CASE REPORT

Eosinophilic Gastroenteritis

Report of a Case of Thirty-Two Years' Duration

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Eosinophilic gastroenteritis is an uncommon disease characterized by recurrent self-limited episodes of abdominal pain, distension, nausea, vomiting, and diarrhea (1). The striking finding is the eosinophilia of the peripheral blood as well as eosinophilic infiltration of the gastrointestinal tract. Optimal treatment is conservative and corticosteroids are beneficial (2, 3). This case is described because it represents the longest documented course of this uncommon disease, and because there were unusual associated findings of granulomatous nodules in the liver and calcifications with metaplastic ossification in the liver and lymph nodes. This case provided an opportunity to observe and document the natural history of this disease and to recognize that even when untreated it does not necessarily pose a threat to life.

CASE REPORT

In 1934 a 29-year-old female (MD), entered Minneapolis General Hospital* for the first of 38 hospital admissions, 30 of which were directly related to her problem of eosinophilic gastroenteritis (Table 1). A history of nausea, vomiting, and abdominal pain of 2 weeks' duration as well as 4 days of diarrhea was elicited. On admission, marked abdominal distension and tenderness were noted. The WBC was 24,900, with 73% eosinophils. Because of some periorbital edema plus the marked peripheral eosinophilia, trichinosis was strongly suspected but never substantiated by muscle biopsy. The patient improved with bed rest.

As evident in Table 2, a summary of the 30 pertinent hospital admissions, the patient's most prominent complaint was that of abdominal pain. The most common finding on physical examination of the abdomen was tenderness. Roentgenographic studies demonstrated gastric retention or intestinal obstruction during 11 of 16 admissions in which these studies were performed. Delayed gastric emptying, with gastric retention of barium for over 6 hours, was also noted (Figure 1). Other significant findings on admission to the hospital included: abdominal enlargement, weight gain, tenderness of the midepigastrium with shifting dullness, and the presence of a fluid wave.

In December of 1946, a cholecystectomy was performed and revealed two calcified concretions near the hilus of the liver. Many fibrous adhesions were found in the area of the liver. One of the smooth, white concretions was removed, and on section the center was cystic and the walls were noted to be calcified.

In April of 1947, repair of a periesophageal diaphragmatic hernia was accomplished. Several stony hard lymph nodes were noted at the gastroesophageal junction. The nodes were grayish white with central calcification. Microscopic examination revealed loss of lymphoid structure, marked accumulation of fat, fibrosis with bundles of collagen, and dilated vascular channels.

In December of 1947, physical findings of abdominal distension, tenderness, and diminished bowel sounds, with radiologic evidence of partial small bowel obstruction led to an exploratory laparotomy. At surgery, hard discrete nodules were palpable throughout the mesentery as well as several small whitish nodules on the liver surface. An extremely firm area was palpated high up on the small bowel and the abdominal wall. Microscopically, the tissue removed from the mesentery showed evidence of extensive fibrosis and foreign body giant cells with foamy cytoplasm. There was some eosinophilic infiltration. The portal areas of the liver were heavily infiltrated with mononuclear cells. Some macrophages with foamy cytoplasm were also seen in these areas. The pleural fluid which developed postoperatively contained large numbers of macrophages and eosinophils.

Repeated muscle biopsies were performed during these admissions and were consistently negative. *Trichinella* skin

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* This patient was followed at Minneapolis General Hospital which became Hennepin County General Hospital in 1963.

Table 1. Review of Selected Admissions

Admission	Gastrointestinal Symptoms: Pain	Vomiting	Diarrhea	Abdominal findings	X-ray findings	WBC	Eos (%)	Associated disease	Surgery
1. 1934 Feb–Mar	+	+	+	Tenderness, distension	—	24,900	73	Eyelid swelling, muscle pain	Muscle biopsy, negative
2. 1937–8 Dec–Jan	+	+	—	Nontender	Stomach, negative	44,750	86	Breast nodule	Biopsy, negative
7. 1945 November	+	+	—	Tenderness, distension, shifting dullness	Right lower quadrant, calcified mesenteric nodes	32,000	73	—	Bone marrow eosinophilia
10. 1947 Apr–May	+	+	—	Tenderness	—	12,800	50	Orthopnea	Para-esophageal hernia repair
11. 1947 August	+	+	+	Tenderness	Colon, negative	9,000	46		—
14. 1947–8 Dec–Jan	+	+	+	Tenderness, distension	Partial small bowel obstruction	36,500	73	Postoperative pleural effusion	Explorative laparotomy
16. 1949 Feb–Mar					Gastric retention, pyloric narrowing	10,000	9	Upper respiratory infection	—
26. 1952 Mar–Apr	+	+	+	Tenderness, distension, absent bowel sounds	Paralytic ileus	42,000	86	Wheezes	Bone marrow eosinophilia
30. 1956 January	+		—	Tenderness, distension, shifting dullness	Gastric retention	10,000	47	Wheezing, *Trichinella* skin test negative	
38. 1966 June–July	+		+	Tenderness	Curvilinear calcification, right upper quadrant, hydronephrosis, hydroureter	17,300 17,800	69 2	Acute pyelonephritis, wheezing postoperatively, cardiopulmonary arrest. Death.	Left nephroureterectomy

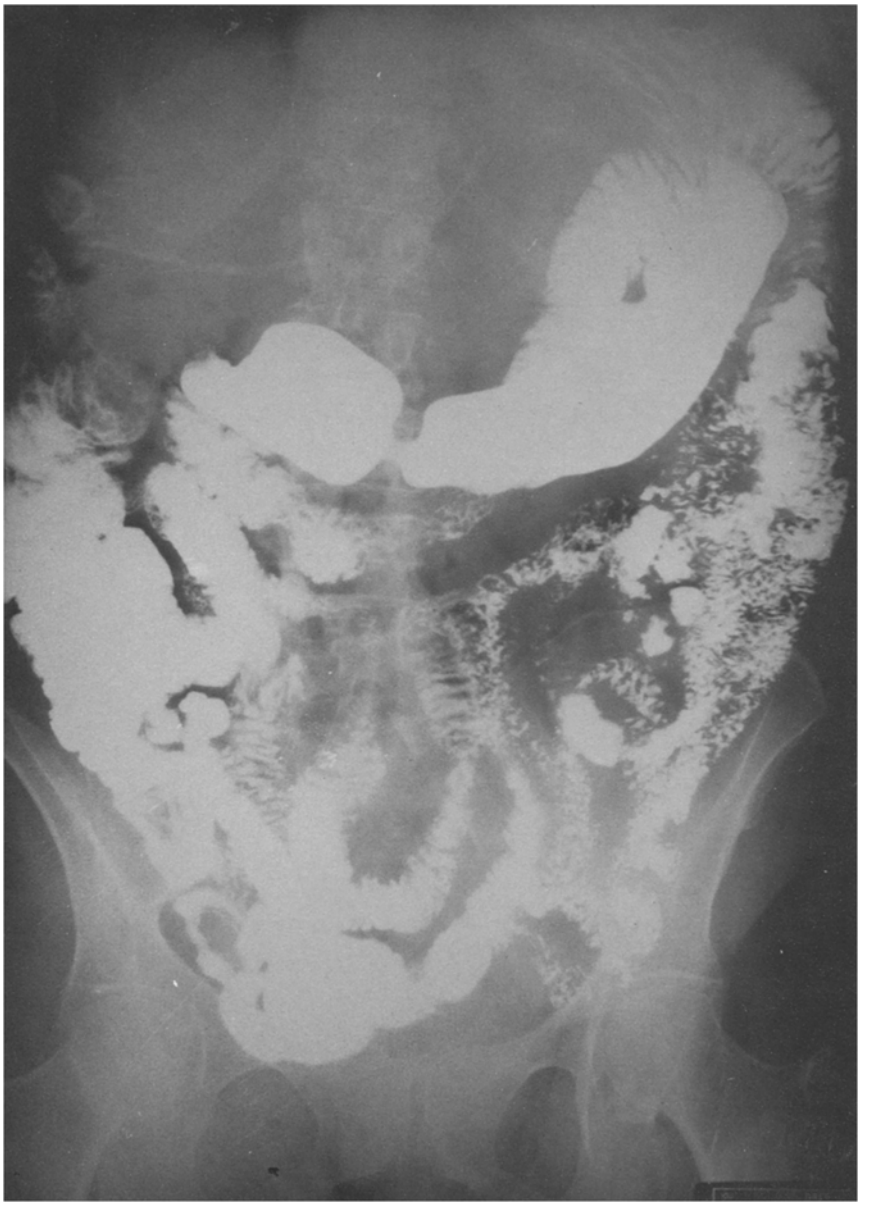

Fig 1. Gastric retention of barium for 6 hours.

tests were applied, and were also negative.

In March of 1952, the patient was readmitted with nausea, vomiting, bloating, abdominal distension and pain. Serum amylase was 92 Somogyi units/100 ml. For the first time, physical examination revealed wheezes to be present bilaterally on examination of the lungs. A bone marrow was normocellular, with large numbers of mature eosinophils and eosinophilic precursors. There was no evidence of a malignancy. Subsequent admissions were primarily for bouts of asthma. Unfortunately, the Allergy Service did not have an opportunity to evaluate the patient.

In addition to the many hospital admissions, the patient

Table 2. Eosinophilic Gastroenteritis—Summary of 30 Hospital Admissions

Gastrointestinal symptoms	
Abdominal pain	22
Emesis	16
Diarrhea	7
Abdominal findings	
Tenderness	23
Distension	13
Obstruction	7
Ascites	4
Roentgenographic findings	
Abnormal	11
Gastric retention (4)	
Bowel obstruction (7)	
Normal	5
Not done	14

visited the Outpatient Clinics and Emergency Room an even greater number of times for similar symptoms of lesser severity.

In June of 1966, the patient's final admission was precipitated by severe left-sided flank pain, with fever and diarrhea. Examination of the chest revealed marked expiratory wheezing. The abdomen was extremely tender. Radiologic studies revealed a curvilinear calcification in the right upper quadrant, and hydronephrosis with hydroureter secondary to obstruction. A left nephro-ureterectomy was performed for acute pyelonephritis. The patient became hypotensive during anesthesia and suffered a cardiopulmonary arrest 1 day postoperatively. The WBC was 17,300 with 69% eosinophils preoperatively, and 17,800 with 2% eosinophils postoperatively.

Pathologic Findings

At autopsy, severe atherosclerosis of the coronary arteries was present, with hemorrhage into an atherosclerotic plaque in the anterior descending coronary. This was presumably the immediate cause of death, although recent emboli were present in several of the smaller pulmonary arteries, a finding which could have contributed to the terminal signs and symptoms.

The abdominal cavity contained approximately 100 ml of reddish tinged serous fluid, along with numerous adhesions. The serosal surface of much of the intestinal tract was studded with discrete grayish yellow patches measuring 1 to 2 cm in diameter.

There were areas of calcification along the diaphragmatic surface of the liver. On sectioning the liver, a 1 × 1.5 cm area of calcification extending approximately 11 cm along the posterior, inferior aspect of the right lobe of the liver was noted. There were punctate yellowish areas throughout the liver.

The mucosa of the gastrointestinal tract was normal in appearance. There was no evidence of antral obstruction. Calcified lymph nodes were found in the mesentery of the right side. In the head of the pancreas, some hemorrhage

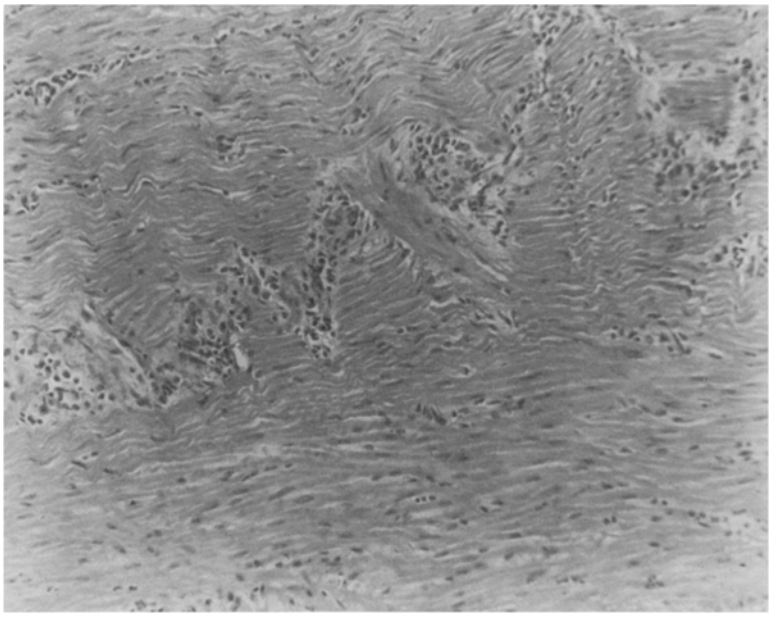

Fig 2. Outer muscle layer of small intestine showing eosinophils separating muscle bundles. (H&E, × 300)

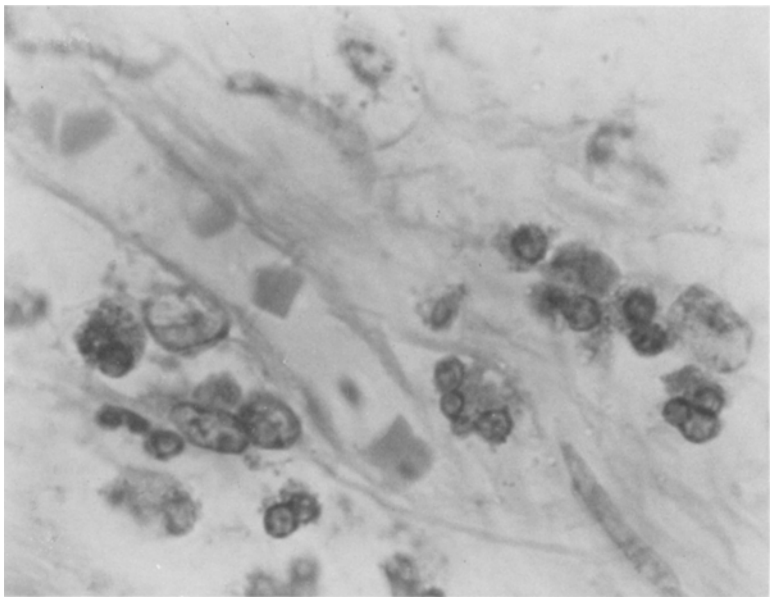

Fig 3. Several bi-lobed eosinophils lying between muscle bundles. (H&E, × 1200)

and fat necrosis was noted.

Microscopically, throughout the length of the small intestine, the serosa was markedly thickened and contained extensive infiltration with eosinophils. The grossly described gray-yellow patches corresponded to focal proliferations of mesothelial cells admixed with eosinophils. Eosinophils were also evident in the external and internal muscular layer and were most numerous in a perivascular distribution. Muscle bundles tended to be divided by eosinophils (Figures 2 and 3). Eosinophils were also prominent in the submucosa but were rare in the lamina propria. Except for an occasional histiocytic cell, the eosinophils were unassociated with other cell types. No granulomas were found at any level of the gastrointestinal tract. Eosinophils

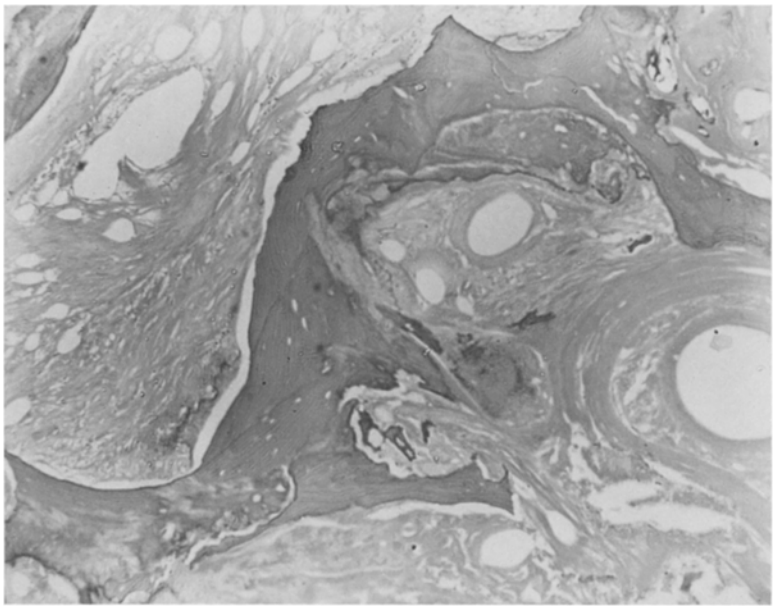

Fig 4. Metaplastic bone formation in liver. (H&E, × 100)

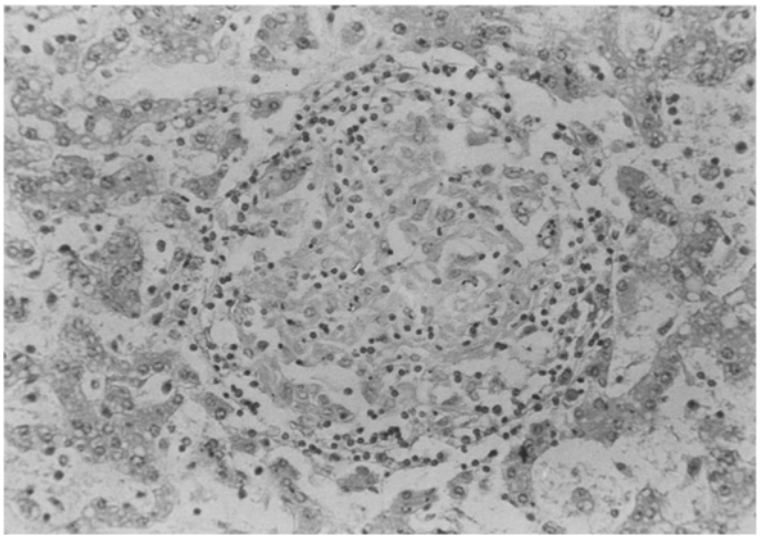

Fig 5. Granuloma in liver. (H&E, × 300)

were present in a similar distribution but to a lesser degree in the musculature and serosa of the colon and in the serosa of the stomach. Unfortunately no microscopic sections of the gastric antrum were available for study.

The calcified lesion in the liver proved to be bone (Figure 4). In other areas of the liver, small, circumscribed granulomas were present (Figure 5). These consisted of central epithelioid cells surrounded by macrophages with foamy cytoplasm and a peripheral layer of lymphocytes. No eosinophilic infiltration was present in these granulomas. Similar granulomas were also seen at the periphery of the metaplastic bone. Methenamine silver, PAS, and Ziehl–Nielson stains were negative for organisms.

Sections of pancreas revealed focal areas of fat necrosis and mild periacinar infiltration with polymorphonuclear leukocytes and eosinophils. There was no evidence of fibrosis in the microscopic sections. Sections of lung revealed occasional eosinophils in a peribronchial distribution. No alteration of bronchial mucosa or musculature typical of asthma was noted. The surgically removed kidney was severely hydronephrotic and had focal chronic pyelonephritis. The other kidney, at autopsy, was unremarkable; specifically, no evidence of arteritis was found in the kidneys or other tissues.

COMMENT

The distribution of eosinophils in this case is similar to that described by Ureles et al in his polyenteric type of eosinophilic gastroenteritis (4). It has been suggested that the layer of bowel primarily involved may determine the presenting symptoms (5). Eosinophilic infiltration of the muscularis, often with hypertrophy, may result in obstructive symptoms, while mucosal involvement may result in bleeding. In cases with serosal involvement, peritonitis is often manifested. Elevated gray or yellow plaques on the serosal surface noted by many authors usually prove to be subserosal collections of acute inflammatory cells with a large percentage of eosinophils (1, 6, 7).

Both sexes appear to be equally affected (8). The predominant age range is from the second to the sixth decade (5). The duration of symptoms ranges from only a few weeks to 32 years (9). The latter occurred in our case and represents the longest duration of symptoms reported in the literature. The symptoms, as described, were intermittent, unrelieved, and characterized by spontaneous remissions. The illness leading to hospital admissions, and at times surgical intervention, was usually a recurrence of severe unremitting symptoms.

The patient studied by us exhibited many of the findings associated with eosinophilic gas-

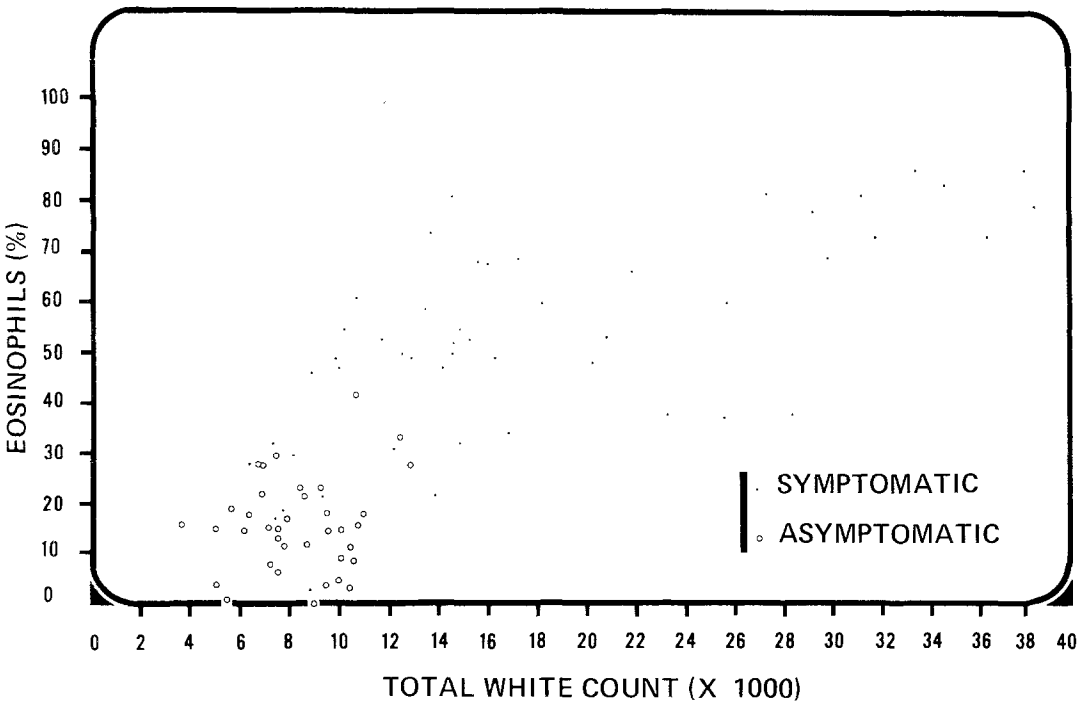

Fig 6. Relation of total white count and degree of eosinophilia to symptoms in Patient MD.

troenteritis, such as marked peripheral eosinophilia (3, 10), asthma (5, 11), delayed gastric emptying (12–15), intermittent abdominal pain, diarrhea, peritonitis, and ascites. As often occurs, the level of eosinophilia correlated with the presence and severity of symptoms (Figure 6). Periorbital edema and hiatal hernias have also been described, but their association with this disease entity is uncertain (13, 16). The fall in eosinophils postoperatively in 1966 was most certainly related to the stress of surgery which resulted in increased cortisol secretion and resulting eosinopenia. Although the patient was never treated with corticosteroids, this response to surgical stress would be expected to mimic such treatment. Other findings, however, such as hepatic granulomas, metaplastic bone formation, and pancreatitis were distinctly unusual and have not been previously reported.

The relative importance of pancreatic disease in our patient's recurring clinical findings is uncertain. It is possible that recurrent pancreatitis could have accounted for many of her signs and symptoms. Eosinophilia, pleural effusion, and ascites have been described in pancreatitis (17). However, serum amylases, when performed, were always normal during episodes of abdominal pain, and repeated laparotomies failed to reveal evidence of pancreatitis. The terminal pancreatitis is most likely related to either the recent surgical procedure or the renal insufficiency.

The cause of metaplastic bone formation in the liver is unknown. Since the bone formation is primarily along the inferior surface, it is most likely due to external irritation of the liver secondary to the recurrent bouts of peritonitis. It could also relate to trauma from previous sur-

gery. However, granulomas were noted at the periphery of the metaplastic bone as well as scattered diffusely through the liver. This spatial association of hepatic granulomas and hepatic ossification in a patient with eosinophilic gastroenteritis might suggest an interrelationship of these entities.

A report by Zuelzer and Apt (18) on visceral lesions associated with eosinophilia in children might aid in relating these findings. These authors describe 4 cases of severe eosinophilia in children in whom they felt they could demonstrate a transition from granulomas in the liver to areas of fibrosis and calcification. They felt the etiologic agent led to hepatic granuloma formation, which, if present for a long enough period of time, healed by fibrosis and calcification. It is well-known that pathologic ossification can occur in areas of chronic inflammation and calcification. It is quite possible that the findings in the liver in our patient represent the end stage of repeated insults of unknown nature, resulting in granuloma formation followed by fibrosis, calcification, and ossification.

The frequent occurrence of asthma and the recent suggestions of food allergy associated with causation of symptoms in these patients, as well as the association of eosinophils with allergic phenomenon, have led to the general acceptance of this disease entity having an allergic or immunologic basis. The exact nature of the inciting agents or antigens is unknown, as is the type of immunologic response. The presence of hepatic granulomas would lend further support to the immunologic etiology of this disease. Experimental work relating to granuloma formation and to the function of eosinophils, might suggest that antigen–antibody complexes were involved in the genesis of disease in our patient (19–21). It is quite possible that the eosinophils were present in the wall of the gastrointestinal tract as a result of the continuing reaction of antibody with an unknown antigen absorbed through the mucosa of the gut following ingestion. Presumably, some of these immune complexes could leave the wall of the gut and reach the abdominal lymph nodes or the liver, giving rise to granuloma formation followed by fibrosis, calcification, and ossification. Those patients in whom exacerbation of signs and symptoms of eosinophilic gastroenteritis followed ingestion of certain food would lend support to this theory (5, 11, 22–24). It is possible that our patient improved during hospitalization in part because of alteration of her diet.

However, extensive studies by Leinbach and Rubin of a young male with eosinophilic gastroenteritis failed to demonstrate any prolonged clinical or histologic improvement using different food elimination diets. They concluded that elimination diets were not therapeutically beneficial and that the disease was a self-perpetuating one responding only to steroids (25).

Recent publications by Basten and Beeson suggest that peripheral eosinophilia is more closely associated with the cellular immune response than with the humoral response (26–28). In addition, the work of Cohen and Ward would strongly support the concept that attraction of eosinophils is dependent on both these immune mechanisms (29, 30). In eosinophilic gastroenteritis, it is possible that both a cellular and a humoral immune response to an unknown antigen work in concert to produce the striking degree of eosinophilic reaction usually seen.

There are similarities between our case and cases originally described by Churg and Strauss as allergic granulomatosis (31). In both, chronic asthma and marked hypereosinophilia are a prominent part of the course. Microscopically, both have involvement of the gastrointestinal tract, with granulomatous and eosinophilic infiltration. Abell et al described a case of allergic granulomatosis in which granulomas were found in the liver as well as stomach (32). In our case, granulomas were found only in the liver and not in the wall of the intestine. An important difference in our case was the lack of arterial involvement. However, Churg and Strauss comment that in cases with prolonged

clinical course, the arterial lesions can be difficult to demonstrate.

In a case report of allergic granulomatosis by Sokolov and co-workers, both granulomas and numerous eosinophils were found in the wall of the colon and liver (33). A definite resemblance between cases of allergic granulomatosis and other diseases such as periarteritis nodosa, Wegener's granulomatosis, Loeffler's syndrome, rheumatic carditis, temporal arteritis, and hypersensitivity angitis was emphasized. A clever triangular relationship between these diseases was proposed in which some of these diseases have primarily arterial involvement, while others have progressively more eosinophilic and granulomatous involvement (33). If such an interrelationship of diseases is valid, it would seem reasonable to include eosinophilic gastroenteritis in the group with mainly tissue rather than vascular involvement. Perhaps our case, with granulomas in the liver, represents a transition between typical cases of eosinophilic gastroenteritis with exclusively an eosinophilic response, and allergic granulomatosis.

It should be borne in mind that the diagnosis is of more than scholarly interest, as treatment for eosinophilic gastroenteritis is established and should be conservative (5). The disease appears to be self-limited and is characterized by remissions and exacerbations (5). Perioral biopsy of the small intestine has been used with some success in obtaining tissue for diagnosis, but may well be unsatisfactory in view of the less frequent eosinophilia of the mucosa and lamina propria (4, 11, 34). If surgery is performed either to establish the diagnosis, or to relieve pyloric obstruction or bleeding, the most conservative procedure should be done. In cases in which biopsy alone was performed and the lesions left in situ, a satisfactory result was obtained (2, 6).

A response to adrenocortical steroids, as demonstrated by relief of symptoms, return of normal intestinal motility, and a decrease in the number of eosinophils in the peripheral blood, may be used as diagnostic criteria (2). Patients treated with steroids for the most part had prompt remission of symptoms (2–4, 35–37). Only the case reported by Harley failed to respond to steroids (38). If eosinophilic gastroenteritis is strongly suspected, steroid therapy is the treatment of choice (2).

SUMMARY

This case represents the longest documented course of eosinophilic gastroenteritis reported in the literature. It is proposed that a recurrent immunologic challenge was occurring, which led to fluctuating bouts of hypereosinophilia, asthma, eosinophilic infiltration of the gut, and granuloma formation in the liver. As demonstrated in liver and abdominal lymph nodes, the hypersensitivity reaction of many years' duration progressed through various stages of granuloma formation, calcification, and bone formation. Conservative treatment, including steroids, is definitely the therapy of choice for this disease entity.

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