

# Diffuse endoscopically visible, predominantly low grade dysplasia in Barrett's esophagus (with video)



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## Bibliography

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## ABSTRACT

**Background** Low grade dysplasia (LGD) in Barrett's esophagus (BE) has generally been considered as undetectable endoscopically.

**Aim** To describe a phenotype which consists of diffuse, endoscopically visible, predominantly low grade dysplasia in Barrett's esophagus (DEVLB), with often subtle but visible endoscopic changes seen with high definition white light (HDWL) and narrow-band imaging (NBI).

**Method** A systematic search of a prospectively collected database for patients satisfying predefined criteria for DEVLB and a review of endoscopic and histological features of biopsies and endoscopic mucosal resection (EMR) specimens.

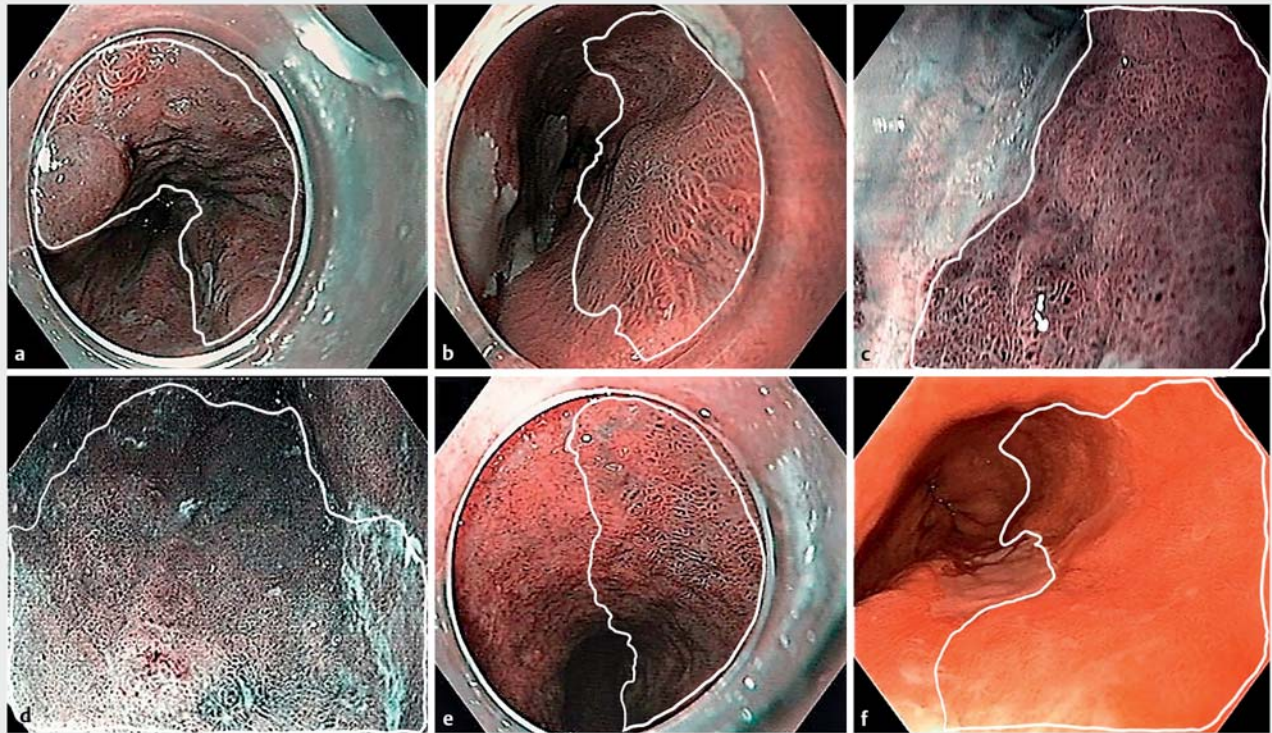
**Results** Out of a total of 419 patients referred to our expert center for assessment of dysplastic Barrett's esophagus during the period January 2009 to March 2018, there were 7 patients (1.7%) who satisfied the criteria defined for DEVLB, identified on their initial assessment endoscopy. All patients were treated by EMR of visible abnormal mucosa during their assessment endoscopy at our tertiary referral center. There was a total of 47 EMR specimens obtained, with a median of 6 (IQR 5–9) EMR resection pieces per patient, of which 36 (77%) contained LGD, 8 (17%) high grade dysplasia (HGD), 2 (4%) non-dysplastic Barrett's esophagus (NDBE), and 1 (2%) contained early esophageal adenocarcinoma (EAC).

**Conclusion** DEVLB is a distinct phenotype seen in a small but significant proportion of individuals with dysplastic Barrett's esophagus. Patients with DEVLB have widespread LGD, with many having areas of focal HGD or early cancer within this area. We believe these patients are best treated with extensive EMR of the visibly abnormal area.

## Introduction

There has been significant technological advancement in endoscopic imaging over the last decade [1]. This has led to a reliable detection of high grade dysplasia (HGD) and early esophageal adenocarcinomas (EAC) in Barrett's esophagus [2,3]. However, low grade dysplasia (LGD) is generally considered to be undetectable endoscopically, despite our best imaging modalities [3,4]. The progression rate of LGD varies significantly in the literature from 0.4% to 13.4% [5,6]. This is in part due to the large interobserver variability among pathologists in diagnosing LGD [7,8]. Many studies have described risk factors for

progression from LGD to EAC, and these include: a confirmed diagnosis of LGD by expert pathologists, multifocal dysplasia, persistent LGD, and use of biomarkers; however, the natural history of progression of LGD is still unpredictable [9–12]. We have recognized a small subgroup of patients with an area of subtle endoscopic features within their Barrett's segment; the histology from the resection specimens within this area contains widespread LGD and often harbors more advanced dysplasia or even EAC.



► **Fig. 1** Well demarcated diffuse subtle nodularity or variation in mucosal pattern from each patient. **a** Patient 2. **b** Patient 3. **c** Patient 4. **d** Patient 5. **e** Patient 6. **f** Patient 7.

## Aim

We aim to describe a case series of a specific phenotype of Barrett's esophagus that we have termed Diffuse Endoscopically Visible predominantly Low-Grade Dysplasia in Barrett's (DEVLB), with features that are defined below and that can be identified on endoscopic examination with high definition white light (HDWL) and narrow-band imaging (NBI).

## Methods

This observational study was performed at a tertiary referral expert center for management of dysplastic Barrett's esophagus.

### Definition of DEVLB and identification of study patients

We have defined DEVLB as consisting of a large area (cutoff for this study defined arbitrarily as at least 6 cm<sup>2</sup>) with: 1) diffusely abnormal mucosa with either: a) patchy loss of or variation in mucosal pattern, and/or b) widespread, subtle nodularity; 2) a clear demarcation from normal looking smooth Barrett's mucosa, and 3) histology showing predominantly multifocal LGD though sometimes with areas of more advanced dysplasia.

Patients who fitted the criteria for DEVLB on their initial assessment endoscopy were identified by manual review of endoscopic and histological data collected prospectively on our Barrett's database from all patients referred with dysplastic Barrett's esophagus for assessment and management.

## Equipment and referral center

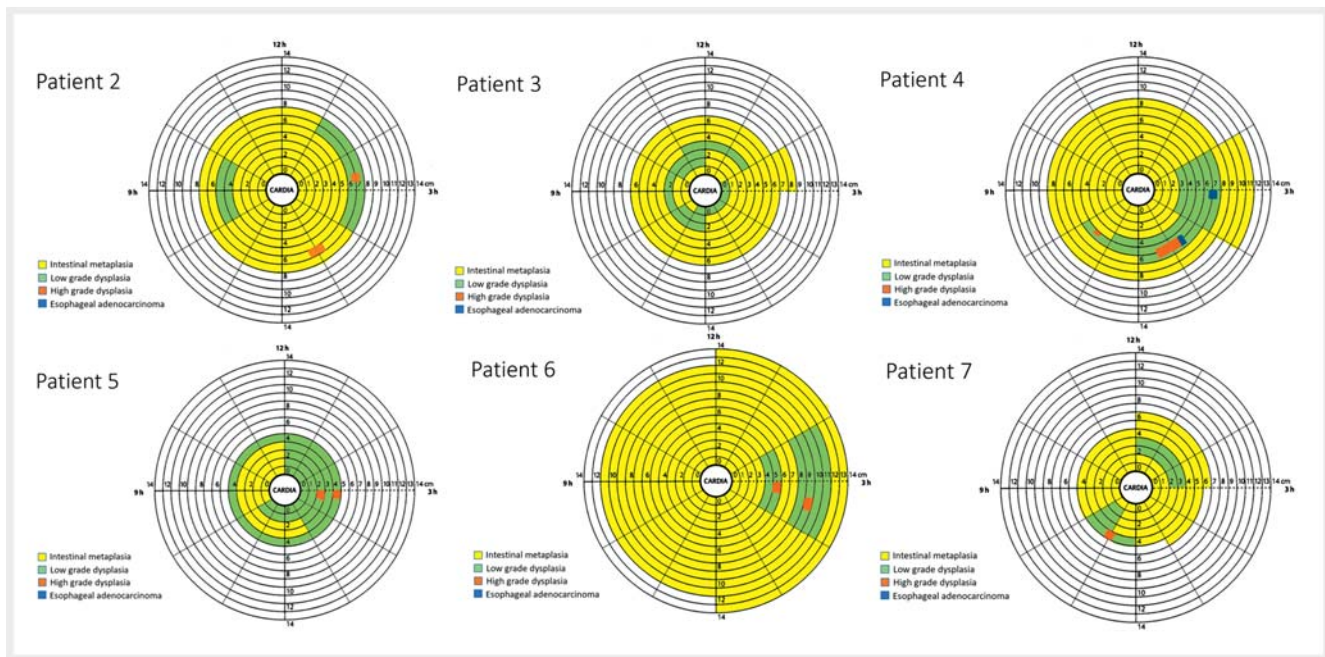
Our hospital is a tertiary teaching hospital and a major referral center for management of dysplastic Barrett's esophagus. All patients had their assessment endoscopy performed with an Olympus HQ180 or HQ190 gastroscope by a single expert endoscopist (AT) with extensive experience in assessment of dysplastic Barrett's esophagus.

### Prospectively collected Barrett's database

A prospective database was established in 2009 documenting all patients referred with dysplastic Barrett's esophagus. Information such as patient demographics, medical history, endoscopy results, histology results, and multidisciplinary meeting outcomes are all recorded. To date, there are a total of 419 patients referred with dysplastic Barrett's esophagus.

## Results

Out of a total of 419 patients referred to our expert center for assessment of dysplastic Barrett's esophagus during the period January 2009 to March 2018, there were seven patients (1.7%) who satisfied the definition of DEVLB, identified on their initial assessment endoscopy (► **Fig. 1**). All were male with a median age of 70 years (IQR:61–72). The median maximum length of Barrett's segment was 9 cm [IQR: 7–12]. Four patients (57%) had DEVLB predominantly on the right wall of the esophagus only (12–6 o'clock position) and three patients (43%) had



► **Fig. 2** Distribution of dysplasia within Barrett's esophagus for patients 2–7.

DEVLB on both the left wall (6–12 o'clock position) and the right wall of the esophagus. Patients were treated initially with endoscopic mucosal resection (EMR) of abnormal looking tissue and had biopsies of the remaining smooth or less abnormal Barrett's mucosa. Radiofrequency ablation was used to treat residual smooth Barrett's mucosa at a later date. There was a total of 47 EMR specimens obtained with a median of 6 (IQR: 5–9)

EMR specimens per patient. There was a total of 80 post-EMR targeted biopsies of the remaining smooth or less abnormal Barrett's mucosa, with a median of 9 (IQR: 0–22) targeted biopsies performed per patient. Of the 47 EMRs performed, 36 (77%) contained LGD, 8 (17%) HGD, 2 (4%) non-dysplastic Barrett's esophagus (NDBE) and 1 (2%) contained EAC. Of the seven patients, one patient had EAC as the worst pathology after review by an expert gastrointestinal pathologist, four patients had HGD as the worst pathology and only two patients had LGD as the worst pathology after review by an expert gastrointestinal pathologist. Of the 80 post-EMR targeted biopsies from the remaining smooth or less abnormal Barrett's mucosa, 64 (80%) were NDBE, 14 (17.5%) LGD, and 2 (2.5%) were HGD (► **Fig. 2**).

Below is a case study accompanied by a video and images of DEVLB under HDWL and NBI.

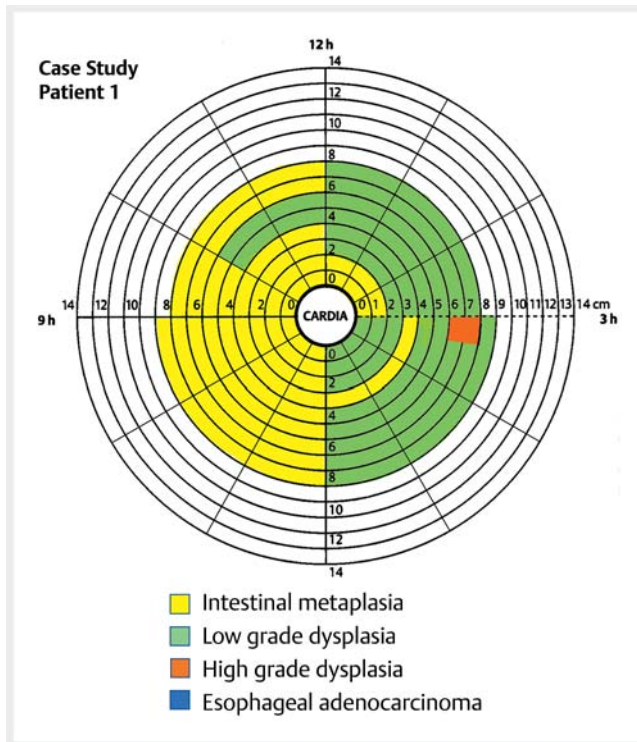
### Case study – Patient 1 (► **Video 1**)

A 69-year-old retired man was referred for investigation of long-standing reflux symptoms requiring proton pump inhibitor therapy for symptom control. His past medical history included previous smoking, ischemic heart disease, and aortic stenosis, treated with coronary artery bypass surgery and bovine aortic valve replacement. The initial gastroscopy performed in the community demonstrated a long segment of Barrett's esophagus (C8M9) and a 3 cm hiatus hernia; there were no strictures. Careful examination with HDWL and NBI revealed multiple subtly abnormal areas that were extensively biopsied, revealing multifocal LGD with focal HGD. The stomach and duodenum were normal.

He was referred to our center for further management. His assessment gastroscopy revealed a C8M9 Barrett's esophagus.



► **Video 1** This video demonstrates the area with diffuse, endoscopically visible, predominantly low grade dysplasia in Barrett's esophagus (DEVLB) in high definition white light and narrow-band imaging. Within this area, there is diffusely abnormal mucosa with patchy loss of mucosal pattern and widespread subtle nodularity. There is a clear demarcation from normal looking smooth Barrett's mucosa which is marked in preparation for extensive endoscopic mucosal resection of the DEVLB area.



► **Fig. 3** Patient 1. Distribution of dysplasia within Barrett's esophagus. Area with diffuse, endoscopically visible, predominantly low grade dysplasia in Barrett's esophagus (DEVLB) consisting of mainly low grade dysplasia (LGD) with focal high grade dysplasia (HGD) (from nodule at 30–31 cm, 3–4 o'clock).

On the right wall extending around 30–60% of the circumference, there was an abnormal area consisting of diffuse, subtle nodularity with variable loss of vascular and mucosal pattern (Paris 0–2b), with a more abnormal lesion at 30–31 cm, 3–4 o'clock with 1 cm raised lesion and with a central depression (Paris 2a+c). The left wall was flat and appeared smooth on HDWL and NBI. Extensive EMR was performed with nine pieces in total removed resulting in 40–70% circumferential resection (70% in mid-distal area).

Histological assessment revealed an extensive covering of LGD mucosa in eight of the nine EMR specimens, and two of these also contained focal HGD (both from the area of the nodule at 30–31 cm, 3–4 o'clock) (► **Figs. 3–5**). One EMR specimen contained no dysplasia. Using a standard biopsy forceps, 15 biopsies were taken from the remaining less abnormal mucosa, including several from the margins of the EMR. Eight of these showed no dysplasia, six contained LGD, and one contained focal HGD.

Four further gastroscopies were performed over the subsequent 7 months. Two endoscopic balloon dilatations were performed, and the residual Barrett's mucosa was then treated with Halo 360 radiofrequency ablation (RFA) then Halo 90 RFA. At the most recent gastroscopy, there was no stricture present; argon plasma coagulation (APC) was performed for residual small Barrett's islands and biopsies from these islands showed no residual dysplasia.

## Discussion

DEVLB is a phenotype which has not been described previously. We defined DEVLB as an endoscopically visible area with predominantly extensive low grade dysplasia within Barrett's mucosa which consists of: a large area with (which we defined as at least 6 cm<sup>2</sup>): 1) diffusely abnormal mucosa with: a) patchy loss of or variation in mucosal pattern and/or b) widespread, subtle nodularity; and 2) a clear demarcation from normal looking smooth Barrett's mucosa, and 3) histology showing predominantly multifocal LGD though sometimes with areas of more advanced dysplasia.

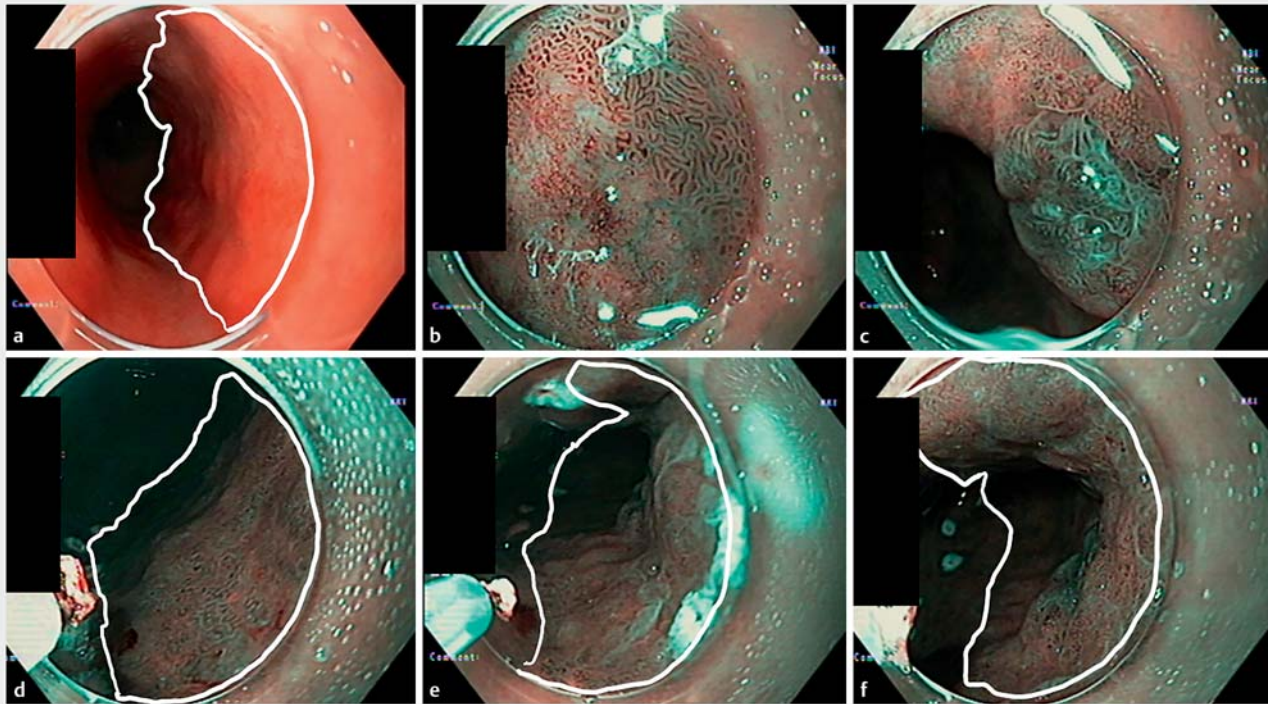
The above case (and Video 1) depicts the typical appearance of DEVLB and the management course.

The median maximal length of Barrett's segment was 9 cm (IQR:7–12), suggesting that DEVLB occurred mainly in long segment BE. Of the seven patients with DEVLB, the majority of the EMR specimens contained dysplasia (96%), of which 77% were LGD. This indicates that the diffuse nodularity in the DEVLB area was comprised predominantly of LGD. This DEVLB area often contained focal HGD or EAC, suggesting that the widespread multifocal LGD in DEVLB may be a more aggressive or advanced phenotype than in most other patients with LGD who have endoscopically invisible LGD. In addition, we have noticed that the occasional HGD or EAC is very difficult to identify and distinguish from the surrounding LGD. Given the potential for HGD and intramucosal carcinoma (IMC) within DEVLB, we believe these patients are better managed with EMR of the abnormal DEVLB area, while reserving RFA for the residual flat mucosa. EMR of DEVLB often involves a large area of the esophagus and could result in esophageal strictures as a complication requiring subsequent dilation.

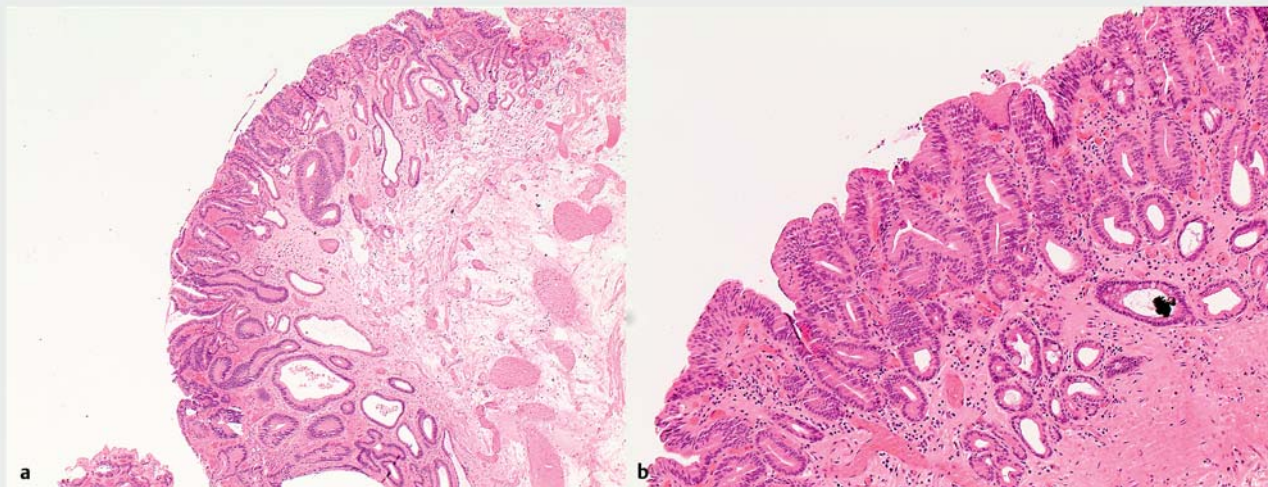
DEVLB predominantly affects the right wall of the esophagus. Similarly, several authors have reported that advanced neoplasia is more likely to be identified on the right wall of the esophagus [13–16]. A potential explanation for this finding may be due to the asymmetrical increased exposure to acid reflux on the right wall of the esophagus as demonstrated by Omae et al. who performed 25-hour pH monitoring on 33 patients with Barrett's related adenocarcinoma [16]. Their study revealed that, in 90.9% of cases, the location of adenocarcinoma coincided with the direction of acid or non-acid reflux.

Furthermore, of the targeted biopsies of the remaining smooth or less abnormal Barrett's mucosa post-EMR, 80% were NDBE, suggesting that DEVLB is often well circumscribed with a clear demarcation from smooth, non-dysplastic Barrett's mucosa.

It is important for all endoscopists to identify patients with DEVLB from a management perspective as these patients tend to require extensive EMR of the affected area before RFA. From the risk stratification point of view, further work and long-term follow-up data are needed to decipher the natural disease progression of DEVLB. Further studies are also needed to determine whether this phenotype is a biologically distinct form of Barrett's esophagus with more aggressive behavior, or simply a more advanced stage.



► **Fig. 4** Patient 1. **a, d, e, f** Marking of a well demarcated area consisting of diffuse subtle nodularity. **b** Patchy loss of mucosa pattern. **c** Nodule at 30–31 cm, 3–4 o'clock (focal high grade dysplasia (HGD)).



► **Fig. 5** Patient 1. **a, b** Histology slide from two different areas showing tissue lined by columnar lined mucosa with intestinal metaplasia and widespread low grade glandular epithelial dysplasia.

In conclusion, this case series illustrates a subset of patients with a distinct phenotype of Barrett's esophagus which we have termed DEVLB. The histology within this segment of Barrett's esophagus usually contains widespread LGD, and can be identified on endoscopy as a diffusely abnormal mucosal appearance over a large, well defined area within a long Barrett's segment often affecting the right wall. In many cases, there are areas of

focal HGD or EAC which are difficult to identify within the large abnormal area. We believe these patients are best managed with a referral to an expert center for extensive EMR of the DEVLB area.

## Competing interests

None

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