CASE REPORT

# Adenosquamous carcinoma of the oesophagus in a dog

H. Okanishi*, H. Shibuya†, T. Miyasaka†, K. Asano‡, T. Sato† and T. Watari*

*Laboratory of Veterinary Internal Medicine, Department of Veterinary Medicine, Faculty of Bioresource Sciences, Nihon University, Fujisawa, Kanagawa 252-0880, Japan

†Laboratory of Veterinary Pathology, Department of Veterinary Medicine, Faculty of Bioresource Sciences, Nihon University, Fujisawa, Kanagawa 252-0880, Japan

‡Laboratory of Veterinary Surgery, Department of Veterinary Medicine, Faculty of Bioresource Sciences, Nihon University, Fujisawa, Kanagawa 252-0880, Japan

**A six-year-old mixed-breed male dog weighing 7.0 kg was presented with chronic vomiting and regurgitation. Endoscopic examination revealed prominent oesophageal dilation in the thoracic region, multiple small greyish-white nodules over the oesophageal lumen and cauliflower-like masses in the caudal oesophagus. Histopathological studies revealed a characteristic pattern of coexisting elements of infiltrating adenocarcinoma and squamous cell carcinoma. Immunohistochemical staining with anti-cytokeratin AE1+AE3 was positive in both types of neoplastic cells. Neoplastic glandular cells stained positively for cytokeratin 8 while neoplastic squamous cells stained positively for cytokeratin 5/6. On the basis of these findings, the dog was diagnosed with oesophageal adenosquamous carcinoma. The case history and findings suggest that the malignancy might have developed from Barrett's oesophagus following irritation of the oesophageal mucosa due to chronic vomiting and regurgitation.**

*Journal of Small Animal Practice* (2015) **56**, 521–523
DOI: 10.1111/jsap.12333

Accepted: 28 November 2014; Published online: 27 January 2015

## INTRODUCTION

Oesophageal tumours are rare, accounting for less than 0.5% of all tumours in dogs and cats (Ridgway & Suter 1979). The commonly reported malignant tumours of the canine oesophagus include *Spirocerca lupi*-associated osteosarcoma and fibrosarcoma (Ivoghli 1978, Ranen *et al.* 2004a), osteosarcoma (Ranen *et al.* 2004b) and squamous cell carcinoma (SCC) (McCaw *et al.* 1980). The main clinical signs of oesophageal tumours include regurgitation, lethargy, depression, anorexia and weight loss. Haematological findings include neutrophilia and microcytic hypochromic anaemia. Endoscopy is a reliable tool in the diagnosis of these tumours, but a definitive diagnosis requires histopathology. The treatment of choice is surgical removal; no conclusions have been drawn regarding the effectiveness of adjunctive chemotherapy (Ranen *et al.* 2004b).

Adenosquamous carcinoma (ASC) of the oesophagus is a rare tumour in humans and typically exhibits coexisting elements of infiltrating adenocarcinoma (AC) and squamous cell carcinoma (SCC). The malignancy has been reported in cats previously (Shinozuka *et al.* 2001). To the authors' knowledge, ASC of the canine oesophagus has not yet been described. This report presents a case of oesophageal ASC in a dog.

## CASE HISTORY

A six-year-old mixed-breed male dog weighing 7.0 kg was presented for evaluation of vomiting and regurgitation. The dog had been vomiting once every two days for five years but was in good general condition. The dog had also been frequently regurgitating and losing weight for two months.

Initial haematological tests revealed sodium concentration of 119 (reference interval, 141–152) mmol/L, potassium concentration of 4.1 (3.6–5.5) mmol/L, chloride concentration of 75 (102–122) mmol/L, blood urea nitrogen concentration of 10.2 (2.5–9.6) mmol/L, creatinine concentration of 194.5 (44.2–159.1) µmol/L, glucose concentration of 10.2 (4.1–7.9) mmol/L and neutrophil count of 48.1 (3.6–12) $\times 10^9$/L. Faecal examination, urinalysis (urine specific gravity, 1.030) and abdominal ultrasonography did not reveal clinically significant abnormalities. Thoracic radiography revealed a shadowy mass in the caudal oesophagus and a moderate amount of air on the cranial portion of the mass.

Endoscopic examination (VQ-8142A flexible video-endoscope; Olympus Medical System Corporation, Tokyo, Japan) revealed prominent oesophageal dilation in the thoracic region and multiple small greyish-white nodules and viscous foamy fluid

in the oesophageal lumen. Cauliflower-like masses were observed in the caudal oesophagus proximal to the cardia (Fig 1A). Endoscopic ultrasound revealed a 5.8-mm-thick hyperplastic mucosa.

Surgical removal of the tumours and oesophageal reconstruction with a small intestinal graft were attempted (Fig 1B). However, complete excision was difficult because of extensive involvement of large blood vessels adjacent to the oesophagus, although no gross lesion was observed in the gastric mucosa. The dog was euthanased at the owner's request, but postmortem examination was not permitted.

For histopathology, the tumours were fixed in 10% neutral buffered formalin and embedded in paraffin as per routine procedures. Tissue sections were stained with haematoxylin and eosin (HE) or Alcian blue-periodic acid-Schiff (AB-PAS). The tumours showed two cellular patterns: columnar or cuboidal neoplastic glandular cells and large neoplastic squamous epithelium-like cells with keratin pearls (Fig 2A–C). The polyhedral, irregularly sized cells had large atypical nuclei and clear nucleolus. Their cytoplasm contained AB-PAS-positive materials, as did the tubular lumen in the AC part. Metastasis of both cell types was observed in a juxta-oesophageal lymph node.

Immunohistochemical staining was performed by means of the streptavidin–biotin technique with mouse cytokeratin AE1/

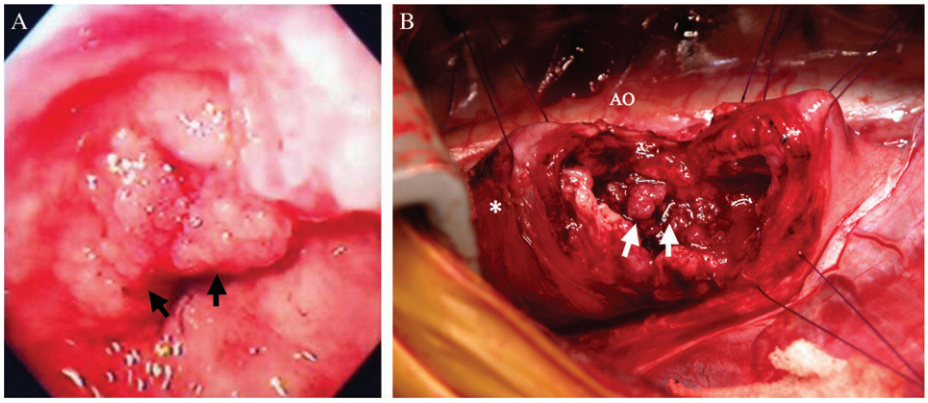


**FIG 1. Gross findings of the oesophageal nodules. (A) Endoscopic view showing cauliflower-like masses in the caudal oesophagus (black arrows). (B) Surgical view showing neoplastic masses in the caudal oesophagus (white arrows). The asterisk indicates the oesophagus. AO, aorta**

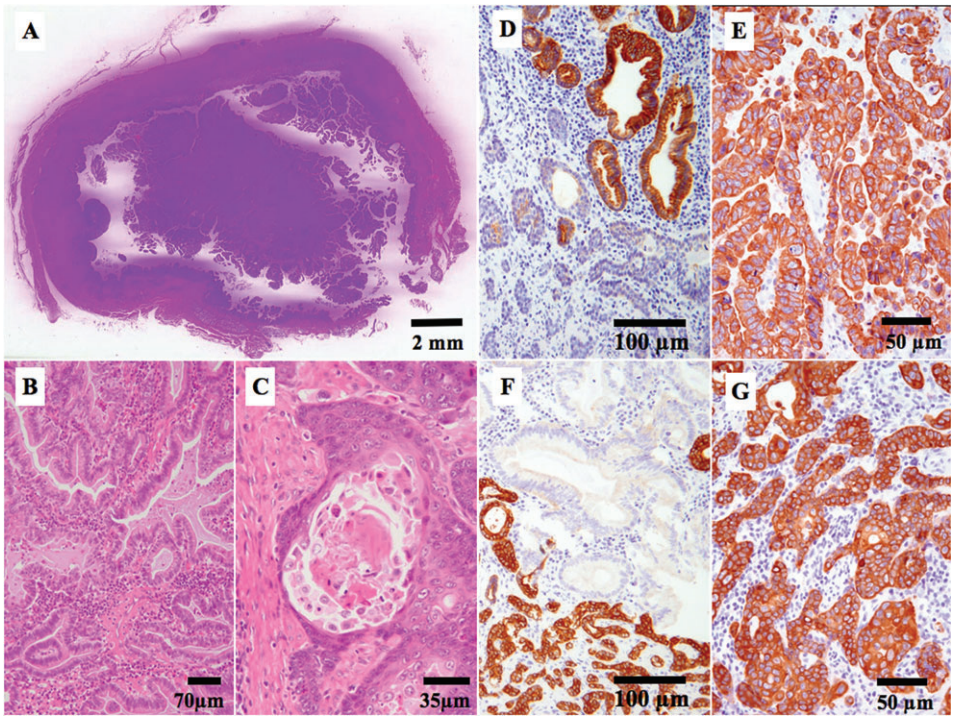


**FIG 2. Histopathological findings of the oesophageal tumours. (A) Cross-section of the caudal oesophagus including part of the tumour, (B) sample of the adenocarcinoma (AC) and (C) sample of the squamous cell carcinoma (SCC). (A–C) Haematoxylin and eosin (HE) staining. (D) Columnar or cuboidal neoplastic glandular cells stained positively for cytokeratin 8 (upper half of the field); neoplastic squamous cells show no staining (lower half of the field). (E) Magnified view of neoplastic glandular cells stained positively for cytokeratin 8. (F) Neoplastic squamous cells stained positively for cytokeratin 5/6 (lower half of the field); neoplastic glandular cells show no staining (upper half of the field). (G) Magnified view of neoplastic squamous cells stained positively for cytokeratin 5/6**

AE3, cytokeratin 8 (which is expressed in simple epithelium but not in stratified squamous epithelium) and cytokeratin 5/6 (which is expressed at low levels in AC and high levels in SCC) monoclonal primary antibodies (DAKO, Tokyo, Japan). Both neoplastic cell types positively stained for cytokeratin AE1/AE3. Further, the neoplastic glandular cells were positively stained with cytokeratin 8 (Fig 2D, E) and the neoplastic squamous cells stained positively for cytokeratin 5/6 (Fig 2F, G).

Electron microscopy showed microvilli-like structures and glycogen granules on the luminal surface of the neoplastic glandular cells and cytoplasmic tonofilament-like fibrils and intercellular desmosome-like structures in the neoplastic squamous cells.

On the basis of these findings, the dog was diagnosed with oesophageal ASC.

## DISCUSSION

A retrospective study of canine oesophageal neoplasms showed only two cases of oesophageal tumours (SCC and leiomyoma) in 49,229 dogs (Ridgway & Suter 1979). There are also two reports of oesophageal AC (Randolph *et al.* 1984) and gastro-oesophageal AC (Takiguchi *et al.* 1997). The former resulted in metastases to the lung, diaphragm and gastric cardia and the latter caused gastric cardia, gastric body and pyloric metastases. In a study of oesophageal ASC in humans, lymph node metastases were found in 10 of 18 cases (55.6%), with no tumours at the gastro-oesophageal junction (Yachida *et al.* 2004). In the present case, invasion into the stomach was not observed, but juxtaposed lymph node metastasis was found.

A study of chemically induced oesophageal carcinoma using *N*-ethyl-*N*′-nitro-*N*-nitrosoguanidine in dogs revealed the formation of multiple small nodules in the oesophagus (Sugihara 1988). Similar greyish-white nodules were noted in the present case. These nodules might be a characteristic feature of canine oesophageal ASC and AC.

Some hypotheses have been proposed about the aetiology of oesophageal carcinoma. Cotchin (1966) suggested that feline oesophageal carcinoma is caused by ingestion of an unknown carcinogen during self-grooming. However, exposure to environmental carcinogens was unknown in the present case. Another possibility is progression from Barrett's oesophagus (BE) to oesophageal ASC. In BE, squamous epithelium is replaced by glandular epithelium (Barrett 1950). Its development is clinically associated with prolonged duodeno-gastro-oesophageal reflux, which replaces the normal squamous mucosa of the oesophagus with columnar mucosa (Buskens *et al.* 2006). BE is considered a premalignant condition because of stepwise progression from intestinal metaplasia to dysplasia and finally AC (Cameron *et al.* 1995) and ASC (Noguchi *et al.* 2002). A case of canine BE with an oesophageal adenomatous polyp has recently been reported (Gibson *et al.* 2010). In the present case, ASC might have developed from BE following irritation of the oesophageal mucosa due to chronic vomiting and regurgitation, because the oesophageal mucosa consisted of not only neoplastic but also non-neoplastic columnar epithelial cells.

According to the World Health Organization, malignant epithelial tumours of the upper alimentary tract in domestic animals are classifiable into four types: SCC, AC, undifferentiated carcinoma and secondary carcinoma (Head *et al.* 2002). Similar to the classification in humans, ASC should be categorised as a malignant epithelial tumour of the upper alimentary tract in domestic animals.

In conclusion, this report presents a case of oesophageal ASC in a dog. Further studies are required to clarify the clinical and pathological characteristics of canine oesophageal ASC.

## Acknowledgements

The authors would like to thank the residents and interns of the Animal Medical Centre of Nihon University for clinical assistance.

## Conflict of interest

None of the authors of this article has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

## References

Barrett, N. R. (1950) Chronic peptic ulcer of the oesophagus and oesophagitis. *British Journal of Surgery* **38**, 175-182

Buskens, C. J., Hulscher, J. B., van Gulik, T. M., *et al.* (2006) Histopathologic evaluation of an animal model for Barrett's esophagus and adenocarcinoma of the distal esophagus. *Journal of Surgical Research* **135**, 337-344

Cameron, A. J., Lomboy, C. T., Pera, M., *et al.* (1995) Adenocarcinoma of the esophagogastric junction and Barrett's esophagus. *Gastroenterology* **109**, 1541-1546

Cotchin, E. (1966) Some aetiological aspects of tumours in domesticated animals. *Annals of the Royal College of Surgeons of England* **38**, 92-116

Gibson, C. J., Parry, N. M., Jakowski, R. M., *et al.* (2010) Adenomatous polyp with intestinal metaplasia of the esophagus (Barrett esophagus) in a dog. *Veterinary Pathology* **47**, 116-119

Head, K. W., Else, R. W. & Dubielzig, R. R. (2002) Tumors of the alimentary tract. In: Tumors in Domestic Animals. Ed D. J. Meuten. Iowa State Press, Iowa, USA. pp 401-482

Ivoghli, B. (1978) Esophageal sarcomas associated with canine spirocercosis. *Veterinary Medicine and Small Animal Clinician* **73**, 47-49

McCaw, D., Pratt, M. & Walshaw, R. (1980) Squamous cell carcinoma of the esophagus in a dog. *Journal of the American Animal Hospital Association* **16**, 561-563

Noguchi, T., Uchida, Y., Fumoto, S., *et al.* (2002) Adenosquamous carcinoma arising in Barrett's esophagus. *Japanese Journal of Thoracic and Cardiovascular Surgery* **50**, 537-540

Randolph, J. F., Center, S. A., Flanders, J. A., *et al.* (1984) Hypertrophic osteopathy associated with adenocarcinoma of the esophageal glands in a dog. *Journal of the American Veterinary Medical Association* **184**, 98-99

Ranen, E., Lavy, E., Aizenberg, I., *et al.* (2004a) Spirocercosis-associated esophageal sarcomas in dogs. A retrospective study of 17 cases (1997–2003). *Veterinary Parasitology* **119**, 209-221

Ranen, E., Shamir, M. H., Shahar, R., *et al.* (2004b) Partial esophagectomy with single layer closure for treatment of esophageal sarcomas in 6 dogs. *Veterinary Surgery* **33**, 428-434

Ridgway, R. L. & Suter, P. F. (1979) Clinical and radiographic signs in primary and metastatic oesophageal neoplasms of the dog. *Journal of the American Veterinary Medical Association* **174**, 700-704

Shinozuka, J., Nakayama, H., Suzuki, M., *et al.* (2001) Esophageal adenosquamous carcinoma in a cat. *Journal of Veterinary Medical Science* **63**, 91-93

Sugihara, T. (1988) Histopathologic and feulgen-cytophotometric DNA analysis on early changes of chemically-induced esophageal carcinoma in dogs. *Japanese Journal of Gastroenterological Surgery* **21**, 2695-2702

Takiguchi, M., Yasuda, J., Hashimoto, A., *et al.* (1997) Esophageal/gastric adenocarcinoma in a dog. *Journal of American Animal Hospital Association* **33**, 42-44

Yachida, S., Nakanishi, Y., Shimoda, T., *et al.* (2004) Adenosquamous carcinoma of the esophagus. Clinicopathologic study of 18 cases. *Oncology* **66**, 218-225