Pathology and histology of the oesophagus and stomach

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Abstract

The presenting symptoms of dysphagia and dyspepsia can be caused by gastro-oesophageal reflux disease, malignancy or, less commonly, disorders of dysfunctional motility, such as achalasia. Most neoplasms of the oesophagus and stomach are epithelial in nature. Benign epithelial neoplasms usually take the form of polypoid lesions, such as oesophageal squamous papillomas, gastric adenomas, hyperplastic and fundic gland polyps. Malignant epithelial neoplasms of the oesophagus are divided into squamous cell carcinoma and adenocarcinoma, whereas malignant gastric neoplasms are predominantly adenocarcinomas. Each tends to develop in the context of dysplastic epithelial changes. Gastric carcinomas and lymphomas are associated with *Helicobacter pylori* infection. Stromal tumours of the stomach are important in that they have a distinctive molecular pathology and linked targeted therapy. This educational article provides an overview of the incidences, aetiologies and histological features of some of the most common mechanical, inflammatory and neoplastic pathologies encountered in the oesophagus and stomach. The emphasis is on clinical application.

Keywords Achalasia; adenocarcinoma; atresia; Barrett's oesophagus; gastrointestinal stromal tumour; *Helicobacter pylori* gastritis; marginal zone lymphoma; oesophagus; squamous cell carcinoma; stomach

Mechanical disorders

Atresia

During embryonic development of the upper gastrointestinal tract, the laryngotracheal diverticulum develops from the ventral foregut during week 4 of gestation. Gradual formation of an oesophago-tracheal septum along the length of this laryngotracheal diverticulum separates the ventral respiratory and dorsal digestive tubes. Anomalies occur from faulty division of the foregut into these oesophageal and tracheal channels. Tracheal dominance with oesophageal stenosis or atresia is the more common form of unequal division and a fistula is usually present. Pure oesophageal atresia without a fistula is rare. Oesophageal atresia with tracheo-oesopheal fistula is a relatively common congenital anomaly with an incidence varying from 1 in 800 to 1 in 10,000 live births. Congenital heart defects are seen in 30% of cases of oesophageal atresia and imperforate anus occurs in approximately 10%. The atresia may extend over a variable length, or rarely may consist of a single transverse diaphragm that may, or may not be imperforate. Additional congenital malformations are common, some of which are described under the VATER syndrome, which comprises vertebral defects, anal atresia, tracheo-oesophageal and renal dysplasias, in addition to cardiac and limb abnormalities. A number of anatomical variants of oesophageal atresia have been described. In around 85–90% of cases, the upper end of the oesophagus ends in a blind pouch, the anterior wall of which often fuses with the trachea but rarely communicates with it. The lower oesophagus is normal at the cardia but becomes progressively narrower proximally and usually communicates with the trachea within 20 mm of the bifurcation and occasionally ends in one, or other of the main bronchi. During breathing, air enters the stomach via the fistula and as the stomach becomes distended, gastric secretions pass through the fistula into the lungs, causing pneumonia. Attempts at feeding produce regurgitation and aspiration. Surgery, involving multiple procedures is usually an option.

Achalasia

This condition has an annual incidence in the UK of 0.5 in 10,000 and a prevalence of 8 in 10,000. It causes obstruction to the passage of food at the level of the cardia and presents clinically with pain, regurgitation, dyspepsia and secondary aspiration pneumonia. Manometry studies demonstrate failure of relaxation of the lower oesophageal sphincter in response to swallowing, absence of peristalsis in the smooth muscle of the oesophageal body, low amplitude non-peristaltic contractions, a normal or high resting lower oesophageal sphincter pressure and increased intra-oesophageal pressure. Radiologically, there is a narrow, constricted, distal segment with gross proximal dilatation. Macroscopically, the appearance of end-stage achalasia is of an enormously dilated and lengthened oesophagus (mega-oesophagus), occupying the mediastinum and filled with stagnant fluid and partially digested food debris. There is considerable hypertrophy of the muscularis propria. Histologically, there is a marked reduction or a complete absence of ganglion cells within the myenteric plexus, within reactive inflammatory epithelial features. Studies suggest that achalasia results from a primary inflammatory process, causing myenteric ganglion and nerve cell destruction, the cause of which is unknown. There is a significant association with DQA1 and DQB1 alleles. There is an increased risk for subsequent development of squamous cell carcinoma. Treatments for the condition have included endoscopic pneumatic dilatation, Heller's myotomy and botulinum toxin injection.

Oesophageal neoplasia

Squamous papilloma

Squamous papilloma is the most common benign neoplasm of the oesophagus, which usually occurs in the lower third. The lesions have a multi-lobulated appearance with a granular, or warty surface and a firm consistency. They are usually small (15 mm diameter) and may be multiple. Histologically, they usually

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have a papillary architecture and a central core of vascular connective tissue covered by acanthotic stratified squamous epithelium. There is no atypia, or dysplasia. Cytological changes suggestive of human papilloma virus (HPV), such as nuclear hyperchromasia and bi-nucleation may be present. Viral genome can be confirmed in tumour tissue by in-situ hybridization. Benign non-epithelial tumours of the oesophagus are commonly submucosal lesions derived from smooth muscle (leiomyomas). True gastrointestinal stromal tumours (GIST) are very rare in the oesophagus.

Squamous carcinoma

Around 80% of squamous cell carcinomas of the oesophagus occur in developing countries. The highest rates are found in Asia, extending from Turkey to Northern China and there are marked differences in incidence between regions that lie only a few miles apart. Pockets of high incidence occur in Europe, for example in Normandy and Brittany. Causative agents may differ between high-risk and low-risk areas and may act synergistically. An increased risk of squamous cell carcinoma is associated with achalasia, diverticulae, Plummer-Vinson syndrome and coeliac disease and is associated with tumours in the oropharynx and larynx, which may be related to shared risk factors such as alcohol intake and smoking. Recent studies have focussed on a possible causative role for HPV infection. However, the International Agency for Research on Cancer (IARC) have concluded that there is inadequate evidence in humans for carcinogenicity of HPV in the oesophagus. Chronic oesophagitis is common in populations where there is a high incidence of oesophageal cancer, which may appear as white patches endoscopically. Squamous dysplasia is a precursor to squamous cell carcinoma and may appear endoscopically as areas of friable, or erythematous mucosa, erosions, plaques, or nodules. Squamous carcinoma is most common in the middle third of the oesophagus and macroscopically may be exophytic, ulcerating or infiltrating. The tumour often results in a stricture, which is usually friable and haemorrhagic. Histologically, well-differentiated tumours show well-defined nests of tumour cells with intercellular bridges and keratinization, whereas poorly differentiated lesions show sheets of undifferentiated cells with no evidence of keratinization. It spreads through the muscularis propria to involve adjacent structures such as the trachea, aorta, or pericardium may occur. The overall 5-year survival rate is 30–40%. The tumour stage is the most important prognostic indicator in patients treated with oesophagectomy.

Barrett's oesophagus

Barrett's oesophagus/columnar lined oesophagus (CLO) is defined as replacement of the lower oesophageal squamous mucosa by metaplastic glandular mucosa, as a result of chemical injury, secondary to gastro-oesophageal reflux disease (GORD), or bile reflux. Macroscopically, the changes occur most commonly in the distal oesophagus and appear red and velvety, with preserved pale squamous islands. The histogenesis remains unproven and candidate cells include multi-potent stem cells at the basal aspect of the squamous mucosa and the cells lining the oesophageal gland ducts. The metaplastic glandular epithelium is often of a simple columnar, mucinous type but goblet cell differentiation (intestinal metaplasia) is frequent (Figure 1). Classical Barrett's, or long segment CLO, is essentially an endoscopic diagnosis, requiring accurate information on the site of biopsy, which histology corroborates. Although a definitive diagnosis can be made on histology if glandular metaplasia is seen adjacent to native oesophageal structures, this situation occurs in only approximately 15% of cases. Histology can be of use when endoscopic appearances are equivocal, or when there is extensive ulceration, or stricturing. As there is a natural variation between the squamo-columnar junction and gastro-oesophageal junction of up to 20 mm, the disease was initially said to be present when at least 30 mm of columnar lined mucosa was present. Short segment CLO (SSCLO) was introduced to describe those cases in which less than 30 mm of columnar lined epithelium was present in the lower oesophagus. Ultrashort segment CLO (USSCLO) is a controversial term that was introduced to describe cases in which there is intestinal metaplasia at the cardia and is essentially a gastric disease, which can only be diagnosed histologically. The association of Barrett's with hiatus hernia can be complicating, as it can be difficult to distinguish the two endoscopically and little is known about the mucosal pathology of hiatus hernia, particularly with respect to the prevalence of intestinal metaplasia.

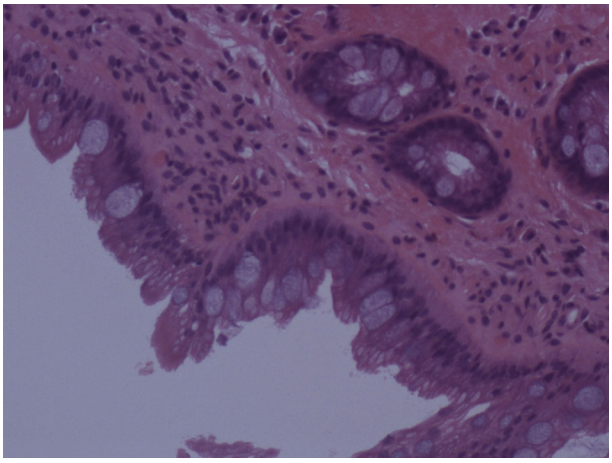

Figure 1 Oesophageal biopsy showing metaplastic columnar epithelium of Barrett's oesophagus; this is confirmed by the presence of intestinal metaplasia (note the pale blue goblet cells).

Endoscopic definition and pathological confirmation of Barrett's oesophagus is important because of the risk of progression to cancer (see below). Though evidence of efficacy is not definitive, most clinical guidelines recommend endoscopic surveillance in patients with established CLO. This generates a considerable workload for endoscopy and pathology units.

Dysplasia in Barrett's oesophagus

The metaplastic epithelium in Barrett's/CLO is less stable than the native epithelium it replaces and morphological dysplastic changes are more likely to occur. It is primarily for the detection or exclusion of dysplasia that biopsy is required. Dysplasia in Barrett's is classified as low or high grade and is a risk factor for development of adenocarcinoma. High-grade dysplasia has been detected in biopsies from macroscopically normal or minimally abnormal mucosa (as assessed by conventional endoscopy). There are architectural changes within the epithelium, with a lack of maturity towards the surface. The cytological features of dysplasia include nuclear enlargement, nuclear pleomorphism,

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