Cervical inlet patch-optical coherence tomography imaging and clinical significance

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AIM: To demonstrate the feasibility of optical coherence tomography (OCT) imaging in differentiating cervical inlet patch (CIP) from normal esophagus, Barrett’s esophagus (BE), normal stomach and duodenum.

METHODS: This study was conducted at the Veterans Affairs Boston Healthcare System (VABHS). Patients undergoing standard esophagogastroduodenoscopy at VABHS, including one patient with CIP, one representative patient with BE and three representative normal subjects were included. White light video endoscopy was performed and endoscopic 3D-OCT images were obtained in each patient using a prototype OCT system. The OCT imaging probe passes through the working channel of the endoscope to enable simultaneous video endoscopy and 3D-OCT examination of the human gastrointestinal (GI) tract. Standard hematoxylin and eosin (H and E) histology was performed on biopsy or endoscopic mucosal resection specimens in order to compare and validate the 3D-OCT data.

RESULTS: CIP was observed from a 68-year old male with gastroesophageal reflux disease. The CIP region appeared as a pink circular lesion in the upper esophagus under white light endoscopy. OCT imaging over the CIP region showed columnar epithelium structure, which clearly contrasted the squamous epithelium structure from adjacent normal esophagus. 3D-OCT images obtained from other representative patients demonstrated distinctive patterns of the normal esophagus, BE, normal stomach, and normal duodenum bulb. Microstructures, such as squamous epithelium, lamina propria, muscularis mucosa, muscularis propria, esophageal glands, Barrett’s glands, gastric mucosa, gastric glands, and intestinal mucosal villi were clearly observed with OCT and matched with H and E histology. These results demonstrated the feasibility of using OCT to evaluate GI tissue morphology in situ and in real-time.

CONCLUSION: We demonstrate in situ evaluation of
INTRODUCTION

Cervical inlet patch (CIP) is characterized by the presence of heterotopic columnar gastric mucosa in the upper esophagus, most commonly located just below the upper esophageal sphincter (UES). Other sites for heterotopic gastric mucosa have been reported in the duodenum, jejunum, cystic duct, ampulla of Vater, gallbladder, rectum and the anus[2-9], but their etiology and pathological significance remain unclear. The incidence of CIP has been reported from as low as 0.01%[10] to as high as 0.3% to 2.3%, depending upon the endoscopist’s awareness of this entity and thoroughness of examination[11,12]. Despite generally asymptomatic, CIP can present with dysphagia[13], stricture[14], ulcers[15] or bleeding[16] or fistula[17]. It is unclear whether CIP is congenital or acquired. One postulate is that CIP originates from incomplete embryonic replacement of the stratified epithelium, which normally starts at the 4th month of gestation. The greater incidence of CIP seen in pediatric populations and in the upper esophageal pouch of children with tracheoesophageal fistula supports this hypothesis[18,19]. Although generally asymptomatic, CIP can present with dysphagia, stricture, ulcers, bleeding or fistula. It is unclear whether CIP is congenital or acquired. One postulate is that CIP originates from incomplete embryonic replacement of the stratified epithelium, which normally starts at the 4th month of gestation. The greater incidence of CIP seen in pediatric populations and in the upper esophageal pouch of children with tracheoesophageal fistula supports this hypothesis[18,19]. Also, immunohistochemical studies suggest an embryologic origin for CIP on account of differences in endocrine markers such as serotonin, glucagon, pancreatic poly-
3D-OCT imaging of cervical inlet patch

Figure 1 Endoscopic view of cervical inlet patch.

formed using the Evis Extra III high definition system (Olympus America, Center Valley, PA), and endoscopic 3D-OCT images were obtained using the system described below.

Optical coherence tomography system

The 3D-OCT endomicroscopy system was developed in collaboration with LightLab Imaging - St Jude Medical, Inc. and is similar to the system previously described by our group[37]. A Fourier Domain Mode Locking swept laser with a center wavelength of 1310 nm and average output power of 42 mW at a sweep repetition rate of 59 kHz was used as the light source. The full-width-half-maximum bandwidth of the laser sweep was about 120 nm, which supports about 5 µm axial resolution in tissue. The system sensitivity was 103 dB with 13 mW of incident power. The imaging probe, with an outer diameter of 2.5 mm, was introduced through a standard working channel of a high-definition endoscope (Olympus GIF-Q180) to enable simultaneous video endoscopy and 3D-OCT imaging examination. The output beam from the probe was focused to a about 15 µm spot and was emitted at an angle of about 80 °C from the probe axis by a prism. The internal optics in the probe was rotated rapidly for radial scanning at 60 (or 70) frames per second (fps). Each image frame had about 512 × 1000 pixels at 60 fps (or about 512 × 900 pixels at 70 fps). To acquire a spirally scanned, volumetric OCT data set of the GI tract, the probe was pulled back at 1.0 mm/s along the sheath, which corresponds to a frame-to-frame spacing of 14-17 µm. At this image acquisition speed, a 20 mm × 8 mm × 2 mm 3D-OCT data set was acquired in 20 s.

Individual 2D-OCT frames were displayed on screen for real-time preview. The volumetric data sets were acquired and streamed to a hard drive. During post-processing, each 2D radial frame was unwrapped to create a rectangular frame. A custom program was written to detect the surface of the plastic probe sheath in each frame, which is used to flatten the image. The flattened 3D-OCT data sets were then loaded into Amira (Resol-veRT, Mercury Computer Systems) for 3D rendering and visualization in different orthogonal imaging planes.

RESULTS

The endoscopic view of a CIP in a 68-year old patient referred for endoscopic treatment for long-segment BE is shown in Figure 1. During retraction of the endoscope, a pink circular lesion was observed under white light endoscopy in the upper esophagus (about 20 cm from the tooth). The histology of the biopsies taken from the lesion later confirmed the finding of CIP (Figure 2C). Endoscopic OCT imaging was performed over the CIP under direct simultaneous visualization with a white light endoscope. From cross-sectional OCT images shown in Figure 2A and B, regions with CIP and the adjacent squamous epithelium can be identified. In addition, the CIP region clearly shows shallower light penetration compared with the adjacent normal esophagus. This is similar to typical images from normal gastric mucosa of representative other subjects. Zoomed views shown in Figures 2D and E clearly demonstrate columnar and squamous epithelium in the CIP and the adjacent normal esophagus, respectively. The columnar features observed in the CIP are consistent with the corresponding H and E histology shown in Figure 2C.

For comparison, OCT images of a normal gastro-esophageal junction (GEJ) obtained from a representative patient with chronic heartburn symptom (Figure 3). The en face OCT projection image at 350 µm underneath the tissue surface clearly shows the GEJ. The OCT imaging probe scans a large field (20 mm × 8 mm) on the tissue, which is about 100× larger compared to the region sampled by a standard biopsy (1-2 mm²). Regions with gastric glandular mucosa (left) and esophageal squamous mucosa (right) exhibit clearly different patterns. Cross-sectional OCT images in Figure 3B-D show the GEJ and esophageal squamous epithelium along the probe pullback and rotation directions, respectively. The GEJ, squamous epithelium, lamina propria/muscularis mucosa, and esophageal glands underneath the squamous epithelium are clearly observed. Features observed in OCT images also match the representative histology of a normal GEJ shown in Figure 3E.

3D-OCT images from a representative patient with a long segment BE confirmed with histology (Figure 4). The en face projection OCT image at 200 µm underneath the tissue surface shows a similar angulated pattern compared with the en face image shown in the gastric mucosa (Figure 4A). Cross-sectional OCT images (Figure 4B and D) clearly show layered structures, where the original squamous mucosa in the esophagus is replaced by the columnar BE mucosa. Two hyper-scattering layers are

Histology analysis

Standard hematoxylin and eosin (H and E) histology was performed by the pathology service at VABHS on biopsy or endoscopic mucosal resection (EMR) specimens in order to compare and validate the 3D-OCT data. Photomicrographs of the H and E slides were taken under a standard Olympus B ×40 microscope using a 4× objective.
observed underneath the BE mucosa, where the top layer corresponds to the newly formed muscularis mucosa layer which replaces the lamina propria, and the bottom layer corresponds to the muscularis propria. These OCT features are confirmed with corresponding histology of an EMR specimen obtained at the imaging area in the

Figure 2  Endoscopic optical coherence tomography imaging of cervical inlet patch. A: Cross-sectional optical coherence tomography images of cervical inlet patch (CIP); B: Adjacent squamous epithelium, respectively; C: Corresponding hematoxylin and eosin histology obtained from a biopsy at the CIP site; D: 3× magnification of the CIP; E: Squamous epithelium (SE) region marked in (A). Scale bars: 1 mm.

Figure 3  3D-optical coherence tomography images of a normal gastro-esophageal junction. A: En face projection optical coherence tomography (OCT) image at a depth of 350 µm; B: Regions with gastric mucosa and squamous mucosa show distinct features; Cross-sectional OCT image along the probe pullback direction showing the gastro-esophageal junction (GEJ) and normal squamous epithelium (SE) clearly; C, D: Cross-sectional images of the GEJ and SE, corresponding to the green and blue dashed lines marked in (A), respectively. Structures, such as SE, lamina propria (LP)/muscularis mucosa (MM), esophageal glands (arrows) (EG), and gastric mucosa, can be clearly identified; E: Representative histology at the GEJ. Scale bars: 1 mm.
Representative OCT images of normal stomach from a patient with chronic heart burn symptom (Figure 5). The en face projection image (Figure 5A) at a depth of 250 µm under the tissue surface represents the typical an-gulated gastric glandular mucosa pattern. Cross-sectional OCT images (Figure 5B and C) clearly show the gastric glandular mucosa. Gastric pits and gastric glands can be observed from cross-sectional OCT images and the image features match the representative histology of gastric mucosa shown in Figure 5D. Light penetration in normal gastric tissues is also shallower compared with normal esophagus and Barrett’s esophagus.

Furthermore, 3D-OCT images of normal duodenum from a patient with chronic heart burn symptom are shown in Figure 6. Distinctive features of the intestinal mucosal villi are observed in the en face OCT projection image (Figure 6A), as well as in the cross-sectional OCT images (Figure 6B and C). The length of individual villi, measured to be around 300-600 µm, matches the corresponding histology shown in Figure 6E. These results demonstrate the feasibility of using OCT to evaluate GI tissue morphology in situ and in real-time.

DISCUSSION

CIP is an under-appreciated entity in general gastroenterologist’s practice. In this study, we present imaging results from OCT, a relatively new imaging technology, to describe the gastric type of epithelial patterns in CIP, as clearly distinct from normal esophageal squamous epithelium, Barrett’s esophagus, or from normal duodenum. Under OCT, CIP exhibits similar columnar structures compared with normal gastric mucosa, and the imaging depth in both CIP and gastric tissues are low. In practice, obtaining biopsies from CIP in patients with troublesome supra-esophageal or laryngeal symptoms may be difficult owing to poor view just below the UES. OCT may allow “optical biopsy” of the CIP epithelium without the need for obtaining tissue specimens, and may be used to assess changes suspicious for malignancy in the future. Given its small diameter (2.5 mm) and flexibility, the OCT probes may be introduced orally or nasally without an endoscope, and with better tolerance and potentially less motion artifacts. This may further negate the need for sedation, nursing, or use of the endoscopy unit which has implications beyond endoscopy costs.

There are a number of case reports of adenocarcinoma arising from heterotopic gastric mucosa in the upper esophagus[23-26,40]. To our knowledge, 31 cases have been reported in the literature where esophageal adenocarcinoma was found arising from an inlet patch[41,42] and two cases where laryngeal squamous cell carcinoma was found associated with or bordering inlet patches[47]. The
A pathogenetic link between BE and CIP raises concerns of dysplastic transformation in CIP. Using immunohistochemical markers to address potential cellular origins, Lauwers et al. [48] demonstrated similar mechanisms of pathogenesis for CIP and BE on the basis of similarity between immunohistochemical staining patterns between the two entities. Furthermore, the similarity in the expression pattern for cytokeratins 7 and 20 and MUC6 mucin protein were not influenced by the presence or absence of GERD in these CIP patients [49-50]. Based on these findings, Lauwers et al. [48] suggested that CIP may arise as a metaplastic change occurring in the esophageal epithelium. In light of these findings and the pathogenetic similarity between CIP and BE based on the cyto-

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**Figure 5** 3D-optical coherence tomography images of a normal stomach. A: En face projection optical coherence tomography (OCT) image at a depth of 250 µm; B: Cross-sectional OCT image along the probe pullback direction, corresponding to the red dashed line marked in (A); C: Cross-sectional images of the gastric mucosa, corresponding to the blue dashed line marked in (A). Gastric pits (GP) and gastric glands (arrows) (GG) can be identified; D: Representative histology of a gastric mucosa. Scale bars: 1 mm.

**Figure 6** 3D-optical coherence tomography images of a normal duodenum. A: En face projection optical coherence tomography (OCT) image at a depth of 350 µm; B: Cross-sectional OCT images of the duodenum along the probe pullback direction; C: Cross-sectional OCT image, corresponding to the blue dashed line marked in (A); Mucosal villous structures (Vi) in the duodenum are clearly seen; D: Corresponding histology of the duodenum showing the villi. Scale bars: 1 mm.
Cervical inlet patch (CIP) is an under-appreciated entity encountered by gastroenterologists in general practice. Although rare, several reports suggest that CIP may progress to adenocarcinoma. Optical coherence tomography (OCT) is an emerging medical imaging technology that enables micron-scale, cross-sectional, and 3D imaging of biological tissues in situ and in real-time.

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Zhou C et al. OCT imaging of cervical inlet patch

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S- Editor Gou SX  L- Editor O’Neill M  E- Editor Li JY