

Multiple Gastric Xanthomas in a 3-Year-Old Patient

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Mucosal lesions of unclear significance are occasionally seen during endoscopy. Gastric xanthomas can develop as solitary or multiple yellowish-white small nodules or plaques in the gastric mucosa. First described by German pathologists, gastric xanthomas consist of fat accumulations in foamy histiocytes in the lamina propria. Due to their benign nature, gastric xanthomas have not been reported frequently in the literature. Hypercholesterolemia, atrophic gastritis, and *Helicobacter pylori* infection have all been proposed as possible etiologies of gastric xanthomas. Furthermore, gastric xanthoma lesions may mimic gastric malignancies in their appearance.

All cases of gastric xanthomas that have been previously reported in the literature have involved adult patients. We report the occurrence of gastric xanthomas in the youngest patient to date (to our knowledge) with no identifiable etiology.

Case Report

A 3-year-old boy presented with chronic abdominal pain of 1 year's duration. The pain was intermittent, with no particular pattern, and was not related to meals or ingestion of specific foods. There were no associated gastrointestinal symptoms. Both the patient's weight and height were at the 50th percentiles for his age. His family history was deemed to be a noncontributory factor of his pain. His physical examination, including an abdominal examination, was normal. Initial laboratory work-up included normal findings for a complete blood

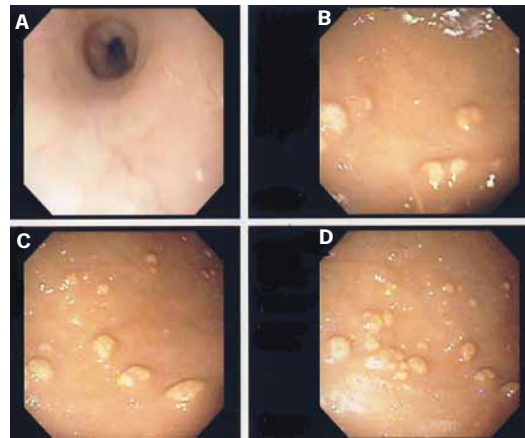


Figure 1. Normal endoscopic view of the esophagus (A). Multiple xanthomas seen by endoscopy involving gastric mucosa (B-D).

count, sedimentation rate, and metabolic panel. An esophageogastroduodenoscopy with biopsies revealed multiple (more than 10) whitish-yellowish nodules (1–2 cm) in the antrum (Figure 1). Histologic sections of the stomach showed antral mucosa with marked foveolar hyperplasia, regenerative epithelial changes, and a lamina propria that was expanded by a population of bland cells with small eccentric nuclei and abundant clear-to-finely-vacuolated cytoplasm (Figure 2). The differential diagnosis included a mucinous/signet cell-type epithelial neoplasm, granular cell tumor, atypical mycobacteria infection, and gastric xanthoma. Special stains, including dPAS (Figure 3) and immunohistochemical pancytokeratin (Figure 4), helped to rule out other entities and supported a diagnosis of gastric xanthoma. Subsequently, a lipid panel was checked and reported normal findings.

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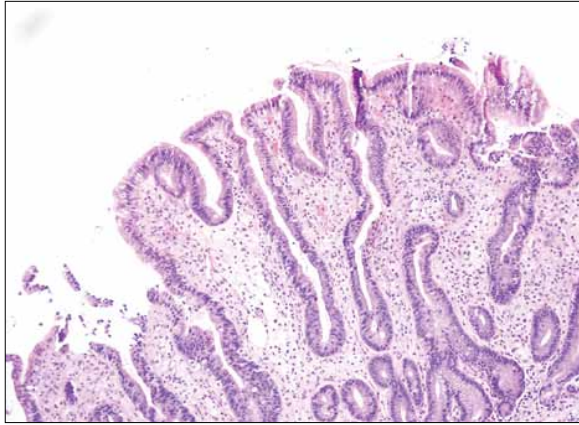


Figure 2. Hyperplastic and reactive foveolar epithelium overlies the lamina propria, which is expanded by an infiltrate of foamy macrophages (hematoxylin and eosin stain).

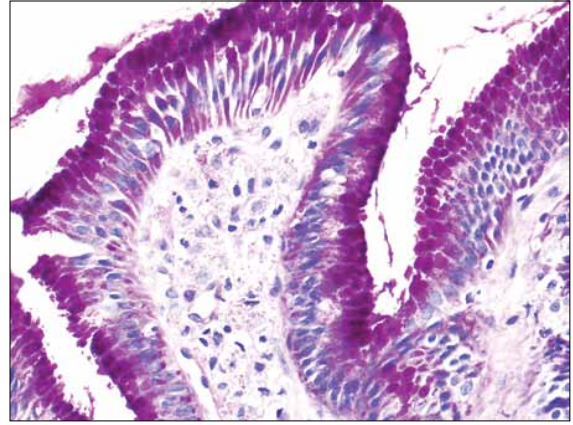


Figure 3. The lamina propria is expanded by histiocytes showing clear cytoplasm with faint periodic acid Schiff stain-positive granules. This finding is consistent with the presence of foamy macrophages in a gastric xanthoma.

The patient was diagnosed with idiopathic functional abdominal pain and given levsin 0.125 mg orally every 6 hours, as needed. Over the subsequent 3 months, this medication was used to achieve complete resolution of the patient's pain. An esophageogastroduodenoscopy was then repeated and found no interim change in endoscopic or histologic findings.

Discussion

The incidence of gastric xanthomas was reported to be 0.018% in a European series of 21,000 patients.¹ In a Japanese study of 131 elderly patients (42 men and 89 women), gastric xanthomas were observed in 17 men (40.5%) and 23 women (25.8%). The frequency of gastric xanthomas tended to increase with age and was highest in patients in their 70s (40.0%). Among xanthoma cases, 42.5% had solitary lesions and 17.5% had more than 5 lesions. More than 70% of the lesions were seen in the antral and pyloric regions. On biopsy, atrophic changes were reported in 89% of the patients. This finding suggested the presence of a mucosal aging process in the form of a disturbance of the local lipid metabolism, as well as the possibility that gastric xanthomas may be a marker of the pathologic aging changes of the gastric mucosa.²

In a Chinese series of 3,870 patients, 30 patients (0.8%) were found to have gastric xanthomas. A moderate predominance of men over women (3.3:1) was again noted. The frequency of gastric xanthomas peaked in patients 40–60 years of age (53.3%). Most patients had small (2–3 mm), single lesions, 67.8% of which were

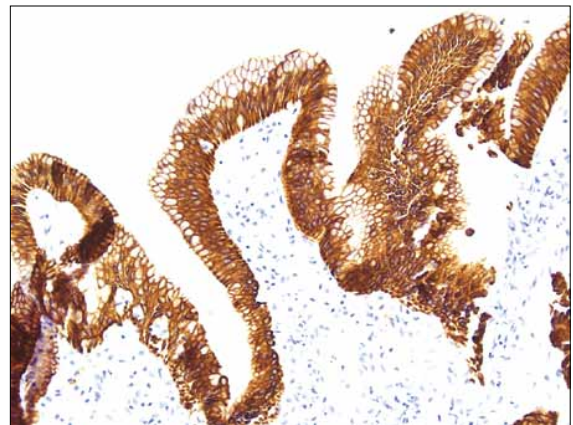


Figure 4. Lamina propria cells with clear cytoplasm fail to react to a cytokeratin immunohistochemical stain, supporting the theory of a nonepithelial origin of the clear xanthoma cells.

found in the antrum. Chronic gastritis was reported in the surrounding tissue of 30 patients.³ No explanation was offered as to the reason for the very high incidence in this study.

Muraoka and associates⁴ reported xanthoma cell proliferation in an early gastric carcinoma diagnosed incidentally during the biopsy of a small gastric polyp.

On rare occasions, gastric xanthomas can mimic carcinoids of the clear cell variety.⁵ Gastric xanthomas can also be confused with signet-cell gastric carcinoma.⁶ Although Masson trichrome stain and immunohisto-

chemical stains using antibodies against macrophages and cytokeratins have been shown to be useful in distinguishing gastric xanthomas from adenocarcinoma,⁶ the absence of nuclear atypia and unique characteristics of foam cells will ensure the correct diagnosis.

A possible association between hypercholesterolemia and gastric xanthomas has been proposed.⁷⁻⁹ The absorption of oxidized low-density lipoprotein by macrophages in xanthomas suggests that oxidized low-density lipoprotein may have a role in the development and persistence of these lesions.

H. pylori infection has also been proposed as an etiology of gastric xanthomas.¹⁰ Isomoto and coworkers studied 67 patients with gastric xanthomas for *H. pylori* infection and compared them to 67 age- and sex-matched control subjects. The prevalence of *H. pylori* infection was significantly higher in patients with gastric xanthomas compared to control patients (94% vs 72%). *H. pylori* antigens were frequently identified in the cytoplasm of xanthoma cells in *H. pylori*-positive specimens of gastric xanthomas (54/63 specimens; 86%). No immunoreactivity for *H. pylori* antigens was detected in gastric xanthoma-negative specimens. It has been proposed that a proportion of gastric xanthomas may be provoked by *H. pylori* infection.^{10,11}

Two cases of gastric xanthomas have been reported in the literature in severe cholestasis.¹² In both cases (1 with acute cholestasis and 1 with chronic cholestasis), gastric xanthomas disappeared with the resolution of the cholestasis.

In our patient, we could not identify any of the abovementioned etiologies, as no hypercholesterolemia, *H. pylori* infection, malignancy, or gastritis was observed. The symptoms resolved despite the persistence of the lesions, which indicates the absence of a causal relationship between abdominal pain and gastric xanthomas. Our patient is the youngest reported to date with gastric xanthomas, to our knowledge. Furthermore, we identified a multiple-lesions pattern in the patient, which has previously been reported to be less common than a single-lesion pattern.^{2,3}

Conclusion

The clinical significance of gastric xanthomas remains unknown. Given the rare occurrence of neoplasias that may have a similar appearance, performing biopsies for histopathology and searching for the presence of *H. pylori* infection appears to be reasonable. Basic metabolic analysis to assess for hyperlipidemia or cholestasis should be considered. Gastric xanthomas can be seen in children as well as in older patients.

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Review

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Gastric xanthomas are uncommon endoscopic lesions that may cause diagnostic confusion in patients at risk for neoplasia. Although population studies have shown an incidence of 0.018% for gastric xanthomas,¹ endoscopic studies have reported an incidence of 2–9%.^{2,3} Peak incidence of these lesions increases with age (up to 40%). In addition, gastric xanthomas are more frequently found in patients with both active and healed gastric ulcers and in patients who have undergone gastric resection.

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Gastric xanthomas are usually solitary lesions in the gastric antrum or prepyloric areas. Findings may include multiple lesions (in 24% of cases) and plaques. Although involvement in all areas of the gastrointestinal tract have been reported, involvement in the stomach predominates. Size is variable (up to 3 cm), but most gastric xanthomas are less than 1 cm. Histologically, gastric xanthomas are characterized by lipid-laden macrophages, often called foam cells, that infiltrate the lamina propria. Foam cells contain cholesterol with or without neutral fat.^{4,5}

Identification of the cause of gastric xanthomas has been controversial. Gastric damage is a common association, with a high incidence in ulcer and surgical patients.⁶ The repair of the damage produced by chronic inflammation leaves behind lipid-laden debris, which is phagocytized by histocytes and forms foam cells. Gastric xanthomas were found in 6.3% of nonoperated, age-matched control patients and 6.2% of patients 1–3 years after gastric surgery. Twenty-three years after gastric surgery, the incidence of gastric xanthomas increased to 60%. Cholesterol levels, lipid levels, and the patient's age were unrelated. Intestinal metaplasia with bile reflux has been shown to increase cellular lipid transport. Permanent cellular change was hypothesized and supported by the fact that the lesions did not change in appearance over time. Increased frequency in the elderly (up to 40%), increased gastric atrophy, and decreased pepsinogen production are consistent with this theory.

Helicobacter pylori infection is closely associated with gastric atrophy. Age- and gender-matched patients with and without gastric xanthomas showed a higher incidence of *H. pylori* infection in patients with gastric xanthomas (94% vs 72%). Extensive gastric atrophy was also more common both endoscopically and histologically in xanthoma patients. The serum pepsinogen I and pepsinogen II/pepsinogen I ratio were lower in patients with gastric xanthomas, which is a finding that is consistent with proximal gastric atrophy. *H. pylori* antigens were also found in most gastric xanthoma foam cells (86%), whereas immunoreactivity was not found for *H. pylori* antigens in *H. pylori*-negative specimens of gastric xanthomas.⁷

Lipid levels have had an unclear role in gastric xanthomas.⁸ Two cases of profound gastric xanthomatosis have been reported in patients with profound cholestasis. Resolution of the gastric xanthomas occurred with the resolution of cholestasis and the return of normal cholesterol and triglyceride levels. This finding supports the idea that not all xanthomas are permanent.⁹

As both gastric ulceration and gastric resection carry an increased risk for gastric cancer, signet-cell gastric adenocarcinoma is in the differential diagnosis of gastric xanthomas. Standard histology of xanthomas usually shows regular nuclear cells centrally located in the foam cells, though atypical cells can be seen in cytology preparations. Masson trichrome staining can be positive in both entities. Periodic acid Schiff staining is uniformly negative in gastric xanthomas and strongly positive in gastric signet-cell adenocarcinoma.¹⁰

Halabi and associates reported the case of a 3-year-old boy with chronic abdominal pain who underwent upper gastrointestinal endoscopy, which revealed multiple xanthomas. Clinical concern for malignancy made the differential diagnosis difficult. Periodic acid Schiff staining and pancytokeratin staining confirmed the diagnosis of gastric xanthoma, though no potential cause for the xanthomas was seen (ie, no inflammation, *H. pylori* infection, gastric atrophy, or cholestasis). The abdominal pain resolved, though the gastric xanthoma persisted in short-term follow-up. Long-term re-evaluation was not available. This case, which involved multiple lesions, was the first pediatric case reported in the literature, according to the authors.¹¹

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