

ARTICLE

Clinical research status of gastric xanthoma

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Abstract

Gastric xanthoma is a lipid deposition disease of the gastric mucosa. It is a rare, asymptomatic benign lesion of the stomach, named for its yellowish-white appearance, and its histopathology is the accumulation of lipid-filled foam cells. The etiology and treatment of this disease is still not clear, in recent years, there have been studies that gastric xanthoma is related to gastric malignant tumors, may be a predictor of gastric cancer, this article reviews the latest clinical research progress of gastric xanthoma, to provide a reference for clinical diagnosis and treatment of gastric Xanthoma.

Keywords: gastric xanthoma; Clinical research status

Xanthoma, also known as xanthelasma or lipid island, occurs in the digestive tract, esophagus, stomach, small intestine, and colon [8]. It is a benign lesion with typical features of foamlike cells detected in the mucous lamina propria. These cells, also known as xanthoma cells, are lipid-containing histiocytes or macrophages. Stomach is the most common lesion site of digestive tract xanthoma, but due to the low incidence, there are few related literature reports, and its pathogenesis and clinical significance are still unclear. In recent years, studies have reported that the incidence of gastric xanthoma is on the rise, and some studies have shown that it is closely related to early gastric cancer [1], and it is believed that gastric xanthoma can be used as a marker of early gastric cancer [2–3]. Studies on gastric xanthoma at home and abroad are limited to morphology and histopathology, and no systematic and comprehensive reports have been reported so far [4].

1. Epidemiology

There is no large-scale population epidemiological survey on the incidence of gastric xanthoma [5], and most literature reports are single-center data. In 1999, the European PetovS epidemiological survey showed that the incidence of gastric xanthoma in the European population was 0.018%. With the popularization of electronic gastroscopy, the detection rate gradually increased, and many scholars began to pay attention to and study gastric xanthoma, and our understanding of this lesion was gradually deepened. A 2004 study of 7,320 patients in Turkey reported a detection rate of about 0.23% for xanthoma, and another study of 1,400 patients in 2016 showed an incidence of 4.9%. In Japan, where the incidence of gastric xanthoma was reported to be 0.2% in 2004, the detection rate of gastric xanthoma was 7.7% and 5.9%, respectively, in studies involving 3,238 subjects and 1,823 patients completed in 2013 and 2015. A study in South Korea in 2007 showed that the detection rate of gastric xanthoma was 7%. In 2014, Luo Yuanbin *et al.* collected a total of 3293 cases of gastric mucosa biopsy data and diagnosed 30 cases of gastric xanthoma, with a detection rate of 0.9%. The detection rate of xanthoma was close to 0.78% in a large retrospective analysis conducted by Professor Chen Yi of the First Affiliated Hospital of Zhejiang University in 2017. As for the incidence of gastric xanthoma in countries around the world, there is a temporary lack of epidemiological data with large multi-center samples. From the above data, it can be seen that: (1) the incidence of gastric xanthoma is different in geographical distribution, and the incidence is slightly higher in Asia, which may be related to the higher infection rate of *Helicobacter pylori* in Asian population [6]; (2) The detection rate of gastric xanthoma was significantly higher than before, which may be related to the popularity of gastrointestinal endoscopy in recent years, the upgrading of digestive endoscopy equipment and examination techniques [7], and the gradual increase in clinical workers' attention and in-depth understanding of xanthoma.

2. Etiology and pathogenesis

The current research indicates that the etiology and pathogenesis of gastric xanthoma may be as follows.

(1) Physical or chemical stimulation: the stomach, especially the gastric antrum, has more peristalsis, and receives more physical stimulation of the esophagus, which can cause increased local tissue proliferation and lymphoid circulation disorder resulting in lipoprotein accumulation, and is phagocytic by histiocytes through the above mechanism to form xanthoma. Chronic inflammation of gastric mucosa leads to exposure of mucosal or submucosal tissues to strong acid environment, which can cause local tissue metabolic disorders and form gastric xanthoma.

(2) Chronic inflammation and aging of gastric mucosa: Long-term chronic inflammation of gastric mucosa and aging of cells can interfere with local lipid metabolism and lead to the rupture and necrosis of mucosal cells. The membranes of necrotic cells release a large amount of lipids. Due to excessive local lipids and the obstruction of lipid metabolism and transport, a large amount of lipids are deposited and phagocytosed by local histiocytes and mononuclear macrophages, forming foam cells full of lipids.

(3) Abnormal lipid metabolism: Due to abnormal lipid metabolism, the plasma low-

density lipoprotein, cholesterol, triglyceride and chylomicron increase, and can move out of the gastric mucosal capillaries to the mucosal or submucosal cell space. Under the action of oxygen free radicals, low-density lipoprotein forms oxidized low-density lipoprotein, which changes the surface characteristics of local histocytes and monocytes, and increases the expression of adhesion factors, resulting in monocytosis that adheres to local tissues, and the latter phagocytes oxidized low-density lipoprotein and other lipids through scavenger receptors to transform into foam cells. The foam cells aggregate to form xanthoma. Whether abnormal lipid metabolism is the cause of gastric xanthoma is still controversial.

3. Risk factor

(1) Age and gender: This disease is more common in elderly people over 60 years old clinically, and the incidence increases significantly after 65 years old [10]. Studies suggest that gastric xanthoma is related to the aging process of gastric mucosal cells, so the prevalence will increase with age. Previous literature studies believed that gastric xanthoma is more common in women, but a large number of recent studies agree that this disease is more common in males than females, and the ratio of male to female incidence is about 1.62-3.11:1.

(2) Atrophic gastritis: The incidence of gastric xanthoma is higher in patients with atrophic gastritis. A review by Sekikawa et al. of 1660 patients with atrophic gastritis, 244 (14.7%) had gastric xanthoma, while only 5 (0.3%) of 1578 patients without atrophic gastritis had gastric xanthoma ($P < 0.0001$). A gastroscopic follow-up study of 1823 patients over 3 years found that 106 (12.5%) of 847 patients with atrophic gastritis eventually developed gastric xanthoma, while only 1 (0.1%) of 976 patients with non-atrophic gastritis developed gastric xanthoma ($P < 0.000001$). This indicates that the occurrence of gastric xanthoma is related to the presence of atrophic gastritis.

(3) Diabetes: The incidence of gastric xanthoma in diabetic patients is significantly higher than that in people without diabetes. Gastric xanthoma was found in 24 of 181 diabetic patients (13.3%), compared with 83 of 1642 non-diabetic patients (5.1%, $P < 0.0001$). The incidence of diabetes in patients with gastric xanthoma was significantly higher than that without gastric xanthoma (22.4% vs. 9.11%, $P < 0.00001$).

4. Research progress on the correlation between gastric xanthoma and gastric cancer

In the past, gastric xanthoma was considered a benign lesion, but in recent years, a number of studies have shown that gastric xanthoma is related to the occurrence of gastric cancer [9]. Sekikawa et al. retrospectively analyzed 3228 patients and found that the incidence of gastric cancer in patients with gastric xanthoma was significantly higher than that in those without gastric xanthoma (20.1% vs. 1.8%, $P < 0.0001$). Among the 105 gastric cancer patients, 50 cases (47.6%) had gastric xanthoma, while among the 3133 non-gastric cancer patients, only 199 cases (6.4%) had gastric xanthoma. In the age/sex/atrophy control experiment, 50 (20.8%) of the 240 patients with gastric xanthoma were complicated with gastric cancer, while only 8 (3.3%) of the 240 patients without gastric xanthoma were complicated with gastric cancer ($P < 0.0001$). The study indicated that gastric xanthoma was closely related to early gastric cancer and may be used as a marker for early gastric cancer.

Gastric xanthoma is independently related to the occurrence of gastric cancer, and may be a biological indicator of the occurrence of gastric cancer, and may be a predictor of the occurrence and location of early gastric cancer. Kaiserling *et al.* suggested that the increased release of oxygen free radicals may participate in the formation of gastric xanthoma. It is well known that oxygen free radicals can cause DNA damage and play an important role in the pathophysiology of various malignant tumors. Therefore, it is speculated that oxygen free radicals may play a role in the development of gastric cancer in gastric xanthoma patients.

5. Research prospect

In the past, gastric xanthoma was considered a rare benign lesion that did not require treatment. However, in recent years, not only has its report increased significantly, but also some studies believe that it is significantly correlated with atrophic gastritis and gastric cancer, which may be a predictive marker of early gastric cancer, so it needs to be vigilant. Through transcriptome analysis, this project team identified the signature protein of gastric xanthoma [11], which may be used as an early screening indicator for gastric cancer. If this signature protein is used to develop detection reagents, the incidence of gastric cancer will be reduced to a large extent, bringing huge economic and social benefits.

NOTE

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