Int J Clin Exp Pathol 2017;10(3):3565-3569
www.ijcep.com /ISSN:1936-2625/IJCEP0043182

Case Report

White opaque substance in superficial esophageal squamous cell carcinoma: report of a case

Honglei Wu[1], Jianqiang Guo[1], Chengjun Zhou[2], Zhaosheng Chen[1], Bingxin Guan[2], Kuangi Fu[3]

Departments of [1]Gastroenterology, [2]Pathology, The Second Hospital of Shandong University, Jinan, Shandong Province, China; [3]Department of Gastroenterology, Kanma Memorial Hospital, 2-5 Nasushiobara City, Tochigi, Japan

Received October 30, 2016; Accepted November 20, 2016; Epub March 1, 2017; Published March 15, 2017

Abstract: White opaque substance (WOS) observed in the gastric neoplasia by magnifying endoscopy with narrow band imaging (NBI-ME) has been reported to be useful for differentiation of gastric cancerous and non-cancerous lesions. Using oil red O staining and adipophilin immunostaining reveals WOS in gastric neoplasms as lipid droplets, and WOS is specific for neoplasm with intestinal or gastrointestinal phenotype. We here in report a case of superficial esophageal squamous cell carcinoma with WOS. A male patient in his seventies was found by esophagogastroduodenoscopy to have two superficial esophageal lesions and two superficial gastric lesions. NBI-ME observed WOS in both gastric lesions and in one esophageal lesion. The patient underwent endoscopic submucosal dissection and all the lesions were resected *en bloc* successfully. All four lesions had diffuse positivity for adipophilin on immunostaining. This is the first case reported that WOS was observed in esophageal squamous cell carcinoma.

Keywords: Squamous cell carcinoma, esophageal cancer, white opaque substance (WOS), magnifying endoscopy, narrow band imaging (NBI)

Introduction

Magnifying endoscopy with narrow band imaging (NBI-ME) has enabled visualization of mucosal microvascular and microsurface patterns. Yao et al. have identified the microvascular and microsurface patterns that are typical for early gastric cancers [1-3]. Recently, NBI-ME is also an excellent modality for identifying the boundary delineation of early gastric cancers [4-6]. Meanwhile, white opaque substance (WOS), first reported by Yao et al., is one of the peculiar findings of NBI-ME, it is a white substance in the superficial area of the gastric neoplasia and sometimes interrupts visualization of the precise microvascular morphology, which results in difficulties in discrimination of gastric cancerous and non-cancerous lesions. WOS does not just interferes with visualization of the epithelial microvascular architecture but is also useful for discriminating gastric adenoma from carcinoma according to the presence or absence of regular shapes and distribution of WOS [7]. WOS has been pathologically confirmed to be intramucosal accumulation of lipid detected using oil red O staining of the endoscopic biopsy specimen [8]. Oil red O staining enables direct visualization of lipid droplets; however, it has a limitation in that it can only be applied to fresh frozen samples but not to paraffin embedded sections as the lipid is removed during the process of paraffin fixing. Recently, adipophilin has been used as a novel marker of lipid accumulation which can be applied even to paraffin embedded section. It is an adipose differentiation related protein located on the surface of lipid droplets [9]. It was reported that immunohistochemistry of adipophilin of gastric neoplasia was well correlated with WOS observed by NBI-ME [10]. WOS has been reported to be found in neoplasms located in colorectum, duodenum and esophagogastric junction, where are all covered by columnar epithelium, histologically [11-13]. We herein report a case of superficial esophageal squamous cell carcinoma in which WOS was observed by NBI-ME.

Case presentation

A 77-year-old Chinese man visited our department because of epigastralgia. His medical his-

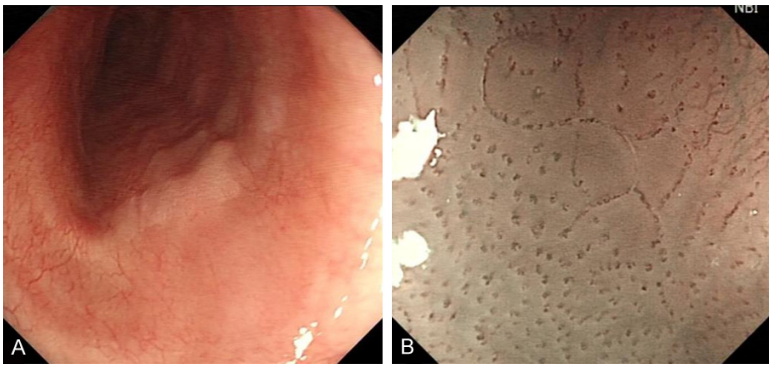

Figure 1. A. A slightly elevated lesion (IIa) of 10 mm in diameter at 28 cm from the incisor teeth. B. NBI-ME followed showed dilatation and irregularity of IPCLs, there was no obviously reticular/speckled WOS observed, the background was slightly whitish.

tories included hypertension, sinus bradycardia and coronary heart disease. He reported a 50-year history of smoking 10 cigarettes daily without alcohol drinking history. His 14C-urea breath test was positive and thus he had eradication therapy for Helicobacter pylori two months ago. No family history of gastrointestinal cancer was identified. Laboratory and physical test results revealed no special abnormalities. His body mass index was 25.

Endoscopic examination showed two superficial lesions in esophagus and two superficial lesions in stomach. Conventional white light imaging showed the whole esophageal mucosa was rough, and two flat lesion (0-IIb according to the Paris classification) of 7 mm and 15 mm in major diameter at 28 cm and 31 cm from the incisor teeth (**Figures 1A**, **2A**). Observing with NBI endoscopy, both lesion could not be detected obviously as brownish areas. Subsequently, NBI-ME, however, showed dilatation and irregularity of intraepithelial papillary capillary loops (IPCLs) (**Figures 1B**, **2B**). Additionally, WOS was observed in the distal lesion, the morphology of WOS was irregular reticular/speckled pattern as reported (**Figure 2B**, **2C**) [7]. Meanwhile, WOS was not detected in the proximal lesion, however there were whitish matter suggesting WOS in the normal mucosa surrounding this lesion (**Figure 1B**). Chromoendoscopy with 1.5% iodine staining showed multiple Lugol-voiding lesions (LVLs) in whole esophagus, and the two lesions were found as non-stained areas. Histologically, biopsy specimens revealed a squamous cell carcinoma limited within the lapmina propria mucosae (m2). Conventional white light imaging showed two additional gastric lesions, one was a flat elevated lesion with central depression (IIa+IIc) of 20 mm in size at posterior wall of upper gastric body, and the other was a flat elevated lesion (IIa) of 15 mm in size at the greater curvature of antrum. NBI showed demarcation line in both lesions. In both lesions, NBI-ME showed irregular microsurface pattern and irregular microvascular structure, and sparse WOS were also observed. Both gastric lesions were diagnosed as well differentiated adenocarcinoma by biopsies histologically. Systemic imaging investigation including computed tomography revealed no evidence of nodal or visceral metastases. We performed endoscopic submucosal dissection (ESD) for all four lesions; all lesions were resected in a single piece without major complications. The postoperative course was uneventful, and the patient was discharged several days after ESD.

Histology revealed intramucosal well differentiated squamous cell carcinomas (m2) in both esophageal ESD resected specimens (**Figure 3A**). No lymphovascular involvement was detected on immunostaining of D2/40. Oil red O staining and immunohistochemical staining of adipophilin of the biopsy specimen of the distal lesion shown lipid droplets scattered in the cytoplasm of squamous carcinoma cells (**Figure 4**). Immunohistochemical staining of adipophilin of the ESD resected specimens revealed that lipid droplets accumulated in both esophageal neoplastic epithelium. Adipophilin was intensely detected in almost all the neoplastic cells in both esophageal lesions, of which the morphology was diffuse and has no polarized structure compared with gastric lesion. In the non-neoplastic squamous epithelium adipophilin was weakly expressed (**Figure 3B**, **3C**). The morphology and density of adipophilin was similar in both lesions. The final diagnosis was well differentiated squamous cell carcinoma of the esophagus, 6×6 mm (28 cm from the incisor teeth)/17×4 mm (31 cm from the incisor teeth), 0-IIb, pT1a-LPM, ly0, v0, pHM0, pVM0 (according to the Japanese

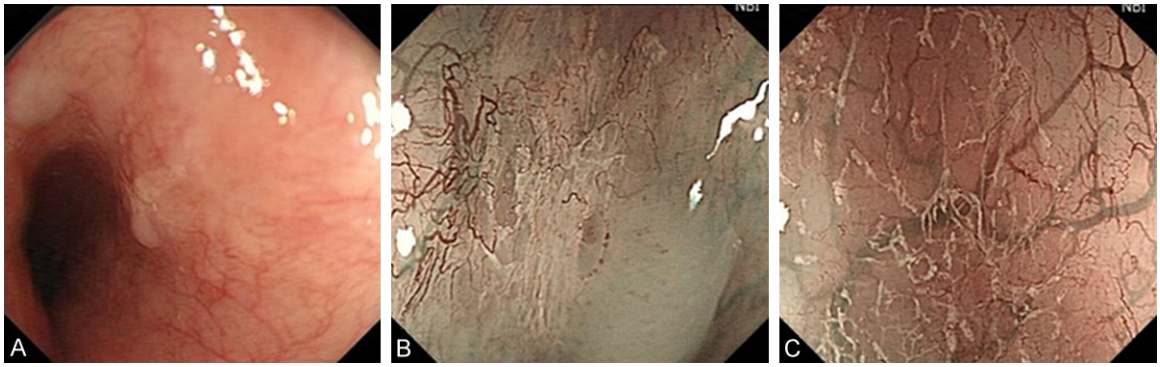

Figure 2. (A) A slightly elevated lesion (IIa) of 15 mm in major diameter at 31 cm from the incisor teeth. (B, C) WOS was observed by NBI-ME and the morphology was irregular reticular/speckled pattern, IPCLs were not distinct. (B) showed the centre of the lesion, (C) showed the margin of the lesion.

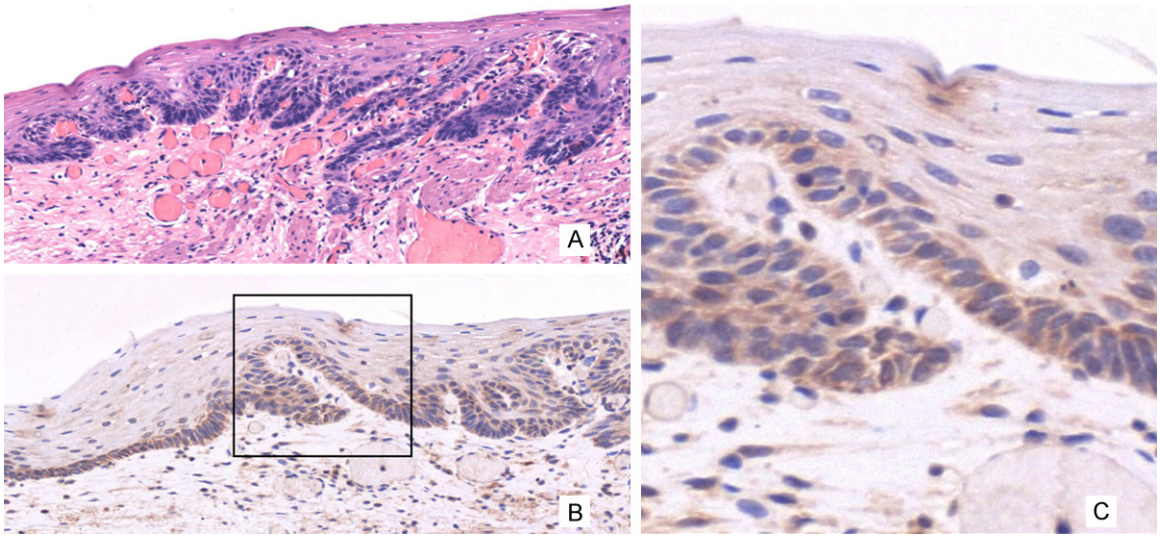

Figure 3. A. Early well differentiated squamous cell carcinoma with microinvasion (basal cell type, M2) with HE staining. B, C. Adipophilin was expressed in the squamous carcinoma cells with cytoplasmic staining and no polarization.

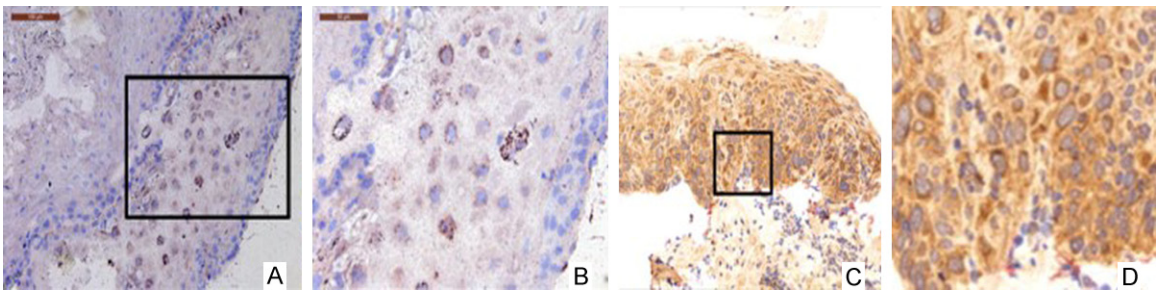

Figure 4. A, B. Oil red O staining of the biopsy specimen of the lesion at 31 cm from the incisor teeth showed lipid droplets scattered in the cytoplasm of squamous carcinoma cells. C, D. In this lesion adipophilin was expressed in the squamous carcinoma cells with cytoplasmic staining and no polarization.

Classification of Esophageal Cancer, the 10th Edition, revised version). Both gastric lesions were histologically diagnosed as intramucosal well differentiated tubular adenocarcinoma (m). No lymphovascular involvement was found. Adipophilin staining revealed that lipid droplets

accumulated in both gastric neoplastic epithelium. Adipophilin was detected in almost all the neoplastic cells in both the surface epithelium of the intervening apical and cryptal epithelium, whereas this was not observed in the non-neoplastic gastric epithelium. The morphology and density of adipophilin staining was similar in both gastric lesions. The final diagnosis was well differentiated adenocarcinoma of the stomach, 18×15 mm (posterior wall of upper gastric body)/16×9 mm (greater curvature of antrum), 0-IIa+IIc/0-IIa, tub1, pT1a-M, ly0, v0, pHM0, pVM0 (according to the Japanese Classification of Gastric Carcinoma, 3rd English Edition).

Discussion

To the best of our knowledge, this is the first report describing a WOS-positive esophageal squamous epithelial neoplasm, and we confirm the phenomenon that lipid accumulation may occur in neoplasms arising from the esophageal squamous epithelium.

The mechanism of the accumulation of lipid droplets in neoplasms is unknown. Yao et al. proposed the following two possible mechanisms of WOS formation in gastric epithelium: the absorption hypothesis and the production hypothesis [8]. The author prefered the former. They reported that WOS positive gastric neoplasms with an intestinal phenotype may be able to absorb digested micellar lipid in stomach. As the mucosal lymphatics in the stomach are anatomically present only in the deepest level of the lamina propria [14], lipid droplets cannot be easily transported into the lymphatics. Consequently, lipid droplets may be retained within the superficial part of the mucosa for a longer period, so adipophilin was expressed primarily in the basal sides of neoplasia cells, forming polarized tubular structures. Recently, few studies showed adipophilin significantly expressed in clear cell renal carcinoma, colorectal adenocarcinoma, lung adenocarcinoma, and esophageal adenocarcinoma [11, 13, 15, 16], where there were no much lipid could be absorbed. It is reasonable to speculate that accumulated lipids in cancer cells might be synthesized by neoplastic cells themselves, rather than be absorbed. So the deficiency of lipid metabolism may be involved in carcinogenesis in variant organs.

In this case adipophilin was detected in esophageal squamous carcinoma and pericarcinous tissue, but the degree of adipophilin's expression was different, which was intense in cancer tissue and weak in pericarcinous normal tissue, so we can detect WOS only in cancerous area by endoscopy. There are two possible reasons about this phenomenon: one is WOS is a sign of neoplasm not only in stomach but also in esophagus; the other is WOS is only a sign of deficiency of lipid metabolism of esophageal squamous cells and has no relationship with esophageal neoplasm, it is accidentally appeared in this WOS-positive gastric cancer patient. We prefer the former because we never detect WOS in patients with normal esophagus or benign esophageal disease. We can speculate that the intense expression of WOS is a sign of neoplasia and the weak expression of WOS is a sign of malignant potential to neoplasia. It is well established that tumor microenvironment plays an important role in cancer development and progression, so the pericarcinous normal tissue expressing WOS weakly would be the soil of neoplasia. WOS may be a key sign of cancerous and precancerous lesion of esophageal squamous epithelium. In this case the endoscopic morphology of WOS is irregular reticular/speckled pattern which is similar to gastric lesion, but morphology of adipophilin expression in squamous cancer cells is diffuse and has no polarized structure compared with gastric lesion. Hence, we can speculate that the mechanism of accumulation of lipid droplets is different in esophagus and stomach. The present findings may provide novel insights into the molecular mechanism of esophageal squamous cell carcinoma development and progression and into the development of new anticancer therapeutics. We need to conduct further studies to clarify the molecular mechanism of WOS in squamous cell carcinoma.

In summary, we present the first case of esophageal squamous cell carcinoma with WOS, which arises from esophageal squamous epithelial. Because WOS can interrupt visualization of the precise microvascular morphology of the esophageal lesion, rather than assessing the IPCLs, the emergence of WOS could be an alternative new optical sign for discriminating cancerous from non-cancerous lesion in esophagus using NBI-ME.

Disclosure of conflict of interest

None.

Address correspondence to: Kuangi Fu, Department of Gastroenterology, Kanma Memorial Hospital, 2-5 Nasushiobara City, Tochigi 325-0046, Japan. E-mail: kevin@asiastm.org

References

[1] Yao K, Iwashita A, Kikuchi Y, Yao T, Matsui T, Tanabe H, Nagahama T, Sou S. Novel zoom endoscopy technique for visualizing the microvascular architecture in gastric mucosa. Clin Gastroenterol Hepatol 2005; 3: 23-6.

[2] Yao K, Iwashita A, Tanabe H, Nagahama T, Matsui T, Ueki T, Sou S, Kikuchi Y, Yorioka M. Novel zoom endoscopy technique for diagnosis of small flat gastric cancer: a prospective, blind study. Clin Gastroenterol Hepatol 2007; 5: 869-78.

[3] Yao K, Anagnostopoulos GK, Ragunath K. Magnifying endoscopy for diagnosing and delineating early gastric cancer. Endoscopy 2009; 41: 462-7.

[4] Kaise M, Kato M, Urashima M, Arai Y, Kaneyama H, Kanzazawa Y, Yonezawa J, Yoshida Y, Yoshimura N, Yamasaki T, Goda K, Imazu H, Arakawa H, Mochizuki K, Tajiri H. Magnifying endoscopy combined with narrow-band imaging for differential diagnosis of superficial depressed gastric lesions. Endoscopy 2009; 41: 310-15.

[5] Ezoe Y, Muto M, Uedo N, Doyama H, Yao K, Oda I, Kaneko K, Kawahara Y, Yokoi C, Sugiura Y, Ishikawa H, Takeuchi Y, Kaneko Y, Saito Y. Magnifying narrowband imaging is more accurate than conventional white-light imaging in diagnosis of gastric mucosal cancer. Gastroenterology 2011; 141: 2017-25.

[6] Nagahama T, Yao K, Maki S, Yasaka M, Takaki Y, Matsui T, Tanabe H, Iwashita A, Ota A. Usefulness of magnifying endoscopy with narrow-band imaging for determining the horizontal extent of early gastric cancer when there is an unclear margin by chromoendoscopy (with video). Gastrointest Endosc 2011; 74: 1259-67.

[7] Yao K, Iwashita A, Tanabe H, Nishimata N, Nagahama T, Maki S, Takaki Y, Hirai F, Hisabe T, Nishimura T, Matsui T. White opaque substance within superficial elevated gastric neoplasia as visualized by magnification endoscopy with narrow-band imaging: a new optical sign for differentiating between adenoma and carcinoma. Gastrointest Endosc 2008; 68: 574-80.

[8] Yao K, Iwashita A, Nambu M, Tanabe H, Nagahama T, Maki S, Ishikawa H, Matsui T, Enjoji M. Nature of white opaque substance in gastric epithelial neoplasia as visualized by magnifying endoscopy with narrow-band imaging. Dig Endosc 2012; 24: 419-25.

[9] Heid HW, Moll R, Schwetlick I, Rackwitz HR, Keenan TW. Adipophilin is a specific marker of lipid accumulation in diverse cell types and diseases. Cell Tissue Res 1998; 294: 309-21.

[10] Ueo T, Yonemasu H, Yada N, Yano S, Ishida T, Urabe M, Takahashi K, Nagamatsu H, Narita R, Yao K, Daa T, Yokoyama S. White opaque substance represents an intracytoplasmic accumulation of lipid droplets: immunohistochemical and immunoelectron microscopic investigation of 26 cases. Dig Endosc 2013; 25: 147-55.

[11] Hisabe T, Yao K, Imamura K, Ishihara H, Hirai F, Matsui T, Iwashita A. White opaque substance visualized using magnifying endoscopy with narrow-band imaging in colorectal epithelial neoplasms. Dig Dis Sci 2014; 59: 2544-2549.

[12] Yoshimura N, Goda K, Tajiri H, Ikegami M, Nakayoshi T, Kaise M. Endoscopic features of nonampullary duodenal tumors with narrow-band imaging. Hepatogastroenterology 2010; 57: 462-7.

[13] Yoshii S, Kato M, Honma K, Fujinaga T, Tsujii Y, Maekawa A, Inoue T, Hayashi Y, Akasaka T, Shinzaki S, Nishida T, Iijima H, Tsujii M, Morii E, Takehara T. Esophageal adenocarcinoma with white opaque substance observed by magnifying endoscopy with narrow band imaging. Dig Endosc 2015; 27: 392-396.

[14] Gannon B. The vasculature and lymphatic drainage. In: Whitehead R, editor. Gastrointestinal and oesophageal pathology. Edinburgh: Churchill livingstone; 1995. pp. 129-99.

[15] Yao M, Huang Y, Shioi K, Hattori K, Murakami T, Nakaigawa N, Kishida T, Nagashima Y, Kubota Y. Expression of adipose differentiation-related protein: a predictor of cancer-specific survival in clear cell renal carcinoma. Clin Cancer Res 2007; 13: 152-60.

[16] Lee H, Fawcett J, Kim D, Yang JH. Correlates of Hepatitis B Virus-related Stigmatization Experienced by Asians: A Scoping Review of Literature. Asia Pac J Oncol Nurs 2016; 3: 324-334.