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Case Report

ADVANCED PERIODONTAL DISEASE IN A YORKSHIRE TERRIER WITH CONCURRENT NASAL CAVITY MALIGNANCY

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Summary: An eleven-year-old male Yorkshire terrier weighing 2.6 kg with a primarily indoor lifestyle was presented for cardiopulmonary examination due to a 6-month history of difficulty breathing. No cardiopulmonary abnormalities were detected but the history included bilateral serous nasal discharge and oral abnormalities were evident. Examination under general anaesthesia confirmed advanced periodontal disease with oronasal fistulae detected at the maxillary canine teeth. Dental treatment, including repair of the oronasal fistulas, appeared to resolve the respiratory signs but the discharge re-appeared at the left nostril 1 month later. There was no evidence of persistent or recurrent oronasal fistula, so rhinoscopy was performed identifying a mass in the left nasal cavity. Histopathological examination identified the biopsy specimen as a low-grade predominantly papillary-cystic adenocarcinoma combined with transitional carcinoma.

Key words: periodontal diseases; rhinitis; nose neoplasms – pathology; adenocarcinoma; dogs

Introduction

Nasal discharge is a common problem in dogs (1). It may be the result of nasal or paranasal disorders or be related to systemic disease (1). In older animals chronic nasal discharge is commonly due to extension of dental disease to involve the nasal cavities (oronasal fistula or tooth root abscessation) or neoplasia (1, 2). Other differentials include fungal infection, chronic foreign bodies, allergic and non-specific rhinitis as well as systemic disease (1, 3). Both fungal rhinitis and nasal foreign bodies tend to be seen in dogs that spend a lot of time outdoors (1). Except for viral infections and systemic diseases, the nasal discharge in animals with nasal conditions is usually unilateral or may become bilateral with disease progression (1).

The case presented here illustrates some of the difficulties in diagnosis and treatment of nasal conditions in dogs.

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Clinical case

Presentation

An eleven-year-old male Yorkshire terrier weighing 2.6 kg with a primarily indoor lifestyle was referred to the Clinic for Surgery and Small Animal Medicine of the Veterinary Faculty in Ljubljana for cardiopulmonary examination in January 2007. On presentation at the clinic the dog had a six month history of difficulty breathing, especially during the night and the owner mentioned a serous nasal discharge, more pronounced from the left nostril. The dog had been treated with furosemide (Edemid; Lek Ljubljana, Slovenia; 1mg/kg/day p.o.) and ramipril (Tritace; Aventis Pharma, Austria; 0.5 mg/kg/day p.o.) for one month prior to referral. No other problems were reported in the history. Complete blood count (CBC) values were within normal limits. On auscultation no cardiac abnormalities were detected, lung sounds and pulse were normal, but there was a pronounced expiratory stertor due to partial nasal airflow obstruction. Oral examination revealed the presence of advanced periodontal disease. As the dog's problem appeared to be related to the upper airway, cardiopulmonary examinations were post-

poned and the previously prescribed cardiologic treatment was discontinued pending the results of upper aerodigestive tract examination. The dog was scheduled for general anaesthesia the next day to permit a more thorough oral examination and treatment of the dental disease.

Anaesthesia

The dog was premedicated with methadone (Heptanon; Pliva, Croatia; 0.4 mg/kg i.m.) and carprofen (Rimadyl; Pfizer Animal Health S.A., UK; 4 mg/kg i.v.) prior to induction of anaesthesia using propofol (Propofol 1% Fresenius; Fresenius Kabi, Austria; 7.5 mg/kg i.v.). Following endotracheal intubation, anaesthesia was maintained with isoflurane (Forane; Abbott Laboratories Ltd., GB) given to effect (approximately 1.5%) in oxygen (2 l/min) using a Mapleson F anaesthetic circuit. Amoxicillin and clavulanic acid (Synulox; Pfizer Italia S.r.l., Italia; 20 mg/kg s.c.) was administered preoperatively as the start of a 10 day course of treatment (20 mg/kg/12h p.o.), carprofen treatment also being continued for 5 days (4 mg/kg/day p.o.) to maintain analgesia during the postoperative period. During anaesthesia body temperature, respiratory rate, inspired and expired isoflurane, heart rate, ECG, pulse oximetry, end tidal CO_2 and blood pressure with Doppler manometer were monitored. During the procedure and recovery from anaesthesia fluid homeostasis was maintained by administration of Ringer's lactate solution 26 ml/h (Hartman's solution; B.Braun Melsungen AG; Germany) i.v.

Oral findings

The dog's oral cavity was assessed by means of periodontal examination and recording, plus radiography of disease affected areas. Tooth presence, probing depth, periodontal attachment loss, furcation involvement and tooth mobility were graded. Supra- and subgingival scaling were then performed, followed by polishing and gingival lavage with water, prior to extraction of compromised teeth.

Oral examination revealed advanced periodontal disease with generalised plaque and calculus accumulation. Many teeth were already missing. Oronasal fistulae were detected palatal to both maxillary canine teeth with deep periodontal pockets being present buccally; probing depths were 10 mm on the left and more than 12 mm on the right. Generalised gingival recession of about 2 mm was detected affecting those mandibular premolar and molar teeth that were still present. Of the remaining incisor teeth, only the left maxillary third incisor tooth was stable, the rest being highly mobile. There was generalized bleeding on periodontal probing, due to the extent of gingivitis and periodontitis.

Dental treatment

Left and right infraorbital and mental nerve blocks were performed using bupivacaine (Marcaine 0.5%; AstraZeneca, UK; 0.05 ml per site). Gross deposits were removed from the teeth and the oral cavity rinsed thoroughly prior to extraction of compromised teeth. Extraction was performed after sectioning of multirooted teeth (using cutting burs in a high-speed dental handpiece with copious water spray). A combination of closed elevation and luxation of mobile single-rooted teeth/tooth segments, and open extraction technique, raising muco-gingival access flaps with or without alveolar bone removal as required to facilitate elevation/luxation of the remaining teeth/roots. All the right maxillary incisor teeth, the canine, the right maxillary first, second and third premolar teeth, the left maxillary second incisor tooth, all the mandibular incisor teeth and the right mandibular canine tooth were extracted. There was extensive bleeding while raising mucogingival access flaps in the severely inflamed gingival tissues leading to significant blood loss (estimated from the number of swabs used and their degree of blood saturation to about 40 ml) resulting in a blood pressure drop which required use of a plasma expander (6% HES; Fresenius Kabi Deutschland GmbH, Germany; 10 ml bolus and Hartman's solution 50 ml/kg/h). In view of this, and a drop in the body temperature (to 35 °C), it was decided not to complete the treatment in a single session but to stage it with the aim of performing extractions of the remaining compromised teeth at a later date.

Second presentation and dental treatment

One and a half months after the initial treatment the dog was generally well, however, there was still a serous nasal discharge from the left nostril and an oronasal fistula was still present palatal to the left maxillary canine tooth. All CBC values were still within normal limits so, two months after the first treatment (March 2007), the dog was re-examined under general anaesthesia, using the same protocol as previously. Oral examination revealed severe plaque accumulation, however, gingival recession previously affecting the mandibular premolar and molar teeth has healed only after scaling and polishing, as had the mucogingival access flaps, al-

though the monofilament resorbable suture material (Biosyn 5-0; United States Surgical, USA) was still present. After thorough oral cleaning (scaling and polishing), the left maxillary canine tooth, left mandibular canine tooth and left mandibular first premolar tooth were extracted using the techniques described previously, the oronasal fistula being closed with a single layer mucogingival flap. A thorough examination of the larynx, pharynx, soft palate and caudal nasal cavity using a dental speculum, mirror and retractor was performed, but no additional abnormalities were found. Due to the presence of the oronasal fistula the dog was maintained on amoxicillin and clavulanic acid (20 mg/kg/12 hours p.o.) for 10 days following the dental treatment, with carprofen (4 mg/kg/day) also being given for the first 4 days.

Further presentations and diagnostic procedures

One month after the second dental treatment (April 2007) the owner reported reappearance of the serous nasal discharge from the left nostril, it having stopped shortly after the previous treatment, and mild difficulties breathing. As no recurrence of the oronasal fistula was detected on clinical examination, the owner agreed to have another examination under general anaesthesia, but the owner scheduled this for 1 month later (May 2007). At this time all CBC values, urea, creatinine, alkaline phosphatase and alanine aminotransferase were still within normal limits. Examination under general anaesthesia (induced and maintained as previously, but without antibiotics and carprofen) revealed no abnormalities in the oral cavity. Radiographs of the head (lateral, open-mouth and intra-oral occlusal dorsoventral projections) were obtained but were not diagnostic. Rhinoscopy with a 2.7 mm rigid endoscope passed via the nostrils was performed revealing no abnormalities in the right nasal cavity, however, in the left nasal cavity at a depth of approximately 3 cm there was a mass estimated to be 1 cm^3 in size, appearing to be based caudally. The surrounding nasal tissues were visibly inflamed. Nasal flush was performed to clear any discharge before biopsy to obtain material for histopathology. As the drainage lymph nodes were small no attempt was made to perform fine needle aspiration at this stage, invasive biopsy remaining an option if the nasal biopsy confirmed neoplasia. The dog was discharged with a course of meloxicam for analgesia (Metacam; Boehringer Ingelheim Vetmedica GmbH, Germany; 0.1 mg/kg/day p.o.).

Histopathology results and further treatment

Histopathology results revealed an inflamed low-grade malignant nasal tumour, composed of two distinct subtypes predominant papillary and cystic adenocarcinoma with mucus secretion and formation of small cysts (Figure 1) and a smaller part of the transitional carcinoma, which is also referred to as respiratory epithelial carcinoma or nonkeratinizing squamous cell carcinoma (Figure 2) (4). The adenocarcinomatous part was mostly composed of

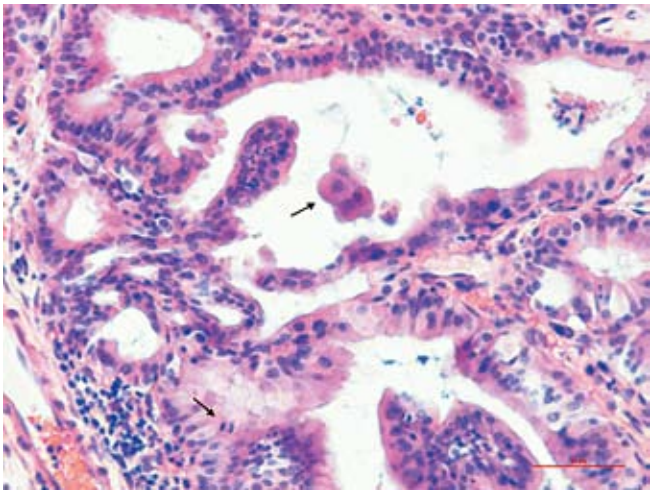

Figure 1: Papillary cystic adenocarcinoma. Part of the tumour shows a less well differentiated tall columnar epithelium with mild cellular and nuclear pleomorphism. A group of pleomorphic epithelial cells can be seen in the middle (arrow) and a mitotic figure in the left lower corner (arrow). There is abundant lymphocytic infiltrate and neutrophils in the stroma. HE staining, x200

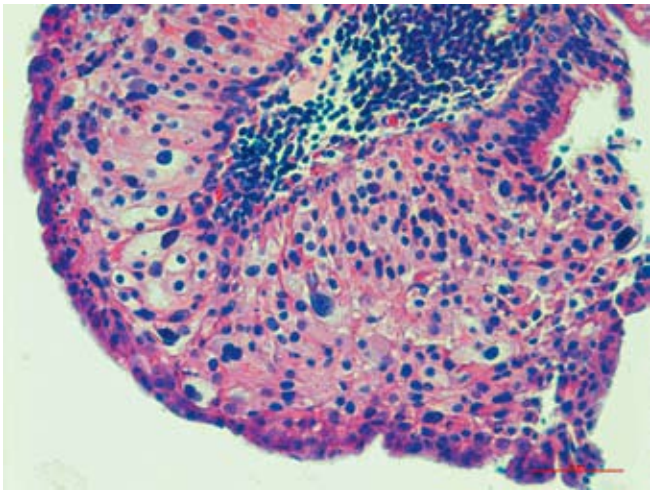

Figure 2: Transitional carcinoma. Cellular and nuclear pleomorphism is clearly evident. Abundant lymphocytic infiltration can be seen in the stroma. HE staining, x200

well differentiated cuboidal or tall columnar epithelial cells with mild pleomorphism, only limited areas showing greater pleomorphism. The cells of a transitional carcinoma subtype revealed greater variability of cell shape and size, from smaller basaloid cells to larger tall columnar and spindle-shaped or polygonal cells with moderate amount of pale eosinophilic cytoplasm and hyperchromatic nuclei containing one or two, and rarely several, small nucleoli. Mitotic figures were rare in both parts.

The dog was much better while on meloxicam and the owner was advised to proceed with staging. In view of the final diagnosis the owner was offered referral for a CT scan prior (3, 5) to possible radiation therapy.

Discussion

Periodontal disease is the most common chronic infectious disease in dogs affecting a majority of the mature population (6, 7), with small breeds being predisposed to it (8). Tumours of the nasal and paranasal sinuses are rare in most domestic species but are recognised most frequently in dogs. The prevalence, however, is only 0.3 to 2.4%, with medium to large dolichocephalic breeds being more often affected. The higher risk associated with a long nose may be related to the larger surface area of nasal epithelium and with the filtering capability, although a genetic basis in some breeds is also suspected (9). Incidence of nasal tumours also increases with age of the dog, the mean age being reported as 9 to 10 years (10, 11). Despite the low prevalence, however, Tasker (12) reports that neoplasia is the most common diagnosis in dogs with persistent nasal disease (one third of cases), where as periodontal disease is only recognized as the cause in 10% of cases. Adenocarcinoma is the most frequent malignant nasal tumour recognized in dogs (9, 10) with transitional carcinoma being the second most common, both being rare or not reported in other animal species (4). Acinic cell carcinoma or even neuroendocrine carcinoma can not been ruled out completely in this case as differentiation requires immunohistochemistry, which was not performed. As neuroendocrine carcinoma is an uncommon sinonasal tract neoplasm with aggressive clinical behaviour (13, 14) this differential diagnosis was not consistent with clinical and histomorphological findings in the presented case.

The diagnostic approach to a patient with nasal discharge includes obtaining a complete history supported by thorough physical examination and routine blood tests to rule out systemic disease (1). If the results are normal as in the presented case, complete oral examination is the next step as well as nasal swabs for cytology and culture if fungal disease is suspected, before proceeding to imaging and rhinoscopy with biopsy sampling (1). However, blood test results may be normal in dogs with nasal neoplasia as paraneoplastic disorders associated with nasal tumours are rare in dogs (10).

As advanced periodontal disease with oronasal fistulae at the maxillary canine teeth was detected in this case, the chronic serous bilateral nasal discharge was suspected to be of dental origin, especially when the nasal discharge completely disappeared on the right side after the first dental treatment (extraction of the right maxillary canine tooth and closure of the fistula at that site), but remained on the untreated site. As the discharge from the left nostril also temporarily disappeared after extraction of the left maxillary canine tooth and antibiotic and anti-inflammatory treatment, dental disease must have had an influence on the nasal discharge, though the improvement may have been due to suppression of secondary bacterial infection in the nasal cavity with the use of antibiotics (11). After unilateral recurrence of the signs, inadequate healing of the oronasal fistula was considered the most likely differential diagnosis (15). Once this was ruled out further investigation was required to identify the cause. Nasal neoplasia most often presents initially with unilateral nasal discharge, epistaxis, epiphora and facial deformity occurring in more advanced cases (11). When there is only serous discharge and expiratory stertor, as our case, chronic rhinitis and nasopharyngeal dysfunction have also to be considered.

It is impossible to say, what the primary disease was or if there is any link between the two diseases in the present case as periodontal disease is extremely common in older small breed dogs and adenocarcinoma, although not a common condition, is seen most often in older dogs. Both conditions have chronic courses, clinical signs persisting for months (1, 6, 10, 11). It is well established that chronic inflammation and/or infection with certain organisms (particularly toxin producing spirochetes) prediposes to carcinoma in certain sites but there have not been any reports suggesting a link between periodontitis and nasal carcinoma (16, 17). Oral lichen planus, a chronic inflammatory disease seen in man is reported to be clinically associated with

development to oral cancer, most likely due to oxidative and nitrative DNA damage caused by chronic inflammation (17-19). Therefore it is possible that the two diseases in the reported case could be related as it has been established that cancer can be promoted and/or exacerbated by inflammation and infections and vice versa (17, 20, 21). The cytokines produced by activated innate immune cells are reported to be important components in this linkage (20, 22-24), many of them are also elevated in periodontal disease (25). TNF-α can contribute to tumour initiation by stimulating production of genotoxic molecules, such as nitric oxide (NO) and reactive oxygen species (ROS), that can induce DNA damage and mutations (20). Stimulated polymorphonuclear leucocytes (PMN), increased in periodontal disease, can also produce reactive oxygen and nitrogen species (ROS, RNS) (17, 25). In periodontal disease there is also a marked production of NO in gingival tissues (26-28). Additionally, activation of toll-like receptors (TLR) on host macrophages or directly on tumour cells by bacterial lipopolysaccharides (LPS), which leads to the activation of NF-κB signaling pathway can enhance tumour development and to a lesser extent tumour regression as well (17, 20, 29). Bacteria can add to cancer development also by production of carcinogenic metabolites (16).

After diagnosing the nasal mass, the dog was placed on meloxicam as the drug not only relieves pain and inflammation but also has the potential to slow the progression of some tumours this effect being suggested to be through the selective inhibition of cyclooxygenase-2 (COX-2), which is upregulated in epithelial nasal tumours (30, 31). Whilst side effects may occur with long term use of meloxicam (32), the risk is so low that it does not outweigh the potential benefits of its use. The owners of the dog have been recommended to consider more definitive treatment for the tumour, i.e. radiation therapy, as this currently provides the best results for nasal carcinomas (10).

References

1. Cooke K. Sneezing and nasal discharge. In: Ettinger SJ, Feldman EC, eds. Textbook of veterinary internal medicine. 6th ed. St.Louis, Missouri: Elsevier Saunders, 2005: 207 - 210.

2. MacEwen EG, Withrow SJ, Patnaik AK. Nasal tumors in the dog: retrospective evaluation of diagnosis, prognosis, and treatment. J Am Vet Med Assoc 170 (1), 1977: 45-8.

3. Lefebvre J, Kuehn NF, Wortinger A. Computed tomography as an aid in the diagnosis of chronic nasal disease in dogs. J Small Anim Pract 46 (6), 2005: 280-5.

4. Dungworth DL, Hauser B, Hahn FF, Wilson DW, Haenichen T, Harkema JR. Histological classification of tumours of the respiratory system of domestic animals. WHO International Histological Classification of tumours of domestic animals, Second Series, Volume VI. Washington: Armed Forces Institute of Pathology, 1999: 16-23.

5. Park RD, Beck ER, LeCouteur RA. Comparison of computed tomography and radiography for detecting changes induced by malignant nasal neoplasia in dogs. J Am Vet Med Assoc 201 (11), 1992: 1720-4.

6. DeBowes LJ. The effects of dental disease on systemic disease. Vet Clin North Am Small Anim Pract 28 (5), 1998: 1057-62.

7. DeBowes LJ, Mosier D, Logan E, Harvey CE, Lowry S, Richardson DC. Association of periodontal disease and histologic lesions in multiple organs from 45 dogs. J Vet Dent 13 (2), 1996: 57-60.

8. Harvey CE, Shofer FS, Laster L. Association of age and body weight with periodontal disease in North American dogs. J Vet Dent 11 (3), 1994: 94-105.

9. Hayes HM, Jr., Wilson GP, Fraumeni HF, Jr. Carcinoma of the nasal cavity and paranasal sinuses in dogs: descriptive epidemiology. Cornell Vet 72 (2), 1982: 168-79.

10. Fox LE, King RR. Cancers of the respiratory system. In: Morrison WB, eds. Cancer in dogs and cats. Medical and surgical management. 2nd ed. Jackson, Wyoming: Teton NewMedia, 2002: 497 - 512.

11. Ogilvie GK, LaRue SM. Canine and feline nasal and paranasal sinus tumors. Vet Clin North Am Small Anim Pract 22 (5), 1992: 1133-44.

12. Tasker S, Knottenbelt CM, Munro EA, Stonehewer J, Simpson JW, Mackin AJ. Aetiology and diagnosis of persistent nasal disease in the dog: a retrospective study of 42 cases. J Small Anim Pract 40 (10), 1999: 473-8.

13. Babin E, Rouleau V, Vedrine PO, et al. Small cell neuroendocrine carcinoma of the nasal cavity and paranasal sinuses. J Laryngol Otol 120 (4), 2006: 289-97.

14. Tarozzi M, Demarosi F, Lodi G, Sardella A, Carrassi A. Primary small cell carcinoma of the nasal cavity with an unusual oral manifestation. J Oral Pathol Med 36 (4), 2007: 252-4.

15. Holmstrom SE, Frost Fitch P, Eisner ER. Veterinary dental techniques for the small animal practitioner. 3rd ed. Philadelphia, Pennsylvania: Saunders, 2004.

16. Parsonnet J. Bacterial infection as a cause of cancer. Environ Health Perspect 103 Suppl 8, 1995: 263-8.

17. Kawanishi S, Hiraku Y. Oxidative and nitrative DNA damage as biomarker for carcinogenesis with special reference to inflammation. Antioxid Redox Signal 8 (5-6), 2006: 1047-58.

18. Chaiyarit P, Ma N, Hiraku Y, et al. Nitrative and oxidative DNA damage in oral lichen planus in relation to human oral carcinogenesis. Cancer Sci 96 (9), 2005: 553-9.

19. Kawanishi S, Hiraku Y, Pinlaor S, Ma N. Oxidative and nitrative DNA damage in animals and patients with inflammatory diseases in relation to inflammation-related carcinogenesis. Biol Chem 387 (4), 2006: 365-72.

20. Lin WW, Karin M. A cytokine-mediated link between innate immunity, inflammation, and cancer. J Clin Invest 117 (5), 2007: 1175-83.

21. Shacter E, Weitzman SA. Chronic inflammation and cancer. Oncology (Williston Park) 16 (2), 2002: 217-26, 229; discussion 230-2.

22. Okamoto T, Sanda T, Asamitsu K. NF-kappa B signaling and carcinogenesis. Curr Pharm Des 13 (5), 2007: 447-62.

23. Rose-John S, Schooltink H. Cytokines are a therapeutic target for the prevention of inflammation-induced cancers. Recent Results Cancer Res 174, 2007: 57-66.

24. Rhodus NL, Cheng B, Myers S, Miller L, Ho V, Ondrey F. The feasibility of monitoring NF-kappaB associated cytokines: TNF-alpha, IL-1alpha, IL-6, and IL-8 in whole saliva for the malignant transformation of oral lichen planus. Mol Carcinog 44 (2), 2005: 77-82.

25. Sculley DV, Langley-Evans SC. Salivary antioxidants and periodontal disease status. Proc Nutr Soc 61 (1), 2002: 137-43.

26. Ugar-Cankal D, Ozmeric N. A multifaceted molecule, nitric oxide in oral and periodontal diseases. Clin Chim Acta 366 (1-2), 2006: 90-100.

27. Skaleric U, Gaspirc B, McCartney-Francis N, Masera A, Wahl SM. Proinflammatory and antimicrobial nitric oxide in gingival fluid of diabetic patients with periodontal disease. Infect Immun 74 (12), 2006: 7010-3.

28. Leitao RF, Ribeiro RA, Chaves HV, Rocha FA, Lima V, Brito GA. Nitric oxide synthase inhibition prevents alveolar bone resorption in experimental periodontitis in rats. J Periodontol 76 (6), 2005: 956-63.

29. Medzhitov R. Toll-like receptors and innate immunity. Nat Rev Immunol 1 (2), 2001: 135-45.

30. Kleiter M, Malarkey DE, Ruslander DE, Thrall DE. Expression of cyclooxygenase-2 in canine epithelial nasal tumors. Vet Radiol Ultrasound 45 (3), 2004: 255-60.

31. Knottenbelt C, Chambers G, Gault E, Argyle DJ. The in vitro effects of piroxicam and meloxicam on canine cell lines. J Small Anim Pract 47 (1), 2006: 14-20.

32. Luna SP, Basilio AC, Steagall PV, et al. Evaluation of adverse effects of long-term oral administration of carprofen, etodolac, flunixin meglumine, ketoprofen, and meloxicam in dogs. Am J Vet Res 68 (3), 2007: 258-64.

NAPREDOVALA PARODONTALNA BOLEZEN IN MALIGNI TUMOR NOSNE VOTLINE PRI JORKŠIRSKEM TERIERJU

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Povzetek: Enajst let star, 2,6 kilograma težek jorkširski terier, ki živi pretežno v stanovanju, je bil napoten na kardiološki pregled zaradi 6 mesecev trajajočih težav z dihanjem. Pri pregledu kardiopulmonarne težave niso bile ugotovljene, pes pa je imel težave zaradi kroničnega seroznega nosnega izcedka ter sprememb v ustni votlini. Pregled ustne votline v splošni anesteziji je potrdil sum napredovale parodontalne bolezni z oronazalnima fistulama ob zgornjem desnem in levem grabilcu. Serozni nosni izcedek se je ponovil 1 mesec po sanaciji ustne votline, tokrat le iz leve nosnice. Ker oronazalne fistule ni bilo, je bila izvedena rinoskopija z odvzemom tkivnih bioptov mase v levi nosnici. Patohistološko je bil v levi nosni votlini dokazan maligni tumor, papilarno-cističen adenokarcinom, kombiniran s prehodnim karcinomom.

Ključne besede: parodontalne bolezni; rinitis; nos, novotvorbe – patologija; adenokarcinom; psi