

Esophageal Xanthoma in Barrett's Esophagus Associated with Non-Steroidal Anti-Inflammatory Drugs Use

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1. Abstract

Xanthomas are benign tumor-like lesions, composed of accumulation of foamy lipid-laden histiocytic cells. Usually, xanthomas appear in the skin and tendons, while visceral location is uncommon. These lesions can be found anywhere along the gastrointestinal tract, commonly in the stomach and colon.

Esophageal xanthoma (EX) is exceedingly rare lesion which can be incidentally found during endoscopy. A few case reports of EX from 1984 up to now have been reported. We present the first case of EX in Barrett's esophageal mucosa on the background of non-steroidal anti-inflammatory drugs use.

2. Introduction

Xanthomas are an uncommon non-neoplastic lesions resulting from the local accumulation of foamy histiocytes. Most commonly xanthomas are seen in the skin and tendons, while visceral xanthomas are uncommon. The reported incidence in the upper gastrointestinal tract varies among endoscopy series, the most frequent location being the stomach, followed by the duodenum and esophagus [1]. The gastrointestinal xanthomas were first described in 1887 as "lipid-laden macrophages in gastric mucosa" and their histopathological findings are identical regardless of their location [1].

Esophageal xanthoma (EX) is a very rare tumor-like lesion [2-8]. The etiology of it is unknown, but *Uehara K. et al.* suggest that EX

is associated with late inflammatory and reparative processes long after the initial injury of the esophageal squamous epithelium [3].

We present a 52-year-old man with EX in Barrett's esophagus (BE) found on the background of non-steroidal anti-inflammatory drugs (NSAIDs) use.

To the best of our knowledge, this is the second published report of EX in association with BE and the first of such combination on the background of NSAIDs-treatment.

3. Case Report

A 56-year-old man was presented with epigastric pain dating from one year, but exacerbated, with suspicion for myocardial infarction. The patient received an anti-inflammatory drugs (NSAIDs) (Aspirin and Ibuprofen) at a dose of 2-4 tablets per a week for the last year. He had a past medical history for peritonitis and no other significant diseases or family history.

Physical examination revealed only mild epigastric tenderness, with no lymphadenopathy. The performed electrocardiogram is normal. RR: 150/93mmHg. Pulse: 71bts/min. T°: 36.7°C. SpO2: 97%. Blood counts and other haematological investigations were, otherwise, within limits. His lipid profile showed total cholesterol 250 mg/dL, tryglycerides 260 mg/dL, high-density lipoprotein 30 mg/dL and low-density lipoprotein 180 mg/dL.

An esophagogastroscope was performed: the stomach showed no macroscopic changes and in the distal part of esophagus, a 2mm

yellow nodular lesion was found. Biopsies were carried out and sent for histopathological evaluation.

Pathological examination: the biopsy specimens obtained from the distal part of esophagus and stomach were stained with hematoxylin-eosin-saffron and periodic acid-Schiff with diastase pre-digestion (PAS.D). The detected macroscopically lesion of the esophageal area showed features of gastric cardiac mucosa. There were few inflammatory cells, and no metaplasia, dysplasia or malignancy. In the center of this BE-mucosa, is observed a polypoid lesion with edematous chorion and accumulation in the lamina propria, of medium to large groups of foamy macrophages with small nuclei centrally or eccentrically located (Figure 1a). The cells were negative for PAS.D (Figure 1b). The immunohistochemical staining revealed that the cells were strongly positive for CD68 and negative for cytokeratin AE1/AE3 (Figures 1c and 1d). Histological examination of the biopsies taken from stomach showed normal histology and were negative for *H. pylori* (data not shown). The lesion was diagnosed histologically as EX of the BE. Extremely rare diagnosis.

The second follow-up esophagogastroscope performed after five months showed endoscopically and histologically (data not shown) stable and unchanged BE, without presence of EX, metaplasia or dysplasia.

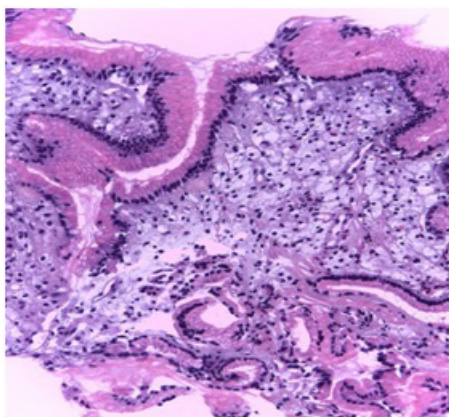


Figure 1a

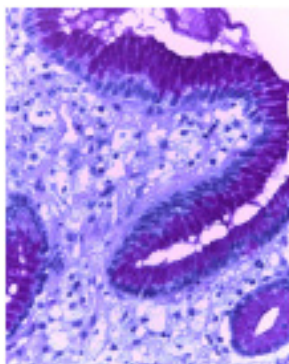


Figure 1b

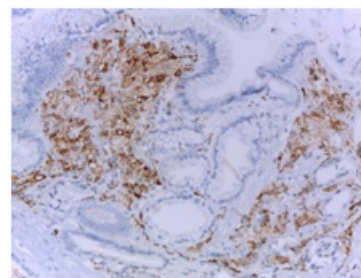


Figure 1c

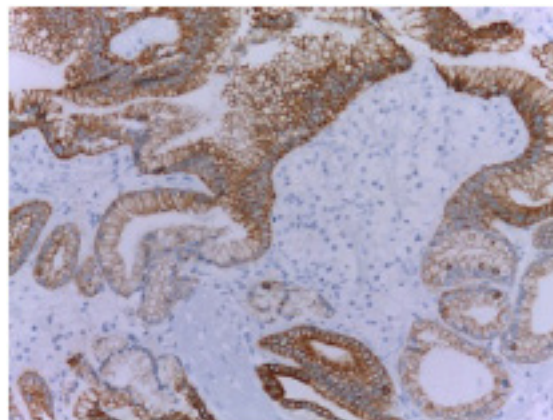


Figure 1d

4. Discussion

Xanthomas (Greek word xanthos meaning “yellow”) are an uncommon non-neoplastic lesions resulting from the accumulation of foamy lipid-laden histiocytic cells that can appear anywhere in the body. They are localized within tissues as papules, plaques, or nodules. The incidence of upper gastrointestinal xanthomas was reported as 0.23% [1]. One study showed the most common location of xanthoma in the gastrointestinal tract was the stomach (76%), followed by the esophagus (12%) and duodenum (12%) [1].

Although EX is thought to be rare, its precise incidence is not known, because only a limited number of cases have been reported. EX was first reported in 1984, by *Remmele and Engelsing* [2]. and since then, 23 cases have been published in the English literature [1-8]. According to the reported cases, esophageal xanthoma is generally a solitary, small (usually 2-5 mm, maximum 10 mm), yellowish elevated lesion [2-8]. Most patients have mild or no gastrointestinal symptoms and the malignant transformation of EX has never been reported [2-8]. Histologically, the lesion is composed by various sized aggregations of foamy cells showing small round shaped nuclei with periphery location and an abundant cytoplasm.

Differential diagnosis includes poorly differentiated carcinoma, storage diseases, infections, macroglobulinemia, and muciphages [1-8]. The clinical presentation together with the past medical history, symptoms of storage diseases, acquired immuno-deficiency syndrome, and/or macroglobulinemia, is essential. In addition,

special stains such as Gram, Ziehl-Neelsen, Gomori methenamine silver, PAS, and PAS-D and immunohistochemistry for cytokeratin AE1/AE3 can be helpful [1-8].

The clinical significance of xanthomas arises due to the resemblance of features on endoscopy with other benign or malignant lesions. Understanding the endoscopic and pathologic features of xanthomas and other lesions is crucial for their detection and differential diagnosis as that may help physicians to appropriately manage these lesions.

The importance and etiology of gastrointestinal xanthomas remain largely unclear [1,4,6].

Few theories have been proposed by authors, explaining the possible trigger or etiology behind the pathogenesis of xanthomas. Xanthomas are considered as a sign of aging by few authors as the incidence of xanthomas increases with age: the incidence of 53.3% is in the age group of 40–60 years, although it can be seen in people of all ages [1].

Mucosal injury has been presumed to contribute significantly to their pathogenesis as it yields lipid-containing debris, ultimately phagocytized by histiocytes forming foamy cells [7]. This hypothesis would clarify why gastric xanthomas seem, by all accounts, to be more successive than EX, as traumatism and irritation might be better endured by esophageal squamous epithelium than by gastric columnar epithelium [8].

BE is a premalignant condition caused by repeated reflux of gastric contents into the distal esophagus. It is found in approximately 1% of the adult population and 3-5% of the population with gastro-esophageal reflux disease. The increase risk of developing adenocarcinoma is 35–125 times that of the general population [6].

Coexistence of EX and BE is rarely mentioned in the literature. Our literature search showed that only one reported case of similar association was recorded [6]. Our case is the first that describes tree conditions diagnosed in one patient -EX in BE in association with NSAIDs use. It is reasonable to ask whether this combination is normal or there is some logical (or pathogenetic) explanation. The patient has started taking NSAIDs after the onset of epigastric pain, apparently related with BE. Whether there is a pathogenetic link between the secondary probably occurrence of EX in the metaplastic BE-gastric mucosa, can only be speculated. It can also be speculated whether, like gastric xanthoma [10], EX presents an important marker of esophageal precancerous lesions in the BE. The follow-up esophagogastrosocopy performed so far does not show such changes. A recent study, using data from the Seattle BE-program, reported a reduced incidence of esophageal adenocarcinoma in Barrett's esophagus patients currently using NSAIDs, suggesting that NSAIDs may help prevent the progression from BE to esophageal adenocarcinoma [9].

Further case reports or large series investigations are required in order to prove this relationships.

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