Particular problems of the male oesophagus

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Peter Fairclough describes two oesophageal conditions that are more common in men than in women: Barrett's oesophagus and eosinophilic oesophagitis.

Although Barrett's oesophagus is well known, the management is evolving as new data become available. Eosinophilic oesophagitis is a surprisingly common disease, which has been described relatively recently, but is still quite poorly recognised.

BARRETT'S OESOPHAGUS

Recently published best-practice advice from the Clinical Guidelines Committee of the American College of Physicians (ACP) prompts me to write about recommendations we should be making about screening for Barrett's oesophagus, and the role reflux symptoms should play in our advice. Barrett's oesophagus is more common in men than in women, and more than two-thirds of the associated cancers occur in men. The European mortality rate for oesophageal cancer in males is 13.3/100 000 and rising; that for females is 4.8, and not rising nearly so rapidly.

We know that symptomatic reflux is common, that reflux is associated with Barrett's oesophagus, though reflux symptoms are absent in many Barrett's.

Figure 1. Barrett's oesophagus. (a) Endoscopic view of the distal oesophagus at 34cm from the incisors. The squamo-columnar junction is normally found more distally, at around 40cm. The normal pale pink mucosa of the oesophagus is replaced by darker pink mucosa. The mucosa is smooth and there are no signs of dysplasia. (b) Endoscopic view of the distal oesophagus at 36cm. There is a nodular area of high-grade dysplasia (circled) (courtesy of Dr S.L. Preston)
patients, and that Barrett’s oesophagus is premalignant. We also know that Barrett’s oesophagus is, for practical purposes, diagnosable only by endoscopy (Figure 1). There are attempts to make screening cheaper, including molecular tests on cells recovered from a swallowed sponge, but these are not yet widely available. So, given that screening the entire population by endoscopy is economically impossible, which patients are at highest risk and should be advised to have endoscopy?

It is worth knowing that, although we screen for Barrett’s oesophagus and survey those with the condition, there is as yet no good evidence that we reduce the chances of adenocarcinoma of the oesophagus, or of death caused by oesophageal cancer. This is at least partly because our screening strategies are imperfect and not regularly and uniformly applied, so that fewer than 10 per cent of oesophageal adenocarcinoma patients are known to have Barrett’s oesophagus before the diagnosis of malignancy. However, ablation therapies for dysplasia are now available and these give promise for diagnosed individuals with dysplasia.

Risk of cancer
It is becoming clear that the risk of cancer in Barrett’s oesophagus is lower than we thought. Initial estimates were that cancer was 30– to 40-fold more common in patients with Barrett’s oesophagus, but recent estimates are around 11-fold.2

A recent study from the largest Barrett’s registry in the world, in Northern Ireland, shows that the risk of progression to dysplasia or cancer in non-dysplastic Barrett’s oesophagus is 0.1–0.5 per cent per patient year.3 The risk of cancer in patients with high-grade dysplasia is much higher (6–19 per cent per patient year), so these are the group in whom ablation is most likely to be appropriate. We do not yet know if proton pump inhibitors (PPIs) – or any other drugs – reduce the tendency to dysplasia or cancer.

There has been much discussion about the possibility of ablation therapy for patients with non-dysplastic disease. Although some would recommend ablation for this group, the number of patients involved would be large and the cost correspondingly huge, the patients need to stay on PPIs for life, and overall the risks outweigh the benefits when the risk of cancer is low, as it is.

Other risk factors for Barrett’s oesophagus give some hope of a more coherent screening policy. Barrett’s oesophagus is thought to be the major risk factor for adenocarcinoma of the oesophagus and cardia, and most of those affected are men over the age of 50 years.

For women with reflux disease, the situation is quite different. Cancer is uncommon. Indeed, the risk of Barrett’s cancer in women is about the same as the risk of breast cancer in men. As far as I know, nobody in the world screens unselected populations of men for breast cancer!

Which patients should be advised to have endoscopy?
The US guidelines are as expected for patients – men or women – with symptoms of serious import such as dysphagia, pain on swallowing, bleeding or weight loss. These people are serious candidates for urgent endoscopy.

If a patient has severe oesophagitis on initial endoscopy, it is often unclear whether they have Barrett’s oesophagus or just oesophagitis. So it is worth re-endoscoping such patients of either gender after eight weeks on high-dose PPIs to distinguish those with Barrett’s. Because biopsy results may be misleading in the presence of severe inflammation, the biopsies from the interval endoscopy are more reliable.

The ACP also recommends endoscopy for patients who do not respond to four to eight weeks of twice-daily PPI (who should all have oesophageal biopsies to seek eosinophilic oesophagitis – see below), and for those with symptomatic strictures.

With regard to screening, the ACP does not recommend screening for Barrett’s oesophagus for women, as discussed above. They do recommend one-off screening for men over 50 with symptomatic reflux, especially if they have another potentiating factor such as smoking or abdominal obesity.

If Barrett’s oesophagus is absent on the first endoscopy, it is probably not worth looking again. I have personally never seen a patient develop Barrett’s oesophagus under observation, but it does happen, albeit at a low rate. A recent study found that Barrett’s oesophagus developed in 2.4 per cent of reflux sufferers over the course of five years.6

Given that the progression to dysplasia and cancer takes decades in most patients, re-endoscopy is unlikely to be of benefit.

EOSINOPHILIC OESOPHAGITIS
Eosinophilic oesophagitis is a more recently described and increasingly recognised oesophageal disease that is markedly more common in men than in women.

First described in 1978, the paper in 1993 by Stephen Attwood, a British surgeon then working with Tom Demeester in the USA,7 has been followed by an explosion in publications on eosinophilic oesophagitis. It turns out that the condition is more common than usually realised. In a recent UK series, 86 per cent were male, although the male-to-female gender ratio is normally 3:1.8

Eosinophilic oesophagitis can occur at any age and in most racial and ethnic groups, but the prototypic adult is a young or early middle-aged male who complains of dysphagia or chest pain, or presents with episodes of oesophageal bolus obstruction, where up to 50 per cent have eosinophilic oesophagitis.1 Upper abdominal pain and
heartburn are also common symptoms; eosinophilic oesophagitis has been reported to account for 10–100 per cent of PPI-resistant heartburn.

Eosinophilic oesophagitis is also quite common in children, in whom the symptoms are often less well defined and include failure to thrive, feeding intolerance, abdominal pain, nausea, vomiting and regurgitation.

Delay of years in diagnosis is very common, because of lack of awareness by primary care doctors resulting in delay in referral for endoscopy, lack of awareness by endoscopists, and misinterpretation of endoscopic findings and pathology specimens. In patients undergoing endoscopy for upper gastrointestinal symptoms, eosinophilic oesophagitis has been found in approximately 10 per cent, and the population prevalence is around 50/100 000, so it is about as common as Crohn’s disease or ulcerative colitis. Most GP practices will have at least one such patient, albeit unrecongnised.

Around half of eosinophilic oesophagitis patients have a history of asthma or allergy to medications, grass, pollens, and foods including nuts, chocolate and wheat.

The characteristic appearances at endoscopy are of stricture, generalised inflammation, persistent oesophageal rings (‘trachealisation’), linear furrows, nodular mucosa, or white exudates or plaques (Figure 2). However, the oesophagus often looks entirely normal, and best practice now is that all patients with dysphagia or bolus obstruction or non-erosive oesophagitis should have oesophageal biopsies taken to look for eosinophilic oesophagitis, even if the mucosa looks normal.

The diagnosis is definitively made on histology of oesophageal biopsies, in which the tissues are infiltrated by eosinophils at greater than 15 per high-power field. Tissue eosinophilia can also be caused by reflux, but in such patients the oesophageal eosinophilia is usually less than 15 per high-power field and decreases after anti-acid therapy with full-dose PPI for eight weeks.

The natural history of eosinophilic oesophagitis is not yet clear. It may be responsible for cases of ‘idiopathic benign stricture’, and as a chronic inflammatory condition may be associated with oesophageal cancer.

Treatment of eosinophilic oesophagitis
Treatment is currently by corticosteroids, dietary restriction or endoscopic dilatation.

Corticosteroids
Topical corticosteroids are a mainstay, usually swallowed asthma preparations, such as fluticasone or budesonide. Although the eosinophil count may reduce to normal, clinical improvement in dysphagia does not always parallel the histological improvement. Topical steroids are well tolerated and there are no reports of adrenal suppression. Oropharyngeal and oesophageal candidiasis may occur in up to a third of patients, but is often asymptomatic.

Systemic steroids can improve symptoms and tissue eosinophilia, and as with topical steroids, symptoms usually recur after the treatment is withdrawn, and systemic steroids are associated with more side-effects, so are not recommended for long-term treatment.

Dietary therapy
Dietary therapy is given to restrict food allergens that are thought to be the basis of eosinophilic oesophagitis in many patients.

Elemental diets containing basic carbohydrates, amino acids and medium-chain triglycerides are allergen-free and often effective within days in treating symptoms of eosinophilic oesophagitis in children. However, elemental diets are restrictive, expensive, unpalatable and affect quality of life in the longer term.

A diet that eliminates the most common allergens (milk, eggs, wheat, soy, seafood and nuts – the ‘six-food elimination diet’) is more practical and almost as effective. During reintroduction studies, wheat and milk were the most common precipitants of recurrent eosinophilic oesophagitis.

Allergy testing may have a place in planning elimination diets, but so far targeted elimination diets have been less successful than a six-food elimination diet.

Endoscopic dilatation
Endoscopic dilatation is used for patients with dysphagia caused by localised oesophageal stricture or more generalised...
narrow calibre oesophagus. Dilatation was initially thought to have a high complication rate in eosinophilic oesophagitis, but later experience shows a perforation rate little different from that in non-eosinophilic oesophagitis patients. Dilatation has no effect on eosinophilia, but does improve dysphagia. A proportion of patients have chest pain after dilatation but the effect on their dysphagia makes it worthwhile for most.

Other therapies
Other therapies that have been tried include leukotriene antagonists and mast cell stabilisers such as montelukast and cromoglycate, but with poor effectiveness. Immunomodulators such as azathioprine and 6-mercaptopurine have been tried in limited numbers of patients, with some good initial results. However, the data are too limited to recommend this treatment at present. Limited trials of existing biological agents against interleukin-5 have shown some promising results, but again there are not enough data to recommend use outside clinical trials. New biological agents are being developed, particularly to target steps in metabolic pathways involved in eosinophilic oesophagitis.

Declaration of interests: none declared.

REFERENCES