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Gastrointestinal involvement in systemic mastocytosis

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SUMMARY Four consecutive patients with systemic mastocytosis were studied. One patient had a malabsorption syndrome with only minor histological changes of the intestinal mucosa. Another patient with ulcer diathesis had a gastric secretory pattern resembling Zollinger-Ellison syndrome. Serum gastrin and histamine levels were consistently normal in all patients. Endoscopy of stomach and colon disclosed urticaria-like papulae either spontaneously or after topical provocation in all patients. No increase of mast cells was found in multiple mucosal biopsies. A markedly increased gastric tissue content of histamine was found, however, in the three patients studied. The findings suggest that urticaria-like lesions associated with a high tissue content of histamine may be more important that hyperhistaminaemia in causing the various gastrointestinal symptoms.

Systemic mastocytosis (SM) is a rare disorder characterized by mast cell proliferation in skin (urticaria pigmentosa), bones, lymph nodes, and parenchymal organs. In rare instances, it may terminate as mast cell leukaemia (Lennert, *et al.*, 1956; Waters and Lacson, 1957; Efrati *et al.*, 1957; Friedman, *et al.*, 1958; Brinkmann, 1959; Schubert and Martin, 1968). Systemic symptoms such as pruritus, flushing, tachycardia, fever, or headache which are probably due to histamine release by the mast cells occur in many patients. Nausea, vomiting, abdominal pain, or diarrhoea may also occur in almost half of the patients (Mutter *et al.*, 1963). A few patients with peptic ulcer (Efrati *et al.*, 1957; Friedman *et al.*, 1958; Remy, 1962; Ultmann *et al.*, 1964; Clémett *et al.*, 1968; Roberts *et al.*, 1968; Keller and Roth, 1970); and four cases with a well-documented malabsorption syndrome have been described (Bank and Marks, 1963; Jarnum and Zachariae, 1967; Broitman *et al.*, 1970; Ammann and Spycher, 1972). Systemic histaminaemia has been claimed to be the causative factor but no consistent relationship between histaminaemia and gastrointestinal symptoms has been found. In a previous publication, the presence of urticaria-like lesions associated with a high tissue histamine content has been postulated as an important factor responsible for the gastrointestinal symptoms (Ammann and Spycher, 1972). To test this hypothesis, four consecutive patients with SM have been investigated and histamine has been determined in serum and in gastric biopsy specimens.

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Methods

Four patients with systemic mastocytosis and gastrointestinal symptoms seen in the medical clinics of the University and the City Hospital respectively have been investigated. The patient W.H. with a malabsorption syndrome has been reported previously (Ammann and Spycher, 1972). Systemic mastocytosis was proved by typical skin changes, skin biopsies, and by the characteristic bone marrow involvement. In each patient a thorough clinical examination and routine laboratory tests were performed repeatedly.

Gastric secretory studies using pentagastrin (6 μg/kg subcutaneously) were performed and basal acid output (BAO) and peak acid output (PAO) were determined (Baron, 1970). Histamine was measured in fasting blood samples spectrofluorometrically according to the method of Evans *et al.* (1973)[1]. Gastric biopsies obtained in three patients were homogenized in 1·4 ml 0·9% saline and treated with trichloroacetic (0·4 N). After centrifugation, histamine was determined spectrofluorometrically in the supernatant. Serum gastrin levels in fasting state (three patients) and after a standard meal (two

cases) were assessed by radioimmunoassay as previously described (Säuberli *et al.*, 1974). 5-hydroxy-indol-acetic acid excretion (5-HIAA) in samples of 24 h urinary collections were determined in two patients.

Pancreatic function was assessed by repeated serum amylase determinations, by the estimation of the faecal chymotrypsin activity (Ammann, 1974), and by the glucose tolerance test. Small bowel function studies included faecal fat excretion (Van de Kamer *et al.*, 1949), D-xylose test, Schilling test, and the 'small bowel profile' (serum protein, calcium, phosphate, cholesterol, iron, prothrombin time, and alkaline phosphatase).

Panendoscopy with multiple mucosal biopsies of stomach and duodenum was carried out in each patient. In three of the patients, fibresigmoidoscopy was performed and multiple mucosal biopsies were taken. A small bowel biopsy was carried out in one patient (W.H.).

A provocative test for histamine release utilizing topical application of a peptone solution (1%) and polymyxin (0·5%) (Orfanos, 1966) was performed under endoscopic control in duodenum, stomach and/or colon in four patients. In five control subjects, this provocative test did not result in any visible endoscopic or histological changes in stomach, duodenum, or colon. All biopsies stained by haematoxylin and eosin and by Giemsa method were studied by light microscopy.

Results

All four patients were male with a mean age at onset of urticaria pigmentosa of 35 years and a mean duration of the disease of 14 years (Table 1). Two patients (A.A., R.C.) were referred with recurrent epigastric pain and intermittent flushing, one patient with haematemesis.

Bone involvement secondary to SM was demonstrated radiologically in two patients. Splenomegaly was present in one patient, probably liver involvement in two others, and kidney involvement was suspected in one patient with constant albuminuria of 0·4-2·9% (Table 1).

FUNCTION OF PANCREAS AND OF SMALL BOWEL

The results of the laboratory tests are summarized in Table 2. Pancreatic exocrine and endocrine function was consistently normal. Evidence of malabsorption was found in the patient (W.H.) reported previously (Ammann and Spycher, 1972). Steatorrhea and subnormal results of D-xylose- and Schilling test (with intrinsic factor) were compatible with a malabsorption syndrome secondary to diffuse mucosal involvement of the small intestine.

Normal values for 5-HIAA urinary excretion were observed in the three patients studied.

GASTRIC SECRETION AND SERUM GASTRIN VALUES

The results of gastric secretory studies and of the serum gastrin values are summarized in Table 3. A secretory pattern suggestive of Zollinger-Ellison syndrome with a very high BAO and a high BAO/PAO ratio was observed in patient M.H. with erosive gastroduodenitis. Patient R.C. also exhibited a markedly elevated BAO and PAO but without endoscopic evidence of ulcer. In both patients, the

Patient	*Sex*	*Age at onset (yr)*	*Duration of symptoms (yr)*	*Chief complaints*	*Flush*	*Involved organs*				
						Marrow	*Bone*	*Liver*	*Spleen*	*Kidney*
A.A.	M	35	7	Epigastric pain	+	++	−	±	−	+
R.C.	M	24	12	Epigastric pain	+	++	−	−	++	
W.H.	M	31	32	Diarrhoea, bone pain	−	++	Porosis	−	−	
M.H.	M	51	5	Gastric bleeding, diarrhoea	−	++	Sclerosis	±	−	

Table 1 *Systemic mastocytosis (SM): clinical data*

Tests of small bowel and pancreatic function	*A.A.*	*R.C.*	*W.H.*	*M.H.*	*Normal values*
Faecal fat (g/24h)	0·7	—	20.2	—	<7·0
D-xylose (g/5h)	9·1	6·7	3·6	5·3	>5·0
Schilling (%/24h)	—	17·6	0·5	—	>8·0
Glucose tolerance	Normal	—	Flat	Normal	
5-HIAA (mg/24h)	12·5	—	1·8	10	<15
Serum-B_{12} (pg/ml)	—	405	0	—	200-900
Serum folate (ng/ml)	—	10·6	4·3	—	5-15
Serum amylase (SU)	151	97	194	—	<200
Faecal chymotrypsin conc. (μg/g)	622	205	714	—	>120

Table 2 *Systemic mastocytosis: laboratory findings*

Patients	*Gastric analysis*		*Gastrin profile (pg/ml)*		
	BAO (H^+mEq/h)	*PAO (H^+mEq/h*	*Basal*	*Poststimulation*	
				Maximum	*After 2h*
A.A.	4·2	15·3	23	28	22
R.C.	9·1	45·3	40	62	44
W.H.	0·1	0·1	—	—	—
M.H.	41·5	53·8	52	—	—
Normal values	0-5	15-35	20-50	80-120	60-80

Table 3 *Gastric acid secretion: serum gastrin values*

normal serum gastrin values are strong evidence against a Zollinger-Ellison syndrome.

HISTAMINE CONCENTRATION IN SERUM AND GASTRIC BIOPSIES

As indicated in Table 4, normal fasting serum histamine values were found in all four patients. The histamine content of gastric biopsies, however, was markedly elevated in all three patients studied (two to four times above normal).

Patients	*Fasting serum histamine (ng/ml)*	*Gastric biopsy histamine content (μg/g fresh tissue)*
A.A.	3·6	62·5
R.C.	3·6	46·3
W.H.	4·4	—
M.H.	4·9	43·6
Normal values	5·5*	14±4†

Table 4 *Histamine content of serum and gastric biopsies*

*Evans *et al.* (1973). †Jarnum *et al.* (1967).

ENDOSCOPIC AND HISTOLOGICAL FINDINGS

In patient M.H., panendoscopy performed in 1973 because of haematemesis revealed erosive gastroduodenitis and marked mucosal oedema. During remission, a second panendoscopy revealed multiple urticaria-like papulae in stomach and duodenum in response to topical application of polymyxin and peptone solution but no erosions. A large bleeding gastric ulcer of the body of the stomach was visualized two days after snare biopsy. The bleeding stopped after truncal vagotomy and ligation of the responsible artery. Six days postoperatively, a second severe haemorrhage due to two large prepyloric gastric ulcers necessitated a second intervention with gastric resection and Billroth II anastomosis. Bleeding has not recurred.

In patients W.H. and R.C. endoscopy was normal. In both patients, however, provocation tests at different sites in the duodenum with peptone solution and/or polymyxin induced varying degrees of spotty papular oedema and hyperaemia. In patient A.A. endoscopy revealed multiple scattered oedematous and hyperaemic papulae along the greater curvature. The normal duodenal mucosa showed a spotty hyperaemic reaction after polymyxin application. The colonic mucosa was also normal on fibersigmoidoscopy but provocation with polymyxin and/or peptone solution induced spotty hyperaemic and oedematous changes in all three patients tested. The most striking findings of the small intestinal biopsy of patient W.H., performed in 1970, were a moderately distorted villous pattern, an intact epithelium, and a marked accumulation of eosinophils in the lamina propria. The mucosal biopsies of stomach, duodenum, and colon in the four patients of the present series disclosed a uniform pattern characterized by a rather dense infiltration of the lamina propria predominantly by plasma cells, lymphocytes, and varying amounts of eosinophils. Only a few scattered mast cells were visualized in the specially stained slides. In one snare gastric biopsy (M.H.) which enclosed some submucosa, a focal perivascular accumulation of mast cells (about 10 per high power field) was observed.

Discussion

Gastrointestinal symptoms frequently occur in systemic mastocytosis (SM). They may be due to systemic histaminaemia, other humoral factors released by the mast cells, or to high tissue concentrations of histamine.

Hyperhistaminaemia and histaminuria have frequently been observed in urticaria pigmentosa or SM, often without gastrointestinal symptoms (Brogren *et al.*, 1959; Bloom *et al.*, 1960; Birt *et al.*, 1961; Remy, 1962; Demis, 1963; Ultmann *et al.*, 1964). Episodic flush, tachycardia, fever, and headache are easily explained by hyperhistaminaemia (Gonella and Lipsey, 1963). Evidence that histamine release into the systemic circulation causes gastrointestinal symptoms, however, is not conclusive (Rider *et al.*, 1957; Havard and Scott, 1959; Szweda *et al.*, 1962; Bank and Marks, 1963). Broitman *et al.* (1970), in a patient with malabsorption syndrome due to SM, found a normal excretion of histamine in the urine, even after histidine load. Similarly, in our patient with malabsorption (W.H.),

the serum histamine concentration was normal. The fact that severe gastrointestinal involvement is not regularly associated with hyperhistaminaemia suggests that there is no direct causal relationship between the two conditions.

Serotonin seems unlikely to be the cause of gastrointestinal symptoms, since human mast cells do not produce serotonin (Bloom, 1942; Sjoerdsma *et al.*, 1957; Birt *et al.*, 1961; Demis, 1963; Selye, 1965), and urinary 5-HIAA excretion was found to be normal in most patients (Brodgren *et al.*, 1959; Remy, 1962; Bank and Marks, 1963; Ultmann *et al.*, 1964; Jarnum and Zachariae, 1967; Keller and Roth, 1970; Broitman *et al.*, 1970; Debray *et al.*, 1973).

Among the patients with gastrointestinal symptoms, there are only a few with either gastroduodenal ulcer and steatorrhea respectively. It seems important to investigate more closely the pathogenetic mechanism in these groups of patients.

A number of cases with peptic ulcer in SM have been reported (Clémett *et al.*, 1968; Roberts *et al.*, 1968) but there is no proof that the overall incidence of peptic ulcer has increased. Keller and Roth (1970) described a patient with gastric ulcer associated with a secretory pattern resembling Zollinger-Ellison syndrome and hyperhistaminaemia. But during administration of brocresine, a specific inhibitor of histidine decarboxylase, the urinary histamine excretion diminished significantly, whereas no significant decrease of the basal acid output occurred. Gastric acid output in the few patients studied was found to be normal or decreased in the majority of patients with urticaria pigmentosa or SM (Jeanselme and Touraine, 1919; Ellis, 1949; Berlin, 1955; Zak *et al.*, 1957; Remy, 1962; Szweda *et al.*, 1962; Bank and Marks, 1963; Jarnum and Zachariae, 1967; Broitman *et al.*, 1970). In the present series, the gastric acid secretion was normal or depressed in two patients (Table 3). In one patient with erosive gastroduodenitis a secretory pattern resembling Zollinger-Ellison syndrome (M.H.) was present. The fasting serum histamine and serum gastrin values were both normal (Table 3 and 4). The same was true in the fourth patient with a less marked increase of the BAO (R.C.). Markedly elevated tissue contents of histamine in gastric biopsies were, however, detected in three patients studied (Table 4). Similar high levels of histamine in biopsies of stomach and small intestine were observed by Jarnum and Zachariae (1967) in one patient each with urticaria pigmentosa and SM respectively. All these findings together suggest that the high tissue content of histamine rather than systemic hyperhistaminaemia may be the important factor for hyperchlorydria and ulcer diathesis, at least in some patients with SM.

A malabsorption syndrome in association with SM has been well documented in four cases only (see Amman and Spycher, 1972). The pathogenetic mechanism has not yet been elucidated. There is a striking discrepancy between the biological abnormalities suggesting a diffuse mucosal involvement as in the primary malabsorption syndrome (steatorrhoea, normal pancreatic function, subnormal D-xylose test, and Schilling test) and the minor histological changes of the intestinal mucosa (Ammann and Spycher, 1972). In particular, villous pattern, epithelium, and lamina propria disclose no major abnormalities (Ammann and Spycher, 1972). There is, however, increasing evidence that oedema and urticaria-like lesions of the mucosa may represent the morphological substrate of malabsorption. Oedema, thickening of the Kerckring folds, and a peculiar nodular mucosal pattern of stomach and small intestine have been demonstrated radiologically in SM (Janower, 1962; Remy, 1962; Bank and Marks, 1963; Bloom, 1965; Jarnum *et al.*, 1967; Clémett *et al.*, 1968; Schongut *et al.*, 1968; Debray *et al.*, 1973). Endoscopically, urticaria-like lesions have been visualized in stomach, duodenum (Clémett *et al.*, 1968; Debray *et al.*, 1973), or in the rectum (Berlin, 1955). Such changes were found also in the four patients of the present series, in some of them only after topical provocation. It seems, therefore, that malabsorption and probably other gastrointestinal symptoms may be related to these urticaria-like mucosal lesions. The variable intensity and transient character of such lesions render their demonstration difficult, particularly by biopsy technique.

Cutaneous urticaria and high tissue contents of histamine in association with accumulation of mast cells are characteristic findings of urticaria pigmentosa. However, no such accumulation of mast cells have been demonstrated in multiple mucosal biopsies at different sites of the gastrointestinal tract in the present series or by other investigators (Bank and Marks, 1963; Broitman *et al.*, 1970; Ammann and Spycher, 1972). Only in the patient of Jarnum *et al.* were a large number of mast cells found particularly in the submucosa in a surgical biopsy of small bowel. According to other investigators, mast cells are normally most abundant in the submucosa of the small bowel (Norris *et al.*, 1963; Astaldi *et al.*, 1966; Dobbins *et al.*, 1969). Thus they could by their location theoretically escape routine mucosal biopsy procedures. The problem of distribution of mast cells in the gastrointestinal tract in SM needs further investigations. Indirect evidence for high tissue contents of histamine derives from the fact that a markedly increased infiltration of the lamina propria by eosinophils has often been noted (Rider *et al.*, 1957;

Bank and Marks, 1963; Broitman *et al.*, 1970; Ammann and Spycher, 1972). Eosinophils are said to possess antihistaminic activity (Kovacs, 1950; Riley and West, 1952; Archer, 1958; Fernex, 1962; Remy, 1962; Bank and Marks, 1963; Cohen, 1974; Wassermann *et al.*, 1974).

Although the cause of gastrointestinal symptoms and dysfunction remains speculative, the evidence of the present investigations suggests that the gastrointestinal tract is frequently involved in SM, and that gastrointestinal manifestations are related to the high tissue content of histamine rather than to systemic hyperhistaminaemia.

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