

# Non-gastric Gastrointestinal Xanthomas: Case Series and Literature Review

Cristina Díaz del Arco<sup>1</sup>, Ángel Álvarez Sánchez<sup>2</sup>, M. Jesús Fernández Aceñero<sup>2</sup>

1) Department of Surgical Pathology;  
2) Department of Gastroenterology, Hospital Clínico San Carlos, Madrid, Spain

**Address for correspondence:**  
Dra. Cristina Díaz del Arco  
Department of Surgical Pathology  
Hospital Clínico San Carlos  
C/Profesor Martín Lagos s/n  
28040 Madrid, Spain  
[crisdelarco@gmail.com](mailto:crisdelarco@gmail.com)

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## ABSTRACT

Gastrointestinal xanthomas are infrequent non-neoplastic lesions characterized by the accumulation of foam cells in the lamina propria. They are commonly seen in association with dyslipidemia, chemotherapy or radiotherapy, and infections in immunosuppressed patients. However, no clear connection to hyperlipidemia has been found. They occur more frequently in the stomach, and are very rare in the small bowel and esophagus. We identified all cases of non-gastric xanthoma or xanthomatosis reported in the English literature by searching the PubMed database and retrospectively reviewed the clinical, endoscopic, and histopathologic features of the 11 cases of non-gastric gastrointestinal xanthomas diagnosed in our hospital. Nine lesions were located in the large bowel, one in the duodenum and one in the esophagus. All xanthomas were small (<5 mm) sessile polyps except the esophageal xanthoma, which measured 13 mm. Two cases in the large bowel and the case in the small bowel were multiple. Most patients with large bowel xanthomas had hypercholesterolemia, unlike esophageal and small bowel cases. The esophageal lesion occurred in a patient with a history of partial fundoplication due to gastroesophageal reflux disease and the small bowel case was associated to chronic atrophic gastritis with intense activity. In our search of the English literature, we found 19 cases of xanthoma or xanthomatosis in the esophagus, 13 cases in the small bowel and 61 cases in the large bowel. In conclusion, gastrointestinal xanthomas, other than the gastric ones, are rare, and are usually incidental findings.

**Key words:** xanthelasma – xanthoma – xanthomatosis – esophagus – small bowel – large bowel.

**Abbreviations:** AIDS: Acquired immunodeficiency syndrome; CESD: Cholesterol ester storage disease; ChT: Chemotherapy; CMV: Cytomegalovirus; GERD: Gastroesophageal reflux disease; HCL: Hypercholesterolemia; HCV: Hepatitis C virus; HPV: Human papilloma virus; MAI: *Mycobacterium avium intracellulare*; PCR: Polymerase chain reaction; RT: Radiotherapy.

## INTRODUCTION

Gastrointestinal (GI) xanthomas are infrequent non-neoplastic lesions characterized by the accumulation of large foam cells in the lamina propria [1]. They have not been reported frequently in the literature [2]. Originally termed “lipoidinseln”, more recently these lesions are named xanthelasma or xanthoma [3, 4]. They are commonly seen in patients with dyslipidemia or other conditions such as previous chemotherapy, radiotherapy, and infection [disseminated *mycobacterium avium intracellulare* (MAI) and

*cytomegalovirus* (CMV) colitis] in immunosuppressed patients (AIDS) [5]. Gastric xanthomas arise in the pathologic gastric mucosa (chronic gastritis, intestinal metaplasia, atrophic gastritis, gastric ulcer and changes due to excess bile reflux). The reported incidence is quite variable (0.018%-0.8%) in the endoscopy series, but reached 58% in an autopsy series [4]. The incidence is higher in elderly patients [5, 6].

Xanthomas are usually incidental findings [2] and complaints of symptomatic patients are unlikely to be related to them [6].

Gastrointestinal xanthomas usually occur in the gastric antrum (68%) along the lesser curvature, or as a part of xanthoma disseminatum [1]. They rarely occur in the small intestine, colon or esophagus [7]. Outside the GI tract, xanthomas are more frequent in soft tissues and skin. However, their histopathological features are identical regardless of location [3].

Endoscopy shows small (1-2 mm) single or multiple yellow, orange or white well-demarcated sessile macules with irregular outlines that rarely exceed 5 mm [3]; larger lesions

may be nodular and elevated [1]. Microscopically, they are composed of compactly aggregated nests of large periodic acid-Schiff (PAS)-negative round cells with small nuclei and foamy cytoplasm [3]. Most cells are histiocytes, although plasma cells, smooth muscle cells and Schwann cells may contribute to the whole picture [6].

Differential diagnosis includes poorly differentiated carcinoma, storage diseases, infections (Whipple disease, mycobacterium, and AIDS), macroglobulinemia, and muciphages. The clinical picture together with the past medical history, symptoms of storage diseases, AIDS and/or macroglobulinemia, is essential. In addition, special stains such as Gram, Ziehl-Neelsen, Gomori methenamine silver, PAS and PAS-Diastase and immunohistochemistry for cytokeratin AE1-AE3 can be helpful [5].

Although more than 100 years have elapsed since the first description of "lipid-laden macrophages in gastric mucosa" (Orth, 1887), the significance and etiology of gastrointestinal xanthomas remain largely unclear [6]. Biliary reflux could be an important etiological factor [1]. Mucosal damage has been presumed to play a major role in their pathogenesis as it produces lipid-containing debris, which are eventually phagocytized by histiocytes forming foam cells [3]. This theory would explain why gastric xanthomas appear to be more frequent than esophageal xanthomas, as traumatism and inflammation may be better tolerated by esophageal squamous epithelium than by gastric columnar epithelium [2]. However, the increased detection in these patients could be biased by the fact that they are more frequently subjected to endoscopy and other additional tests than healthy population. Xanthomas are usually asymptomatic and can go undetected if the patient has no associated GI lesions. Other authors suggest that they may be a sign of aging of the gastric mucosa [6].

Ultrastructural studies have shown that the foam cells originate from two sources, histiocytes and smooth muscle cells [1]. Chemical analysis of these lesions has shown the presence of cholesterol, neutral fats, low-density lipoprotein and oxidized low-density lipoprotein [6]. However, there is no documented relationship between gastric xanthoma and hyperlipidemia [3, 8].

We review GI xanthomas diagnosed in a single hospital between 2000 and 2015. Our cases include one xanthoma in the esophagus, another one in the duodenum and nine cases in the colon and rectum. We have reviewed all cases of non-gastric xanthoma or xanthomatosis reported in the English literature by searching the PubMed database.

## CASE SERIES

**Esophagus:** A 56-year-old female with prior history of recurrent pneumonia was admitted for medical examination because of respiratory symptoms, fever and gastroesophageal reflux disease. An upper GI series and an esophageal manometry revealed a mild esophageal motility disorder. She had normal serum fat levels. An upper GI endoscopy showed a 13 mm sessile polyp with white vascular surface (Table I). Microscopically the polyp was composed of localized subepithelial nests of foam cells with small round eccentric nuclei intermixed with polymorphonuclear neutrophils (Fig. 1). The epithelium showed no changes. Histochemical stains for microorganisms and

PCR for *Tropheryma whippelii* were negative. The pathological diagnosis was esophageal polypoid xanthoma.

**Small bowel:** A 72-year-old male with no medical history of interest presented for epigastric pain. He had normal serum fat levels. The endoscopy showed dispersed white dots in duodenal and proximal jejunal mucosa (Table II). The small bowel biopsy showed multiple localized collections of foam cells in the lamina propria (Fig. 2). PAS and Ziehl-Neelsen were negative. Gastric biopsy evidenced chronic atrophic gastritis with intense activity (without evidence of *H. pylori*).

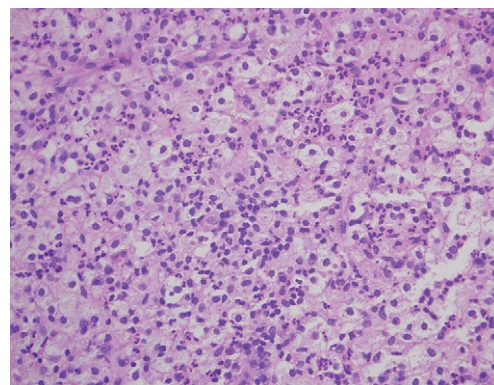
**Large bowel:** We identified nine cases of large bowel xanthoma in our institution (Table III). Mean age was 67.5 years with female preponderance. Most lesions were located in the rectum and two involved the sigmoid colon. Eight lesions were solitary and there were multiple lesions in only one case. All of them were sessile polyps, and microscopically they were composed of accumulations of foam cells (Figs. 3, 4). Six patients had hypercholesterolemia.

## DISCUSSION

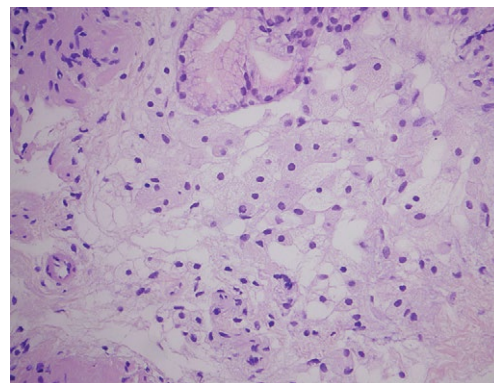
### Esophagus

The first case of esophageal xanthoma was reported by Remmele and Engelsing in 1984 [10] and since then only 19 more cases (including our case and 4 verruciform xanthoma cases) have been reported (Table I).

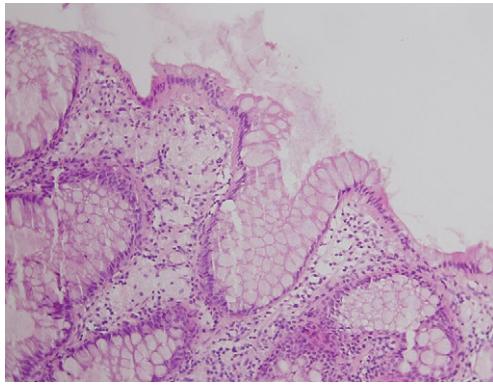
Benign esophageal lesions have a wide spectrum of clinical and pathologic features. Shu-Jung Tsai et al. studied



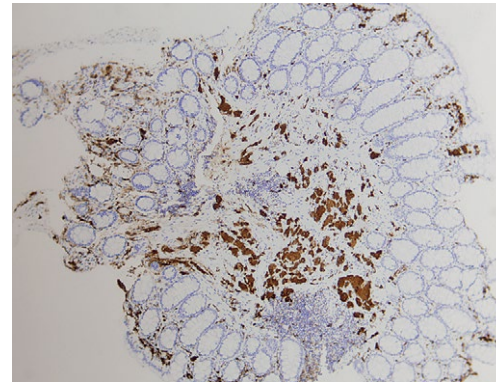
**Fig. 1.** Esophagus. Accumulation of foam cells intermixed with polymorphonuclear neutrophils (H&E x400).



**Fig. 2.** Small bowel. Foam cells: large round cells with small nuclei and finely bubbly cytoplasm (H&E x400).



**Fig. 3.** Large bowel. Accumulation of foam cells in the lamina propria (H&E x200).



**Fig. 4.** Large bowel. Foam cells showing strong CD68 staining (CD68 x100).

**Table I.** Characteristics of esophageal xanthomas and verruciform xanthomas

Case [Ref]	Sex/Age (years)	Location No.	Size (mm)	Macroscopic aspect	Other conditions
1 [10]	M/54	Upper Solitary	10	Yellow spot	Gastrectomy
2 [21]	M/45	Middle Three	<1	Yellow flat elevations	Hyperlipidemia, diabetes mellitus
3 [1]	F/37	Lower Multiple	2-5	Yellowish nodular	Gastric xanthoma
4 [3]	F/52	Lower Solitary	2	Yellowish granular	Duodenal ulcer
5 [3]	M/67	Lower Solitary	2	Yellow spots	Hepatocellular carcinoma, hypertension, coleditiasis
6 [22]	M/61	Middle Solitary	5	Verruciform	Non-Hodgkin lymphoma of the testis
7 [6]	NS	NS Multiple	<5	Yellow-white colored plaques	NS
8 [6]	NS	NS Solitary	<5	Yellow-white colored plaques	NS
9 [23]	M/49	Lower Solitary	3	Yellowish elevated granular lesión	Atrophic gastritis
10 [24]	M/74	Middle Solitary	4	Yellowish white patch	NS
11 [24]	M/74	Upper Solitary	2	Whitish protruding lesion	NS
12 [13]	M/49	Upper Solitary	3	Verruciform	NS
13 [2]	M/72	Lower Solitary	3	Yellowish elevated granular lesion	Atrophic gastritis
14 [2]	F/56	Lower Solitary	4	Yellowish elevated lesion	Biermer anemia, antral hyperplastic polyp with focal adenocarcinoma, atrophic gastritis
15 [25]	F/74	Middle Solitary	3	Verruciform	Atrophic gastritis, hyperlipidemia, dementia
16 [12]	M/70	Upper Solitary	20	Verruciform	Hypertension, HCV, hemochromatosis, glottis cancer, hepatocellular carcinoma, tracheal cancer
17 [26]	M/67	Lower Solitary	2	White-yellowish elevated lesion	Ileocecal lymphoma
18 [11]	M/70	Upper Solitary	3	Yellowish granular elevated lesion	Gastric and duodenal ulcer
19 [9]	M/62	Middle and lower Multiple	2-10	Well-defined, fern-like and yellowish lesions	NS
<b>Our case</b>	F/56	Lower Solitary	13	Sessile polyp with white vascular surface. Probably submucosal	Recurrent/persistent pneumonia. Segmental pneumonectomy due to bronchiectasis. Partial fundoplication due to GERD

M: male; F: female; NS: not specified

2,997 patients and observed that the subepithelial lesions more common in esophagus were hemangioma, leiomyoma, dysphagia aortica, granular cell tumor and xanthoma (in order of occurrence). The prevalence of benign esophageal tumors is less than 0.5%, but they represent 20% of esophageal neoplasms on autopsy. With the widespread use of endoscopy, radiologic imaging and increased awareness of the disease, these lesions could be detected more often [9].

Macroscopically, they usually are 2-10 mm yellow granular or slightly elevated lesions, resembling gastric xanthoma. Some authors suggest that granular or spotty configuration may be characteristic of esophageal xanthoma, because lipid islands are present between the rete ridges and absent beneath

them. Microscopically, lipid islands are usually located just underneath the squamous epithelium [3].

Esophageal xanthoma must be distinguished from ectopic sebaceous glands, squamous papilloma, granular cell tumor, carcinoid tumor and signet ring cell carcinoma (PAS and cytokeratin positive, opposed to CD68 positivity of xanthoma cells) [11].

Verruciform xanthomas are rare benign lesions that occur mainly in the oral cavity (70%) but can also occur in skin, especially in the anogenital area [12]. They are usually solitary lesions, but multifocal cases have been reported [13]. First described by Shafer in 1971 [1, 5], only four esophageal cases have been reported [11]. Two of them occurred in patients who

**Table II.** Characteristics of small bowel xanthomas/ xanthomatosis

Case [Ref]	Sex/Age (years)	Symptoms	Location No.	Size (mm)	Serum fat levels	Other conditions
1 [6]	F/NS	No	Duodenum Multiple	5-10	NS	Gastric dysplasia, Barrett's esophagus. Son with esophageal xanthoma
2 [6]	NS	No	Duodenum Multiple	5-10	NS	NS
3 [8]	M/68	Severe abdominal pain and constipation	Jejunum Solitary	93	Normal	Diverticulosis of sigmoid colon. Nodular melanoma in left arm. CT scan for melanoma staging with mass in the lower abdomen.
4 [27]	F/3	Dysphagia for solids with frequent vomiting	Duodenum Multiple	NS	NS	CHILD syndrome
5 [5]	F/51	Copious vomiting and intermittent abdominal pain	Jejunum Solitary	NS	NS	CT scan: adynamic ileus with jejunal loop thickening and inflammatory changes suggestive of foreign body obstruction
6 [17]	F/70	Incidental finding in colon and small bowel resection for ischemia.	Ileum Solitary	NS	NS	Ruptured infrarenal abdominal aortic aneurysm. Sigmoid resection because of metabolic acidosis and necrosis.
7 [28]	M/22	Malignant obstruction of common bile duct with HCL and xanthomatosis	Duodenum + lymph nodes Multiple	NS	Increased. Normalized after surgical treatment	Duodenal carcinoma
8 [7]	M/22	Intestinal obstruction. Total parenteral nutrition	Ileum Multiple	1-2	NS	Ewing sarcoma of the right hip treated with radiation therapy
9 [29]	M/54	Autopsy finding	Jejunum Multiple	1-3	NS	Hepatocholangiocarcinoma with bone metastases, RT and ChT. Wine-colored stool and endoscopy with dilatation of jejunum and regular thickening of mucosal folds
10 [30]	M/33	Intermittent abdominal pain, partial small bowel obstruction	Ileum + cecum NS	NS	NS	AIDS. Pneumocystis pneumonia and disseminated MAI, successfully treated. CMV colitis
11 [31]	M/67	Skin xanthomatization	Duodenum + rectum + skin Multiple	NS	Normal	Multiple myeloma ChT
12 [32]	F/54	Multiple skin xanthomas	Ileum NS	NS	HCL	Pericholangiolar biliary cirrhosis
13 [33]	M/70	Epigastric pain, weight loss	Jejunum + stomach Multiple	NS	NS	Gastrectomy Billroth II, stomatitis, bile reflux
<b>Our case</b>	M/72	Epigastric pain	Duodenum + jejunum Multiple	NS	Normal	Chronic atrophic gastritis with intense activity (without evidence of infection by H. pylori)

HCL: Hypercholesterolemia; RT: Radiotherapy; ChT: Chemotherapy

**Table III.** Characteristics of colorectal xanthomas (our patients)

Sex	Age (yrs)	Location	Size (mm)	No.	Macroscopy	Serum fat	Other conditions
Female	52	Rectum	1-2	Solitary	Sessile polyp	HCL	
Female	81	Rectum	4	Solitary	Sessile polyp	HCL	
Female	67	Rectum	<5	Solitary	Sessile polyp	HCL	Diverticulosis of sigmoid colon
Male	77	Sigmoid colon	<5	Solitary	Sessile polyp	Normal	Sigmoidectomy for adenocarcinoma stage IVA (pT3 pN0 pM1, hepatic metastases)
Male	64	Sigmoid colon	3	Solitary	Sessile polyp	HCL	
Male	68	Rectum	2-3	Multiple	Sessile polyps	HCL	Sigmoidectomy for adenocarcinoma stage IIIB (pT3 pN1)
Male	60	Rectum	3-4	Solitary	Sessile polyp	Normal	Lung adenocarcinoma stage IV (bone metastases), obesity
Male	74	Rectum	3	Solitary	Sessile polyp	NS	
Male	65	Rectum	2	Multiple	Sessile polyps	HCL	Recurrent low-grade papillary urothelial carcinoma of the bladder

HCL: hypercholesterolemia

underwent thoracic radiotherapy for systemic non-Hodgkin lymphoma and squamous carcinoma of the tracheal carina. Microscopically, the lesions are characterized by an epithelial mucosa with papillomatosis, acanthosis, hyperkeratosis with a prominently eosinophilic thickened parakeratin layer and neutrophilic intraepithelial exocytosis [12]. The histological differential diagnosis includes squamous papilloma, verrucous carcinoma and papillary squamous cell carcinoma.

As for the pathogenesis, this lesion may represent an unusual reaction to localized epithelial trauma or damage and radiotherapy has also been advocated as a potential etiologic factor. The etiology is unknown, and most cases are not related to human papilloma virus (HPV) infection. The presence of HPV in the epithelial cells has been demonstrated in only two reported lesions in the oral mucosa [15] and scrotum [16].

### Small bowel

We found 13 previous cases of small bowel xanthoma or xanthomatosis in the English literature: 3 xanthomas (localized) and 10 cases of xanthomatosis (diffuse) (Table II).

Several disorders of the small intestine can show accumulations of vacuolated macrophages including single or multiple xanthelasmata, Wolfman's disease, cholesterol ester storage disease (CESD), xanthomatogranulomatotic disease and xanthelasma disseminatum. Xanthelasma disseminatum is a rare mucocutaneous xanthomatosis characterized by cutaneous xanthomas and xanthoma in the gastrointestinal tract, though only exceptionally in the intestine [8].

Pathogenesis of small bowel xanthoma or xanthomatosis is unknown. Intestinal xanthomatosis is a non-neoplastic diffuse lesion that can lead to obstruction and can present as a mass-like lesion mimicking malignant tumor obstruction due to prominent fibrosis and inflammation. It occasionally involves several compartments of the gastrointestinal tract [17], and it is not associated with predisposing conditions such as hyperlipidemia or lymphoproliferative lesions [5].

### Large bowel

We found 61 cases of large bowel xanthoma in the English literature: 54 of them were reviewed in three major studies by

Nakasono et al. [18], Miliauskas [19] and Okano et al. [20]. In our institution, we found 9 cases of colorectal xanthoma (Table III).

Nakasono et al. studied 28 polypoid colorectal xanthomas in 25 patients [18]. Median age was 64 years, and there were 15 males and 10 females. Seven patients had prior history of hyperlipidemia; 60% of cases were located in the sigmoid colon and the remaining cases in the rectum. Macroscopically, 23 polyps were sessile; 60% of them were reddish and only two polyps revealed a yellowish tone, a fact that can be due to the capillary proliferation behind the epithelium; mean size was 5 mm (2-14 mm). Microscopically, the foam cells were confined to lamina propria, and in 78% of cases the superficial epithelium showed a hyperplastic change. In two patients a synchronous carcinoma was found. The macroscopic findings of colorectal xanthomas are different from gastric and esophageal xanthomas, which are usually non-polypoid and yellowish. They also have microscopic peculiarities so the authors propose the term "xanthomatous polyp" for these large bowel lesions.

Large series of cases [19, 20] have shown a slight female preponderance and no association to hyperlipidemia.

The differential diagnosis must include collections of muciphages (PAS and alcian blue positive), Whipple disease, melanosis coli, malakoplakia (the colon is the most common site of involvement by malakoplakia outside the urogenital tract) and xanthogranulomas (composed of foamy histiocytes with fibroblasts, lymphocytes and plasma cells) [18].

As for the pathogenesis, Remmele and Engelsing [10] considered that toxic factors from the intestinal lumen damage the mucosa, and colorectal xanthoma could be a sign of previous mild damage. The cause of damage may be focal occult infection or a mechanical force of the feces. Okano et al. [20] suggested that there could be an association between colorectal xanthoma and carcinoma, and this relationship could be due to the slow transit time of feces in the sigmoid colon and rectum. A low intake of dietary fiber prolongs transit fecal time and increases the mucosal damage and exposure to potential carcinogens such as bile acids. Moreover, a high intake of animal fat and high serum

lipid levels also support a possible relationship between these entities [20].

## CONCLUSION

Gastrointestinal xanthomas other than the gastric ones are rare. They are usually incidental findings and their pathogenesis is not entirely elucidated.

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**Authors' contribution:** C.D.del A.: study concept and design, data acquisition, analysis and interpretation, drafting of the manuscript; Á.Á.S.: study concept and design, data analysis and interpretation, critical revision; J.F.A.: study concept and design, drafting of the manuscript, data analysis and interpretation, critical revision.

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# Xantoamele gastrointestinale non-gastrice: o serie de cazuri și revista literaturii

## ABSTRACT / REZUMAT

Xantoamele gastrointestinale sunt leziuni non-neoplazice puțin frecvente, caracterizate prin acumularea de celule spumoase în lamina propria. Ele se asociază adesea cu dislipidemia, cu chimioterapia sau radioterapia, și cu infecțiile la pacienții având imunodepresie. Cu toate acestea, nu s-a găsit o legătură clară cu hiperlipidemia. Xantoamele se localizează mai frecvent în stomac, și sunt foarte rare în intestinul subțire sau esofag. Noi am identificat toate cazurile de xantoame non-gastrice raportate în literatura de limbă engleză prin căutarea în baza de date PubMed, și am revăzut retrospectiv modificările clinice, endoscopice și histopatologice ale celor 11 pacienți cu xantoame gastrointestinale non-gastrice diagnosticați în spitalul nostru.

Toate xantoamele din cazuistica noastră au fost polipi sesili mici (<5 mm) cu excepția celui esofagian, care a măsurat 13 mm. Leziunile au fost multiple la doi pacienți cu localizare în colon și la pacientul cu localizare în intestinul subțire. Cei mai mulți pacienți cu xantoame în colon aveau hipercolesterolemie, spre deosebire de pacienții cu xantom esofagian sau în intestinul subțire. Leziunea esofagiană a fost prezentă la un pacient cu fundoplicație parțială în antecedente pentru boală de reflux gastro-esofagian, iar localizarea în intestinul subțire s-a asociat cu gastrită cronică atrofică cu activitate intensă. În cazuistica din literatură am găsit 19 cazuri de xantoame sau xantomatoză localizate în esofag, 13 în intestinul subțire și 61 în colon. În concluzie, xantoamele gastrointestinale, altele decât cele gastrice, sunt rare, și sunt de obicei descoperite incidental.