Goblet cells in Barrett's oesophagus: cancer precursor, risk marker, or irrelevance?

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Abstract

It is popularly held that cancer risk in Barrett's oesophagus is conferred by intestinal metaplasia (IM), defined by goblet cells. This belief is difficult to test, partly because it is impossible to prove an *absence* of goblet cells in a particular oesophagus: no matter how many biopsies without them have been examined, it is always possible there may be some in the very next biopsy.

Also, little is known about the spatial distribution and temporal drift of the intestinal phenotype in Barrett's oesophagus; and ignorance of relationships between duration, extent and phenotypic diversity in a Barrett segment on the one hand, and dysplasia and its progression on the other is a problem.

Cancer-related genetic and epigenetic abnormalities in non-intestinal glandular mucosa further call in question the belief that intestinalized mucosa alone is at increased risk of malignancy.

Accurate determination of patient-specific cancer risk in Barrett's oesophagus will require more sophisticated understanding of how mucosal phenotype is determined (cell fate specification) and how dysplasia evolves than presently available, and is unlikely to be reducible to whether intestinal metaplasia is 'present' or 'absent'. That intestinal metaplasia is a necessary precondition for Barrett's adenocarcinoma is a dogma hindering understanding of carcinogenesis in metaplastic oesophageal mucosa and at the oesophago-gastric junction, and has no value in the definition of Barrett's oesophagus.

Keywords adenocarcinoma; Barrett's oesophagus; columnar lined oesophagus; goblet cells; intestinal metaplasia; metaplasia

Introduction

In Barrett's 'columnar lined' oesophagus, normal squamous epithelium is replaced by metaplastic glandular mucosa in response to chronic gastro-oesophageal reflux of acid, pepsin and bile. Barrett's oesophagus predisposes to oesophageal adenocarcinoma, and over recent decades the incidence of Barrett's oesophagus and adenocarcinoma have risen to the point that oesophageal adenocarcinoma is now relatively common in the United Kingdom,[1] Europe and the USA, while remaining rare in the far east.

Many different mucosal types can be recognized in a Barrett segment, including autochthonous squamous mucosa; neosquamous epithelium, following ablative therapies; immature transitional forms; squamous islands around ostia of oesophageal submucosal gland ducts; classical incomplete intestinal metaplasia, with goblet cells; cardia-like mucosa; and cardio-oxyntic and oxyntic mucosae, with parietal (oxyntic) cells.

It is widely considered that metaplasia to a mucosa with goblet cells is specifically associated with premalignant dysplasia (intraepithelial neoplasia) and risk of progression to oesophageal adenocarcinoma.[2] In the USA and Germany intestinal metaplasia (IM) has come to be regarded as a prerequisite for the diagnosis of Barrett's oesophagus and enrolment into endoscopic surveillance.[3] On the other hand, neither the British Society for Gastroenterology not the Japan Esophageal Society require intestinal metaplasia for a diagnosis of Barrett's epithelium, which can be made when columnar mucosa of cardiac (junctional), oxyntic or intestinal types are found in a mucosal biopsy[4] confirmed as oesophageal in origin.

Studies over the last half-century are often said to show that Barrett's dysplasia and adenocarcinoma develop in the presence of, and perhaps from intestinal metaplasia. However, there is molecular evidence suggesting that Barrett's 'columnar lined' oesophagus, even without IM (i.e. without goblet cells) may have malignant potential.[5] We reviewed original evidence for a specific role of intestinal metaplasia as the usual precursor of oesophageal adenocarcinoma, and consider whether its presence or absence is really an appropriate precondition for a diagnosis of Barrett's oesophagus.

Literature search

A literature search was performed using PubMed, Embase and Ovid for English language literature since 1900 using MESH terms "Barrett", "Barrett's esophagus/oesophagus", "columnar lined esophagus/oesophagus", "esophageal/oesophageal adenocarcinoma", "intestinal metaplasia", "metaplasia" and "goblet cells". All articles identified were screened by title and abstract when available by the authors and included if relevant.

History of Barrett's oesophagus

As early as 1906 the distinguished American physician and educator Wilder Tileston (1875–1969), then at Harvard, described three cases of oesophageal peptic ulceration and a 'close resemblance of the mucous membrane about the ulcer to that normally found in the stomach'.[6] In 1950, Norman Barrett (1903–1979) proposed a definition of the oesophagus as 'that part of the foregut, distal to the cricopharyngeal sphincter, which is lined by squamous epithelium'.[7] He went on to describe peptic ulceration of gastric-like mucosa in a tubular organ, with associated oesophageal stricture. In keeping with his definition of the oesophagus, he concluded that this tubular viscus was a segment of stomach tethered within the chest by a congenitally short oesophagus. This paper was one of the first to link oesophagitis, gastro-oesophageal reflux hiatus hernia.

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In 1953 Allison and Johnstone argued that Barrett's tubular, columnar lined structure was actually "an oesophagus lined with gastric mucous membrane".[8] They showed it had no serosal covering, and contained submucosal glands typical of the oesophagus. Acknowledging Barrett, then editor of *Thorax*, they called ulceration in a glandular-lined oesophagus "Barrett's ulcers". By 1957, Barrett had accepted Allison and Johnstone's theory and proposed the name "lower oesophagus lined by columnar epithelium". However, the name "Barrett's oesophagus" has stuck even though the present concept is not as Barrett initially described. Barrett himself did not mention intestinal metaplasia in his reports, but many subsequent definitions note, and some have required goblet cells for its diagnosis.[9] We use 'Barrett's oesophagus' and 'columnar lined oesophagus' (CLO) as exact synonyms.

Further studies supported the view that the columnar lined oesophagus was caused by gastro-oesophageal reflux. Moersch et al (1959) reviewed 36 oesophageal resections for oesophagitis, and concluded that the columnar (glandular) mucosa of Barrett's oesophagus was acquired following repeated exposure of the distal oesophagus to gastric refluxate.[10] Bremner and colleagues supported this theory with an animal model in 1970, and the congenital theory was abandoned.[11]

Histology of Barrett's oesophagus

As early as 1937 Lyall noted that the columnar lined oesophagus (not yet so named) contained cells similar to those normally found near the pylorus of the stomach.[12] After Allison and Johnstone, other investigators identified a mosaic of histological types in the histologically heterogenous columnar lined oesophagus. Bosher and Taylor (1951) described a woman with a long oesophageal segment lined by a gastric-like mucosa composed of glands with goblet cells, but no parietal cells.[13] In 1952, Morson and Belcher identified a patient with oesophageal adenocarcinoma in whom the adjacent mucosa was intestinal, with many goblet cells.[14]

In 1961, Hayward suggested that glandular metaplasia in the distal oesophagus protected the mucosa from peptic injury.[15] Paull et al. (1976) gave a clear histological description of the columnar lined oesophagus in their series of 11 patients with Barrett's mucosa, identifying three types of columnar epithelia above the lower oesophageal sphincter: a gastric fundic type, with parietal and chief cells; a junctional type with cardiac mucous glands (Figure 1), and a distinctive 'specialized' type with mucous glands and intestinal-like goblet cells (Figure 2).[16] This 'specialized' columnar epithelium, found especially at the proximal end of the columnar lined oesophagus was the most prevalent, and was associated with a long dysplastic segment in one patient.

Events in the metaplastic transformation of squamous to columnar epithelium are still not clear, nor where the columnar cells come from.[17] Chandrasoma has proposed that even 'normal' cardiac mucosa is itself acquired by metaplasia following reflux injury to squamous epithelium of the distal oesophagus.[18] Manometry and pH studies suggest that the extent of cardiac mucosa is increased in people with acid reflux, and there is no cardiac mucosa in children in the absence of reflux: the entire oesophagus is normally lined by squamous epithelium with an abrupt transition to gastric oxyntic mucosa at the gastro-oesophageal junction.[19] This state may persist in some adults: Figure 3 shows a very abrupt transition from squamous to fundic mucosa at the squamo-columnar junction of a middle-aged man who had an oesophagectomy for squamous carcinoma. Cardiac type mucosa may develop above the anastomosis of a gastric pull-up following oesophagectomy, in keeping with an acquired condition.[20] Other types of glandular mucosa may evolve from this mucosa by developing specialized cells (parietal cells, chief cells, goblet cells), and severity of reflux is associated with length of the columnar lined segment.[21] Oesophageal submucosal ducts are a useful marker of oesophageal location in biopsies (Figure 3).

Intestinal metaplasia and cancer risk

Intestinal metaplasia in the stomach is strongly associated with gastric adenocarcinoma,[22] and it is *plausible* that intestinal metaplasia of the oesophagus is premalignant, but there are few original studies which really test this idea,[23] and even gastric intestinal metaplasia itself may be no more than a marker of cancer-promoting chronic mucosal injury and inflammation caused by autoimmune gastritis or *Helicobacter* infection, and not a direct cancer precursor *per se*.

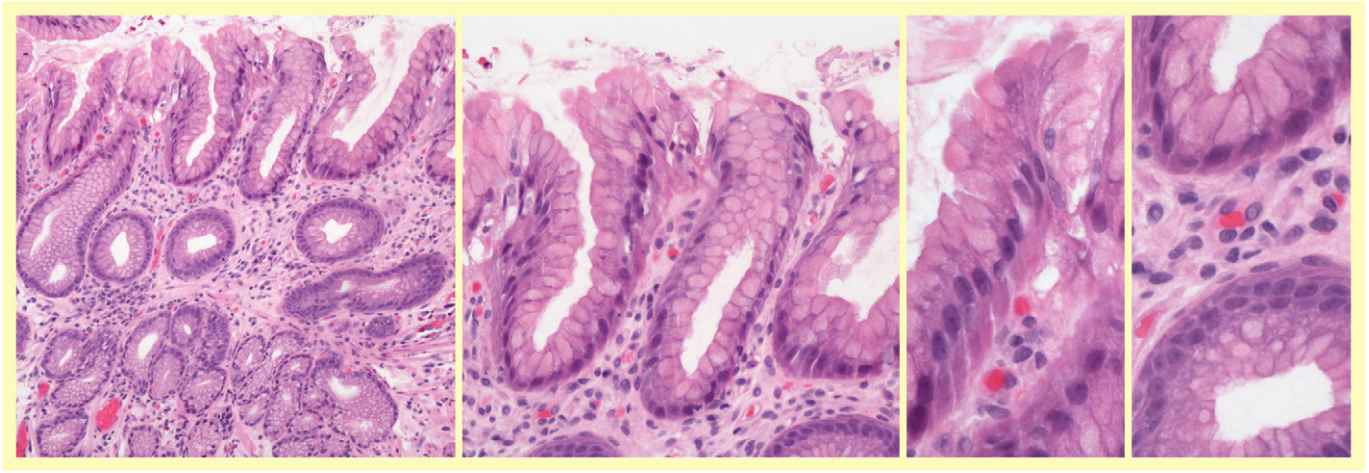

Figure 1 Barrett's mucosa of a purely cardiac phenotype. No goblet cells are present. Such a purely cardiac mucosa is actually quite uncommon in Barrett's oesophagus. There is no dysplasia.