Villous atrophy with crypt hyperplasia in malignant histiocytosis of the nose

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SUMMARY Intestinal changes, mainly in the jejunum, were investigated in 13 cases of malignant histiocytosis at necropsy and who had presented as lethal midline granuloma. Villous atrophy with crypt hyperplasia was observed in all cases, and a proliferation of atypical histiocytes was observed in seven cases. In the remaining cases, histiocytes with normal morphology increased in number. These findings showed that a prolonged abnormal proliferation of histiocytes was present in the small intestine of these cases concurrently with the nasal lesions.

The term malignant histiocytosis was introduced by Rappaport, for "a systemic, progressive, and invasive proliferation of morphologically atypical histiocytes and their precursors".¹ Malignant histiocytosis of the intestine has been described in connection with malabsorption and ulcerative jejunitis.² In these cases, peroral jejunal biopsy and surgical resection specimens showed villous atrophy with crypt hyperplasia even in the jejunum remote from areas of ulceration or frank lymphoma. Villous atrophy with crypt hyperplasia was suggested as a prolonged cryptic phase of malignant histiocytosis.

Six cases with malignant histiocytosis presenting as lethal midline granuloma have been reported by us.³ These patients usually complained of nasal obstruction and discharge, fever, and other symptoms restricted to the face. Abdominal symptoms including malabsorption were not noticed at the initial presentation. Physical examinations revealed ulcerative and granulomatous lesions in the nasal cavity. Deterioration in these patients progressed rapidly, and mean survival was 13 months. In two cases, multiple ulcers with perforations were found in the intestine at necropsy and the lesions were due to the infiltration of atypical histiocytes.

In this paper, changes in the jejunum are described in 13 cases with malignant histiocytosis presenting as lethal midline granuloma examined at necropsy.

Material and methods

The 13 cases presented here were examined between 1958 and 1980. They showed typical histopathological findings of malignant histiocytosis. Sections

from the jejunum were available in all cases. In one case, material from the jejunum was also obtained at operation. Adequate clinical data were available in 11 cases.

Results

CLINICAL FINDINGS

The 13 cases showed progressive and destructive lesions in the nose and adjacent structures, which presented as clinical lethal midline granuloma. Nasal obstruction and discharge were most common symptoms with prodromal periods ranging from 2 to 15 months. The clinical courses were rapid and survivals ranged from 0.3 to 40 months (mean 13 months). Subcutaneous nodules were noticed in five cases terminally. Nine patients suffered from abdominal symptoms (Table 1) terminally, and the duration of these from the onset to death were two days to 2.5 months (mean 0.8 months). No patient had diarrhoea or steatorrhoea.

PATHOLOGICAL FINDINGS

Multiple ulcers in the gastrointestinal tract were found in four cases at necropsy, and perforation of the jejunum occurred in one case. Perforations of stomach or jejunum were operatively resected in two cases. The histological examinations of these lesions showed infiltration of atypical histiocytes in five cases.

Pathological findings in the jejunum in 13 necropsy cases are shown in Table 2. Villous atrophy and crypt hyperplasia was observed in all. In seven cases there was a proliferation of atypical histiocytes (Figs. 1, 2). Phagocytosis was not uncommon among the atypical histiocytes (Fig. 3). The proliferation of

Table 1 Clinical data of thirteen cases

Case	Age	Sex	Abdominal symptoms	Operation	Survival (months)
1	32	M	No	No	0.3
2	45	M	Abdominal pain	No	4
3	32	F	Tarry stool	No	5
4	57	M	No	No	6
5	37	M	Abdominal pain	Gastrectomy for perforation	6
6	44	M	Abdominal distension, Haematemesis	No	6
7	50	F	Abdominal distension	No	8
8	22	M	Abdominal pain	No	13
9	41	F	Abdominal pain	No	16
10	21	F	No	No	19
11	36	F	Abdominal distension	No	21
12	26	M	Abdominal pain, Haematemesis	Ileocejunotomy for perforation	24
13	49	M	No	No	40

Table 2 Pathological findings of jejunum in 13 necropsy cases

Case	Macroscopical findings	Microscopical findings		
		VACH	PAH	LPI
1	Submucosal bleeding	+	-	+
2	No	+	+	+
3	No	+	-	+
4	No	+	-	+
5	No	+	-	+
6	No	+	+	+
7	Submucosal bleeding	+	+	+
8	Multiple ulcers with perforation	+	+	+
9	No	+	-	+
10	NA	+	+	+
11	NA	+	+	+
12	Multiple ulcers	+	+	+
13	No	+	-	+

VACH = villous atrophy with crypt hyperplasia.

PAH = proliferation of atypical histiocytes.

LPI = lymphoplasmacytic infiltration.

NA = not available.

atypical histiocytes was usually accompanied with lymphoplasmacytic infiltration. Eosinophils were uncommon. Grossly visible tumour masses were found in four cases (cases 2, 7, 8, 12) and in these villous atrophy with crypt hyperplasia was observed even in intestine remote from the lesions. In cases without proliferation of atypical histiocytes, histiocytes with normal morphology were increased in number in the layers beneath the muscularis mucosae.

Necropsy findings in other organs were systemic and invasive proliferation of atypical histiocytes without tumour formation. Multinucleated atypical histiocytes were occasionally found. Phagocytosis with variable frequencies was observed in all cases. Lymph nodes were diffusely permeated by atypical histiocytes, but residual lymph follicles and maintenance of sinus structures were common. In the

Fig. 1 Villous atrophy with crypt hyperplasia and lymphoplasmacytic infiltration in the lamina propria. Infiltration of atypical histiocytes can not be observed. Haematoxylin and eosin $\times 130$.

Fig. 2 Villous atrophy with crypt hyperplasia and infiltration of atypical histiocytes. Lymphocytes and plasma cells also infiltrated in the lamina propria. Haematoxylin and eosin $\times 130$.

Fig. 3 Detail of infiltrates underlying the ulcer. Erythrophagocytosis is noted in the centre (arrow). Haematoxylin and eosin, original magnification $\times 700$.

Fig. 4 Intrasinusoidal infiltration in the liver. Phagocytosis is noted in the centre. Haematoxylin and eosin $\times 800$.

livers, intrasinusoidal infiltrations were marked (Fig. 4). In the spleen, the infiltration was mainly found in the red pulp.

Discussion

Patients with malignant histiocytosis usually show fever, lymphadenopathy, general fatigue, and malaise.⁴ Common physical findings are a high temperature, localised or generalised lymphadenopathy and hepatosplenomegaly. Malignant histiocytosis with abdominal symptoms occurs, and necropsy may reveal tumour masses in the intestines.⁵⁻⁷ Greenberg *et al* reported that frequency of abdominal symptoms in 146 cases with malignant histiocytosis was 15%.⁸

Isaacson and Wright described a relation between malignant histiocytosis, malabsorption and ulcerative jejunitis.^{2,9} The patients suffered from abdominal pain and malabsorption followed by intestinal obstruction or perforation. Although the disease usually progressed rapidly, a case with prolonged history of malabsorption was described. Macroscopically, non-indurated ulcers or tumour masses were observed in the intestines. Microscopically, villous atrophy with crypt hyperplasia was observed even in the uninvolved mucosa. They regarded this as a histological feature of a prolonged cryptic phase of malignant histiocytosis in the intestine. Malabsorption and ulcerative jejunitis were observed in this phase. Malignant histiocytosis in a preneoplastic or in neoplastic stage accompanied by a host inflammatory reaction was invoked as the explanation

for cryptic phase of malignant histiocytosis.

Malignant histiocytosis presenting as lethal midline granuloma has been reported by us.³ These cases showed prodromal symptoms for 2 to 15 months. Nasal obstruction and discharge were frequently found but abdominal symptoms were never observed at the initial stage. Abdominal symptoms were present terminally in each case. Necropsy revealed a systemic proliferation of atypical histiocytes, and intestines were involved in five of six cases. It was suggested that this disease had been previously included in the midline malignant reticulosis.¹⁰

The 13 cases described here are malignant histiocytosis presenting as lethal midline granuloma, and abdominal symptoms were present terminally in nine cases. This ratio is much higher than that reported by Greenberg *et al* (15%).⁸ Malabsorption was not found but histological examination of the jejunum revealed villous atrophy with crypt hyperplasia, with the proliferation of atypical or normal histiocytes. Atypical histiocytic proliferation was found in 7 (54%) of our cases, which is higher than that reported by Warnke *et al* (33%).⁴ Lymphoplasmacytic infiltration was also a constant finding. Although the lesions in the face stand out clinically in our cases in the initial stages, the presence of villous atrophy suggest that the face and small intestine were simultaneously involved by a systemic histiocytosis.

Radiotherapy has been suggested for the treatment of midline malignant reticulosis.^{11,12} Eichel *et al*¹¹ reported a good prognosis of midline malignant reticulosis treated by radiation and nine stage 1

cases all survived 5 yrs. However, Fu and Perzin reported a poor response to radiation and all their followed cases died due to tumour.¹³ In malignant histiocytosis improved progress has been reported after intensive systemic combination chemotherapy.¹⁴ When apparently only the facial area is involved midline malignant reticulosis and malignant histiocytosis may be indistinguishable. Since our investigations suggest simultaneous involvement of the face and small intestine in malignant histiocytosis presenting as lethal midline granuloma, we recommend that combination chemotherapy and radiation be preferred to radiation alone in the treatment of midline malignant reticulosis or malignant histiocytosis.

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