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CASE REPORT

Esophageal xanthoma with nearby coexistent squamous cell carcinoma observed using magnifying endoscopy with narrow-band imaging

Tomohiko Mannami[1] · Tsukasa Sakaki[1] · Takehiro Tanaka[2] · Yasushi Fukumoto[1] · Toshiyuki Wakatsuki[1] · Shinichi Furutachi[1] · Shin'ichi Shimizu[1] · Tsuyoshi Umekawa[1] · Mayu Mitsumune[1] · Hanako Nagahara[1] · Genyo Ikeda[3] · Nobukiyo Fujiwara[3]

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Abstract

We report the case of a 63-year-old man who underwent annual surveillance esophagogastroduodenoscopy, during which a small squamous cell carcinoma and a tiny yellowish granular lesion were found in the middle esophagus, slightly apart from each other. Magnifying endoscopy with narrow-band imaging of the yellowish granular lesion showed yellowish spots and blots scattered within an approximately 2-mm area. The larger spots appeared nodular and were overlaid with tortuous microvessels. Subsequently, both the lesions were excised en masse via endoscopic submucosal dissection, and the yellowish lesion was determined to be xanthoma. Histologically, an aggregated nest of foam cells surrounded by intrapapillary capillary vessels filled the intraepithelial papillae; the foam cells also extended inferiorly, below the rete ridges, and were sparsely distributed through the lamina propria mucosae. To our knowledge, the latter finding is the first to be described in literature, which leads us to postulate that the number of foam cells in the lamina propria mucosae may affect how thick and yellow a xanthoma appears on endoscopy. We believe that this case that presents a highly detailed comparison between endoscopic and histologic findings improves our understanding of the endoscopic appearance of esophageal xanthomas and may facilitate a precise diagnosis of this rare disease.

Keywords Xanthelasma · Endoscopic features · Intrapapillary capillary loop (IPCL) · One-to-one correspondence between endoscopic and histologic findings · Endoscopic submucosal dissection (ESD)

Introduction

Xanthomas are non-neoplastic lesions caused by the accumulation of lipid-containing foamy histiocytes and can occur anywhere in the body; they are commonly observed on the skin and in soft tissues. Xanthoma of the upper gastrointestinal tract can be incidentally discovered during gastrointestinal endoscopy for investigation for other diseases. The incidence of xanthomas of the upper gastrointestinal tract detected on endoscopy is 0.23%, with most cases found in the stomach [1]. Esophageal xanthomas are extremely rare; the first case was reported in 1984 [2], and only 27 cases have been reported since then [2–19]. This type of xanthoma is asymptomatic and usually manifests as a solitary lesion. Its endoscopic appearance may include yellowish granular spots, yellowish elevated lesions, yellowish-white colored plaques, and yellow verruciform lesions of 2–20 mm (usually ≤ 5 mm) [15]. Due to the rarity of the disease, the available literature contains very little data on esophageal xanthoma observed via magnified endoscopy [15, 17, 19]. Herein, we present a case of esophageal xanthoma and a nearby squamous cell carcinoma. Close observation using a magnifying endoscopy with narrow-band imaging (NBI) followed by en bloc endoscopic submucosal dissection enabled a more accurate evaluation of the

✉ Tomohiko Mannami
tmannami-gi@umin.ac.jp

[1] Department of Gastroenterology, National Hospital Organization Okayama Medical Center, 1711-1 Tamasu, Kita-ku, Okayama 701-1192, Japan

[2] Department of Pathology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama 700-8558, Japan

[3] Department of Internal Medicine, Chugoku Central Hospital, Fukuyama 720-0001, Japan

endoscopic and histological appearances and their correlations, thereby providing some new characteristic findings of esophageal xanthoma.

Case report

A 63-year-old man underwent esophagogastroduodenoscopy (EGD) for esophageal cancer surveillance. The patient had a history of *Helicobacter pylori* infection, which had been eradicated, and he had undergone treatment for esophageal cancer through endoscopic submucosal dissection (ESD) 2 years previously without recurrence. The patient used to drink and smoke heavily in the past. The patient's father had been diagnosed with esophageal cancer. The patient's vital signs were normal and no abnormalities were noted on physical and radiologic examinations and laboratory tests.

Conventional white-light endoscopy (GIF-H260Z; Olympus Co., Tokyo, Japan) revealed a faintly depressed, slightly red lesion of ~ 5 mm in the middle esophagus, which was suspected to be esophageal cancer (Fig. 1). In addition, a tiny yellowish granular lesion was observed at a small distance from the depressed lesion. Using NBI produced better contrast between the two lesions and the surrounding mucosa than white-light imaging (Fig. 2a). Slight magnification revealed that the yellowish lesion comprised several small, light-yellow dots (Fig. 2b). Maximum magnification with NBI revealed light-yellow spots and blots of up to 0.1 mm in diameter scattered at intervals within an area of approximately 2 mm. The larger spots appeared nodular and each had tortuous microvessels directly above it. No irregular caliber or variation in shape was apparent (Fig. 2c). Differential diagnosis suggested xanthoma or ectopic sebaceous glands but a definitive diagnosis using endoscopy alone was difficult. On the other hand, the slightly depressed reddish lesion was judged as squamous cell carcinoma with an invasion depth to the epithelium or lamina propria mucosae based on the nature of the accompanying microvessels. The microvessels were abnormally irregular with loop-like formations, which corresponded to the magnifying endoscopic classification of type B1 vessels as per the Japan Esophageal Society [20] (Fig. 2d), whereas those in the yellowish lesion were type A1 vessels. Due to their proximity, the yellowish granular lesion was resected en masse along with the squamous cell carcinoma within the same resection area. Resection was performed through ESD.

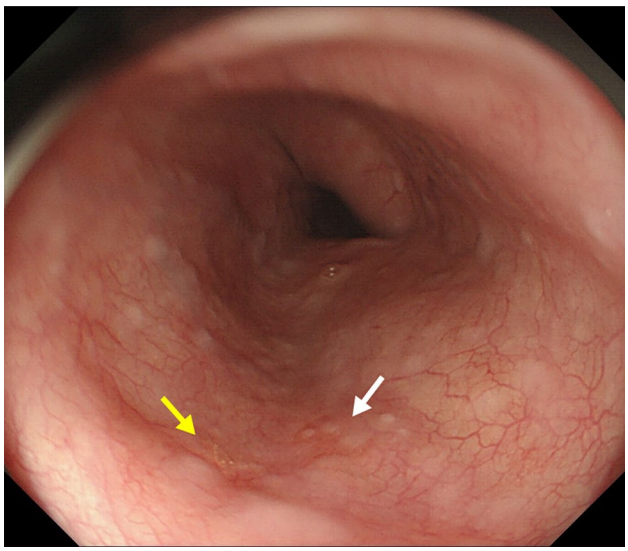


Fig. 1 Conventional white-light endoscopic image of the esophagus of the patient in this case. The image showed a faintly depressed, slightly red lesion with a diameter of approximately 5 mm (white arrow) and a smaller, yellowish granular lesion (yellow arrow) located < 1 cm away, in the middle esophagus (GIF-H260Z; Olympus Co., Tokyo, Japan)

The resected specimen contained both the depressed as well as the yellowish granular lesion, which were 3 mm apart, with sufficient horizontal and vertical surgical margins (Fig. 3a, b). Microscopy confirmed that the depressed lesion was a squamous cell carcinoma in situ with a diameter of 4 mm (Fig. 3c). Histological examination of the yellowish lesion revealed that the intraepithelial papillae were filled with compactly aggregated nests of foam cells (Fig. 3d). These had small round or oval-shaped nuclei located centrally or eccentrically and finely vacuolated cytoplasm (Fig. 3e, f). Positive CD68 immunohistochemical staining confirmed that these cells were foamy macrophages (Fig. 3g, h). Few tiny foam cells were also found in the squamous epithelium. The foam cells also extended downward beneath and below the rete ridges and were sparsely distributed in the lamina propria mucosae. The foam cells in the lamina propria were confined to the area beneath the yellowish lesion and were not present beneath the carcinoma or elsewhere. These morphologic findings combined with the immunohistochemical profile allowed for the definitive diagnosis of the yellowish lesion as esophageal xanthoma. The patient was followed up for 20 months after the resection and no recurrence was noted.

The endoscopic findings for the esophageal xanthoma were adjusted to the corresponding histologic findings (Fig. 4a–d) through a detailed comparison of histologic, macroscopic, and endoscopic images using a modification of the method previously described by Fujita et al. [21]. The larger yellowish spots observed on endoscopy corresponded histologically to larger papillae filled with more abundant foam cells at shallower locations. Conversely, smaller yellowish spots corresponded histologically to smaller papillae less abundantly packed with foam cells at deeper locations (Fig. 4e, f). A round yellowish area on endoscopy corresponded to the aggregated foam cells seen after hematoxylin and eosin staining, whereas the tortuous microvessels over

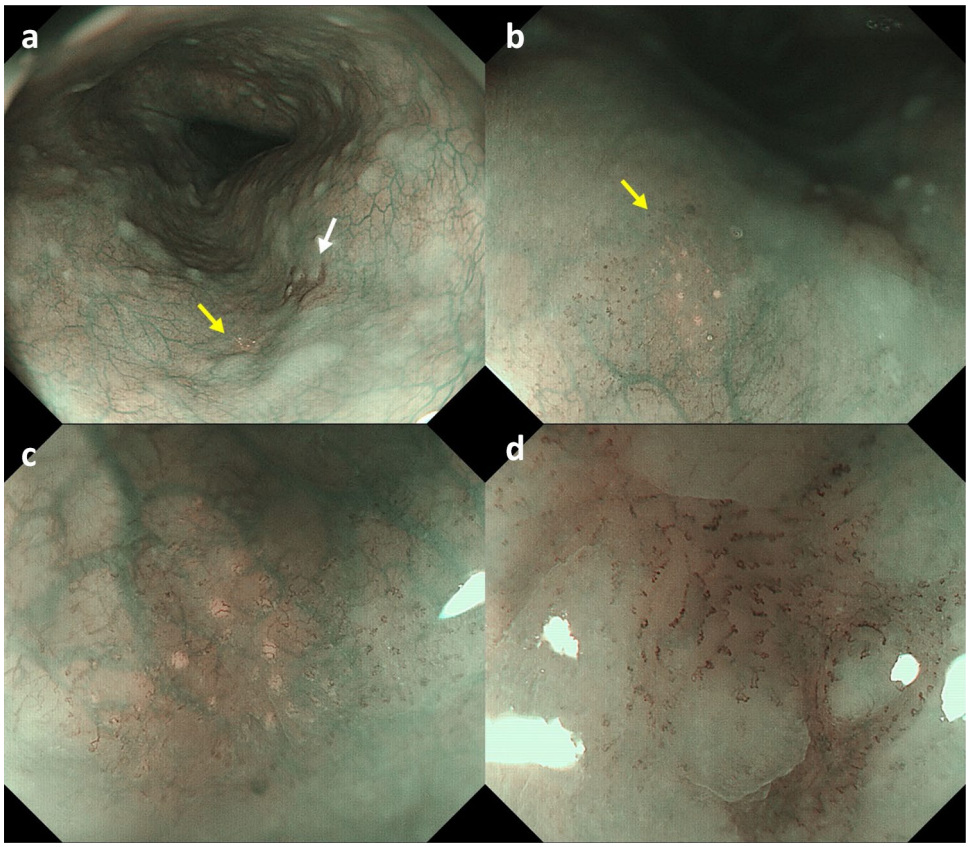


Fig. 2 Endoscopic images with narrow-band imaging of the esophageal abnormalities observed in this case. **a** Endoscopic observation using narrow-band imaging (NBI) provided better contrast with the surrounding mucosa than white-light imaging when viewing the slightly depressed lesion (white arrow) and the yellowish granular lesion (yellow arrow) in the middle esophagus of our patient. **b** Closer observation with slight magnification showed the yellowish granular lesion (yellow arrow) to consist of several small yellowish dots. **c** Maximum magnification revealed yellowish spots and blots of different sizes, up to 0.1 mm in diameter, scattered at intervals across an area of approximately 2 mm. Each of the relatively larger spots, appearing nodular, had tortuous microvessels directly above it, without irregular caliber and shape variation. In images **c** and **d**, up is toward the mouth and down is toward the stomach. **d**. Maximum magnification of the depressed lesion showed abnormally irregular microvessels with a loop-like formation, suggesting squamous cell carcinoma with an invasion depth somewhere between the level of the squamous cell epithelia and the lamina propria mucosae. Intervascular background coloration was also observed

the yellowish area corresponded to capillary vessels in the papillae (Fig. 4g).

The patient had undergone annual endoscopic checks at our institution for the past 4 years. A retrospective review of all endoscopic images of the patient found that the xanthoma had been present in images taken 3 years ago. At the time, the endoscopist had misdiagnosed it as an ectopic sebaceous gland. The morphology of the lesion in the older images appeared virtually identical to the current images but slightly more prominent (Fig. 5a, b).

Discussion

Two important clinical observations were made in this case. First, magnifying endoscopy with NBI showed the esophageal xanthoma as an aggregation of tiny yellowish spots and blots of different sizes overlaid with tortuous microvessels. Second, histologic analysis revealed that the xanthoma cells not only formed an aggregated nest in the intraepithelial papillae, but also extended downward below the rete ridges and were sparsely distributed in the lamina propria mucosae.

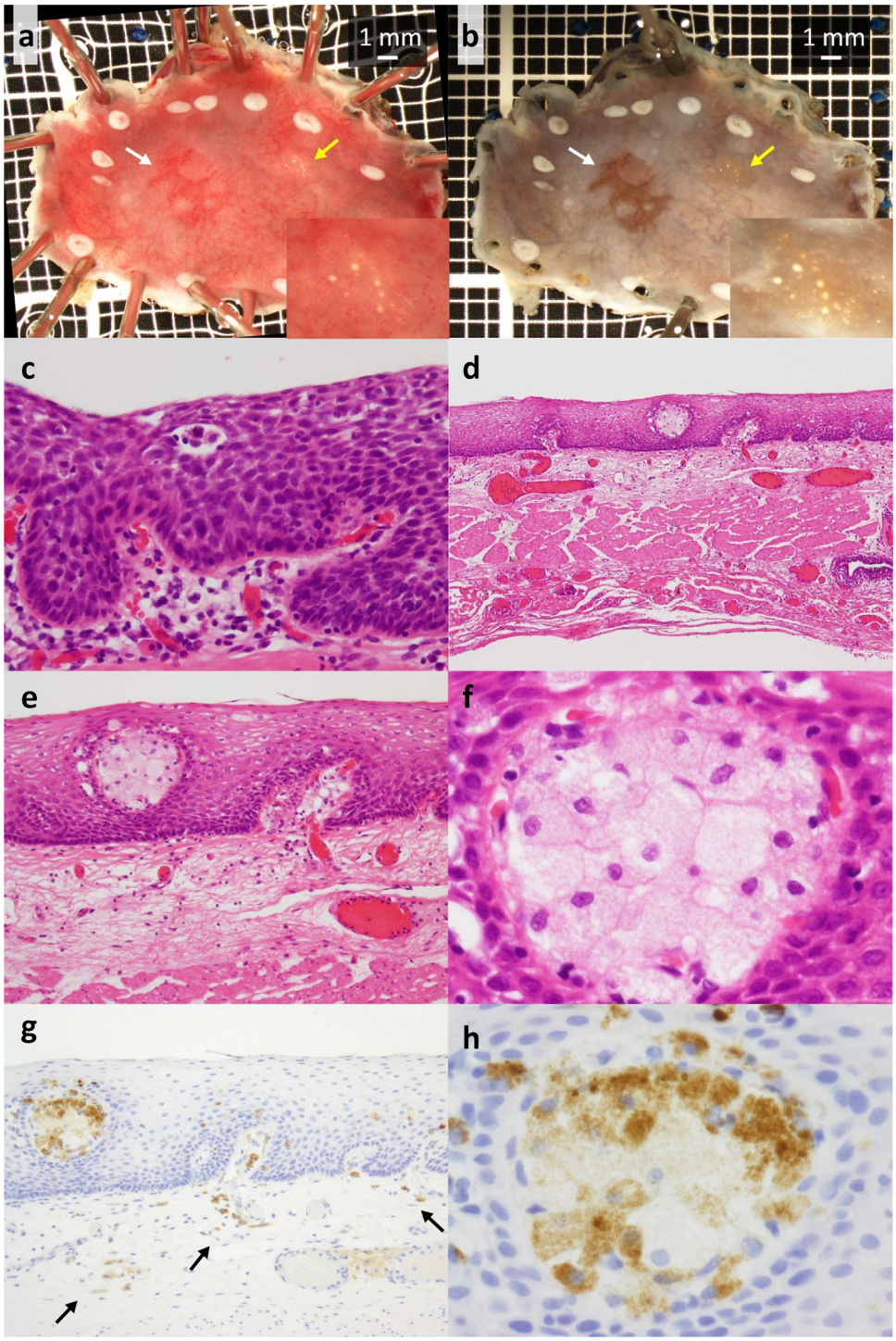
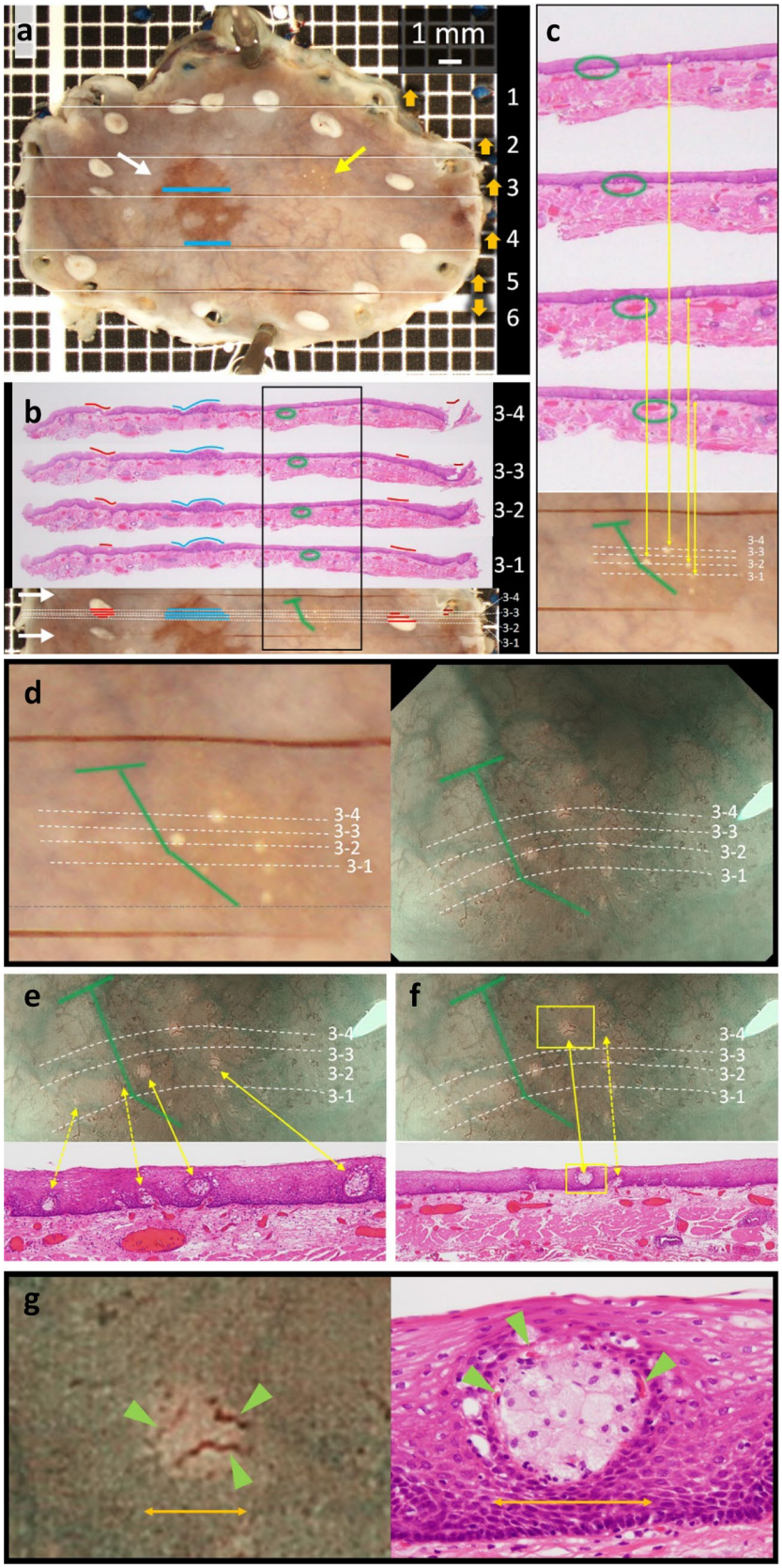


Fig. 3 Histopathological findings from the endoscopic submucosal dissection specimen in this case. **a**, **b** Macroscopic views of the resected specimen before and after formalin fixation. The specimen contained both the depressed lesion (white arrow) and the yellowish granular lesion (yellow arrow). Inset images of each show further magnification of the yellowish granular lesion. The upward direction in the images indicates the oral side of the resected specimens. A single square in the background is equivalent to 1 mm. **c** Microscopic appearance of the depressed lesion (hematoxylin and eosin (HE) staining, 20 × magnification). The tumor cells proliferated in the squamous epithelium, causing inflammation, pleomorphism, hyperchromasia, and loss of polarity. **d** Microscopic appearance of the yellowish lesion (HE staining, 4×). Compactly aggregated nests of foam cells filled the intraepithelial papillae. **e, f** Histological findings (HE staining, magnified 10× and 40×, respectively). The foam cells had finely vacuolated cytoplasm and small round or oval-shaped nuclei located centrally or eccentrically. **g, h** Immunohistochemical findings (10× and 40×, respectively). The foam cells that filled the papillae were positive for CD68. A small number of tiny foam cells were also found in the squamous epithelium. The foam cells also extended downward beneath and below the rete ridges and were distributed sparsely in the lamina propria mucosae (arrows)

First, esophageal xanthoma in our case showed an aggregation of tiny yellowish spots and blots of different sizes overlaid with tortuous microvessels as a characteristic finding on magnifying endoscopy. This endoscopic appearance correlated well with the histological findings. This finding is in concordance with the observations noted in the few existing case reports on the magnified endoscopic appearance of esophageal xanthoma [15, 17, 19]. Among these is a case series of seven patients diagnosed at a tertiary cancer center in which non-magnifying endoscopy revealed esophageal xanthoma to manifest with two distinct morphologies: flat areas with yellowish granular spots and slightly elevated yellowish lesions [15]. Regardless of these two endoscopic shapes, all lesions included in the case series reportedly demonstrated characteristic findings on magnifying endoscopy, such as areas of aggregated minute yellowish spots overlaid with tortuous microvessels, which were very similar to those observed in our case. The authors of the case series suggested that the use of magnifying endoscopy with NBI may reduce the need for biopsies in the diagnosis of this disease. Interestingly, there have been case reports wherein magnifying endoscopy with NBI has found very similar characteristic features in pharyngeal xanthoma [22, 23]. The similarities in histological architecture are somewhat expected as the esophagus and the pharynx are covered with stratified squamous epithelium. Another intriguing finding from our case was that the histological findings corresponding to the endoscopically observed yellowish spots had size-dependent variations. Thus, larger yellowish spots were in shallower locations with larger papillae filled with more foam cells, whereas smaller yellowish spots were in deeper locations with smaller papillae less densely filled with foam cells. This finding is unique to our case and has not previously been observed. Hence, this case report is able to corroborate the findings from previous studies and provide new data on the features of esophageal xanthomas.

Xanthoma cells are known to form an aggregated nest in the intraepithelial papillae. Our novel and second important clinical observation was that xanthoma cells extend inferiorly beneath and below the rete ridges and are lightly distributed in the lamina propria mucosae. Several studies have shown that xanthoma cells may be present in lamina propria mucosae [2, 5–7, 10, 12, 15, 17, 19]. However, their precise distribution in squamous cell epithelium, papilla, and the lamina propria mucosae was not previously known as most reported cases have been diagnosed via biopsy. In the present case, the esophageal xanthoma was resected en bloc via ESD, thus allowing a more accurate histologic evaluation of the distribution of foam cells and their relationship with the surrounding tissue. This led us to describe the histopathological findings that have not been described previously. A case report by Mori et al. describes a 75-year-old woman with slightly raised 5-mm xanthoma of the thoracic esophagus. This was resected using ESD as a total excisional biopsy because the possibility of a neoplastic lesion could not be excluded [17]. Histopathological examination revealed foamy macrophages positive for CD68 accumulated densely as a band-like mass in the lamina propria mucosae. These two cases, that of ours and that described by Mori et al., infer that foam cells may be sparsely or densely distributed in the lamina propria mucosae in esophageal xanthoma. Of note, the differing distributions of foam cells in the lamina propria mucosae found histologically in these two cases were reflected in different endoscopic appearances. In the current case where the distribution of foam cells in the lamina propria mucosae was sparse, the endoscopic findings showed only yellowish granular spots but no yellow background coloration. However, in the case reported by Mori et al. where foam cells accumulated densely in the lamina propria mucosae, the endoscopic findings showed not only yellowish granular spots in the superficial layer, but also dense yellowish background areas with plaque-like morphology and slight elevation of the entire area. Hamada et al. have proposed that differences in the endoscopic appearance of esophageal xanthoma represent differences in the density of foam cell-filled papillae [15]. In addition to that, we suggest that the degrees of yellow coloration and apparent thickness observed in esophageal xanthoma endoscopically appear to reflect the amount of foam cell deposition in the lamina propria mucosae.

The etiology of esophageal xanthoma remains unclear. It has been postulated that chronic inflammation causes focal mucosal damage by promoting the production of lipid-laden debris. This is eventually phagocytized by histiocytes to form foam cells [5]. Previous research has found associations between esophageal xanthoma and a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◂**Fig. 4** Correspondences between the endoscopic and histologic representations of the esophageal xanthoma in this case. **a** Macroscopic view of the fixed specimen with incision showing the area of carcinoma in situ (white arrow) and the xanthoma (yellow arrow). The blue line indicates the extent of the carcinoma as determined with histopathology. The white lines indicate the sectioning lines. The numbers to the right are the specimen numbers. The orange arrows show the direction of each sectioning. **b** Since the initial sections were considered less representative of the histopathology of the xanthoma, deeper sections were made for specimen 3. The upper four pictures are histological images of the four section depths (numbered from 3–1 to 3–4); the lower image is a macroscopic view of specimen 3. White arrows indicate mucosa-cut lines. Both images are lined up to create size correspondence, with both ends aligned. The exact lines in which the hematoxylin and eosin (HE) stain section was made are shown on specimen 3 (white broken lines from 3–1 to 3–4 corresponding to the deeper sections above). These were determined by observing and comparing landmarks, such as cautery markings (red lines), holes made by mounting pins (brown lines), and branching vessels running below the epithelium (green lines). An enlarged image of the black square seen here is shown in **c**. **c** Double-headed arrows indicate correspondence between histologic and macroscopic xanthoma findings. **d** Comparison of the magnified narrow-band endoscopy images (right side) and the macroscopic view (left side). The exact lines in which the HE stain section was made are shown on the endoscopic image (broken white lines from 3–1 to 3–4 corresponding to the deeper sections in **b**. **e**, **f** The upper image shows magnifying endoscopy with NBI; the lower image is the histology of the corresponding area. A detailed comparison between histologic and macroscopic images was conducted (**c**), followed by a detailed comparison between macroscopic and endoscopic images (**d**) as described above. Thereby, complete adjustment of the endoscopic findings for the esophageal xanthoma in line with the corresponding histologic findings was achieved. The double-headed arrows show the one-to-one correspondence between endoscopic and histologic xanthoma findings. The comparisons revealed that larger yellowish spots observed on endoscopy corresponded to shallower larger papillae more densely filled with foam cells (unbroken double-headed arrows), and smaller yellowish spots corresponded to deeper smaller papillae filled with fewer foam cells (broken double-headed arrows). Comparison between the images designated in squares is shown in **g**. **g** A one-to-one correspondence between one of the yellowish nodules seen with magnifying endoscopy with NBI (left side) and a papilla filled with foam cells identified histologically (right side). An endoscopic finding of a round yellowish area corresponded to the aggregated foam cells of the HE stain section (double-headed arrows). An endoscopic finding of tortuous microvessels on a yellowish area corresponded to the capillary vessels in the papillae (arrowheads)

history of radiation therapy or chemotherapy, infection, and biliary reflux [3, 4, 9]. A medical history of esophageal as well as head and neck cancer has also shown strong correlations with esophageal xanthoma [15]. In our case, the patient had previously had esophageal cancer, which had been resected by ESD. A distinctive feature of our case was the simultaneous presence of superficial esophageal cancer close to the esophageal xanthoma. Similarly, Yang et al. have reported a case of esophageal xanthoma coexisting with superficial esophageal cancer in a 68-year-old man [19]. In Yang et al.'s patient, white-light endoscopy revealed a semicircular, irregular, yellow granular lesion of approximately 5 cm diameter in the middle and lower esophagus. Histologically, the resected specimen was revealed to be a squamous cell carcinoma in situ with extensive foamy cells in the superficial mucosal layer, indicating that the esophageal xanthoma and esophageal cancer had coexisted and overlapped. In both the Yang case and ours, the patient was an elderly man with a history of heavy drinking and smoking. These behaviors may have contributed to mucosal irritation that led to both esophageal cancer and esophageal xanthoma. Conversely, their case differed from ours in that magnifying endoscopy showed microvessels with irregular caliber. These are defined as type B1 vessels by the magnifying endoscopic classification system of the Japan Esophageal Society. Such vessels are far more closely associated with squamous cell carcinoma than nonneoplastic lesions [20]. To the best of our knowledge, no other cases reported so far, including the present case, have found B1 microvessels at the xanthoma site. It is possible that xanthomas and carcinomas in the same location may present such a vascular structure. Nevertheless, it is questionable whether this was actually a xanthoma since Yang's case is exceptionally broader than others reported. Thus, it might more accurately be classed as xanthomatous change or xanthomatosis. Regardless, it is worth considering that xanthomatous lesions of the esophagus may be associated with squamous cell carcinoma, although it is rare.

In conclusion, close observation using magnifying endoscopy with NBI followed by en bloc ESD enabled a more accurate evaluation of endoscopic and histological findings of esophageal xanthoma. This case not only corroborates the characteristic features of magnifying endoscopy with NBI, which was previously reported, but also enhances our understanding of the endoscopic appearance of this disease. Additional cases are required to further verify the consistency of these endoscopic findings, thereby ensuring their utility in the diagnosis of esophageal xanthoma.

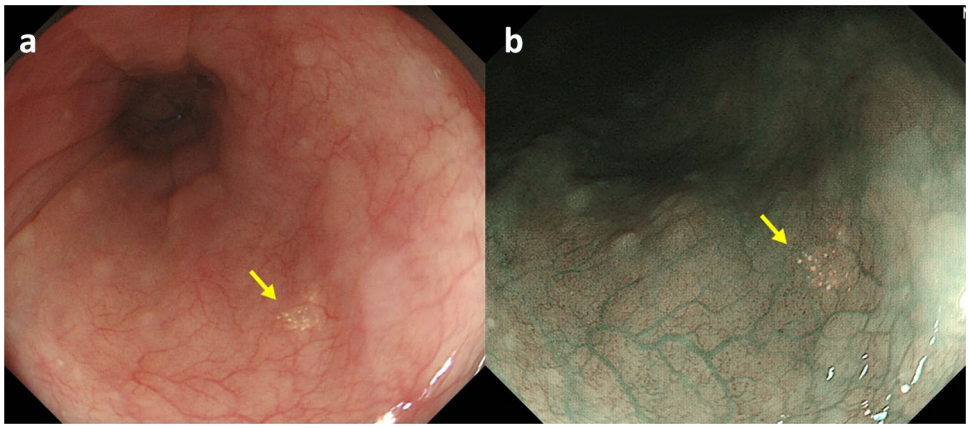

Fig. 5 Retrospectively reviewed endoscopic images of an esophageal xanthoma. Endoscopic images of the patient's esophagus were taken three years ago. Retrospective recognition of the same lesion in those images found almost identical morphology to that seen in the recent images. Although, the xanthoma appears slightly more prominent in the older images. **a** Conventional white-light endoscopic image of an esophageal xanthoma. **b** Magnifying endoscopic image of an esophageal xanthoma with narrow-band imaging

Declarations

Conflict of interest The authors have no conflicts of interest, financial or otherwise, to declare.

Ethical approval All procedures in this study were performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all patients included in the study.

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