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Research Progress on Gastric Xanthelasma

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Abstract

Gastric xanthoma, also known as gastric xanthelasma or lipid island of the stomach, is a benign lipid deposition lesion occurring in the gastric mucosa. It is named for its yellowish-white macroscopic appearance and is histopathologically characterized by the accumulation of lipid-laden foam cells. The etiology and pathogenesis of this disease remain unclear, but it has been hypothesized to be associated with chronic gastritis, *Helicobacter pylori* (*H. pylori*) infection, diabetes mellitus, and hyperlipidemia. Recent studies indicate a significantly increased risk of gastric cancer in patients with gastric xanthoma, though the precise association between the two remains unclear. Therefore, this review comprehensively examines gastric xanthoma.

Keywords

Gastric Xanthelasma, *Helicobacter pylori*, Diabetes Mellitus, Gastric Cancer

1. Introduction

Gastric xanthoma, also known as gastric xanthelasma, gastric lipid island, or reticuloendotheliosis of the stomach, presents endoscopically as raised, granular, yellowish lesions scattered across the gastric mucosal surface. Gastric xanthoma represents a proliferative response of histiocytes to plasma lipid alterations, constituting a non-neoplastic, reactive tumor-like hyperplastic lesion [1]. Orth first designated this condition as "gastric xanthoma" in 1887 [2]. In recent years, with the widespread adoption of gastrointestinal endoscopy and changes in environmental/dietary factors, the incidence and detection rates of gastric xanthoma have shown an increasing trend. Gastric xanthoma has been attracting increasing attention from researchers. The etiology and pathogenesis of gastric xanthoma remain incompletely understood, but may be associated with chronic gastritis, *Helicobacter pylori* (*H. pylori*) infection, diabetes mellitus, and hyperlipidemia. This article elaborates on gastric xanthoma regarding its etiology, pathogenesis, epide-

miology, diagnosis, and treatment.

2. Epidemiology

The incidence of gastric xanthelasma exhibits regional variations and can occur across all age groups. Its prevalence shows a positive correlation with age, with the highest incidence observed in individuals aged 50 - 70 years. Additionally, the condition is more common in males than in females [3]. Anatomically, gastric xanthelasma predominantly occurs in the gastric antrum [4]. Recent years have witnessed a significant increase in the detection rate of gastric xanthomas, potentially attributable to the widespread adoption of endoscopy, advancements in endoscopic equipment and techniques, as well as changes in environmental and dietary factors.

3. Diagnosis

Gastric xanthomas lack typical clinical manifestations and are usually asymptomatic. They are often incidentally detected during gastroscopy in some patients due to various reasons. The diagnosis of gastric xanthomas primarily relies on endoscopic examination and histopathological evaluation. Endoscopically, typical gastric xanthomas present as yellowish-white nodules or plaques, which may be solitary or multiple, measuring approximately 1 - 10 mm in size, with a rough surface and well-defined margins [5]. The characteristic histopathological manifestation of gastric xanthomas consists of lipid-laden mononuclear cells and macrophages transformed into foam cells, which aggregate in clusters within the mucosa and submucosa, as observed under light microscopy [6]. However, differentiation from certain malignant tumors (e.g., signet-ring cell carcinoma [7]) is essential. In diagnostically challenging cases, further histological and immunohistochemical staining should be performed. The diagnostic value of CD68 or other macrophage markers is relatively high, when routine histology is equivocal.

4. Etiology and Pathogenesis of Gastric Xanthelasma

The exact etiology and pathogenesis of gastric xanthomas remain incompletely understood. However, current research suggests several plausible mechanisms.

4.1. Disordered Lipid Metabolism

Whether abnormal lipid metabolism is an etiological factor for gastric xanthomas remains controversial. Previous reports have documented cases where xanthomas spontaneously regressed after correction of underlying dyslipidemia. However, studies have also demonstrated that patients with gastric xanthomas often exhibit no significant abnormalities in serum lipid levels. Several studies [4] [8] have demonstrated that patients with gastric xanthomas exhibit significantly elevated triglycerides (TG) and low-density lipoprotein (LDL) levels, along with reduced high-density lipoprotein (HDL), compared to those without gastric xanthomas. Nevertheless, definitive conclusions have not been reached, considering factors

such as discrepancies in sample sizes and study heterogeneity. It is generally hypothesized that abnormal lipid metabolism may facilitate the translocation of lipoproteins from gastric mucosal capillaries into the intercellular spaces of the gastric mucosa or submucosa, where they undergo oxidation by reactive oxygen species (ROS) to form oxidized lipoproteins. Subsequently, through chemotactic mechanisms, these oxidized lipoproteins migrate into the intercellular spaces, where they are phagocytosed by monocytes and macrophages, ultimately transforming into foam cells. Accumulation of numerous foam cells ultimately forms gastric xanthelasma [9]. However, some researchers propose that localized tissue damage and degeneration in the gastric mucosa lead to intracellular lipid accumulation within mucosal epithelial cells, subsequently forming gastric xanthelasma [10].

4.2. *Helicobacter pylori* Infection

In 1996, Hori *et al.* [11] first detected *Helicobacter pylori* within gastric xanthoma tissue specimens. Multiple studies report a significantly higher prevalence of *Helicobacter pylori* infection in patients with gastric xanthomas compared to those without xanthomas [12] [13]. These studies demonstrate a significant association between *Helicobacter pylori* infection and xanthoma formation. Therefore, it is hypothesized that *Helicobacter pylori* infection may promote the development of gastric xanthomas and could serve as an independent risk factor. The potential mechanism involves *Helicobacter pylori*-induced inflammatory damage to the gastric mucosa and localized metabolic disturbances.

4.3. Atrophy and Intestinal Metaplasia

Compared to patients without xanthelasma, those with gastric xanthelasma exhibited significantly more severe gastric mucosal atrophy and intestinal metaplasia [12]. Some studies have indicated that gastric xanthelasma is associated with gastric atrophy and intestinal metaplasia [14]. One possible explanation is that in patients with chronic atrophic gastritis and intestinal metaplasia, the gastric mucosa is in a state of prolonged chronic inflammation and cellular senescence, leading to mucosal damage and metabolic dysfunction.

A possible etiology is *Helicobacter pylori* infection leading to gastric atrophy and intestinal metaplasia, which may subsequently contribute to the formation of gastric xanthelasma. In summary, the presence of gastric xanthelasma should be considered during the diagnosis of gastric atrophy and intestinal metaplasia, as this association may provide diagnostic clues for detecting xanthelasma.

4.4. Diabetes Mellitus

A large-scale study [4] demonstrated that elevated fasting blood glucose is an independent risk factor for gastric xanthelasma. Another study [15] revealed that patients with gastric xanthelasma had significantly higher HbA1c levels compared to those without xanthelasma, along with a significantly higher prevalence of diabetes mellitus. Previous studies have demonstrated that hyperglycemia increases

oxygen free radical production, thereby contributing to gastric xanthelasma formation [16] [17].

4.5. Reflux Gastritis

Studies suggest that bile reflux-induced intestinal metaplasia upregulates cellular lipid transport mechanisms [18], providing a pathogenic basis for bile reflux gastritis to promote gastric xanthelasma formation. However, the exact underlying mechanisms remain unclear, warranting further investigation to elucidate the precise pathogenic pathways.

4.6. Hyperplastic Polyps

In 2009 [19], Japan reported a rare case of a mixed lesion consisting of gastric xanthelasma and hyperplastic polyp. Turkish researchers also identified a rare co-occurrence of hyperplastic polyps with xanthelasma in a pathological study [20]. Although the etiopathogenesis of gastric xanthelasma and hyperplastic polyps, as well as the rationale for their co-occurrence, remain unclear, it may be hypothesized that local inflammatory responses to mucosal injury play a contributory role.

4.7. Others

Some studies suggest an association between gastric xanthelasma and immunosuppressant use [21], though further research is needed to establish a definitive link.

5. Association between Gastric Xanthelasma and Gastric Cancer

Gastric cancer (GC) ranks as the fifth most common malignancy and the fourth leading cause of cancer-related mortality worldwide [22], posing a significant burden on global health. Therefore, early diagnosis and treatment of gastric cancer are of critical importance. Existing evidence confirms that chronic atrophic gastritis and *H. pylori* infection are well-documented risk factors for gastric cancer [23]. Since these conditions are also associated with gastric xanthelasma, it is imperative to explore whether gastric xanthelasma itself contributes to gastric cancer development. Several studies have reported a significantly higher prevalence of gastric xanthelasma in patients with gastric cancer compared to the general population [24]. Furthermore, multivariate analyses have identified gastric xanthelasma as an independent risk factor for gastric carcinoma [25]. Studies indicate that gastric xanthelasma is not only associated with gastric cancer development, but also significantly correlates with its differentiation status [26]. Miura *et al.* [27] compared 54 rapidly progressive gastric cancer (GC) cases with 60 slow-progressing GC patients, revealing a significant association between gastric xanthelasma and aggressive tumor progression. Previous studies [16] [17] suggest that increased release of oxygen free radicals may contribute to the pathogenesis of gastric xanthelasma. Moreover, oxygen free radicals can induce DNA damage and play a piv-

otal role in the pathophysiology of various malignancies. Thus, there is compelling rationale to hypothesize that reactive oxygen species (ROS) may contribute to gastric carcinogenesis in patients with gastric xanthelasma. These findings collectively indicate a close association between gastric xanthelasma and the initiation/progression of gastric cancer, suggesting its potential as a predictive biomarker for malignancy.

6. Treatment

Traditionally, gastric xanthelasma was considered to require no specific treatment but warranted surveillance endoscopy. The demonstrated association between gastric xanthelasma and gastric carcinogenesis necessitates heightened clinical vigilance toward these lesions. Regardless of whether endoscopic treatment is performed, close endoscopic surveillance is mandatory. As a gastric mucosal lesion, xanthoma is currently managed primarily through minimally invasive endoscopic interventions, including microwave coagulation therapy, endoscopic mucosal resection, radiofrequency ablation, and argon plasma coagulation. The decision to pursue endoscopic treatment should be based on patient preference, lesion size, and the presence of concurrent atrophic gastritis or early gastric cancer. In previous reports, a case of gastric xanthoma coexisting with hyperplastic polyps was successfully treated with endoscopic mucosal resection [19]. Endoscopic mucosal resection (EMR) is now widely utilized in clinical practice due to its well-established advantages of high safety and low complication rates.

The etiology of gastric xanthelasma remains unclear. For patients with gastric xanthelasma accompanied by metabolic disorders such as abnormal glucose and lipid metabolism or concurrent atrophic gastritis, particularly those with multiple gastric xanthelasmas, management should include not only endoscopic therapy but also aggressive treatment of metabolic abnormalities and atrophic gastritis. The therapeutic outcomes of non-endoscopic interventions remain inconclusive.

7. Summary

Historically, gastric xanthelasma was regarded as a benign lesion requiring no therapeutic intervention. However, with the significant increase in detection rates of gastric xanthelasma in recent years and deepening understanding of this condition. Although the etiology and pathogenesis of xanthelasma remain incompletely understood, it may be associated with chronic gastritis, *Helicobacter pylori* (*H. pylori*) infection, diabetes mellitus, and hyperlipidemia, particularly demonstrating significant correlations with atrophic gastritis and gastric cancer. Thus, it may serve as a predictive biomarker for early gastric cancer. When gastric xanthelasma is detected during endoscopy, heightened vigilance is required to meticulously examine the gastric mucosa for concurrent gastric cancer or early neoplastic lesions. Further diagnostic evaluation should be pursued as indicated, with endoscopic intervention performed when necessary. Close endoscopic surveillance is mandatory in all cases. However, current evidence is largely limited to

small, single-center studies. Future large-scale, multicenter, and prospective research is needed to validate these findings and provide new insights for clinical management.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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