histiocytosis of the intestine and Hodgkin's disease. None of our cases reacted with Leu M1, however, whereas most Reed-

Sternberg cells express this marker.^{38 39}

Recently, a patient with an abnormal expansion of granular lymphocytes that reacted with both T cell and macrophage markers (Leu7⁺, OKT3⁺, OKT4⁺, OKT8⁻, OKM1⁺) was described.⁴² Although none of our specimens reacted with Leu7 when tested, the neoplastic cells in malignant histiocytosis of the intestine may possibly be related to such a cell expressing markers of T cell and macrophage lineage. Such an expansion of large granular lymphocytes, which were negative for Leu7 but positive for T and monocytic antigens, has been described in a patient.⁴³

Isaacson *et al* recently reported four cases of malignant histiocytosis of the intestine arising in coeliac disease, each of which showed a T cell phenotype. Three of these four cases also showed T cell receptor gene rearrangement.⁴⁴ These findings, along with our results, strongly support the idea that malignant histiocytosis of the intestine is a T cell lymphoma.

When a panel of monoclonal antibodies was applied to cases of malignant histiocytosis of the intestine, we obtained results that revealed a diversity of phenotype expression within the tumour cells. These results show a mixed population of cells in malignant histiocytosis of the intestine, only a proportion of which expressed typical macrophage markers, while most tumour cells expressed T cell markers. These observations confirm the need for a critical re-evaluation of the histogenesis in this group of tumours.

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