Envoi SPECIALIST PATHOLOGISTS *inside insights*

Update No.1 - 2019 Dr Ian Brown

SCC Oesophagus

Squamous cell carcinoma is a malignant epithelial neoplasm most commonly located in the middle one third of the oesophagus. Worldwide two thirds of patients are male, rising to 80% in developed countries. There is marked geographic difference in incidence both between regions and even within individual countries. The highest incidence of disease (exceeding 50 cases per 100,000 population) occurs from Eastern to central Asia.

Aetiology: Aetiological factors and their relative importance vary with location. Main risk factors include:

1) Tobacco – more important in developed countries
2) Alcohol consumption – mutations in aldehyde dehydrogenase and alcohol dehydrogenase (ALDH2 and ALDH1) in East Asian populations; accumulation of carcinogen acetaldehyde.
3) Diet – increased risk with pickled vegetables (generation of carcinogenic mycotoxins and in nitrosamine compounds). Selenium and riboflavin may be protective.
4) Genetic disease
    a. Tylosis - autosomal dominant mutation in the RHBDF2 gene at 17q25. Patients develop oesophageal squamous cell carcinoma in 90% by age 65 years.
    b. Fanconi anaemia.
5) Others
    a. Plumber Vincent syndrome related to deficiency in iron and riboflavin
    b. Achalasia
    c. Radiotherapy
    d. Caustic ingestion

Role for HPV infection: Multiple studies have identified HPV DNA in tissue from oesophageal SCC. The virus appears to be an innocent bystander since viral integration and transcription is uncommon. As such HPV infection is unlikely to represent any significant risk for development of oesophageal SCC apart from tumours immediately beneath the cricopharyngeus.

Pathogenesis: There is a stepwise progression involving progressively more genetic abnormality from histologically normal squamous mucosa to low-grade and high-grade intraepithelial neoplasia (dysplasia) and finally to invasive squamous cell carcinoma. Mutation in TP53 gene is an early driver mutation. Abnormalities in EGFR and silencing of the CDKN2A gene are also important.

Clinically: Early disease is usually asymptomatic and an incidental diagnosis. Advanced disease presents with dysphagia, chest pain, odynophagia, and/or weight loss.

Pathology: Macroscopically the disease may be infiltrative or fungating/polypoidal (see Fig.1). Usual SCC is characterised by cytologically atypical keratinocytes invading beyond the basement membrane. The presence of keratinisation marks better differentiation and tumours are graded on this basis.

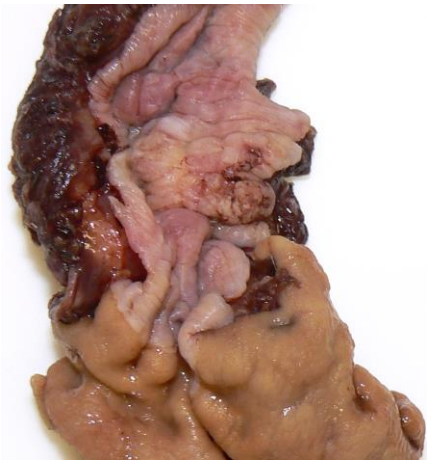

Fig.1 Macroscopic image of polypoidal SCC arising mid oesophagus

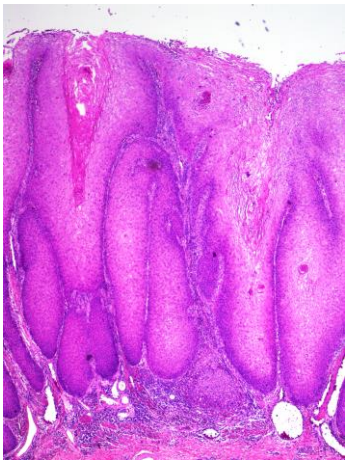

Fig.2 Histological image of verrucous carcinoma showing a thickened proliferation of well differentiated squamous cells

Histological variants:

1) *Verrucous carcinoma* – rare variant arising in a setting of chronic irritation, oesophagitis or previous oesophageal injury. Histologically there is minimal cytological atypia or mitotic activity (see Fig.2). The tumour is slow-growing, and metastases are uncommon.
2) *Carcinoma cuniculatum* – rare and slow growing tumour that only infrequently metastasises. Usually seen in middle to distal oesophagus. Histology shows well-differentiated keratinising squamous epithelium extending deeply into the oesophageal wall.
3) *Spindle cell carcinoma (sarcomatoid carcinoma)* – polypoidal lesion typically in middle or distal oesophagus. Histology shows biphasic pattern with neoplastic squamous epithelium and spindle cells. Despite its frequent large size, the prognosis of this tumour is better than conventional squamous cell carcinoma.
4) *Basaloid squamous cell carcinoma* – seen in upper oesophagus with a marked male predominance. There is no association with HPV infection. The tumour is highly aggressive with poor prognosis.
5) *Lymphoepithelioma like carcinoma* – rare variant seen almost exclusively in Asians. Histology shows rich lymphoid and plasma cell rich inflammatory infiltrate surrounding the tumour. Only rarely associated with EBV and prognosis similar to conventional squamous cell carcinoma.

Two other kindred tumours, *mucoepidermoid carcinoma* and *adenosquamous carcinoma* will be considered as variants of adenocarcinoma in the forthcoming WHO classification of oesophageal tumours, although, particularly in non-Western populations, these lesions may be more closely related to SCC.

Prognosis: Overall five-year survival oesophageal SCC 10- 15%. However, in superficial invasive disease, five-year survival is approximately 85%. There is a potentially encouraging role for immune checkpoint inhibitors as novel therapy in advanced disease.

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