

CASE REPORT

A "crackeware" oesophagus

M Westerterp, O R C Busch, J J G H M Bergman, F J W ten Kate, J J B van Lanschot

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This case report describes a 70 year old woman with excessive diffuse keratinisation of the oral cavity and oesophagus harbouring a squamous cell carcinoma. This excessive diffuse keratinisation of normally non-keratinised squamous epithelium could not be identified in normally non-keratinised epithelia in other parts of the body (the vagina), arguing against a genetic basis for this disorder. The term "crackeware" oesophagus was used to describe this entity, which has not been described previously in the English literature.

The soft tissues of the human oral cavity and oesophagus are covered by stratified squamous epithelium. The gingiva and the hard palate, being exposed to the mechanical forces associated with mastication, are covered by keratinised epithelium resembling that of the epidermis, which covers the skin. The floor of the mouth, buccal regions, pharynx, and oesophagus, which require flexibility to accommodate chewing, speech, and swallowing of a bolus, are covered with non-keratinised epithelium.¹

"Keratinisation of the oesophagus is rare and only cases of focal keratinisation have been reported"

To adapt to mechanical or thermal stimuli the non-keratinised epithelium can be stimulated to undergo keratinisation, especially in the oral cavity.

However, keratinisation of the oesophagus is rare and only cases of focal keratinisation have been reported in combination with ulceration, chronic inflammation, and verrucous carcinoma.²

We describe a patient with nearly complete keratinisation of the squamous epithelium of the oral cavity and oesophagus, in which focal dysplasia and a squamous cell carcinoma had developed. To our knowledge, this clinical entity has not been described previously in the English literature.

CASE REPORT

A 70 year old woman presented with a four month history of mild dysphagia, odynophagia, and considerable weight loss after mild but longstanding gastro-oesophageal reflux complaints. She had no history of severe or repeated injury of the oesophagus, aberrant eating behaviour, or skin disorders, did not use medication, and did not drink alcohol, but had smoked 10 cigarettes/day for 40 years. Her further history included a uterus extirpation because of prolapse. Her family history was negative for oesophageal, dermatological, and gynaecological diseases.

Diagnostic investigation

Endoscopy showed a hiatal hernia 37–39 cm from the incisors and a 1 cm Barrett's segment from 36 to 37 cm; macroscopically, there were signs of diffuse keratinisation of the oesophagus proximal to the columnar metaplasia (fig 1).

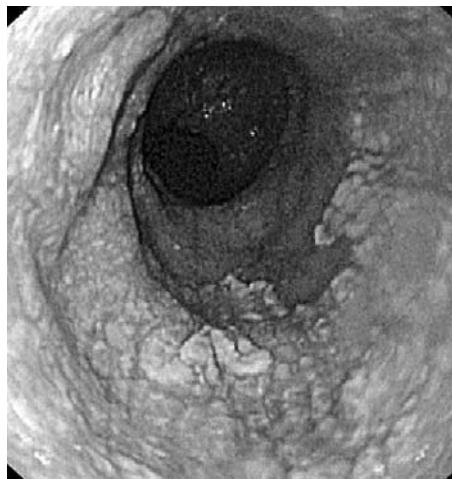


Figure 1 Endoscopic picture of crackeware oesophagus showing the white aspect as a result of keratinisation.

This altered epithelium had a crackeware appearance. A tumour was seen in this hyperkeratotic area, which extended 30–35 cm from the incisors. Endosonographically, the tumour was interpreted as uT3 N0 M0.

Randomly taken biopsies established the diagnosis of diffuse hyperkeratosis and targeted biopsies from the tumour showed a squamous cell carcinoma. Additional biopsies from the cheek and the pharyngeal arch also showed keratinised squamous epithelium. Further preoperative analyses did not show signs of distant metastases.

Treatment

After completion of the diagnostic investigation, the patient received neoadjuvant chemotherapy, consisting of three cycles of cisplatin and etoposide. Four weeks after completion of the chemotherapy, a transthoracic resection of the oesophagus with two field lymph node dissection was performed, followed by reconstruction with a gastric tube. Peroperatively, vaginal biopsies were taken to investigate the possibility of a genetic basis for keratinisation of normally non-keratinised squamous epithelium.

Pathology

Postoperative histology showed a poorly differentiated exophytic squamous cell carcinoma with a diameter of 0.8 cm infiltrating the superficial layer of the mucosa without lymph node metastasis (fig 2). A microscopically radical resection had been achieved (pT1aN0M0ROG3).

Large parts of the mucosal surface of the oesophagus showed extensive keratinisation (figs 2, 3) with focal dysplastic changes. In the distal part of the oesophagus, a Barrett's segment of 3.5 cm was identified with extensive pancreatic metaplasia (fig 4). The vaginal biopsies showed

Abbreviation: CK, cytokeratin

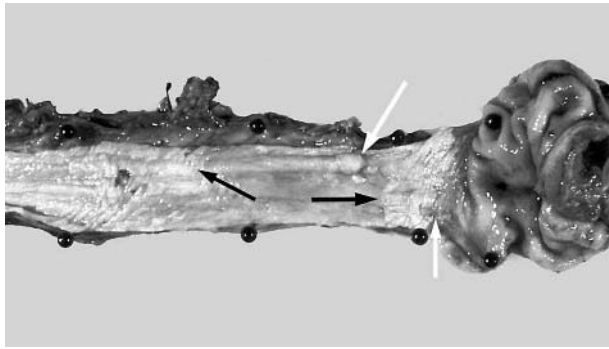


Figure 2 Macroscopic picture of the oesophagus showing the excessive hyperkeratosis (black arrows), the tumour (left white arrow), and the Barrett's segment (right white arrow).

normal squamous epithelium, with no signs of keratinisation.

To identify the origin of the different types of epithelium additional histological analysis of cytokeratin (CK) expression was performed, using immunohistochemical staining of paraffin wax embedded tissues (CK7, CK10, CK14, and CK20).

CK10/14 immunostaining was used to compare the pathological keratinisation of the oesophagus with the normal keratinisation pattern seen in the skin. CK10 expression in the keratinised oesophageal epithelium was comparable to that of the skin, whereas it was not expressed in the non-keratinised epithelium of the oesophagus. As expected, CK14 was expressed in both keratinised and non-keratinised epithelium. The Barrett's segment showed its characteristic CK7/CK20 staining pattern, consisting of diffuse and strong CK7 staining of the surface and glandular epithelium, with weak CK20 staining of the superficial epithelium.^{3, 4}

Finally, the presence of extensive pancreatic metaplasia was confirmed underneath the columnar epithelium and underneath the hyperkeratosis in the distal oesophagus by using sheep antihuman lipase polyclonal antibodies (Immunosource, Swampscott, Massachusetts, USA; fig 4, inset).

DISCUSSION

We present a patient with diffuse excessive keratinisation of the normally non-keratinised squamous epithelium of the oesophagus and the oral cavity in combination with oesophageal squamous cell carcinoma.

Benign focal hyperkeratosis is a well known clinical entity, which is often recognised as a white appearing lesion in the oral mucosa. It can be either hereditary or reactive in origin.⁵ Reactive white lesions may be induced by tobacco or develop as a result of chronic rubbing or friction, causing a protective layer that is analogous to callous of the skin.^{6, 7}

The diffuse pattern of keratinisation in the upper gastrointestinal tract of our patient suggests a genetic background. For that reason we also examined the normally non-keratinised epithelium of the vagina. However, the presence of normal vaginal epithelium in this patient and her negative family history does not support a genetic mechanism. Very rarely, an inherited skin condition called "tylosis" (exceptionally thickened skin on hands and feet) is associated with oesophageal cancer.⁸⁻¹⁰ However, this patient had no known skin disorders.

In addition, our patient had no history of aberrant eating or drinking habits and no professional contact with chemicals. A possible inducing factor might have been chronic gastro-oesophageal reflux disease, which must have



Figure 3 Histological picture of the oesophagus showing the excessive keratinisation of the epithelium (haematoxylin and eosin stain; original magnification, $\times 120$).

occurred, based on the presence of a metaplastic Barrett's segment. However, reflux alone is not known to induce diffuse keratinisation in humans.

"The enzyme secretion of the metaplastic pancreatic cells might have contributed to keratinisation of the injured mucosa"

In the oral mucosa, idiopathic leucoplakia (a clinical term for a white patch or plaque of the oral mucosa that cannot be rubbed off and cannot be characterised clinically as a specific disease, such as lichen planus or candidiasis) is known as a possible premalignant lesion. Histopathological changes of leucoplakia range from hyperkeratosis and dysplasia to carcinoma in situ to invasive squamous cell carcinoma. In contrast to the development of squamous cell carcinoma in the oral cavity, hyperkeratosis is not a well known stage in the multistep development of squamous cell carcinoma in the oesophagus.

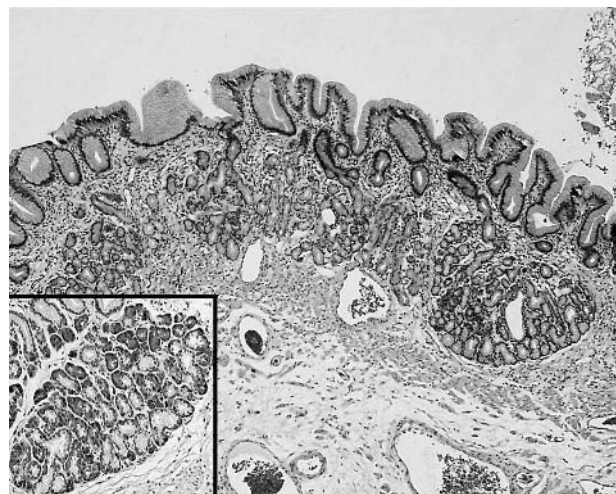


Figure 4 Histological picture of the tubular part of the oesophagus showing the extensive pancreatic metaplasia (haematoxylin and eosin stain; original magnification, $\times 30$), confirmed by immunohistochemistry (inset; sheep antihuman polyclonal antibody; original magnification, $\times 150$).

Take home messages

- We describes a 70 year old woman with excessive diffuse keratinisation of the oral cavity and oesophagus harbouring a squamous cell carcinoma
- This excessive diffuse keratinisation of normally non-keratinised squamous epithelium was not present in the vagina, suggesting that this disorder does not have a genetic basis
- The hyperkeratosis may have been caused by pancreatic reflux and further insight into the role of pancreatic metaplasia in the pathogenesis of diffuse keratinisation of the upper gastrointestinal tract is needed

During this multistep process, non-keratinised squamous epithelium changes into dysplasia and finally to carcinoma. The intermediate step of oesophageal hyperkeratosis is only seen in experimental animal models: experiments in rats studying duodeno–gastro–oesophageal reflux have shown that pancreatic reflux can induce hyperkeratosis.¹¹ Pera *et al* hypothesised that severe oesophagitis develops as a result of the reflux of duodenal content. By exposing the injured epithelium to pancreatic juice, as yet unknown factors in this refluxate promote a multiple differentiation capability in the proliferating stem cells in the basal layer of the squamous epithelium, seen as hyperplasia, acanthosis, and hyperkeratosis. With the addition of 2,6-dimethylnitrosomorpholine these rats developed both adenocarcinoma and squamous cell carcinoma.

In our patient, the presence of columnar metaplasia in the distal oesophagus (Barrett's segment) indicates longstanding reflux disease. According to the hypothesis of Pera *et al*, hyperkeratosis might be caused by pancreatic reflux. Interestingly, abundant pancreatic metaplasia was recognised within the Barrett's segment and confirmed by specific immunohistochemical staining. Therefore, the enzyme secretion of the metaplastic pancreatic cells might have contributed to keratinisation of the injured mucosa. However, it does not explain the extensiveness of the keratinisation from the oral cavity to the distal oesophagus. Therefore, further insight into the role of pancreatic metaplasia in the

pathogenesis of diffuse keratinisation of the upper gastrointestinal tract is needed.

Authors' affiliations

M Westerterp, O R C Busch, J J B van Lanschot, Department of Surgery, Academic Medical Centre/University of Amsterdam, Suite G4-123, Meibergdreef 9, 1105 AZ, The Netherlands
J J G H M Bergman, Department of Gastroenterology, Academic Medical Centre/University of Amsterdam
F J W ten Kate, Department of Pathology, Academic Medical Centre/University of Amsterdam

The patient gave permission for this case report to be published

Correspondence to: Dr M Westerterp, Department of Surgery, Academic Medical Centre/University of Amsterdam, Suite G4-123, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands; m.westerterp@AMC.UVA.NL

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