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CASE REPORT

Histopathological confirmation of similar intramucosal distribution of fluorescein in both intravenous administration and local mucosal application for probe-based confocal laser endomicroscopy of the normal stomach

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Abstract

Probe-based confocal laser endomicroscopy (pCLE) is capable of acquiring *in vivo* magnified cross-section images of the gastric mucosa. Intravenous injection of fluorescein sodium is used for confocal imaging. However, it is still under debate if local administration of the dye to the mucosa is also effective for confocal imaging as it is not yet clear if topical application also reveals the intramucosal distribution of fluorescein. The objective of this study was to evaluate the intramucosal distribution of fluorescein sodium after topical application and to compare the distribution to the conventional intravenous injection used for confocal imaging. pCLE of the stomach uninfected with *Helicobacter pylori* was performed in a healthy male employing intravenous administration and local

mucosal application of fluorescein. The mucosa of the lower gastric body was biopsied 1 min and 5 min after intravenous administration or local mucosal application of fluorescein, and the distribution of fluorescein in the biopsy samples was examined histologically. Green fluorescence was already observed in the cytoplasm of fundic glandular cells in the biopsied deep mucosa 1 min after local mucosal application of fluorescein. It was also observed in the foveolar lumen and inter-foveolar lamina propria, although it was noted at only a few sites. In the tissue biopsied 5 min after the local mucosal application of fluorescein, green fluorescence was more frequently noted in the cytoplasm of fundic glandular cells than in that 1 min after the local mucosal application of fluorescein, although obvious green fluorescence was not identified in the foveolar lumen or inter-foveolar lamina propria. The distribution of intravenously administered fluorescein in the cytoplasm of fundic glandular cells was also clearly observed similarly to that after local mucosal application of fluorescein. Green fluorescence in more cells was observed in many cells 5 min after intravenous administration compared with that after 1 min. The presence of fluorescein in the mucosa was observed within a short time after local mucosal application of fluorescein, suggesting that pCLE images similarly to those after intravenous fluorescein administration can be acquired by local mucosal application of fluorescein.

Key words: Confocal laser endomicroscopy; Fluorescein; Local application; Intravenous; Distribution

Core tip: In this study, we demonstrated the presence of fluorescein administered by local mucosal application in the lamina propria. We consider this study valuable because it demonstrated that confocal laser endomicroscopic images can be acquired by local mucosal application of fluorescein. In addition, the fluorescein distributions after intravenous administration and local mucosal application were the same, which is also of interest.

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INTRODUCTION

Probe-based confocal laser endomicroscopy (pCLE) is a novel endoscopic procedure capable of observing in real time *in vivo* horizontal cross-section images of a fixed depth of the gastrointestinal mucosa with a magnifying power of 1000 times using a probe-type endoscope (Cellvizio; Mauna Kea Technology, Paris, France)[1,2]. To visualize gastrointestinal mucosal tissue by pCLE, staining with a fluorescent dye is necessary, and generally, images are acquired by detecting fluorescence of intravenously administered fluorescein[1-3]. It has been assumed that intravenously administered fluorescein visualizes the capillary vascular network in the superficial layer of the mucosa immediately after administration and leaks gradually into the lamina propria, resulting in visualization of the contour of the mucosal gland structure[3,4]. However, its dynamics has not been investigated in detail.

We have reported that pCLE images equivalent to those acquired employing intravenous fluorescein administration can be acquired by local mucosal application of fluorescein[5-7]. However, it has not been investigated whether or not pCLE images were acquired through the distribution of locally-applied fluorescein in the tissue similarly to that after intravenous administration.

In this study we examined whether the fluorescein locally applied on the gastric mucosal surface penetrates the mucosa tissue by histologically investigating the intramucosal distribution of fluorescein of the biopsy. In addition, it was compared with the distribution of intravenously administered fluorescein in the gastric mucosa to verify the validity of pCLE performed using local mucosal application of fluorescein.

CASE REPORT

Subject

The subject was a 39-year-old healthy male (author, Kouichi Nonaka). Before examination, written informed consent regarding gastrointestinal local mucosal application and intravenous administration of fluorescein was obtained. With respect to examination using pCLE and fluorescein administration, approval was obtained from the Ethics Review Board of our hospital.

pCLE and biopsy

Firstly, pCLE was performed without fluorescein administration in the subject, and one site of the probe-contacted mucosa in the lower gastric body was biopsied as a negative control.

For the local mucosal application of fluorescein, 0.1 mL of 10% fluorescein solution was prepared in advance and applied to the dye-spraying tube, so that the dye alternated with air (Figure 1A). Using the prepared dye-spraying tube, 2 drops of fluorescein were topically applied on the mucosa of the greater curvature of the lower gastric body of the subject, followed by pCLE (Figure 1B). One biopsy specimen of the applied mucosa was obtained after 1 min, and another specimen was biopsied from the same region 5 min after local mucosal application.

pCLE employing intravenous administration of 2.5 mL of 10% fluorescein solution was performed in the same healthy subject after 4 wk. One biopsy specimen was obtained from the mucosa of the greater curvature of the lower gastric body, which was the pCLE observation

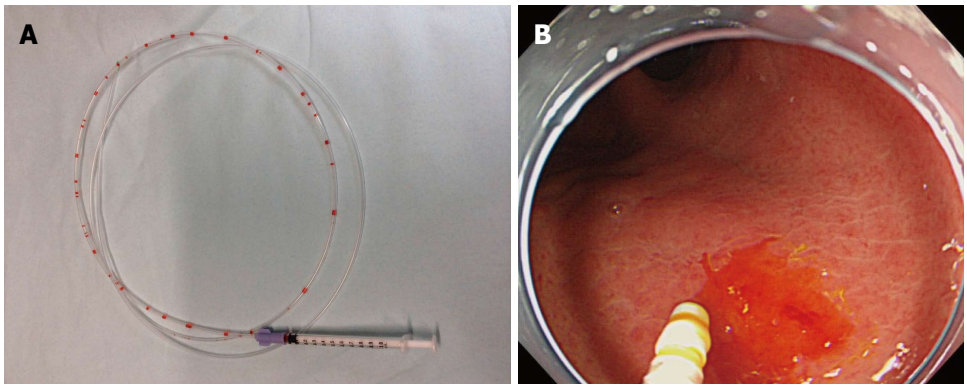

Figure 1 Local mucosal application of fluorescein for probe-based confocal laser endomicroscopy. A: Preparation for local mucosal application of fluorescein. 0.1 mL of 10% fluorescein solution is applied to the dye-spraying tube so that the dye alternates with air; B: Endoscopy findings immediately after local mucosal application of fluorescein onto the gastric body mucosa.

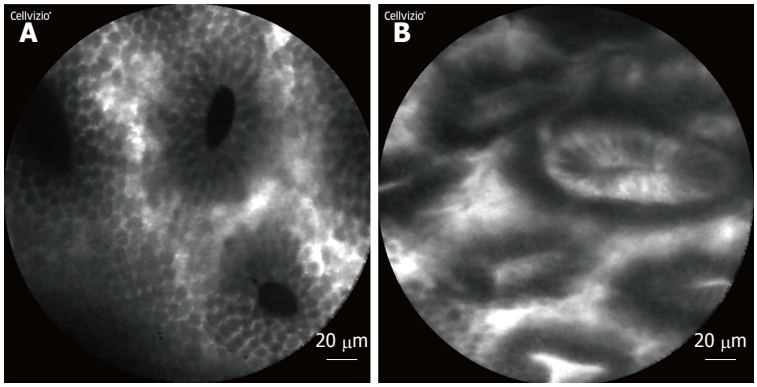

Figure 2 Probe-based confocal laser endomicroscopy images of normal fundic glands mucosa of the stomach. A: Image employing intravenous fluorescein administration. Regular round or oval foveolar lumina with homogeneous epithelial cells are visualized, showing dark images; B: Image employing the local mucosal application of fluorescein. Regular round or oval foveolar lumina with homogeneous epithelial cells are visualized, showing dark images of the foveolar epithelial cells and bright images of the foveolar lumina.

region, one minute after fluorescein administration. One biopsy specimen was similarly obtained from the mucosa of the same region 5 min after administration.

The 5 biopsy specimens of the gastric mucosa were histologically investigated.

Preparation of frozen sections and observation of fluorescence

Each biopsied specimen was embedded in a cryoembedding medium (Tissue-Tek Optical Cutting Temperature Compound; Sakura Finetek Japan, Tokyo, Japan) immediately after biopsy and fresh-frozen in liquid nitrogen. Using a cryomicrotome (CM1860UV; Leica Microsystems, Wetzlar, Germany), frozen sections with a thickness of approximately 5 μm were prepared.

The prepared frozen sections were dried with cold air and rapidly dipped in pure water and 100% ethanol to remove the embedding medium. The sections were dried again with cold air, covered with a cover glass after adding 5 μL of 4'-6-diamidine-2'-phenylindole dihydrochloride (DAPI) of the HER2 FISH KIT (J17539, JOKOH, Tokyo, Japan), and immediately observed under a fluorescence microscope (BIOREVO BZ9000; KEYENCE, Osaka, Japan) at 20 times objective lens magnification (200 times). Images of green fluorescence were acquired at an excitation wavelength of 470 nm, which were merged with images of nuclei derived from DAPI fluorescence.

Probe-based confocal laser endomicroscopy

Regular round/oval foveolar with homogeneous epithelial cells were visualized on pCLE by both intravenous fluorescein administration and local mucosal application of fluorescein (Figure 2). Foveolar epithelial cells were dark on pCLE of both methods. The foveolar lumen was dark in the intravenous administration whereas it was bright in local mucosal application of fluorescein. Although more clear images were obtained in the intravenous administration, images in the local mucosal application of fluorescein were also of sufficient quality for evaluation. No difference of pCLE images was noted between 1 min and 5 min after fluorescein administration both in the intravenous administration and in the local mucosal application.

Histological assessment

In the negative control, no green fluorescence regarded as derived from the administered fluorescein was observed.

In the mucosal tissue obtained one minute after local mucosal application of fluorescein (Figure 3), green fluorescence was observed in the cytoplasm of fundic glandular cells. It was also observed in the foveolar lumen and inter-foveolar lamina propria, although it was noted at only a few sites. Green fluorescence was more frequently noted in the cytoplasm of fundic glandular cells of the biopsy tissue obtained 5 min after local mucosal application of fluorescein compared with that obtained one minute after local mucosal application of fluorescein, although no fluorescence was observed in the foveolar lumen and inter-foveolar lamina propria (Figure 4).

Intravenously administered fluorescein was also

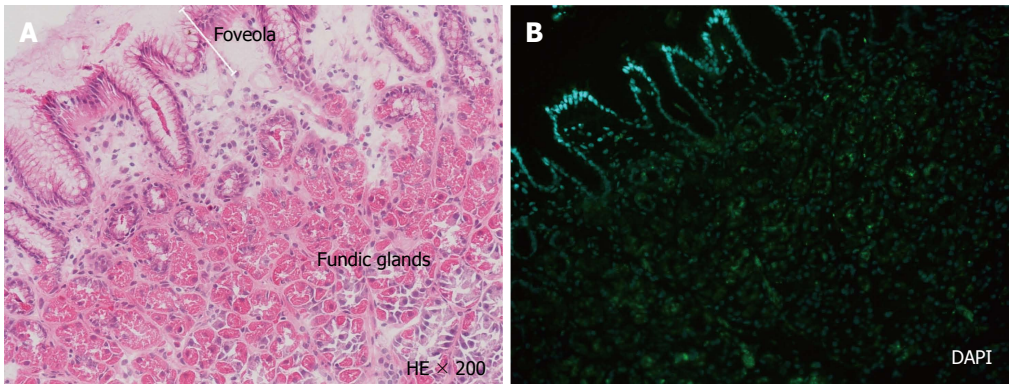

Figure 3 Histology one minute after local mucosal application of fluorescein. A: HE staining of biopsied tissue (original magnification × 200); B: Green fluorescence was observed in the cytoplasm of fundic glandular cells in the deep mucosa (non-HE staining; original magnification × 200). Although it was noted at only a few sites, green fluorescence was also observed in the glandular crypt lumens and lamina propria.

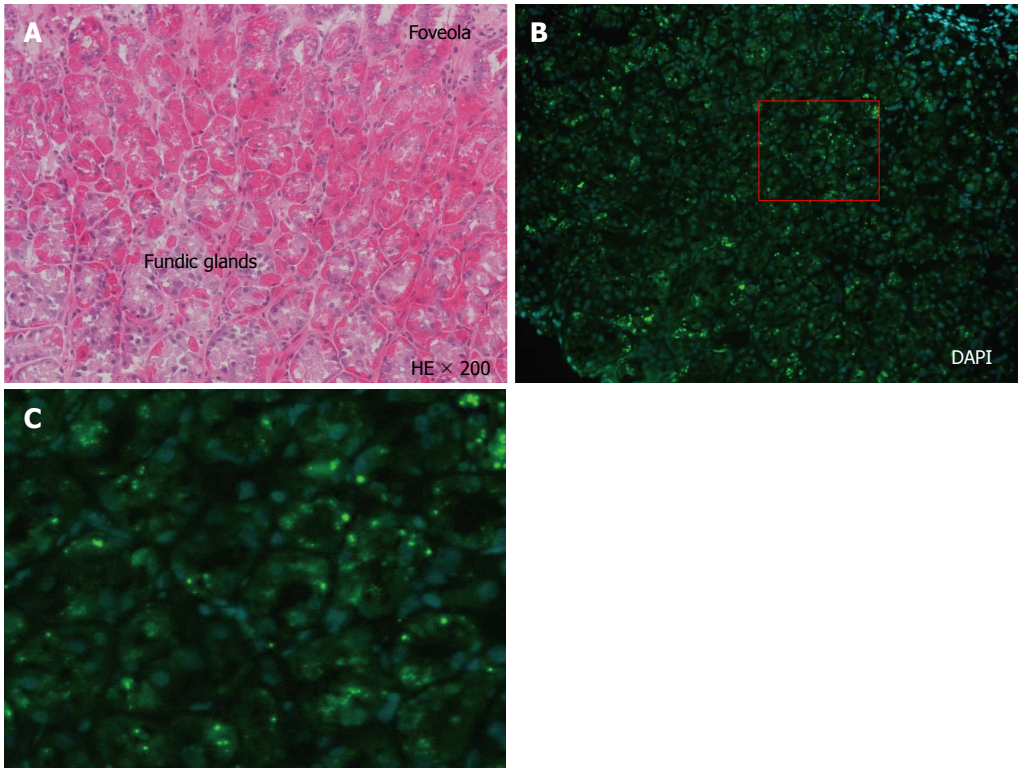

Figure 4 Histology 5 min after local mucosal application of fluorescein. A: HE staining of biopsied tissue (original magnification × 200); B: Fluorescence observed in the serial section of Figure 4A. Green fluorescence is observed in more fundic glandular cells compared with that at one minute (non-HE staining; original magnification × 200); C: The region in the red square is magnified. Green fluorescence is noted around the nuclei (light blue) of fundic glandular cells.

localized in the cytoplasm of fundic glandular cells, and fluorescence was more frequently noted in the biopsy tissue obtained 5 min after administration (Figure 5) than that obtained 1 min after administration (Figure 6), similar to the distribution after local mucosal application of fluorescein.

DISCUSSION

Confocal laser endomicroscopy has been spreading mainly in Europe, and its usefulness to differentiate cancer and non-cancer in the digestive tract and detect dysplasia, cancer in Barrett's esophagus, and inflammatory bowel disease has been reported over the last several years[8-16]. However, only a few studies on the distribution of fluorescein in the mucosa after intravenous administration[4,17], which is essential to acquire black-and-white images of confocal laser endomicroscopy, have been reported. Moreover, the penetration of fluorescein locally applied on the mucosa from the superficial layer has not previously been elucidated, which we investigated in this study.

In this study, in both fluorescein local mucosal application and intravenous administration, the fluorescence was observed in fundic glandular cells showing similar distribution, which suggests that the fluorescein locally

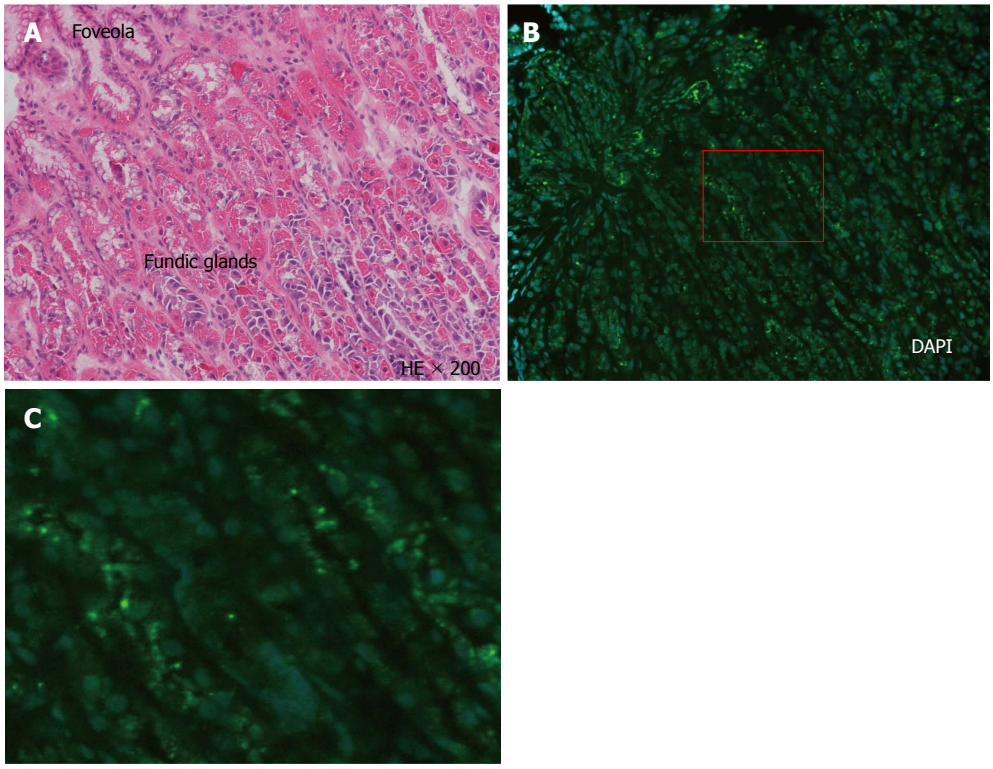

Figure 5 Histology 5 min after intravenous fluorescein administration. A: HE staining of biopsied tissue (original magnification × 200); B: Fluorescence observed in the serial section of Figure 5A. Green fluorescence in the cytoplasm of fundic glandular cells is more clearly observed compared with that at one minute (non-HE staining; original magnification × 200); C: The region in the red square is magnified. Green fluorescence is noted around the nuclei (light blue) of fundic glandular cells, suggesting that fluorescein was incorporated into the cytoplasm of the cells.

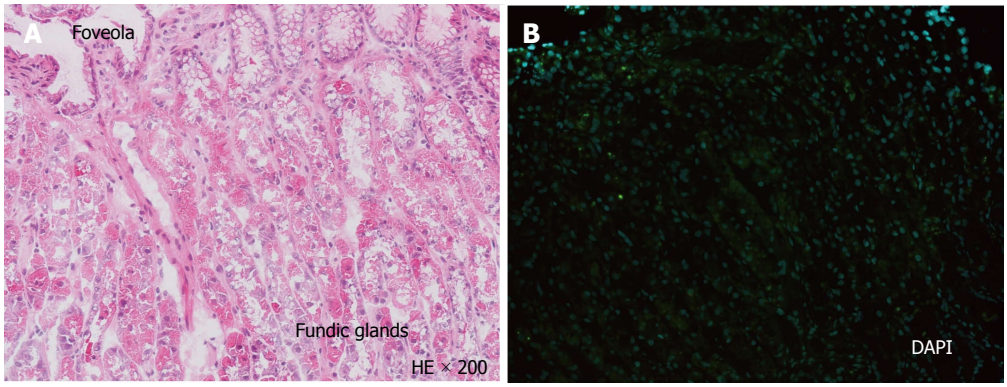

Figure 6 Histology one minute after intravenous fluorescein administration. A: HE staining of biopsied tissue (original magnification × 200); B: Fluorescence observed in the serial section of Figure 6A. Green fluorescence is scattered in the cytoplasm of fundic glandular cells (non-HE staining; original magnification × 200).

applied on the mucosal surface can be incorporated into the mucosal tissue within a short time as with the case for intravenous administration, supporting the validity to pCLE images using local mucosal application of fluorescein.

However, the region observed on pCLE is the foveolar area within the depth of 100 μm from the surface of the mucosa. In this region, just a small amount of fluorescence was observed in the foveolar lumen and inter-foveolar lamina propria of the biopsy sample obtained one minute after local mucosal application of fluorescein. When the air-dried frozen sections were observed without removing the cryoembedding medium in our preliminary experiment, intense fluorescence was noted around the tissue, which made it difficult to identify fluorescence in the tissue (Figure 7). Considering that fluorescein might readily dissolve in the cryoembedding medium (aqueous solution containing polyethylene glycol), the procedure was modified: the sections were dried with cold air and then rapidly dipped in pure water and 100% ethanol to remove the embedding medium surrounding the tissue. Although trying to remove the medium as rapidly as possible, it was plausible that fluorescein was eluted from the tissue while being passed through the solvents (pure water and alcohol).

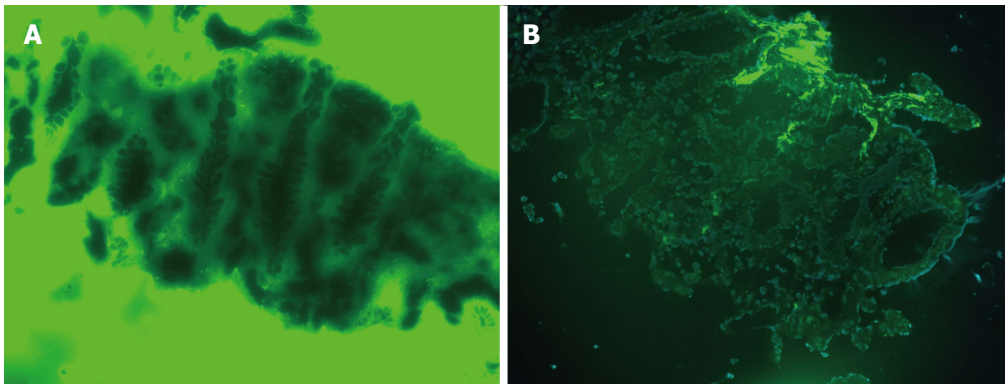

Figure 7 Fluorescence observed in tissue sections with or without removal of the cryoembedding medium. A: Lower gastric body mucosa tissue obtained 5 min after local mucosal application of fluorescein. When fluorescence is observed without removing the embedding medium, intense green fluorescence is noted around the tissue, and it is difficult to observe fluorescence in the tissue; B: Fluorescence in the tissue can be observed clearly after removing the embedding medium.

In addition, the procedure was performed in a room under fluorescent light, which possibly gave rise to additional attenuation of the fluorescence with time. The larger amount of fluorescein might have been present in the tissue before the procedure, and the detection of fluorescence at a low level in the foveolar area may be due to this condition.

Although the level was low, some fluorescence was observed in the foveolar lumen and inter-foveolar lamina propria, which corresponded to bright images of the foveolar lumens on pCLE after local mucosal application of fluorescein and suggested that fluorescein locally applied on the mucosal surface was incorporated into the lamina propria. In contrast, no fluorescence indicating the incorporation of fluorescein into the foveolar epithelium was confirmed, and this may correspond to dark images of foveolar epithelium on pCLE. Ji *et al*[17] reported that gastric epithelium with intestinal metaplasia was positive for fluorescein immunostaining, suggesting that fluorescein is incorporated into the epithelium, but goblet cells were negative. Fluorescein may not be readily incorporated into the foveolar epithelial cells, which have abundant intracytoplasmic mucus similar to goblet cells.

According to the study by Ji *et al*[17], the intercellular permeability of intact foveolar epithelia was low. However, if fluorescein is unlikely to be incorporated into the cytoplasm of foveolar epithelial cells, the locally applied fluorescein is may diffuse into the lamina propria through intercellular spaces of the foveolar epithelia, but it is also possible that it diffuses through the cell membrane and cytoplasm, and reaches the lamina propria without accumulating in the foveolar epithelia. Fluorescein for medical use is water-soluble sodium salt with a molecular weight of 376.27 and a negative charge. The cell membrane is mostly composed of a phospholipid bilayer containing various proteins and glycolipids. Since fluorescein sodium salt is negatively charged as are phospholipids of the cell membrane, repellence of the charge prevents the fluorescein from entering the cell membrane. However, fluorescein has both a hydrophilic region (negatively charged region) and a hydrophobic region corresponding to the lipid fraction, as the lipid bilayer of the cell membrane. This hydrophilic-hydrophobic balance is similar to that of the cell membrane lipid bilayer, which may enable fluorescein to pass through the cell membrane. On the other hand, regarding fundic glandular cells, it was suggested that the fluorescein does not simply pass through the cells, but also is actively incorporated into the cells from the lamina propria or gland lumen side and accumulates in the cells.

This study was performed with only normal gastric mucosa in one subject, so further investigation is necessary. However, it was confirmed that fluorescein locally applied on the gastric mucosal surface was distributed in the mucosa within a short time, validating that pCLE images can be acquired by local mucosal application of fluorescein.

COMMENTS

Case characteristics

A 39-year-old healthy male with no symptoms.

Laboratory diagnosis

All labs were within normal limits.

Imaging diagnosis

Regular round/oval foveolar with homogeneous epithelial cells were visualized on probe-based confocal laser endomicroscopy (pCLE) by both intravenous fluorescein administration and local mucosal application of fluorescein.

Pathological diagnosis

In the mucosal tissue obtained after local mucosal application of fluorescein, green fluorescence was observed in the cytoplasm of fundic glandular cells.

Related reports

Previously it was considered that CLE imaging requires intravenous injection of fluorescein. However, the acquisition of images just by applying a small volume of fluorescein onto the region of interest has been reported recently.

Term explanation

pCLE is a novel endoscopic procedure capable of observing gastrointestinal mucosa at 1000 times magnification in real time.

Experiences and lessons

It was confirmed that fluorescein locally applied on the gastric mucosal surface was distributed in the mucosa within a short time.

Peer-review

The presence of fluorescein in the mucosa was observed after local mucosal application of fluorescein, suggesting that pCLE images similarly to those after intravenous fluorescein administration can be acquired by local mucosal application of fluorescein.

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