XANTHELASMAS OF THE UPPER GASTROINTESTINAL TRACT: THEIR SIGNIFICANCE AND ASSOCIATION WITH DYSLIPIDEMIA

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ABSTRACT

Objective: The significance of gastrointestinal xanthelasmas (GX) is unclear, although sometimes lesions they may be confused with malignant lesions. The aim of this study is to investigate the relationship between GX, atrophic gastritis, Helicobacter pylori (HP), and dyslipidemia.

Material and Method: Upper gastrointestinal endoscopy reports of 8040 patients were evaluated retrospectively. Among them, 20 patients with GX were included into the study and evaluated for endoscopic characteristics, atrophic gastritis, HP infection and serum lipid profiles. The findings were compared with 20 age- and gender-matched control subjects.

Results: The prevalence of GX was 0.24% with no gender difference. As compared with the control group, lipid profiles of GX group showed significantly lower HDL-cholesterol (38.50±9.59 vs 48.80±14.80, p=0.01) and total serum-cholesterol levels (mg/dL) (171.70±26.21 vs 194.25±34.84, p=0.032). LDL-cholesterol and triglyceride levels were not related to the presence of GX. GX showed a close relationship with endoscopically determined atrophic gastritis (30.0% vs 5.0%, p=0.03). HP infection and intestinal metaplasia were not significantly related with GX.

Conclusion: In our serial endoscopy, the prevalence of GX was 0.24% and it showed an increase with age. Dyslipidemia and atrophic gastritis were found to be related to GX. This relation was not observed with HP infection.

Key Words: Xanthelasma, dyslipidemia, Helicobacter pylori, atrophic gastritis Nobel Med 2014; 10(1): 53-57

ÜST GASTROİNTESİTAL SİSTEM KSANTELEZMALARı: ÖNEMİ VE DISLIPIDEMİ İLE İLİŞKİLERİ

ÖZET


Bulgular: Gastrointestinal ksanteleza prevalansı %0,24 olarak bulundu ve cinsiyet açısından farklılık yoku. Kontrol grubu ile karşılaştırıldığında, ksanteleza grubunda HDL-kolesterol (38,50±9,59 vs 48,80±14,80, p=0,01) ve total kolesterol seviyeleri (mg/dL) (171,70±26,21 vs 194,25±34,84, p=0,032) anlamlı olarak daha düşük bulundu. LDL-kolesterol ve trigliserid seviyeleri açısından ise farklılık saptanmadı. Gastrointestinal ksanteleza ile atrofik gastrit varlığında anlamlı bir ilişki mevcuttu (%30 vs %5, p=0,03). HP infeksiyonu ve intestinal metaplası varlığı ile ksanteleza arasında ise anlamlı ilişki bulunmadı.

Sonuç: Endoscopy serimizde gastrointestinal ksanteleza prevalanisi %0,24 olarak bulundu ve yaşa artış göstermektediy. Ksanteleza ile dislipidemi ve atrofik gastrit varlığı arasında anlamlı ilişki tespit edilmemişken HP infeksiyonu ile benzer bir ilişki gözlenmedi.

INTRODUCTION

Gastrointestinal xanthelasmas (GX) are uncommon benign lesions. The etiology and clinical significance of GX is unknown. Chronic gastritis, Helicobacter pylori (HP) infection, diabetes mellitus and hyperlipidemia have been implicated in the etiopathogenesis. The most frequent location of xanthelasma in the upper gastrointestinal (GI) tract is the stomach.\textsuperscript{1} The incidence of GX is reported as ranged from 0.018\% to 0.8\% in endoscopy series and approximately 58\% in autopsy series.\textsuperscript{2,3} Its frequency increases with age, and highest in the seventies.\textsuperscript{4,5} Endoscopic appearance of upper GX is typical. They appear as yellow-white, welldemarcated, single or multiple nodules or plaques, with a size varying from 1 to 10 mm in diameter (Figure 1, 2).\textsuperscript{4,5} Xanthelasmas are composed of large foamy cells containing mixture of lipids, including cholesterol, neutral fat, low-density lipoprotein, and oxidized low-density lipoprotein (Figure 3).\textsuperscript{1}

Although the clinical significance of GX is unclear and they are not uncommon, there are few reports about GX in the literature. They may be confused with malignant lesions.\textsuperscript{5,8}

In this study, we aimed to determine the prevalence of upper GX and their association with HP infection, gastric mucosal changes, atrophic gastritis, intestinal metaplasia and dyslipidemia.

MATERIAL and METHOD

A retrospective analysis of 8040 upper GI endoscopy reports, done at the gastroenterology department of Stuleyman Demirel University between January 2007 and December 2009, was performed. Patients with diagnoses of xanthelasma on upper GI endoscopy and confirmed by histopathologic examination of biopsy specimen, were included into the study. Demographic, clinical, endoscopic and histopathologic features and serum lipid profiles of patients were recorded. Blood samples were taken following 10-12 hours of fasting. Total cholesterol, triglyceride and HDL levels were analyzed with spectrophotometric method using Olympus AV 2700 autoanalyzer. HP infection was detected by rapid urease test and histopathologic examination of mucosa. Histopathologic slides stained with periodic acid-Schiff (PAS) and toluidin blue were evaluated by a single pathologist.

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±SD SSPS 15.0 version (SPSS Inc., Chicago, IL., USA) software was used to analyze the data.

RESULTS

GX was detected in 20 of 8040 patients (0.24\%). Age and gender-matched 20 individuals without GX were included in the control group.

The mean ages of patients in the GX and control groups were 57.25±12.81 (28-79) years and 48.90±11.13 (25-68) years, respectively. There were 9 (45\%) women and 11 (55\%) men in the GX group and 8 (40\%) women and 12 (60\%) men in the control group. There was no difference between the groups in terms of age and gender (p=0.13, p=0.74).

The mean size of lesion was 3.05±1.09 mm in patients with GX. Lesion was located in the stomach in 19 (95.0\%) patients, and in the duodenum in 1 patient (5.0\%). 11 (57.89\%), 6 (31.57\%) and 2 (10.52\%) of the gastric lesions were located in the corpus, antrum and cardia, respectively. Lesion was single in 11 (55.0\%) patients, 2 in six patients, 3 in two patients and 4 in one patient. In patients with multiple lesions, lesions were located in the corpus in 4 patients, in the antrum in 4 patients and in the duodenum in 1 patient (Table 1). Serum HDL (38.50±9.59 and 48.80±1.09 mmol/L, p=0.01) and total cholesterol (171.70±26.21 and 194.25±34.84, p=0.03) levels (mg/dL) were low in the xanthelasma group compared to control group, and this difference was statistically significant. There was no association between GX and serum triglyceride and LDL cholesterol levels.

Atrophic gastritis was detected in 6 (30\%) patients of GX group while in only one patient (5\%) of control group (p=0.03). Intestinal metaplasia was detected in 5 (25\%) patients of GX group and in 4 (20\%) patients of control group (p=0.7). H. pylori infection was detected in 16 (80\%) patients of GX group and in 13 (65\%) patients of control group (p=0.28). Atrophic gastritis was detected significantly higher in GX group while there was no difference between the groups in terms of H. pylori infection and intestinal metaplasia.
Demographic features, serum lipid profiles and histopathologic features of GX and control groups were showed in Table 2.

**DISCUSSION**

GX is a benign lesion characterized by the presence of lipid islands in the gastrointestinal mucosa. The significance and cause of GX still remain unknown. The incidence of upper GX was reported as 0.23% in our population. In the present study, it was found to be 0.24%. However, in a Korean study by Yi, the prevalence was reported as 7%, which was much higher than previous studies. Approximately 76% of the lesions are located in the stomach, particularly in the antrum and pyloric region (70%); they occur less frequently in the esophagus (12%), duodenum (12%) and colon.

Xanthelasma is more frequent in women and its incidence shows an increase with age. Distribution of gender was almost equal (M:F=1.2:1) in our series, however this ratio was reported as 3.3:1 by Oviedo et al. Symptoms in patients with GX were nonspecific and may be variable. One third of patients are asymptomatic; epigastric fullness, anorexia, nausea and precordial pain were reported in symptomatic patients but the association between the lesion and these symptoms was very suspicious. The symptoms of our patients were nonspecific and considered as related to gastritis and duodenal ulcer rather than GX.

Although the clinical significance of GX is unclear, they are important because they may be confused with malignant lesions. Several studies have shown that xanthelasma is associated with gastritis, carcinoma, intestinal metaplasia of the gastric epithelium, or peptic ulcer diseases. Moderate-severe atrophy (89%) and intestinal metaplasia (13%) on the gastric glands around the lesions were reported in previous studies. Pieterse et al. observed that intestinal metaplasia was less frequently seen within the GX specimens as compared to the control specimens. The prevalence of GX was similar in GX and control groups and suggested no correlation between GX and H. pylori infection.

### Table 1: Distribution of patients according to the location and number of xanthelasmas

<table>
<thead>
<tr>
<th>Location</th>
<th>n (%)</th>
<th>Single/Multiple</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>19/20 (95%)</td>
<td></td>
</tr>
<tr>
<td>Cardia</td>
<td>2</td>
<td>2/0</td>
</tr>
<tr>
<td>Corpus</td>
<td>11</td>
<td>7/4</td>
</tr>
<tr>
<td>Antrum</td>
<td>6</td>
<td>2/4</td>
</tr>
<tr>
<td>Duodenum</td>
<td>1/20 (5%)</td>
<td>0/1</td>
</tr>
</tbody>
</table>

### Table 2: Demographic features, serum lipid profiles and histopathologic features of xanthelasmas and control groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Xanthelasma group</th>
<th>Control group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57.25±12.91</td>
<td>49.80±11.13</td>
<td>0.13</td>
</tr>
<tr>
<td>Sex (n) (M/F)</td>
<td>11/8</td>
<td>12/8</td>
<td>0.74</td>
</tr>
<tr>
<td>Serum Lipid Parameters*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>171.70±26.21</td>
<td>194.25±34.84</td>
<td>0.03</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>38.50±9.59</td>
<td>48.80±14.90</td>
<td>0.01</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>101.55±19.55</td>
<td>118.50±31.74</td>
<td>0.053</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>155.25±63.73</td>
<td>138.15±68.83</td>
<td>0.053</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histopathologic feature</th>
<th>Xanthelasma group</th>
<th>Control group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation</td>
<td>16/20 (80%)</td>
<td>20/20 (100%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Activation</td>
<td>7/20 (35%)</td>
<td>12/20 (60%)</td>
<td>0.11</td>
</tr>
<tr>
<td>H. pylori</td>
<td>16/20 (80%)</td>
<td>13/20 (65%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Atrophy</td>
<td>6/20 (30%)</td>
<td>11/20 (50%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Intestinal metaplasia</td>
<td>5/20 (25%)</td>
<td>4/20 (20%)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

*Normal ranges of serum lipid parameters: Total cholesterol: 140-200 mg/dL, LDL-cholesterol: 0-130 mg/dL, Triglyceride: 40-160 mg/dL, HDL-cholesterol: 30-80 mg/dL.

H. pylori antigens were detected in the cytoplasms of xanthelasma cells in some studies and it was hypothesised that these lesions may be initiated by H. pylori infection. Chronic persistent H. pylori infection is considered as an important factor in the development and extent of atrophic gastritis. Turkey is an endemic country for H. pylori infection and its estimated prevalence is approximately 80%. Some studies found a close association between H. pylori infection and gastrointestinal cancers. However, in a study, Yi reported the prevalence of H. pylori was similar in GX and control groups and suggested no correlation between GX and H. pylori infection. H. pylori was detected in 80% of our patients both with histopathologically and rapid urease test. The prevalence of H. pylori infection in GX patients and controls was similar, however atrophic gastritis was detected more frequently in GX patients. Although atrophic gastritis was highly related to H. pylori infection, there was no absolute correlation between atrophy and H. pylori in some endemic areas like Turkey. Also atrophy could be induced by some other reasons, such as autoimmune, idiopathic, reactive, drug-associated, or other gastric disease.
irritant-induced causes. In our cases, GXs were not associated with H. pylori infection. The prevalence of H. pylori infection is high in our country, so we think that the existence of H. pylori infection and gastric xanthelasma may be coincidental.

Although some amount of triglycerides and esterified cholesterol were detected on chemical analyses of these islands, most studies suggest that there is no correlation between GX and hypercholesterolemia. Generalized disturbance of fat metabolism seems not to be essential for lipid islands. Because of the histochemical characteristics resemble those of skin lesions, a possible relationship with lipid metabolism has been investigated, but no obvious association with lipid metabolism disorders or hypercholesterolemia was found. Yi reported lower mean HDL-cholesterol and higher mean LDL-cholesterol levels and Chang et al. reported lower mean HDL-cholesterol and higher mean triglyceride levels in GX subjects in comparison with the controls. In the present study, mean HDL-cholesterol and total serum cholesterol levels were lower in GX subjects than in controls, and this differences were statistically significant. Our investigation showed higher mean triglyceride level in GX subjects than controls, however this elevation was not statistically significant, similar to the results of Yi. We concluded that, abnormalities of lipid metabolism may play a role in presence of GX.

Muraoka et al. observed an association between type Ia early gastric cancer and xanthelasma and speculated that cancer cells may have caused xanthelasma cell proliferation via an autocrine mechanism. In addition, it was recommended that xanthelasma should be differentiated from signet ring cell carcinoma by histochemistry and immunohistochemistry. Predisposing conditions for gastric cancer such as atrophic gastritis, intestinal metaplasia and H. pylori infection may accompany xanthelasmas.

CONCLUSION

Clinical significance of GX is not known. Our findings demonstrated that, atrophic gastritis and dyslipidemia are significantly associated with GX. This association was not detected with intestinal metaplasia and H. pylori infection. Diagnosis of xanthelasmas should be confirmed with histopathologic examination of lesion. Patients with xanthelasmas should be followed-up, because of increased incidence with age, association with atrophic gastritis and H. pylori infection, which could be a predisposan factor for carcinoma, and possibility of interference with malignant lesions.

REFERENCES