Case N°1: Adenocarcinoma of the upper oesophagus developed in heterotopic gastric mucosa

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Clinical history
54 year-old man complaining of recent dysphagia. Long history of pyrosis, not investigated. No other past medical history. On endoscopy, large fungating and ulcerated tumour in the upper oesophagus. The rest of the oesophagus appears normal, including the gastroesophageal junction. Biopsies: moderately differentiated adenocarcinoma. EUS: tumour of the upper oesophagus, staged usT2N0.
Total oesophagectomy.
Follow-up: cervical lymph-node metastasis 18 months after surgery, multiple lung and brain metastases 2 years after surgery.

Description of the slide
On the slide that was submitted for the seminar, taken from the tumour visible on the surgical specimen (Figure 1), there is a malignant tumour that corresponds to a well differentiated adenocarcinoma, with a tubulo-papillary architecture (Figure 2). The tumour cells have moderate atypia. On this slide the invasion is limited to the mucosa and the upper part of the submucosa, but on other slides the entire oesophageal wall is invaded. There are several images of tumour invasion into submucosal lymphatic vessels. There is no lymph-node metastasis in any of the 22 lymph-nodes present in the specimen.
Interestingly, the mucosa is not only of squamous type. In close contact with the adenocarcinoma, there is an area of non-dysplastic glandular mucosa. This mucosa is of gastric type, with surface epithelium and crypts lined by gastric mucus secreting
cells, and with glands of either antral or fundic type (Figure 3). Although the crypts are slightly hyperplastic in that area, there is no intestinal metaplasia nor dysplasia. On extensive sampling of the rest of the oesophagus there is no abnormality. The gastroesophageal junction is normal, with no feature suggesting metaplastic Barrett mucosa (Figure 4).

On immunohistochemistry, p53 protein is strongly overexpressed in the carcinoma (Figure 5), but shows no overexpression in the heterotopic tissue nor in the normal oesophagus. Cytokeratin 7 is expressed in the cancer and in the heterotopic mucosa. Cytokeratin 20 is negative in the tumour and positive in the superficial heterotopic epithelium. Muc2 is negative in both cancer and heterotopia, Muc5AC and Muc6 are negative in cancer but positive in gastric heterotopic tissue, with a pattern corresponding to that observed in normal gastric mucosa. Muc1 is only very mildly expressed in the tumour.

Figure 1: macroscopic view of the tumours of the upper oesophagus

Figure 2: on low power, adenocarcinoma infiltrating the oesophageal wall (HE)
Diagnosis

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Comments

Adenocarcinoma of the oesophagus has become a frequent type of cancer of the oesophagus. In several countries it is now more frequent as squamous cell carcinoma. In most cases it develops in the lower third of the oesophagus, from metaplastic Barrett mucosa, or even in the middle or upper oesophagus when extensive Barrett’s oesophagus is present (1). Barrett oesophagus (endobrachyoesophagus in France) is a complication of gastrooesophageal reflux disease.

On the other side, most carcinomas of the upper oesophagus are squamous cell carcinomas, with chronic alcohol and tobacco consumption as a major cause in most western countries.

The case presented in this slide seminar illustrates the rare occurrence of adenocarcinomas of the upper oesophagus developed from gastric heterotopic mucosa (HGM). HGM is frequent in the cervical oesophagus, but most carriers are asymptomatic (2). It is often termed “inlet patch”, and is usually located within 3 cm of the cricopharynx. It is incidentally found in 0.1 to 10% of patients on endoscopy, but is probably even more frequent in the general population as suggested by some autopsy series. The pathogenesis of HGM of the oesophagus is still debated, but the most widely accepted theory considers that it is a congenital condition, resulting from incomplete squamous metaplasia of the columnar-lined oesophagus from the embryo.

On gross examination, HGM appears as pink velvety patch measuring from 0.5 to 4 cm. When biopsies are taken, which is not mandatory for the diagnosis in uncomplicated cases as endoscopic features are characteristic, they show typical gastric mucosa. This latter is in most cases of the fundic-type, with glands containing parietal cells and chief cells. In some cases the mucosa can be “transitional” with admixed fundic and antral glands, or very rarely purely antral. In most cases there is no inflammation, although there may be in rare instances chronic active inflammation, atrophy and metaplasia, and even *Helicobacter pylori* infection. This infection is present in less than 5% of the cases, and is associated with gastritis. The pattern of expression of cytokeratins and MUC antigens is in keeping with a gastric phenotype, as it was in our case, although this pattern has been considered by some authors as arguing for a common pathogenesis with Barrett mucosa (3).
HGM is asymptomatic in a large majority of cases, but in rare cases it can cause cervical pain, dysphagia and bleeding. Ulcerative strictures, oesotracheal fistula, and upper oesophageal rings are very unusual complications of this lesion. These symptoms and lesions can be caused by inflammation and a crycopharyngeal spasm due to the local production of acid secretion by parietal cells.

Oesophageal adenocarcinomas arising from HGM are exceedingly rare with less than 30 cases reported in the English-literature (2), including a case report from our group (4), which is not the same case as the one presented in this slide seminar. As for Barrett adenocarcinoma, there is a strong male predominance, and all cases have been reported in adults, with a mean age of 61 years. By definition the tumours are located in the upper oesophagus, polypoid or infiltrative, with variable size. Most cases extend to the muscularis propria or the adventitia, with a poor prognosis. On microscopic examination, the tumours are adenocarcinomas with variable degree of differentiation, very similar to adenocarcinomas developed in the stomach or in Barrett oesophagus. In all reported cases there is gastric type mucosa around the tumour, unless the cases would not have been reported as examples of adenocarcinoma plus HGM...

It is highly probable that adenocarcinomas developed in HGM develop along a stepwise pattern similar to changes in other epithelia, including Barrett’s mucosa, with intestinal metaplasia and increasing grades of intraepithelial neoplasia (dysplasia). Some cases are associated with intestinal metaplasia with a phenotype similar to Barrett mucosa (4). However, so far only exceedingly few cases of high grade dysplasia in HGM have been reported. The factors leading to neoplastic transformation in HGM are unknown. It has been hypothesised that as in Barrett oesophagus peptic injury could play a role as irritative factor. The lower exposure of upper oesophagus to peptic injury could explain the rarity of adenocarcinoma (and also of intestinal metaplasia) arising in HGM in comparison to the high incidence of cancer involving the lower oesophagus.

In conclusion, adenocarcinoma of the upper oesophagus in HGM is a very rare tumour. Its pathogenesis is unknown, although it has been suggested that it could share some similarities with Barrett’s adenocarcinoma. This very rare malignant form of the disease does not justify performing endoscopic surveillance of asymptomatic HGM carriers.
References


