

RAPID COMMUNICATION

Dyslipidemia and *H pylori* in gastric xanthomatosis

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Abstract

AIM: To investigate the relationship among gastric xanthomatosis (GX), *H pylori*, dyslipidemia, and gastritis in Korea, a well-known *H pylori* endemic area.

METHODS: A total of 771 patients who had undergone gastroduodenoscopy by one endoscopist were included in this study. Among them, 54 patients with GX were assessed for *H pylori* infection and their endoscopic characteristics and serum lipid profiles. The findings were compared with 54 age- and sex-matched control subjects without GX.

RESULTS: The prevalence of GX was 7% (54/771) with no sex difference. GX was mainly single (64.8%) and located in the antrum (53.7%). The mean diameter was 7 ± 3 mm. Mean body mass index (BMI) of patients with GX was 23.1 ± 2.8 and no one was above 30. Compared with the controls, lipid profiles of GX group showed significantly lower HDL-cholesterol (48.8 ± 12.3 vs 62.9 ± 40.5 , $P = 0.028$) and higher LDL-cholesterol (112.9 ± 29.9 vs 95.9 ± 22.4 , $P = 0.032$). The level of total serum cholesterol, triglyceride and the existence of dyslipoproteinemia were not related to the presence of GX. However, GX showed a close relationship with endoscopically determined atrophic gastritis and histologic severity (24/53, 44.4% vs 8/54, 14.8%, $P = 0.0082$). *H pylori* infection and bile reflux gastritis were not significantly related with GX.

CONCLUSION: The prevalence of GX is 7% and it may be an increasing entity in Korea. Moreover, dyslipidemia and atrophic gastritis are found to be related to GX, but *H pylori* infection is not.

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Key words: Xanthomatosis; Dyslipidemia; *H pylori*; Gastritis

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INTRODUCTION

Xanthomatosis is a yellow tumor-like lesion of the skin or deeper structure characterized by the presence of lipid-containing histiocytes. Its presence may be a manifestation of a metabolic disturbance, such as hyperlipidemia, although it usually represents an isolated phenomenon. Many clinicians believe that yellowish plaque in the gastric mucosa is a benign lesion, and it has no clinical significance. Feyrter^[1] reported the first recorded observation of a small yellow macule in the gastric mucosa representing a fatty deposit. Since gastric xanthomatosis (GX) was first named in 1929 by Lubarsch and Borchardt^[2] as a gastric lipid island, a variety of possible causes, such as an abnormality of the lipid metabolism or inflammatory changes in the gastric mucosa, have been suggested^[3-5]. However, the detailed developmental mechanism remains unknown.

H pylori is the most important etiologic factor of peptic ulcer disease and chronic active gastritis. Chronic gastritis is thought to be involved in the gastric glandular atrophy and intestinal metaplasia sequence, which is considered a precursor of gastric cancer. Recently, Hori and Tsutsumi^[6] found *H pylori* infection on the surface of foveolar cells in 48% of biopsy samples of GX. Isomoto *et al*^[7] also reported a close relationship among *H pylori* infection, GX, and atrophic gastritis, and GX may be provoked by *H pylori* infection.

Since GX has received little attention in the Korean literatures, we undertook this study to evaluate the prevalence and the clinical significance of GX endoscopically, and to investigate the relationship among GX, *H pylori* infection and dyslipidemia.

MATERIALS AND METHODS

Patients

From August 2003 to March 2004, a total of 771 patients (398 males and 373 females) who had undergone gastroduodenoscopy by one endoscopist were included in this study. Subjects' age ranged from 17 to 88 (mean 60) years. Of these 771 patients, 54 cases (27 men and 27 women; mean age 54 and range 33-77 years) had GX. Of these 54 patients, chronic gastritis was diagnosed in 41, gastric ulcer in 4, duodenal ulcer in 4, gastric polyp in 3, gastroesophageal reflux disease (GERD) in 3, Mallory-Weiss syndrome in 1, gastric cancer in 1, congestive gastropathy in 1, and normal gastric mucosa in 2. Among them, 6 cases were

Table 1 Serum lipid profiles of gastric xanthomatosis and age- and sex-matched controls (mean \pm SD)

	GX (n = 54)	Control (n = 54)	P
Total cholesterol (mg/dL)	188.7 \pm 32.8	189.2 \pm 30.9	NS
LDL-cholesterol (mg/dL)	112.9 \pm 29.9	95.9 \pm 22.4	0.032
HDL-cholesterol (mg/dL)	48.8 \pm 12.3	62.9 \pm 40.5	0.028
TG	125.9 \pm 71.0	119 \pm 67.8	NS

NS: Not significant. TG: Triglyceride; HDL: High-density lipoprotein; LDL: low-density lipoprotein.

combined with chronic gastritis; those were gastric polyp in 2, gastric ulcer in 2, duodenal ulcer in 1 and GERD in 1.

There were no systemic signs of xanthomatosis in GX patients. Fifty-four age- and sex-matched individuals without GX served as controls. During endoscopy, six biopsy specimens had been obtained, two from GXs, two from the antrum, and two from corpus specimens. The two biopsy specimens were available from the area of the xanthomatosis and these were stained with hematoxylin and eosin (HE) for histologic examination. The one antrum and one corpus samples were used for the rapid urease test (CLO test, double chamber: Chongkeundang Co., Seoul, Korea), and stained with HE for evaluation of the activity of gastritis and *H. pylori* positivity. Anti-*H. pylori* IgG antibody was measured by enzyme-linked immunosorbent assay (ELISA) with a commercial kit (Hel-p test, Amrad Co, Melbourne, Australia) before endoscopy. Patients were classified as *H. pylori*-positive if at least two of above tests were positive or as *H. pylori*-negative if all tests were negative.

Endoscopic assessment

GX, a white-yellow nodule measuring less than 10 mm, was observed on the wall of stomach. Enterogastric or bile reflux gastritis was defined as the presence of bile-stained mucosa and a collection of bile juice on endoscopic examination.

Histologic evaluation

The histologic appearance of lipid islands was that the lamina propria was occupied by large ovoid to polygonal histiocytes having an abundant, finely vacuolated (foamy) cytoplasm staining lightly with eosin. The foam cell nuclei were regular, round to ovoid, and occupied a small portion of the cell area. No mitoses were observed. To confirm that foamy cells were present in the GX and derived from macrophages, immunohistochemical study was performed. The foamy cells were positive for the human macrophage marker (HAM-56, DAKO, Carpinteria, CA) and negative for cytokeratins (AE 1/3, Biogenex, San Roman, CA), supporting the diagnosis of xanthomatosis.

Histologic examination of the other biopsy specimens of the mucosa taken at a distance from lipid islands was also done. Biopsy specimens stained with HE and Giemsa were used to detect *H. pylori*. The histologic degree of activity (neutrophil infiltration), inflammation (mononuclear cell infiltration), glandular atrophy, and intestinal metaplasia were classified as none, mild, moderate, and severe in accordance with the updated Sydney System^[8]. Atrophy of

the gastric mucosa is defined as loss of glandular tissue. The observer should attempt to evaluate one feature at the time using a new visual analogue scale that was provided to assist in grading^[9]. Two independent observers evaluated the histologic examination without prior knowledge of the diagnosis or experimental results.

Statistical analysis

Statistical analysis was performed using the Chi-square test, Student's *t* test, and Mann-Whitney *U* test, when appropriate. A *P* value less than 0.05 was considered statistically significant. Data were expressed as mean \pm SD. SPSS 11.0 version software was used to analyze the data.

RESULTS

In this present study, the prevalence of GX was 7% (54/771). Of these 54 GX patients, 27 were men and 27 women, with mean age of 54 (range 33-77) years.

Endoscopic characteristics of GX

The mean number of GX was 1.7 ± 1.1 , and 64.8% (35/54) of cases had a single xanthoma. GX was located at the antrum in 53.7% (29/54), at the body in 35.2% (19/54), and at the fundus in 11.1% (6/54) of cases. The mean size of GX was 7 ± 3 mm, and none of the GX exceeded 10 mm in diameter.

Clinical characteristics of patients with GX

Distribution of BMI: The mean BMI of the GX group was 23.1 ± 2.8 (range, 18.0-28.2), with none over 30, which was similar to the control group (mean 24.1 ± 2.4 , range, 18.5-29.7). No correlation was found between abnormal BMI and the presence of GX.

Lipid profiles: Results of lipid profiles are shown in Table 1. When a normal HDL-cholesterol level of 30 mg/dL was selected as the lower cut-off value, 11 (20.4%) GX cases had HDL-cholesterol level lower than the cut-off value. Hypertriglyceridemia was found in 11 GX patients. However, no difference was found in the serum total cholesterol and triglyceride levels between the GX and control groups. In contrast, GX patients had lower mean HDL-cholesterol and higher mean LDL-cholesterol levels than the controls (*P* = 0.032 and *P* = 0.028, respectively).

Lipoprotein electrophoresis analysis was performed in 32 GX patients. Abnormal patterns were exhibited by only 2 (6.3%) patients, and both of them were dyslipoproteinemia type IV. No correlation was observed between the presence of dyslipoproteinemia and GX.

Underlying diseases: The underlying diseases were diabetes mellitus in 3 (5.5%), essential hypertension in 7 (12.9%), fatty liver in 3 (5.5%), chronic liver disease in 2 (3.7%), and malignancies in 6 (11.1%) GX patients. GX was not significantly correlated with any special underlying diseases.

Endoscopic findings and histologic severity

Table 2 shows the endoscopic findings of the GX patients

Table 2 Comparison of endoscopic distribution of atrophic gastritis in GX patients and controls

	Predominant distribution		
	Antrum	Corpus	Pangastritis
GX patients (24/54, 44.4%) ^b			
Mild (n = 10)	2	1	7
Moderate (n = 8)	3	0	5
Severe (n = 6)	2	0	4
Control (8/54, 14.8%)			
Mild (n = 6)	3	1	2
Moderate (n = 1)	1	0	0
Severe (n = 1)	1	0	0

The distribution and severity of atrophic change in GX patients significantly differed from that in controls (^b $P = 0.0082$).

and controls. The endoscopic distribution and severity of atrophic gastritis were determined in 24 of 54 (44.4%) GX patients as follows: mild form in 10, moderate in 8, and severe in 6. The distribution and severity of atrophic change were significantly higher in GX patients as compared with the controls in terms of both the antral distribution and the pangastritis ($P = 0.048$ and $P = 0.0082$, respectively).

Enterogastric reflux gastritis was noted in only 2 of 54 (3.7%) GX patients without other mucosal injury and in 1 of 54 (1.9%) controls. There was no significant relationship between GX and the presence of enterogastric reflux.

Prevalence of *H pylori* in GX

The positive rate of *H pylori* infection in GX patients (63%, 34/54) was similar to that of the controls (69.2%).

DISCUSSION

Gastric xanthomatosis, once considered a rare lesion, is being reported more frequently. Many reports^[1,3-5,10-12] about GX have shown its frequency of 0.018%-0.8%. Of 7816 patients who had undergone gastroduodenoscopy from January 2001 to August 2002, GX was detected in 76 (0.97%) patients, which is similar to the findings of previous studies^[11,12]. In the present study, the prevalence was found to be 7%, which is very much higher than that reported in Western countries^[12]. This finding indicates that GX is a relatively common disease entity as an increasing trend in Korea, although its etiology remains unclear. This may be associated with an increased awareness and selection bias of endoscopists; however, a large-scaled prospective study is needed in the future. In a Chinese series of 3870 patients, a moderate predominance of male over female (male:female = 3.3:1) was reported^[11], but GX showed no sex predilection in the present study.

Xanthogranulomatous gastritis is characterized by an inflammation of the gastric wall by foamy histiocytes, inflammatory cells, multinucleated giant cells, and fibrosis. The occurrence of this nodular growth in the gastric mucosa is manifested by the presence of lipid-laden macrophages containing cholesterol and natural fats in the lamina propria. The relationship between serum lipid and gastric mucosal injury due to bile reflux has been more clearly defined. After subtotal gastrectomy (Billroth II operation), GX occurred in 6.3% at 1 to 3 years after surgery,

in 35.7% at up to 15 years, and in 43.9% after 20 years^[12,13]. Isomoto *et al*^[7] reported a close relationship between atrophic gastritis or bile reflux gastritis and GX endoscopically. Several studies have shown that xanthoma is associated with gastritis, carcinoma, intestinal metaplasia of the gastric epithelium, or peptic ulcer diseases^[5,14,15]. In the present study, a close relationship was found between atrophic gastritis and GX but there was no correlation between GX and enterogastric reflux.

Endoscopically, a single GX was detected in a majority (64.8%) of GX patients, all GX were less than 10 mm in size, and most of the lesions (88.9%) were located at the antrum and body, which is in agreement with a previous study^[16]. The clinical significance of GX remains unknown and the presence of GX *per se* is probably of little clinical significance. Basic metabolic analysis to assess for hyperlipidemia or hypercholesterolemia should also be considered. Etiologically, these conditions may be associated with a primary dyslipoproteinemic state, such as diabetes, nephrosis, obesity or cholestasis. Chang *et al*^[17] reported lower mean HDL-cholesterol and higher mean triglyceride levels in GX subjects in comparison with the controls. In the present study, abnormal BMI (≥ 30) was not correlated with the presence of GX, while the lower mean HDL-cholesterol and higher mean LDL-cholesterol levels in GX subjects than controls seems statistically interesting ($P = 0.028$ and $P = 0.032$, respectively). Elevated triglyceride levels among GX patients have been occasionally mentioned in a small number of case studies^[18-20]. The present study showed insignificantly higher mean triglyceride level in GX subjects than controls. Abnormalities of lipid metabolism seem to play a role in presence of GX. The higher serum lipid content in GX patients may be partly derived from circulating lipids. Since excessive concentrations of oxygen-free radicals may result in accelerated LDL-cholesterol oxidation and the formation of GX^[7], the plasma levels of LDL-cholesterol and of oxidized LDL-cholesterol are important factors in the pathogenesis of atherosclerosis. GX cases in the present study showed no systemic signs of xanthomatosis and no significant differences were observed between GX patients and controls in the incidences of other conditions, such as diabetes, hyperlipidemia, or hypertension.

Chronic persistent infection with *H pylori* is believed to result in the development and to influence the extent of atrophic gastritis. Korea is one of the well-known *H pylori* endemic countries in the world. Some studies found a close association between *H pylori* infection and GX^[6,7]. Moreover, bacterial infection-induced foamy cell infiltration was observed in the small bowel lesions of Whipple disease^[21]. Therefore, it is possible that macrophage transformation into foamy cells may be secondary to phagocytosis caused by *H pylori* that have penetrated into the lamina propria, as suggested by Hori *et al*^[6]. In the present study, we examined *H pylori* infection by CLO test, histologic examination, or serologic test, and found that the prevalence of *H pylori* was similar in GX patients and controls, suggesting no correlation between GX and *H pylori* infection. This may be associated with high prevalence of *H pylori* infection in Korean adult population. Although the prevalence of *H pylori* infection was similar in GX patients and controls, atrophic gastritis was more frequently ob-

served in GX patients. Although atrophy of stomach was highly related to *H pylori* infection, there was no absolute correlation between atrophy and *H pylori* in some endemic area like Korea^[22]. Also atrophy could be induced by some other reasons, such as autoimmune, idiopathic, reactive, drug-associated, or other gastric irritant-induced causes.

In conclusion, although the reasons remain unclear, GX is an increasing entity in Korea. In addition, GX is associated with dyslipidemia and atrophic gastritis. However, there is no relation between *H pylori* infection or entero-gastric reflux gastritis and GX. It remains to be clarified whether dyslipidemia and atrophic gastritis observed among GX patients play any role in its etiology.

COMMENTS

Background

Xanthomatosis is yellow tumor-like lesion of the skin or deeper structure characterized by presence of lipid-containing histiocytes. This yellowish plaque in gastric mucosa (gastric xanthomatosis, GX) is a benign lesion, and it has no clinical significance. But a variety of possible causes, such as an abnormality of the lipid metabolism or inflammatory changes in the gastric mucosa, have been suggested. The aim of this study was to evaluate the prevalence and the clinical significance of GX endoscopically in Korea, and to investigate the relationship among GX, *H pylori* infection and dyslipidemia.

Innovations and breakthroughs

Although the reasons remain unclear, GX is an increasing entity in Korea. The present study showed the lower mean HDL-cholesterol and higher mean LDL-cholesterol and higher mean triglyceride levels in GX subjects than the controls. Abnormalities of lipid metabolism seem to play a role in presence of GX. However, there was no relation between *H pylori* infection or enterogastric reflux gastritis and GX. Although the prevalence of *H pylori* infection was similar in GX patients and controls, atrophic gastritis was more frequently observed in GX patients.

Applications

Even though GX is benign disease entity, it is definitely related with dyslipidemia and atrophic gastritis. If the patient has GX in endoscopic examination, it needs to evaluate the severity of atrophic gastritis and the level of lipid profile. It remains to be clarified whether dyslipidemia and atrophic gastritis observed among GX patients play any role in its etiology.

Terminology

GX was first named in 1929 by Lubarsch and Borchardt as a gastric lipid island. A variety of possible causes, such as an abnormality of the lipid metabolism or inflammatory changes in the gastric mucosa, have been suggested. The histologic appearance of GX was that the lamina propria was occupied by large ovoid to polygonal histiocytes having an abundant, finely vacuolated (foamy) cytoplasm staining lightly with eosin.

Peer review

It is an interesting and well written paper. The authors investigated the relationship among GX, *H pylori*, dyslipidemia, and gastritis in Korea. They conclude that the prevalence of GX is 7% and it may be an increasing entity in Korea. Moreover, dyslipidemia and atrophic gastritis are related to GX, but *H pylori* infection is not.

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