REVIEW OF BARRETT'S OESOPHAGUS

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The term Barrett's oesophagus is given to the condition in which the distal oesophagus is lined by columnar epithelium, instead of the normal squamous epithelium, that is expected anatomically. This condition, which continues to be a source of controversy, was named after the surgeon Norman Barrett, who described the columnar-lined oesophagus in a paper in 1950.[1] However, he did not recognise that he was describing a condition of the oesophagus, stating that it was actually part of the stomach that was located intra-thoracically and he called the condition 'congenital short oesophagus'. Allison and Johnston had demonstrated in 1953 that the 'columnar-lined oesophagus' was indeed an abnormality of the oesophagus itself.[2]

Seven years later Norman Barrett recognised this condition as being a true replacement of the oesophageal epithelium by a columnar-lining and that this lining was not gastric mucosa.[3] This term 'columnar-lined oesophagus' reflects more accurately the nature of the condition than the eponymous term Barrett's oesophagus.

DEFINITION

Defining Barrett's oesophagus as the presence of columnar epithelium in the distal oesophagus seems simple enough, but in practice using this definition actually may cause problems. This has led to three different approaches in defining Barrett's oesophagus: (1) On the basis of *Endoscopic findings*; (2) on a *Histology* based approach; (3) and on a *Clinico-pathological* based approach.

(1) Endoscopic findings

In many, a columnar epithelium is found at the lower end of the oesophagus as an upward continuation of the gastric mucosa beyond the cardia, and this is regarded as being a normal finding. In the presence of a hiatus hernia, it can be difficult to define exactly where the gastric mucosa stops and there are thus difficulties in the diagnosis of a columnar-lined oesophagus in association with this condition.[4] To overcome these problems, Barrett's oesophagus has been defined as columnar-lined epithelium that extends for greater than 3cms from the oesophago-gastric (OG) junction.[5] However, even this stricter definition has its problems, as in some cases of Barret's oesophogus the columnar epithelium (i.e. a tongue of columnar epithelium or an irregular squamocolumnar junction) extends for less than 3 cms from the oesophago-gastric junction.

(2) Histology

Histology has been used to define what is columnar-lined oesophagus and what is normal stomach. In the columnar-lined oesophagus, three types of metaplastic tissue can be seen: gastric fundic, gastric junctional and intestinal (specialised) metaplasia.[6] The gastric fundic and gastric junctional type metaplastic mucosa could easily have come as an extension from the normal stomach or normal OG junction. This has led many to suggest that the presence of intestinal metaplasia at above the OG junction should be the defining feature of columnar-lined oesophagus / Barrett's oesophagus. However, in the last few years, it has become recognised that even at a 'normal' OG junction, intestinal metaplasia is found in up to 18% of people.[7]

Studies have shown that if the OG junction appears to be normal and there is intestinal metaplasia, the intestinal metaplasia is associated with *H. pylori* infection and not with symptoms of reflux disease. However, if the OG junction is abnormal and there is intestinal metaplasia present, the intestinal metaplasia is associated with reflux disease, but not with *H. pylori* infection.[8]

Using histology to define the presence of Barrett's oesophagus is not foolproof either. Biopsies taken from this area are random and the distribution of the metaplastic tissue in its constituent forms of intestinal metaplasia or gastric fundic or gastric junctional epithelium is also random. In some instances there is a columnar-lined oesophagus greater than 3 cms but no intestinal metaplasia is detected on biopsy. Later biopsies taken at further endoscopies may detect the intestinal metaplasia.[9,10] It is now advocated that when biopsying a columnar-lined oesophagus multiple biopsies should be taken using a systematic intensive biopsy protocol, in order to maximise the chances of detecting intestinal metaplasia and dysplasia. However, even when using an intensive biopsy protocol, a significant risk of missing intestinal metaplasias still remains.[9]

(3) Clinico-pathological

The above problems have led to good working definition of Barrett's oesophagus that rely on endoscopic findings and histology:[11]

A. Columnar-lined oesophagus of greater than 3 cms together with intestinal metaplasia (also known as long segment Barrett's oesophagus).
B. Abnormal oesophago-gastric junction with columnar-lined oesophagus of less than 3 cms, plus intestinal metaplasia (also known as short segment Barrett's oesophagus).

PATHOLOGY

In the majority of patients, a columnar-lined oesophagus is acquired during adult life, although a few cases of congenital columnar-lined oesophagus do occur and may present earlier. Once acquired the extent of columnar-lined oesophagus does not change.[12] The importance of this condition is an increased risk of oesophageal adenocarcinoma with the risk varying from 1 in 50 patient-years to 1 in 180 patient-years; the risk of developing adenocarcinoma as compared to the general population is 40 to150 times higher.[13,14] The most common type of metaplastic tissue which is associated with most cases of oesophageal adenocarcinoma is intestinal metaplasia.[6]

Progression from columnar-lined oesophagus to an adenocarcinoma is gradual with simple metaplasia giving way to low-grade dysplasia, then on to high-grade dysplasia and eventually to adenocarcinoma: this progression is not inevitable.[13,15] However, in approximately 40% of cases of high-grade dysplasia small foci of frank adenocarcinoma are found in the surgically resected specimens.[16,17]

THE CAUSE OF BARRETT'S OESOPHAGUS

The columnar-lined oesophagus is currently believed to be an adaptive response of the non-keratinising squamous epithelium of the oesophagus to exposure of excessive amounts of hydrochloric acid refluxed from the stomach. The metaplastic epithelium appears to arise from the residual cells basal epithelial cells in the submucosa that are exposed to acid after the squamous epithelium has been stripped off. The metaplastic tissue is not due to upward migration of epithelium from the stomach.[18]

It is conventionally held that those with complications of gastro-oesophageal reflux (i.e. Barrett's oesophagus, ulcer, and stricture) have greater oesophageal acid exposure than those with uncomplicated oesophagitis.[19,20] However, others have shown no difference in oesophageal acid exposure between those with Barrett's oesophagus and those with grade II/III oesophagitis.[21-23] As Barrett's patients tend to be older than oesophagitis patients, it has been suggested that increasing age explains the increased duration of acid exposure in the Barrett's group.[23] Barrett's patients do not have more oesophageal acid exposure than those with other complications (ulcer, stricture) do.[24] This suggests that other factors may be involved.

The distal oesophagus is exposed not only to acid but to other substances such as pepsin, pancreatic enzymes and duodenal contents which include bile acids and trypsin.[25,26] One paper argues that levels of bile acid exposure within the distal oesophagus seems to parallel the severity of acid reflux.[27] However most of the exposure to bile acids takes place between pH 4-7;[28] experiments have shown that at an acidic pH (pH<4) there seems to be little additive effect of bile acids on acid-caused damage in the lower oesophagus. However, at (pH 7) bile acids, especially secondary bile acids and deconjugated bile acids, can cause damage;[29-31] this seems to be synergistic in its activity with trypsin.[32] Oesophageal damage can occur without exposure to pathological amounts of acidic gastric contents:[33] exposure to pathological amounts of duodenal contents can have a similar deleterious effect. Severity of oesophageal damage have been shown to correlate with the severity of duodenogastroesophageal reflux. It remains to be seen whether it is either acid or another constituent of the refluxate, or a combination of factors that induces a switch from squamous-lined to columnar-lined oesophagus.

EPIDEMIOLOGY

Symptoms of gastro-oesophageal reflux are common and in one study the incidence of either heartburn or acid regurgitation on a weekly basis is reported as 19.8%.[34] Some authorities report the incidence of Barrett's oesophagus at endoscopy as being as high as 1 in every 100 endoscopies performed. However, recent data suggest that in recent years this may be an under-estimate. A study from Dundee reports that in the year 1992-1993 there were 42.7 cases of newly diagnosed Barrett's per 1000 endoscopies.[35] This study also showed that there was a rise in incidence of newly diagnosed Barrett's at endoscopy which has occurred between the years 1980-1993. This observation has been confirmed elsewhere in the UK.[36]

Another study performed in the US indicates that the incidence of Barrett's in the general population is higher than that suggested by the number of cases diagnosed by endoscopy.[37] It suggests that for every case of Barrett's diagnosed at endoscopy, there are another six that remain undiagnosed in the community.

Barrett's oesophagus tends to be more common in men: one study suggests that for every female with Barrett's there are two males.[12] The incidence of Barrett's oesophagus increases with age and the majority of cases are found in people over 50 years of age.[12,38]

Over the last 30 years there has been a marked increase in the incidence of oesophageal adenocarcinoma. In Scotland between the years of 1975 and 1990 the incidence in males rose from 2.2 to 3.5 per 100,000, and in females from 0.8 to 1.1 per 100,000.[39] A similar rise in the incidence of oesophageal adenocarcinoma has been reported elsewhere in the world.[40,41]

As previously mentioned the main risk factors for oesophageal adenocarcinoma would seem to be pre-exisiting Barrett's oesophagus.[42,43] When one has Barrett's oesophagus, the main risk factors for progressing to adenocarcinoma would appear to be male sex, smoking, and length of the segment of Barrett's oesophagus, presence of a complicating oesophageal ulcer and / or stricture in the same columnar-lined area.[44-46]

SURVEILLANCE

The five-year survival rate of oesophageal adenocarcinoma is approximately 17%. This improves to 24% for those who undergo surgical resection.[47] The studies have however shown that survival depends on the stage of the tumour with better survival rates for those without regional lymph node involvement (stages 0,I, IIa): a five-year survival of 30% as opposed to <10% for those with regional lymph node involvement (stages IIb, III). The five-year survival rate improves to 63% if the tumour is restricted to the submucosa alone (stages 0,I).[47] Surveillance of those with Barrett's oesophagus allows adenocarcinoma to be detected at an earlier stage, thus improving the chances of survival from this malignancy. Two-year survival was 85.9% for surveyed patients and 43.3% for non-surveyed patients.[48]

This strongly suggests that there is an advantage for the individual with Barrett's oesophagus in undergoing surveillance. However, oesophageal adenocarcinoma is not a common cause of death in those who have Barrett's oesophagus.[14,49] Surveillance does not affect the life-expectancy of a group of Barrett's patients who undergo surveillance and most cases of oesophageal adenocarcinoma arise in Barrett's that has not been previously known about.[43,50] We can deduce from this that surveillance of those with known Barrett's oesophagus will not make an impact on death rates in the general population from oesophageal adenocarcinoma.

SURVEILLANCE STRATEGIES

The question of whether patients with Barrett's oesophagus should undergo surveillance remains controversial. If surveillance is to be undertaken it is advised that only those who would be fit enough to undergo an oesophagectomy

should undergo surveillance. This may change in the future as new oncological treatments, in the form of laser or photodynamic therapy, are developed.

For those whose biopsies do not show dysplasia, surveillance endoscopies should take place every one to two years. Quadrantic biopsies should be taken every 2 cms of the portion of the oesophagus which is columnar lined. However, for those with low-grade dysplasia, surveillance endoscopies should take place every six months.[51]

In patients with known high-grade dysplasia some advocate that regular endoscopies, with a biopsy protocol that is more intensive than the one outlined previously, can differentiate between high-grade dysplasia and early adenocarcinoma.[52,53] It should be recalled, however, that that high-grade dysplasia may not progress to carcinoma for many years, if at all. Their protocols for frequency of endoscopy and biopsy taking are very intensive, and place a large burden on the patient and the health care system. Their data also suggest that in spite of all this they do miss the diagnosis of carcinoma in a significant proportion of cases.

Others would suggest a policy of oesophagectomy for high-grade dysplasia,[16,17] on the bases that on average 41% of surgical specimens from oesophagectomies for high-grade dysplasia will also exhibit foci of adenocarcinoma; although most of these are stage I adenocarcinomas, some are stage II or III. Their rationale is that the whole idea of surveillance is to detect a cancer as early as possible, as this enhances the chances of a cure.

TREATMENT

Medical

The main stay of treatment in Barrett's oesophagus is acid suppression therapy with the scope of: (1) *Symptomatic relief*; (2) induction of *Regressio*n of Barrett's mucosa; (3) as *Adjuvant therapy*.

(1) Symptomatic relief

This is aimed at suppressing the symptoms of gastro-oesophageal reflux. However, those with Barrett's oesophagus may not have symptoms of reflux disease.[54] Barrett's oesophagus is less sensitive than a squamous-lined oesophagus to the presence of acid.[55,56] Acid suppression therapy is sometimes used in asymptomatic Barrett's oesophagus, on the assumption that preventing further acid exposure will decrease the risk of adenocarcinoma developing; however, there is no evidence to support or refute this approach.

(2) Regression

Some patients with Barrett's oesophagus, who have taken proton-pump inhibitors on a long-term basis have had regeneration of their squamous epithelium.[57-59] This does not take place in all of the patients and in those in which such epithelial reversal does take place it is only islands of squamous epithelium that regenerate. Biopsies of these squamous islands show that underneath the squamous epithelium there is still columnar epithelium present.

(3) Adjuvant therapy

At present, many centres are evaluating acid suppression therapy combined with local laser therapy. The rationale behind this being that if the actual Barrett's mucosa is removed and the acid stimulation removed, this should allow the squamous epithelium to regenerate spontaneously. This regimen does show some promise in that a large proportion of these patients do have regeneration of squamous epithelium to some extent, but yet again biopsies of the regenerated squamous epithelium still show abnormal mucosa underneath this.[58,60] These studies to some extent relied on the clinical assessment of normalisation of oesophageal pH, although the elimination of reflux symptoms does not imply normalisation of oesophageal pH.[61] One study has shown that with laser therapy and normalisation of oesophageal pH as confirmed by 24 hour oesophageal pH recording, squamous regeneration is successful.[62] However, it is not known whether this regeneration reduces the individual risk of developing adenocarcinoma.

Surgery

Surgery in the form of an antireflux procedure has a role to play in Barrett's oesophagus. It is useful when medical treatment has failed to suppress the symptoms of reflux or if the patient does not wish to take medication for the rest of their life. However, even in the best hands the procedure is not without its problems.

A few small studies have suggested that an antireflux procedure may reduce the risk of malignant transformation in Barrett's oesophagus,[63,64] but to date a large randomised controlled trial has not been done. Surgery does not eliminate the risk and surveillance would still be required.[65] This should be borne in mind given that there is significant morbidity associated with antireflux procedures and the lifetime risk of developing adenocarcinoma in Barrett's oesophagus is approximately 10%.

CONCLUSION

Barrett's oesophagus and oesophageal adenocarcinoma are becoming more common and pose a significant and increasing problem for the health service. At present oesophageal acid exposure is considered to be the main factor in causing Barrett's, but there is increasing evidence that bile acids have a role that may equal or surpass that of gastric acid. Surveillance of those with Barrett's oesophagus benefits the individual patient but will not alter the death rate from oesophageal adenocarcinoma. New modalities in the form of laser therapy and photodynamic therapy show promise in the treatment of Barrett's oesophagus, however it remains to be seen if these methods of treatment will reduce the risk of developing oesophageal adenocarcinoma.

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