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Gastric Xanthomatosis and Cholestasis
A Causal Relationship

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We report two cases of gastric xanthomatosis which developed in patients with marked cholestasis. In both cases, one with acute and one with chronic cholestasis, the gastric xanthomas disappeared with resolution of the cholestasis. A review of the literature is also provided.

Xanthomatosis is characterized by collections of lipid-laden macrophages, or foam cells, forming plaques or nodules in many tissues, most commonly the skin (1–3). Involvement can occur in all regions of the gastrointestinal tract, but is most common in the stomach (2). Once thought to be a rare entity, gastric xanthomatosis has been reported with increasing frequency with the advent of increasing utilization of gastrointestinal endoscopy (2, 4–8). Because gastric xanthomas appear to be more common in patients with gastritis, gastric ulcer, and with duodenogastric reflux after gastric surgery, mucosal damage has been presumed to play a major role in their pathogenesis (2, 4, 6). Although cholesterol and neutral fat are the major constituents of the foam cells, there is no documented relationship between degree of hyperlipidemia or hypercholesterolemia and presence of gastric xanthomatosis. We report two patients with marked xanthomatous infiltration of the stomach which developed concomitant with cholestasis and hypercholesterolemia and disappeared with resolution of the hyperlipidemia.

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MATERIALS AND METHODS

Case 1. C.S., a 36-year-old white female, was in good health until September 1972 when, at the age of 22, she developed intense pruritis and fatigue two weeks after starting oral contraceptives. At that time, her serum bilirubin was 2.0 mg/100 ml, SGOT 150 IU/liter, SGPT 120 IU/liter, and alkaline phosphatase 680 IU/liter. After eight months of dietary treatment for "hepatitis," the patient was hospitalized for severe right upper quadrant pain. Her serum bilirubin was 4.6 mg/100 ml and an alkaline phosphatase was 600 IU/liter. Exploratory laparotomy demonstrated a normal gallbladder and biliary tree. Wedge liver biopsy revealed cirrhosis with a paucity of bile ducts. In several portal areas, nonsuppurative destructive cholangitis with granulomas was also present. A cholecystectomy was performed, and the patient was discharged on prednisone 20 mg on alternate days.

She was seen for the first time at the University of Michigan Medical Center in November 1976 with chief complaints of fatigue, numbness in the hands, and facial nodules. She had scleral icterus, extensive eruptive xanthomas, and hepatosplenomegaly. Her serum bilirubin was 8.2 mg/100 ml and alkaline phosphatase was 1745 IU/liter. Antimitochondrial antibodies were present at a titer of 1:320, serum cholesterol was 2796 mg/100 ml, and triglycerides were 250 mg/100 ml. Endoscopic retrograde cholangiography showed minor intrahepatic bile duct beading and extensive yellowish nodular and plaque-like lesions of the gastric mucosa (Figure 1). Biopsy from the gastric mucosa revealed normal fundic epithelium and marked infiltration of the lamina propria with foam cells (Figure 2). A diagnosis of primary biliary cirrhosis with gastric xanthomatosis was made. Prednisone was discon-

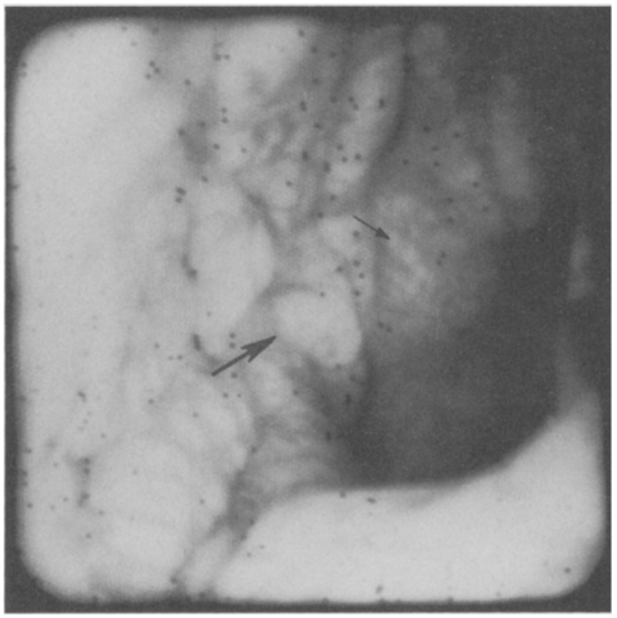

Fig 1. Massive lipid infiltration involving body and antrum of stomach in case 1. Both nodules (small arrow) and plaques (large arrow) are visible endoscopically.

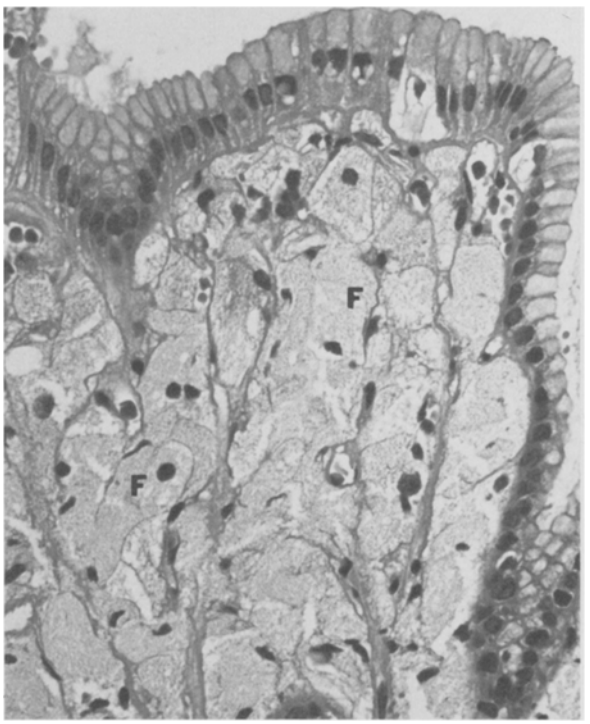

Fig 2. Light microscopic photomicrograph of case 1 showing normal surface epithelium and marked infiltration of lamina propria by foamy macrophages (F). The macrophages were not stained by the PAS reaction. H&E stain, ×250.

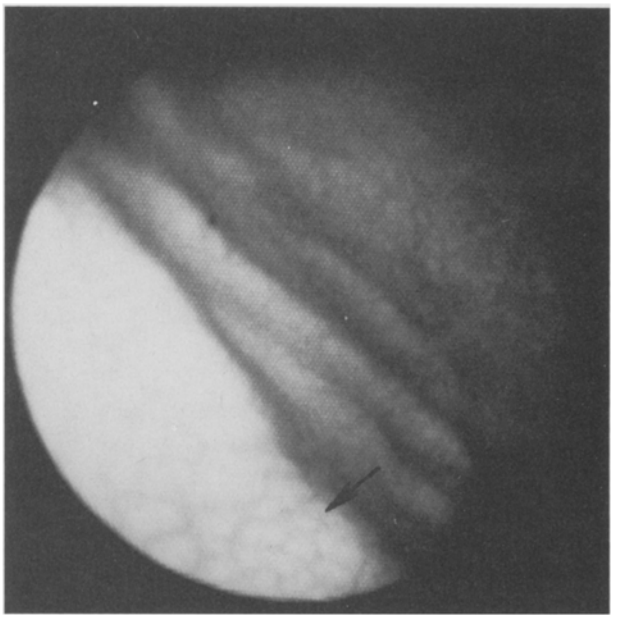

Fig 3. Endoscopic picture of plaquelike xanthomas (arrow) involving greater curve of stomach during acute cholestasis in case 2.

tinued and plasmapheresis was begun for xanthomatous neuropathy.

Despite improvement in her peripheral neuropathy, the patient was lost to follow-up until she presented with massive upper gastrointestinal bleeding in January 1984. her bilirubin was 22 mg/100 ml and alkaline phosphatase was 900 IU/liter. Serum cholesterol was 90 mg/100 ml, and triglycerides were 25 mg/100 ml. Upper gastrointestinal endoscopy revealed bleeding esophageal varices, but no gastric xanthomas. The patient died two days after admission.

Case 2. S.E., a 21-year-old white female was well until November 1984 when she developed tonic clonic seizures. Diphenylhydantoin 100 mg three times a day was instituted after a negative neurological evaluation. Two weeks after beginning diphenylhydantoin, she developed a morbilliform rash and a temperature of 105° F. Her admission serum bilirubin was 1.0 mg/100 ml, alkaline phosphatase 310 IU/liter, and SGOT 685 IU/liter. Hepatitis serologies and antimitochondrial antibodies were negative. A presumptive diagnosis of diphenylhydantoin hepatotoxicity was made, and the drug was discontinued. Two weeks after admission, she improved sufficiently to be discharged.

After discharge, cholestasis persisted and she developed eruptive xanthomas of the fingers and palms. Serum cholesterol was 1610 mg/100 ml and triglycerides were 60 mg/100 ml. Intractable pruritus and vomiting prompted a second hospital admission. Serum bilirubin was 7.3 mg/100 ml, SGOT 145 IU/liter, and alkaline phosphatase 2595 IU/liter. Ultrasound examination demonstrated a normal gallbladder and common bile duct size. Liver biopsy showed marked neocholangiolar proliferation. Esophagogastroduodenoscopy demonstrated yellow plaques

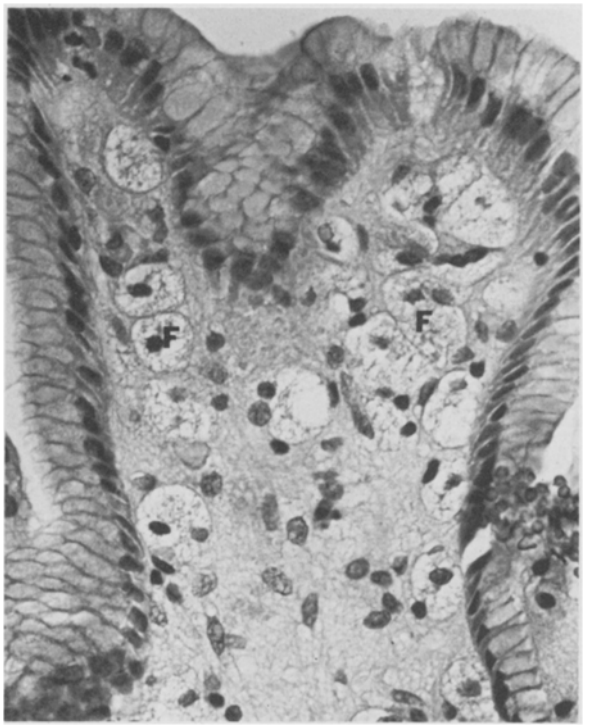

Fig 4. Light microscopic photomicrograph of case 2 showing normal surface epithelium and modest infiltration of lamina propria with foamy macrophages (F). H&E stain, ×250.

and nodules from the midbody of the stomach to the pylorus (Figure 3). Several nodules were seen in the duodenum. Biopsy specimens revealed the presence of foamy histiocytes in both the stomach (Figure 4) and duodenum.

Over the next five months, her laboratory values normalized. Repeat endoscopy and biopsy specimens were normal (Figures 5 and 6).

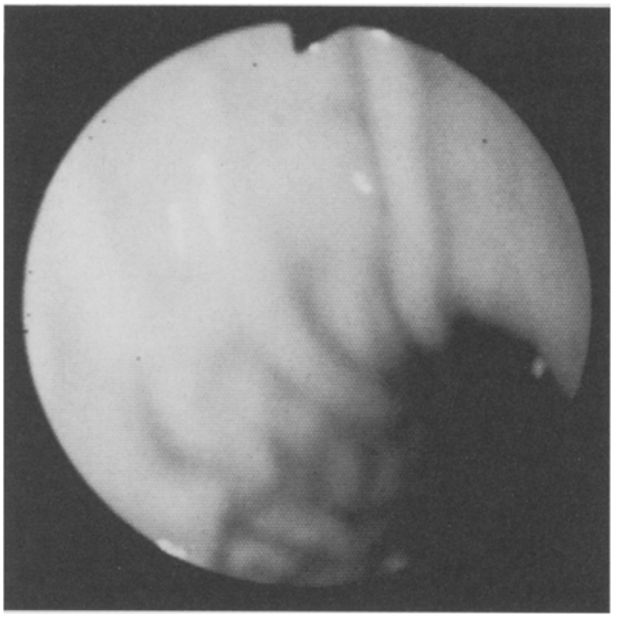

Fig 5. Endoscopic picture demonstrating a normal mucosa along the greater curve of the stomach after resolution of cholestasis in case 2.

DISCUSSION

Endoscopically, gastric xanthomas are yellow plaque-like or nodular lesions of variable size (1–6). They are found in the highest concentration in the prepyloric region along the lesser curvature, although they may be found anywhere in the stomach. The reported incidence of gastric xanthomas in autopsy series varies from 2% to 53% (1, 3). Endoscopic studies show their incidence to be between 1% and 4%. Histologically, gastric xanthomas are characterized by infiltration of the lamina propria by lipid-laden macrophages, often called foam cells. Other lamina propria cells may also be involved with lipid deposits. Chemical analysis has shown that the foam cells contain cholesterol with or without neutral fat (4). No association with hyperlipidemia or hypercholesterolemia has been reported to date (1).

The cause of gastric xanthomas is unknown. The importance of damage to the gastric mucosa is pointed out by the fact that xanthomata largely appear in damaged gastric mucosa (1–6). The association of xanthomas with gastric ulcers and gastritis has occasionally led to difficulties in differentiating this lesion on biopsy from infiltrative signet-cell carcinoma of the stomach. It has been postulated that chronic inflammation may cause focal mucosal damage. Repair of this damage leaves behind lipid-containing debris, which is eventually phagocytized by histiocytes forming foam cells (6).

Domellof et al (6) found a high incidence of gastric xanthomas in patients who had subtotal gastrectomy for treatment of benign gastric ulcers. Gastric xanthomas were found in 6.3% of nonoperated controls and in 6.2% of patients one to three years after surgery. This incidence increased steadily to 60% twenty-three years after gastric surgery. No relation to patient age, lipid levels, or serum cholesterol was found. The stomal location of these lesions led Domellof et al to hypothesize that intestinal reflux with subsequent intestinal metaplasia promoted their production. Intestinalized gastric epithelium in the rat has been shown experimentally to transport lipid, lending support to

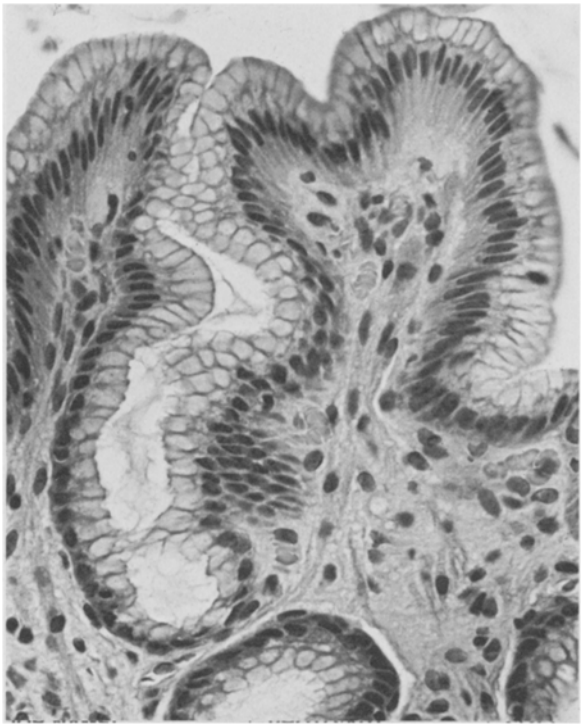

Fig 6. Light microscopic photomicrograph of case 2 showing normal surface epithelium and lamina propria in gastric mucosa following resolution of the cholestasis. H&E stain, ×250.

this concept (9). Domellof et al (6) considered these lipid islands to be permanent alterations in the gastric mucosa, because they did not change in size, location, or appearance during long intervals of observation. The importance of differentiating this lesion from gastric carcinoma was emphasized because of the reported increased incidence of stomal cancers after gastric resection (10).

While hyperlipidemia and cutaneous xanthomas are found in patients with cholestasis, a relationship between gastric xanthomas and cholestasis has not been previously described. Kimura et al (4) examined the association of gastric xanthomas and selected disease states in 186 patients. The prevalence of gastric xanthomas was 28% in patients with bile duct obstruction and 58% in those without obstruction. There was no correlation between serum levels of cholesterol or lipids and presence of gastric xanthomas, and there was no significant difference in the prevalence of gastric xanthomas in patients with or without cholestasis. The close relationship of gastric xanthomas to cholestasis in our cases is strong evidence for a cause-and-effect relationship. In the first case, gastric xanthomas disappeared with progressive hepatic failure, while in the second case, appearance and disappearance were closely correlated with the course of diphenylhydantoin-induced hepatotoxicity. In both cases, disappearance of xanthomas was associated with normalization of serum cholesterol and lipid levels.

We believe that these two patients represent the first reported cases of cholestasis associated gastric xanthomas. The course in these patients points to the fact that these lipid islands may be temporary mucosal changes, possibly related to elevated serum cholesterol and lipid levels, and may disappear with resolution of cholestasis.

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