Leading article

Barrett's oesophagus and proton pump inhibitors: a pathological perspective

In Western communities, the incidence of oesophageal adenocarcinoma continues to increase in an almost epidemic manner, greater than any other common epithelial malignancy.[1 2] There is therefore increasing interest in the treatment strategies that reduce reflux, especially of acid, into the oesophagus in an attempt to reduce the neoplastic potential of Barrett's oesophagus/columnar lined oesophagus (CLO), the most important predisposing factor for oesophageal adenocarcinoma. The effect of surgical antireflux procedures on CLO is still controversial with no clear evidence of regression of CLO after these procedures. There is also no evidence that acid lowering drugs such as the H_2 blockers can reverse the glandular metaplasia of CLO. The efficacy of the powerful acid reducing agents, the proton pump inhibitors (PPIs), in causing regression of CLO is also controversial. Although many believe that these drugs have no great effect on CLO and most accept that these drugs do not result in complete regression of CLO, in a recent issue of *Gut*, Peters and colleagues[3] have shown that high dose PPI therapy does result in partial endoscopic regression of CLO. Perhaps because of the lack of measurable success in treating CLO with acid reflux lowering procedures, there has been a veritable explosion of interest in ablative techniques, including laser, photodynamic therapy and argon beam therapy, in an attempt to reverse the glandular phenotype. This article explores the pathophysiological mechanisms behind these treatment strategies and reviews the pathological changes that result.

Pathophysiology of acid suppression in CLO

It is generally accepted that reflux of gastric contents, particularly acid and pepsin, is the most important factor in the development of CLO in the oesophagus. Notwithstanding the widely held view that partial regression of CLO, however induced, is an inadequate end point, especially as far as cancer risk is concerned,[4] intuitively one would have thought that a reduction in acid concentrations in the oesophagus, by whatever means, should reduce the inflammation, epithelial proliferation, mutagenic potential, and neoplastic risk in CLO. Such an argument assumes that acid reflux is the most important factor, not only in the pathogenesis of CLO but also in accelerating the metaplasia–dysplasia–carcinoma sequence.

In an environment where acid reflux is either substantially reduced or absent, are other factors important? It has been argued that duodenogastro-oesophageal reflux, notably of bile acids and pancreatic trypsin, may be as important as acid and pepsin in the development of neoplastic change in CLO. Nevertheless the role of bile acids in the genesis of the complications of CLO remains uncertain.[5] There is little doubt that acid and bile acids are synergistic in toxicity to the oesophageal mucosa and probably in their induction of CLO.[6–8]

Conjugated bile acids provoke oesophageal mucosal injury at low pH levels and thus require the presence of acid to cause such pathology.[5] However unconjugated bile acids may be more toxic at neutral pH, the environment produced by powerful acid suppressing agents.[5 7] Thus it could be that such powerful acid suppression, induced by PPIs, might perpetuate mucosal damage and cancer risk, because of an increased reflux of unconjugated bile acids and trypsin into the oesophagus.[5] Patients with early adenocarcinoma in CLO seem to have the highest levels of exposure to bile acids in the oesophagus compared with patients with uncomplicated CLO.[9] In this study Nissen fundoplication resulted in complete removal of this bile reflux whereas medical acid suppression did not.[9] Bile acids may have a role in the promotion of the important intestinal phenotypes that occur in high risk CLO, given the close relation between bile acids and the induction of immature intestinal type phenotypes and intestinal type neoplasia, notably in the colorectum and the duodenum. Thus it has been postulated that unconjugated bile acids may be a factor in the progression of the neoplastic sequence of CLO.[10 11] However, although the synergism between acid and bile in the genesis of reflux disease and CLO seems to be undeniable, the relative importance of conjugated and unconjugated bile acids in the induction of mucosal damage and in the pathogenesis of the complications of CLO, especially in those on powerful acid suppressing drugs, remains unclear.[5]

The pathology of PPI therapy in CLO

It is generally accepted that PPI therapy does not result in total regression of CLO, although pathological studies of patients with CLO, treated with PPIs, have shown that there is undoubted evidence of squamous re-epithelialisation over and adjacent to Barrett's type mucosa. One medium term omeprazole trial has shown that, not only is there a small but noticeable regression in the length of CLO, there is also an increase both in endoscopically visible and microscopic squamous islands.[12 13] This partial regression seems to occur early after therapy starts, usually in the first two years[12 14] with little or no evidence of further partial regression after this time.[13]

So what is the pathological explanation for these partial regression changes? The stimulus to squamous re-epithelialisation is evident both by the production of squamous islands and by encroachment of squamous epithelium over glandular mucosa adjacent to the squamocolumnar junction.[12 13] Although this encroachment can be easily explained by migration of oesophageal type squamous mucosa across the surface of the metaplastic mucosa, the development of both macroscopic and microscopic squamous islands represents a further metaplastic phenomenon within CLO itself. Initially thought to derive from progenitor cells within the CLO mucosa,[15] more recently it has been shown that both macroscopic and microscopic squamous islands mainly derive from oesophageal gland ducts, normal structures within the

Abbreviations used in this article: CLO, columnar lined oesophagus; PPI, proton pump inhibitor.

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oesophagus which drain mucus produced by the oesophageal submucosal glands to the mucosal surface.[16] The ability of this native epithelium to undergo metaplasia might suggest that pluripotential cells within these structures are themselves responsible for the genesis of CLO.[16 17] It should be noted that such microscopic (and indeed macroscopic) squamous islands have been recognised previously and may occur in untreated CLO.[18 19] Nevertheless there is clear evidence that these squamous islands are greatly increased in CLO treated with profound acid suppression. Their production may well account for Peters *et al*'s finding that omeprazole has a more pronounced effect on CLO surface area reduction than on CLO length reduction.

These changes of squamous re-epithelialisation are the only definitive pathological effect of PPIs as yet fully recognised. After laser and photodynamic therapy, similar squamous re-epithelialisation is seen but this is much more extensive. These ablative procedures have been performed in concert with profound acid suppression, induced by PPIs, and it is likely that it is the combination of the two treatment strategies that causes the extensive squamous re-epithelialisation. A further type of squamous metaplasia or re-epithelialisation is seen after laser and, in particular, photodynamic therapy.[20] Squamous metaplasia has been noted within the Barrett's glands, giving rise to an appearance similar to that recognised in the cervix as immature squamous metaplasia.[16 20] The morphological features suggest that this squamous change represents a true metaplasia within the Barrett's glands.[16] This would argue that there are pluripotential cells within the glandular epithelium of CLO, as originally intimated by Berenson and colleagues,[15] that have the ability to transform CLO glands to structures composed wholly of squamous cells and thereby, presumably, substantially reducing the neoplastic potential.[16] This feature has not, as yet, been found in patients treated only with PPIs.

A concern with all treatments which induce surface squamous re-epithelialisation is that the surface squamous mucosa has the ability to conceal underlying CLO mucosa.[16 19] One could speculate that the buried CLO epithelium may be protected from the toxic stimuli, be they acid, bile acids, trypsin, or other agents, within the oesophageal lumen with resulting reduction in inflammation, cell proliferation, mutagenic potential, and neoplastic risk. Equally one could argue that the buried CLO mucosa continues to pose a neoplastic risk. After laser and photodynamic treatment of dysplastic CLO, concealed dysplastic epithelium has been found, although there is no evidence to suggest that this neoplastic mucosa was not already present before surface squamous epithelialisation occurred.[16 19 20] Nevertheless the concealment of CLO under squamous mucosa, whether induced by PPI therapy, surgical treatment or ablative therapy, does give rise to concern because such treatment may result in the hiding of, ultimately, advanced malignancy. These findings emphasise the need for adequately deep biopsy in cases where squamous re-epithelialisation has occurred.[16]

If the hypothesis that acid reduction in the oesophagus may lead to stabilisation of the CLO mucosa, notwithstanding the possible effects of continued duodenogastro-oesophageal reflux, is there any pathological evidence of such an effect? There have been very few studies of the morphological, histochemical, and molecular phenotypes of CLO mucosa in patients taking PPIs in comparison with those who are not. One major confounding factor here is that many, indeed most, patients with CLO under medical care have already been prescribed these drugs, often early in their treatment. One study has shown that medium term omeprazole therapy may induce a notable reduction in the proportion of sulphomucin positive mucin.[13] The expression of sulphomucin is characteristic of the incomplete or immature intestinal phenotype, particularly associated with neoplastic change in CLO.[21] Thus profound acid suppression might result in stabilisation of the intestinal phenotype with the production of more complete intestinal metaplasia.[13] Furthermore one group has reported that nuclear cyclin D1 protein expression, notably associated with dysplasia and carcinoma in CLO, may be reduced by treatment with PPIs.[22]

If the hypothesis that acid suppression alone has a powerful stabilising effect on the CLO mucosa, then we require pathological and molecular evidence of such an effect. Recent studies have shown that disturbance of epithelial proliferation, and changes in its relation with apoptosis, are readily demonstrable in the CLO neoplastic sequence and that these may be markers of early neoplastic change.[23 24] Furthermore we now know many of the molecular events that underpin the progression of the CLO neoplastic sequence.[25 26] Functional and molecular studies such as these, in controlled trials, are required to assess whether the neoplastic potential is likely to be maintained in an environment of profound acid suppression.

Conclusions

Current thinking, I believe, should not subscribe to the view that partial regression is, by necessity, an inadequate end point in the management of CLO. Our goals in treating CLO are to ensure control of symptoms and a reduction in complications, most notably neoplastic change. Yes, the continued survival of CLO type glandular epithelium may indeed sustain the neoplastic potential (and could even increase it), if the toxic insult induced by reflux of bile acids, especially unconjugated bile acids, remains. Equally, it could be that, in an environment where the one major stimulus to inflammation, cell proliferation, and oncogenic mutation is reduced, because of a profound reduction in acid and conjugated bile acids in the oesophagus, cells of the CLO phenotypes, be they of non-specialised gastric type or immature intestinal type, may survive and yet mature without, necessarily, the neoplastic potential of untreated CLO. The modest squamous re-epithelialisation that occurs in response to PPI induced acid suppression may be just a surrogate marker of more profound maturation effects on the cells of the CLO phenotypes. Only long term trials of PPI therapy, such as the multi-centre trial currently under consideration by OESO, the BSG and the MRC, which includes assessment of other treatments, can answer the critical question, not whether PPIs result in minimal, partial or complete regression of CLO, but whether they reduce the neoplastic potential of the disease.

Finally, in our drive to reduce the neoplastic potential of CLO by these various management strategies, be they pharmacological, ablative, or otherwise, we must not lose sight of the fact that only about 5% of current cases of oesophageal adenocarcinoma occur in patients already known, to the medical community, to have CLO.[1 27] All of our current treatment strategies for patients with CLO will have very little overall impact on the disquieting increase in the incidence of oesophageal adenocarcinoma in the Western World.

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