Background and study aims: The authors previously reported that the white opaque substance (WOS) in gastric epithelial neoplasia was caused by accumulation of lipid droplets by immunohistochemical and immuno-electron microscopic studies of adipophilin, which was recently identified and validated as a marker of lipid droplets. The aim of the current study was to investigate the characteristics of the histologic differentiation and mucin phenotype in WOS-positive gastric epithelial neoplasms.

Patients and methods: A total of 130 gastric epithelial neoplasias (45 adenomas and 85 early adenocarcinomas) from 120 patients were retrospectively evaluated. The presence or absence of WOS was evaluated by M-NBI. Lipids were examined by immunohistochemical staining for adipophilin. Tissue phenotypes were immunohistochemically classified as intestinal (I), gastrointestinal (GI), and gastric (G) using antibodies against CD10, MUC2, MUC5AC and MUC6. The histologic differentiation and mucin phenotype of WOS-positive neoplasias were characterized and examined according to adipophilin expression.

Results: The presence of WOS by M-NBI was correlated with histologic differences between adenoma or differentiated type adenocarcinoma and mixed type or undifferentiated type adenocarcinoma (P<0.0153). Adipophilin was only expressed in primary adenoma and well to moderately differentiated adenocarcinoma components but not in undifferentiated components. WOS and adipophilin expression were only observed in neoplasias with I or GI phenotypes, but not in those with the G phenotype (P<0.0001).

Conclusions: WOS in gastric epithelial neoplasias might indicate differentiation into a mature histological subtype with GI or I mucin phenotype.

Introduction

White opaque substance (WOS) on magnifying endoscopy with narrow band imaging (M-NBI) was first reported by Yao et al. [1] as a substance in the superficial area of gastric neoplasias that obscured the subepithelial microvascular architecture. In cases in which the presence of WOS prevent visualization of the microvascular architecture, morphologic differences in WOS are used as an optical indicator for discriminating adenomas from adenocarcinomas [1, 2]. Recently, Yao et al. reported that WOS is caused by lipid droplets and used oil-red-O staining to detect the accumulation of lipid droplets in the cells of WOS-positive gastric neoplasms [3]. In a previous study from our group, the accumulation of lipid droplets was confirmed as a cause of WOS in gastric neoplasias by immunohistochemical and immuno-electron microscopic studies of adipophilin, which was recently identified and validated as a marker of lipid droplets [4]. The presence of WOS was recently reported in epithelial neoplasms in other gastrointestinal organs, such as colorectal neoplasias and esophageal adenocarcinoma [5, 6]. Studies on *Helicobacter pylori* infection-associated intestinal metaplasia of the stomach used lipid staining and light microscopy or electron microscopy and showed that the epithelium in intestinal metaplasia has the ability to absorb lipid droplets [7, 8]. Although the mechanism underlying the accumulation of lipid droplets in WOS-positive gastric neoplasias remains unknown, the resynthesis of triglycerides from external lipids was speculated to be involved [3]. In a recent study, Ohtsu et al. demonstrated that WOS is related to external lipids, and that oral ingestion of foods containing emulsified lipids increases the density of the WOS in epithelial neoplasias including adenoma and adenocarcinoma [9]. These novel findings suggest that new techniques can be developed to improve our ability to accurately diagnose gastric neoplasias. However, the types of gastric epithelial neoplasias that can absorb lipids...
and the histologic types that do not have the absorption function remain unclear. Therefore, the possible limitations of fat loading tests need to be defined. Accordingly, the development of a novel functional endoscopy technique that utilizes the lipid absorption capacity of gastric neoplasias requires clarification of the histologic differentiation and mucin phenotypes of WOS-positive neoplasias including adenomas and adenocarcinomas.

Considering that WOS in gastric neoplasia is associated with the absorption of lipid droplets, WOS-positive gastric neoplasms may represent a mature histologic form and a mucin phenotype similar to that of intestinal metaplasia. The mucin phenotype of WOS-positve gastric neoplasias has been identified as either intestinal or gastrointestinal [3]; however, this study was limited by a small sample size. Furthermore, differentiated adenocarcinomas can vary histologically according to tumor size and can contain dedifferentiated components with different mucin phenotypes. Therefore, histologic investigation based on the immunohistochemical detection of adipophilin in a large number of gastric epithelial neoplasias of various histologic types is more desirable for the precise analysis of lipids. In addition, there are currently no reports describing the histologic differentiation of WOS-positive gastric neoplasias. The purpose of the current study was to investigate the histologic differentiation of WOS-positive gastric epithelial neoplasias and their association with a mucin phenotype.

**Patients and methods**

**Patients**

The current study was a retrospective evaluation of the endoscopic image database of Oita Red Cross Hospital Endoscopy Unit. The institutional review board of Oita Red Cross Hospital approved the study. Between July 2009 and June 2013, 161 gastric epithelial neoplasias (adenoma or early gastric cancer) from 151 consecutive patients referred to our departments for tumor resection by endoscopic submucosal dissection (ESD) were subjected to endoscopic examination using M-NBI.

Gastric epithelial neoplasias from consecutive patients who fulfilled the following criteria were included in this study: (1) patients who provided written informed consent; and (2) patients who underwent endoscopic or surgical resection at Oita Red Cross Hospital and who had a confirmed histologic diagnosis of adenoma or early gastric cancer. Exclusion criteria were as follows: (1) neoplasias in which a detailed comparison of histologic and endoscopic findings was difficult; (2) neoplasias measuring < 5 mm; and (3) neoplasias from remnant stomach. The reason for exclusion criterion (2) was that evaluation of immunohistochemical findings is difficult in small lesions. The reason for exclusion criterion (3) was that rich bile acids in the remnant stomach can affect M-NBI observations [10].

Finally, 130 gastric epithelial neoplasias (adenoma or early gastric cancer) from 120 patients who fulfilled the above mentioned criteria were included in the study. Of 130 neoplasias, 123 (94.6%) were resected by ESD, and 7 (5.4%) were resected by surgery.

**Endoscopic procedure**

The instruments used in the current study were a high-resolution magnifying upper gastrointestinal endoscope (GIF-Q240Z; Olympus Medical Systems, Tokyo, Japan) or a high-definition magnifying upper gastrointestinal endoscope (GIF-H260Z; Olympus Medical systems, Tokyo, Japan) and an electronic endoscopy system (EVIS LUCERA Spectrum; Olympus Medical Systems). A soft black hood (MAJ-1988 for the GIF-Q240Z, MAJ-1989 for the GIF-H260Z; Olympus) was mounted at the tip of the endoscope to enable the endoscopist to fix a consistent focal distance between the tip of the endoscope and the gastric mucosa. M-NBI examinations and the recording of endoscopic findings were carried out by four endoscopists (T.U., K.T, Y.Y, and M.F.). The presence or absence of WOS was determined in each of the neoplasias based on the findings of M-NBI. Neoplasias with a partially positive WOS were considered “WOS positive”. For assessment of the background gastric mucosa, atrophy was graded endoscopically according to the Kimura and Takemoto classification [11].

**Immunohistochemical staining and assessment of adipophilin expression and the mucin phenotype**

Sections (4 mm thick) were cut from representative paraffin-embedded blocks of resected tumors and mounted on silane-coated glass slides. One section from each block was stained with hematoxylin and eosin (HE). All sections were deparaffinized in xylene and rehydrated in a graded ethanol series. Endogenous peroxidase activity was quenched by incubation with 3% hydrogen peroxide for 20 minutes at room temperature. The slides were autoclaved in citrate buffer (pH 6.0) at 121 °C for 15 min. Lipid accumulation was detected using a primary antibody against adipophilin (clone AP125, lot 007281, Acris Antibodies GmbH, Hiddenhausen, Germany), which can be used for the detection of lipid droplets in paraffin-embedded sections [12, 13]. For the identification of tissue phenotypes, primary antibodies against MUC2 (clone NCL-MUC2, lot 6008336, Novocastra Laboratories, New-castle upon Tyne, United Kingdom), MUC5AC (lot 6003413, Novo-castra), MUC6 (lot 6003414, Novocastra), and CD10 (lot 6005650, Novocastra) were used. After immersion in normal goat serum (1:10) for 10 minutes, sections were incubated with primary antibody for 2 hours at room temperature, washed, and incubated for 30 minutes with secondary antibodies conjugated to a horse-radish peroxidase-labeled polymer (Envision™, Dako Corporation, Carpinteria, CA). Immunoreacting products were visualized with 0.02% 3,3′-diaminobenzidine tetrahydrochloride and 0.005% hydrogen peroxide, and nuclei were counterstained with Mayer’s hematoxylin. Sections incubated with normal mouse IgG or pre-immune rabbit serum instead of the corresponding primary antibodies and anti-sera were used as negative controls. Positive immunostaining for adipophilin was defined as > 5% of positively stained neoplastic cells in the superficial neoplastic areas. The results of immunostaining for MUC5AC, MUC6, MUC2 and CD10 were defined as described previously [14]. Briefly, the tissue phenotypes were immunohistochemically classified into gastric (G), intestinal (I), and gastrointestinal (GI) types (gastric markers were MUC5AC and MUC6, and intestinal markers were MUC2 and CD10). Positive expression was defined as > 5% of positively stained neoplastic cells. The histologic evaluation was performed by an expert pathologist (H.Y.) who was blinded to the endoscopic findings.

**Histopathologic assessment**

Histopathologic assessment was performed according to the Japanese classification of Gastric Carcinoma (14th edition) [15]. Differentiated-type adenocarcinomas were defined as those with a glandular structure, including well-differentiated tubular adenocarcinoma (tub1); moderately-differentiated tubular adenocarcinoma (tub...
noma (tub2); and papillary adenocarcinoma (pap). Undifferentiated-type adenocarcinomas were defined as those with indistinct or no glandular structure, including solid-type, poorly differentiated adenocarcinoma (por1); non-solid-type, poorly differentiated adenocarcinoma (por2); and signet-ring cell carcinoma (sig); and mucinous adenocarcinoma (muc). Excluding adenomas, adenocarcinomas were classified into the following three histologic types according to the proportions of differentiated and undifferentiated components: differentiated type (composed of differentiated type only), mixed type (mixed predominantly differentiated or mixed predominantly undifferentiated), and undifferentiated type (undifferentiated type only). In this study, we speculated that WOS-positive gastric neoplasms may represent a mature histologic form similar to that of intestinal metaplasia. To evaluate the histologic characteristics of WOS-positive gastric neoplasms, we reclassified adenomas and the three histologic types of adenocarcinomas into two categories: adenoma or differentiated type adenocarcinoma and mixed type or undifferentiated type adenocarcinoma.

The following parameters were evaluated: (1) characteristics of histologic differentiation and mucin phenotype in WOS-positive gastric epithelial neoplasms; and (2) characteristics of histologic differentiation and mucin phenotype according to adiphophilin expression.

**Statistical analysis**

All continuous variables are expressed as the mean±standard deviation (SD). For parametric variables, the Student’s t-test was used to compare the means between two groups; otherwise, a Wilcoxon rank-sum test was used. The chi-square test or Fisher’s exact test was used for comparisons of the prevalence between the groups. Statistical significance was considered at P<0.05. All statistical analyses were performed using JMP 9 (SAS Institute, Cary, NC, USA).

**Results**

**Clinicopathologic characteristics of WOS-positive gastric neoplasias (Table 1)**

A total of 130 gastric epithelial neoplasias (adenoma or early gastric cancer) from 120 patients were included in this study. The average age of the patients was 71 years (range, 45–91 years). The male:female ratio was 91:29. Of the 130 neoplasias, 51 were WOS-positive by M-NBI. Statistically significant differences in macroscopic type, tumor color (whitish vs. reddish), and histologic type (adenoma vs. adenocarcinoma) were observed between WOS-positive and WOS-negative neoplasias. The background gastric mucosa of all WOS-positive neoplasias was categorized as H. pylori-related advanced atrophic gastritis, as defined by endoscopic evidence of advanced mucosal atrophy diagnosed as open-type atrophic gastritis by the Kimura and Takemoto classification [11]. WOS was frequently observed in protruding or superficial-elevated macroscopic type, and associated with whitish tumor color and adenoma predominance (Table 1).

**Immunohistochemical detection of adiphophilin according to the presence of WOS by M-NBI**

The presence of WOS by M-NBI was positively correlated with adiphophilin expression. Of the 51 WOS-positive neoplasias, 50 (98.0%) were positive for adiphophilin, whereas 13 of the 79 WOS-negative neoplasias (16.5%) were positive for adiphophilin (Table 2). A statistically significant correlation between the presence of WOS and the expression of adiphophilin by immunohistochemistry was observed (P<0.0001, Fisher’s exact test).

**Histologic characteristics of WOS-positive gastric neoplasias**

The 130 gastric epithelial neoplasias analyzed comprised 45 adenomas and 85 early adenocarcinomas. Early adenocarcinomas were classified into three types according to the proportions of differentiated and undifferentiated components as follows: 68 differentiated type (55 well differentiated and 13 moderately differentiated tubular adenocarcinomas, and 0 papillary adenocarcinoma); nine mixed type (9 mixed predominantly differentiated type and 0 mixed predominantly undifferentiated type); and eight undifferentiated type (5 poorly differentiated adenocarcinomas, 3 signet ring cell carcinomas, and 0 mucinous adenocarcinoma) (Table 3). The presence of WOS by M-NBI was associated with the histologic difference between adenoma or adenocarcinoma of differentiated type and mixed type or undifferentiated type adenocarcinoma. In WOS-positive neoplasias, 49 of 51 (96.1%) were adenoma or differentiated type adenocarcinoma, whereas two of 51 (3.9%) were mixed or undifferentiated type adenocarcinoma (Fig.1 and Fig.3). In WOS-negative neoplasias, 64 of 79 (81.0%) were adenoma or adenocarcinoma of differentiated type, whereas 15 of 79 (19.0%) were adenocarcinoma of mixed or undifferentiated type (P=0.0153, Fisher’s exact test) (Table 4). The presence of the WOS has a sensitivity of 43.4% and a specificity of 88.2% for
Table 2 Immunohistochemical detection of adipophilin according to the presence of WOS by M-NBI

| Histologic subtype                        | Adipophilin-positive (63) | Adipophilin-negative (67) |
|-------------------------------------------|---------------------------|---------------------------|
| Adenoma                                   | 32                        | 13                        |
| Differentiated type adenocarcinoma         | 28                        | 40                        |
| Mixed predominantly differentiated adenocarcinoma | 3                        | 6                         |
| Mixed predominantly undifferentiated adenocarcinoma | 0                        | 0                         |
| Undifferentiated type adenocarcinoma       | 0                         | 8                         |
| Mucin phenotype                           | 63                        | 67                        |
| Intestinal type                           | (38)                      | (12)                      |
| Gastrointestinal type                     | (25)                      | (31)                      |
| Gastric type                              | (0)                       | (24)                      |

WOS, white opaque substance; M-NBI, magnifying endoscopy with narrow band imaging.

The results of the current study indicated that the presence of WOS by M-NBI was correlated with the histologic difference between adenoma or adenocarcinoma of differentiated type and mixed type or undifferentiated type adenocarcinoma. WOS-positive neoplasias were histologically composed of adenoma or differentiated type adenocarcinoma (96.1%), and mixed or undifferentiated type adenocarcinoma (3.9%). WOS-negative neoplasias were histologically composed of adenoma or adenocarcinoma of differentiated type (81.0%), and mixed or undifferentiated type adenocarcinoma (19.0%) (P=0.0153, Fisher’s exact test). In other words, the presence of the WOS has a sensitivity of 43.4%, specificity of 88.2%, positive predictive value of 96.1%, and negative predictive value of 19.0% for the diagnosis of the lesion classified as adenoma or adenocarcinoma of differentiated type but not mixed or undifferentiated type adenocarcinoma.

Our immunohistochemical studies identified a relationship between detailed histological subtype and the expression of adipophilin. Adipophilin expression, which represents the accumulation of lipid droplets, was only observed in adenoma and well to moderately differentiated adenocarcinoma components but not in undifferentiated component. These findings could potentially be of value in routine medical practice. Recent advances in M-NBI allow endoscopic observation down to the capillary level and some previous reports describe the usefulness of endoscopic findings for differentiating tumor histology. Differentiated type early adenocarcinoma often exhibits two patterns on M-NBI. The first is an uneven network of irregular microvessels with the absence of a microsurface structure [16]. The second is irregular microvessels situated in the irregular papillary microsurface structure [17]. Undifferentiated type early adenocarcinoma often shows corkscrew-like irregular microvessels with the absence of a microsurface structure [16]. Compared with the above-mentioned M-NBI findings, WOS might be superior in that it represents not only a qualitative diagnosis from the aspect of morphologic differences, but also indicates histologic features including differentiation and the mucin phenotype of the tumor itself. Therefore, it is suggested that WOS-positive lesions could be classified as adenoma or differentiated adenocarcinoma (principally well to moderately differentiated tubular adenocarcinoma) with GI or mucion phenotype but not undifferentiated adenocarcinoma regardless of the mucin phenotype. These novel findings could be useful for investigating the pathogenesis of gastric neoplasias and histological differentiation.

Table 3 Histologic and phenotypic features according to the detection of adipophilin

| Histologic subtype                        | Adenoma or differentiated-type adenocarcinoma | Mixed-type or undifferentiated-type adenocarcinoma |
|-------------------------------------------|---------------------------------------------|--------------------------------------------------|
| WOS-positive neoplasias (n = 51)          | 49 (96.1%)                                  | 2 (3.9%)                                         |
| WOS-negative neoplasias (n = 79)          | 64 (81.0%)                                  | 15 (19.0%)                                       |

WOS, white opaque substance; M-NBI, magnifying endoscopy with narrow band imaging.
In the current study, although WOS was associated with the expression of adipophilin, there were 14 exceptions. In 13 of 14 cases, adipophilin expression was positive despite a negative endoscopic result. All of these cases were adenomas or well to moderately differentiated adenocarcinoma with I or GI phenotype. A review of the histologic findings showed that adipophilin was faintly expressed in a small area. Hence, we speculated that the small amount of lipids could not be identified as WOS endoscopically despite being microscopically evident. These findings suggest that an adequate amount of lipid accumulation is necessary for the endoscopic identification of WOS, as WOS is visualized by strong reflection or backward scattering of the projected light [3]. Furthermore, we found that in certain adenomas with intestinal phenotypes, the degree of WOS increased and was evident after oral administration of a proton pump inhibitor (data not shown), which suggests that WOS is not constant and persistent. WOS may be closely associated with factors such as diet or the pH of fasting gastric juice, which can affect the absorption of lipids by neoplasias. A study by Ohtsu et al. showed that WOS positivity and density increase when micellar lipid is loaded before endoscopic examination [9]. Further intensive laboratory work is needed to clarify the effect of micellar lipid on WOS.

Table 5 Phenotypic findings of WOS-positive gastric neoplasias

| Phenotype | I type or GI type | G type |
|-----------|------------------|--------|
| WOS-positive neoplasias (n=51) | 51 (100%) | 0 (0%) |
| WOS-negative neoplasias (n=79) | 55 (69.6%) | 24 (30.4%) |

WOS, white opaque substance; I, intestinal; GI, gastrointestinal; G, gastric.
needed to clarify the association between WOS and the pH of fasting gastric juice.

In the current study, we defined the phenotypic characteristics of WOS-positive and WOS-negative gastric neoplasias. We used two approaches to clarify this issue. One was similar to that used by Yao et al. [3], in which the phenotypic characteristics associated with WOS were evaluated by M-NBI. In the second method, we evaluated phenotype according to adipophilin expression. A total of 51 WOS-positive neoplasias were classified into 33 (64.7%) type I, 18 (35.3%) type GI, and 0 (0%) type G, indicating that WOS was only present in type I or GI phenotypes, but not in the G phenotype (P<0.0001, Fisher’s exact test). Our current results were in agreement with those previously reported by Yao et al. [3]. In addition, similar results were obtained in our immunohistochemical examination of the relationship between tissue phenotypes and the expression of adipophilin. Adipophilin expression was only observed in the type I or GI phenotype, but not in the G phenotype. Taken together with the results of Yao et al. [3], our findings indicate that lipid accumulation is present in the type I or GI phenotypes, but not in the G phenotype. The identification of the phenotype of gastric neoplasias before treatment is important. Differentiated type adenocarcinomas of gastric phenotype are considered highly malignant, possessing high invasiveness and high metastatic potential, compared with those of intestinal phenotype [18]. Among adenomas, those of gastric phenotype are named “pyloric gland adenoma” and have a higher malignant potential than intestinal type adenomas [19]. Ueyama et al. reported that a WOS-positive epithelium indicated dysplastic changes in gastric hyperplastic polyps [20]. Although gastric hyperplastic polyps usually have a gastric pheno-
type, change from a gastric to an intestinal phenotype is associated with malignant transformation [21]. Considering the possibility that the appearance of WOS in gastric hyperplastic polyps may represent their malignant transformation, the case report by Ueyama et al. [20] is interesting and useful for the management of gastric hyperplastic polyps.

The current study had several limitations associated with its retrospective nature. In addition, the study was a single-center study. There could be a population bias in the tumor histology because patients were referred to our department for the purpose of endoscopic resection. This could explain the small number of undifferentiated type adenocarcinomas. We reviewed the medical records of all patients with early gastric cancer, in particular those with undifferentiated type adenocarcinoma who were referred to the Department of Surgery at Oita Red Cross Hospital during the study period using a registry of operation records, although they did not fulfill the inclusion criteria of this study and were not included in the main data. We identified 10 patients with undifferentiated type early gastric cancer. Of these 10 cases, eight received magnifying endoscopic examination and their endoscopic findings were available to examine the presence of WOS. Furthermore, the expression of adipophilin and mucin phenotypes were evaluated in these eight cases. The results were consistent with those of the current study and showed that WOS and adipophilin expression were not observed in undifferentiated type adenocarcinomas regardless of the mucin phenotype. However, further well-designed studies with a large number of cases with undifferentiated type early gastric cancer are necessary to verify the present results.

In conclusion, the current study suggested to us that WOS in gastric epithelial neoplasias might be an indicator of histologic differentiation and mucin phenotype. WOS in gastric epithelial neoplasias might indicate differentiation into a mature histologic subtype with a GI or I mucin phenotype.
Competing interests: None

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