BARRETT'S OESOPHAGUS: A BRIEF OVERVIEW

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Introduction

Mini Review

Barrett's oesophagus (BO) is a condition in which the normal oesophageal squamous epithelium is replaced by columnar epithelium. This process is called metaplasia. BO is considered as a benign pre-stage of distal oesophageal adenocarcinoma and occurs as a result of prolonged gastro-oesophageal reflux, which also causes symptoms of heartburn.

Epidemiology and risk factors

The occurrence of BO differs worldwide with a prevalence of 1.6% in Sweden [1] and 5.6-6.8% in The United States [2]. These percentages are likely underestimated due to the lack of symptoms related to BO. Gastro-oesophageal reflux is the main risk factor to develop BO, yet only 7.8% have symptoms of heartburn [3]. Patients older than 65 years have a higher prevalence of BO with a prevalence of 19.8% and 14.9%, respectively, in patients with and without symptoms of heartburn [4]. Besides reflux and age, other risk factors for the development of BO are central obesity (OR 1.98; 95%-CI 1.52-2.57) [5], male gender (OR 2.16; 95%-CI 1.84–2.53) [6], increased BO segment length (OR 1.25; 95%-CI 1.16–1.36), and the presence of a hiatal hernia, which is present in 76.9% of the patients with BO [7]. Additionally, BO is more frequent in patients who have ever smoked cigarettes (OR 1.67; 95%-CI 1.04-2.67) [8].

Malignant progression

During the last decades, the number of patients with adenocarcinoma has been rising and the incidence has increased sixfold [9]. In patients with BO, the risk of progression to adenocarcinoma is 0.25-0.70% per year, which is 24 times higher than in the general population [10-13]. This risk is higher in men and in patients with long-segment BO. If oesophageal adenocarcinoma has developed, the 1-year and 5-year survival are 50% and 20% respectively, but these rates get better if the cancer is recognised in an early stage [14]. The prognosis of patients with adenocarcinoma is dismal, American Cancer Society brought out the first estimates for 2017; 16,940 new oesophageal cancer cases and 15,690 deaths from oesophageal cancer [15]. To prevent malignant progression, intensive surveillance programs are offered in patients with BO (see paragraph Prevention and Surveillance).

Pathobiology

The oesophageal wall is originally covered by squamous epithelium. In patients with BO, this squamous lining is replaced by columnar epithelium. Gastro-oesophageal reflux leads to inflammation of the oesophageal wall (i.e. reflux oesophagitis). Prolonged oesophageal reflux may alter oesophagitis into BO, followed sequentially by low-grade dysplasia (LGD), high-grade dysplasia (HGD) and eventually oesophageal adenocarcinoma. Specifically, reflux of bile can lead to oxidative stress and is associated with carcinogenesis [16]. Regularly, one BO segment comprises multiple different islands (which coexist like mosaic); one island could contain LGD, while the other contains HGD [17].

Three types of columnar cells are found in a BO segment; 1. the junctional or cardiac type (which is generally located at the gastroesophageal junction), 2. the gastric type, 3. the intestinal type. Mainly the intestinal type is known to predispose malignant progression [18]. Some guidelines advocate that intestinal metaplasia (IM; the replacement of squamous cells by intestinal type cells) is required for BO diagnosis, but other guidelines fear underdiagnosis if replacement by the cardiac or gastric type is not detected [19-21].

Helicobacter pylori (H. pylori) is associated with symptoms of heartburn, chronic gastritis, peptic ulcer disease and IM of the gastric epithelium. However, it is thought that *H. pylori* plays a protective role against BO and the development of adenocarcinoma (OR 0.50) [22].

Symptoms

Metaplasia of the distal oesophagus (BO) itself does not cause any problems. However, gastro-oesophageal reflux disease (GORD) is a major risk factor and has the following symptoms: regurgitation, heartburn and dysphagia [19].

Diagnosis

The healthy oesophageal mucosa has a pale colour, in contrast to BO, which is recognised by bright salmon-coloured mucosa extending above the gastro-oesophageal junction (Figure 1). The gastro-oesophageal junction is defined as the transition zone between the stomach and the oesophagus, which can be recognised as the proximal end of the gastric folds. For diagnosis, histologic confirmation (by taking a biopsy) and a segment of more than 1 cm are required [23]. Another reason of taking biopsies is to rule out coexisting HGD or adenocarcinoma. These biopsies are obtained during gastroesophageal endoscopy according to the Seattle protocol, which comprises targeted tissue sampling of visible nodules and four-quadrant random biopsies (i.e. 12, 3, 6 and 9 o'clock) with 2 cm intervals up to the proximal end of the Barrett's segment. If the segment is shorter than 2 cm, at least four biopsies should be obtained [24].

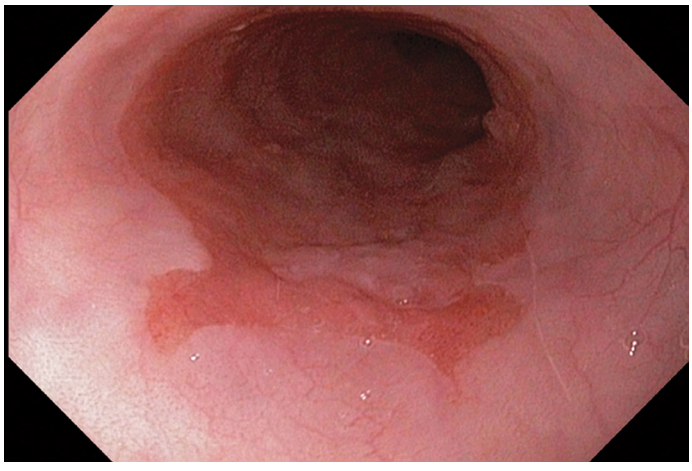

Figure 1: *Endoscopic view of a Barrett's oesophagus segment.*

During endoscopy, the Barrett segment is described with the Prague C&M classification by assessing the circumferential (C) and the maximum (M) length of the salmon-coloured mucosa in centimeters (Figure 2) [25,26]. Histologic analysis according to the Seattle protocol has several drawbacks: 1. it prolongs the procedure time, 2. the adherence to the protocol by the endoscopist is reduced for patients with longer Prague segments 3. this biopsy method often only samples 4-6% of the whole salmon-coloured surface [27], 4. the interobserver agreement between pathologists is often low. During the last decades, new techniques have been developed (e.g. Narrow Band Imaging (NBI), Volumetric Laser Endomicroscopy (VLE), Confocal Laser Endoscopy (CLE), WATS3D) to address this problem [28].

A frequently used technique during endoscopy is NBI. NBI uses high-intensity blue light to enhance capillaries in the mucosa and the mucosal patterns. An irregular mucosal pattern with increased vascularity is suspicious for HGD [29].

Treatment

Acid suppression
Proton-pump inhibition (PPI) is the treatment of choice in patients with BO. This agent suppresses acid production by the inhibition of H+/K+ ATPase of the gastric parietal cells in the fundus and the corpus of the stomach. Hillman et al [30] found a hazard ratio of 20.9 for developing HGD or adenocarcinoma in patients who did not receive PPI-treatment. However, this effect has never been proven in prospective trials.

An alternative to the pharmaceutical approach is to create a mechanical barrier against acid reflux. One example of anti-reflux surgery is Nissen fundoplication; this technique aims to wrap the gastric fundus around the distal oesophagus and narrows oesophageal hiatus with stitches. Various studies have compared the pharmaceutical and surgical approach for anti-reflux therapy, but a statistically significant difference has not been found [31,32]. Yet anti-reflux surgery should be considered in treatment-resistant patients.

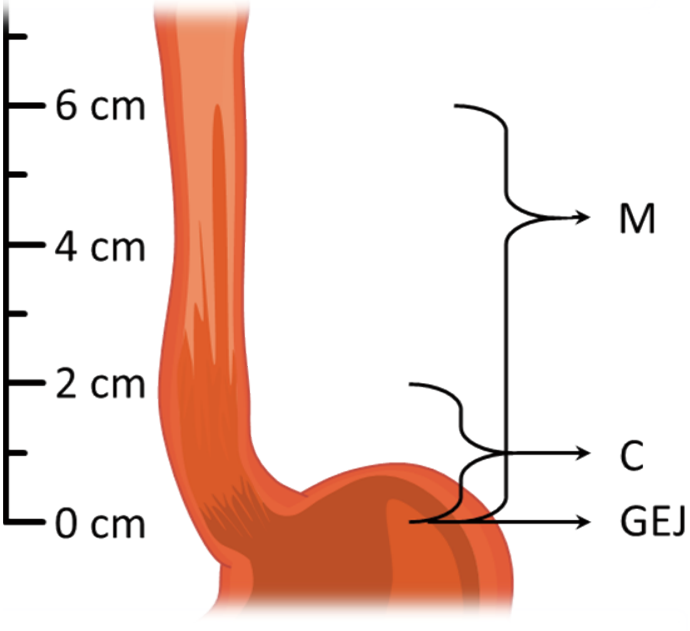

Figure 2: *The C&M Prague criteria. 'C' represents the circumferential Barrett's Oesophageal length in cm measured from the gastroesophgeal junction (GEJ), 'M' represents the maximal extent of the metaplasia in cm (C2M6) measured from the GEJ.*

Endoscopic treatment
Most Barrett's lesions can be treated endoscopically. In case of flat BO (without nodules), the abnormal mucosa is treated with ablative therapy. The approach that is frequently used is Radiofrequency Ablation (RFA), this technique eradicates the superficial layers of the oesophageal wall with high frequency energy. The device is passed through the biopsy channel and can eradicate large areas at once. Orman et al. [33] performed a large meta-analysis and showed complete eradication of IM and dysplasia in 78% and 91% of the cases, respectively. One drawback is stricture formation, which occurs in 5.6% of the cases [33], resulting in dysphagia. The RFA technique reduces the risk of progression to HGD or adenocarcinoma with 25% [34].

In case of nodular disease, endoscopic mucosal resection (EMR) is applied. It can be used prior to RFA or individually. The response rate is high (96.6%), but so is the stricture rate (37-88%) [35].

Oesophagectomy
In case of multifocal dysplastic lesions, oesophagectomy is considered, in which the entire oesophagus is surgically removed. This can be performed 'trans-hiatal', in which the oesophagus is approached from the abdomen through the oesophageal hiatus) or 'trans-thoracic' (e.g. Ivor Lewis procedure with an upper abdominal incision and a posterolateral thoracotomy). Williams et al. [36] studied the histology of oesophagectomy specimens in 38 patients with HGD, in 29% of the cases occult EAC was found. In case of only HGD in the pathology analysis, lymphadenectomy is not required [37,38].

Prevention and Surveillance
Secondary prevention focuses on the detection of a disease in a subclinical stage to treat in an early stage, which is related to better survival rates. Although the risk of oesophageal adenocarcinoma in patients with BO is relatively low [10-13], the high mortality, related to adenocarcinoma, calls for surveillance [14]. A Dutch BO expert panel recommends the following in patients with non-dysplastic BO [39] (see Figure 2 for the Prague C&M classification):

- No follow-up in case of a Prague length (M) of < 1cm
- Follow-up after 5 years in case of a Prague length (M) of 1-3 cm
- Follow-up after 3 years in case of a Prague length (M) of 3-10 cm
- Reference to a BO expert centrum in case of a Prague length (M) of >10 cm

Frequent surveillance in patients without dysplasia, elderly (>75 years) and patients with significant comorbidity is discouraged by recent Dutch (concept) guidelines. Patients with LGD should undergo treatment (e.g. RFA), since the risk that it also harbours HGD or adenocarcinoma is 14% [39] and if left untreated, 13% develops HGD or adenocarcinoma [40]. In case of HGD or adenocarcinoma, there should be a second evaluation by a pathologist experienced with BO. In case of HGD or adenocarcinoma, it is recommended (in the Netherlands) to refer the patient to one of the eight BO expert centres and let a pathologist, experienced with BO, do a second evaluation [39] .

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