Case Report

Nasopharyngeal amelanotic melanoma in cat: A case report

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Abstract

Upper airway obstruction is one of the most important respiratory diseases, which is a life-threatening emergency in cats. A 10-year-old sterilized female domestic shorthair (DSH) cat was referred to the Small Animal Teaching Hospital (SATH), Faculty of Veterinary Science, Chulalongkorn University for diagnosis and treatment. She was quiet, alert, and responsive (QAR) and had a normal appetite. The clinical signs of upper respiratory distress with stridor had been presented for more than three months. Computed tomography (CT) and radiography examination were used for diagnosis, and the results showed a soft tissue mass in the nasopharyngeal region. The morphology and position of the nasopharyngeal mass were demonstrated by retrograde rhinoscopy, which underwent a biopsy simultaneously. Histopathological examination indicated an amelanotic melanoma. Immunohistochemistry staining was positive for S-100 and negative for melan-A. The finding offers a diagnostic approach for amelanotic melanoma, an uncommon occurrence in the nasopharyngeal region.

Keywords: amelanotic melanoma, cat, melanoma, nasopharyngeal mass, nasopharyngeal melanoma

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Introduction

Nasopharyngeal amelanotic melanoma in cats has not yet been reported. Upper airway obstruction is one of the most important respiratory diseases, which is a life-threatening emergency in cats. Clinical signs of upper airway obstruction include stertor, stridor, gagging, increased inspiratory effort, dysphagia, and dyspnea. The etiology of chronic upper airway obstruction, particularly the nasopharynx, is infection, inflammation, polyps, and neoplasia, which are found to be common (Allen *et al.*, 1999; Reed and Gunn-Moore, 2012). In the case of neoplasia, lymphoma was the majority (29–70%), followed by adenocarcinoma (13-25%). The other neoplasia, carcinomas (squamous cell, undifferentiated carcinomas), and sarcomas were rarely documented (Allen et al., 1999; Henderson et al., 2004; Reed and Gunn-Moore, 2012b). Melanoma has a few reports involving feline nasal and paranasal sinus tumors. However, the specific location was not stated (Mukaratirwa *et al.*, 2001)

Small animals with melanoma typically have a poor prognosis owing to the tumor's aggressive nature, which may result in up to 50% of cases of regional metastasis and recurrence (Chamel *et al.*, 2017). In feline non-ocular melanomas (NOMs), metastatic rates have been reported to range from 5 to 30% (Smith *et al.*, 2002). However, melanomas have been less frequently reported in cats, especially NOMs (Luna *et al.*, 2000). Previously, the reports of feline NOMs have been indicated at the pinnae, digits, nares, oral cavity, and skin (van der Linde-Sipman *et al.*, 1997b; Luna *et al.*, 2000).

Melanomas are tumors of melanocytes and melanoblasts, which may be benign or malignant in nature. A melanoblast is a precursor cell to the melanocyte, which is the mature melanin-synthesizing dendritic cell located at the epidermal-dermal junction between the cells of the basal layer of the epidermis. Amelanotic malignant melanoma is a subtype of melanoma with little or no pigment on visual or histological examination (Pizzichetta *et al.*, 2004). The most common statement is that amelanotic characteristics have been associated with a poor prognosis. According to one study, the median survival time (MST) for cats with amelanotic melanoma is 71 days, compared to 179 days for those with pigmented melanomas (Chamel *et al.*, 2017).

This case report describes the first evidence of nasopharyngeal amelanotic melanoma in cats. This finding would fulfill the veterinary knowledge and assist the clinician in making the diagnosis and providing information about nasopharyngeal mass.

Case description

A 10-year-old sterilized female DSH cat was brought to the Small Animal Teaching Hospital (SATH), Faculty of Veterinary Science, Chulalongkorn University, with occasional loud breathing sound for more than three months. The cat lived strictly indoors with another cat and was fed commercial food. She received deworming treatments and prevention occasionally. Her body weight was 4.0 kg with a body condition score of 5/9. She was quiet, alert, and responsive (QAR) and had a normal appetite. Other than a stridor sound without respiratory effort, no abnormal clinical symptoms were seen during the physical examination. Normal hydration status, normal breathing pattern, no ocular and nasal discharge, facial symmetry, no stomatitis, no enlarged lymph node, normal lung and heart sounds, and strong femoral pulse were presented. Blood was drawn for a complete blood count and serum biochemistry. The results were within the normal range (Table 1). The feline immunodeficiency virus (FIV) antibodies and feline leukemia virus (FeLV) antigen were negative using the commercially available rapid test (WITNESS®, Zoetis, Lyon, France).

Computed tomography (CT) was used to localize, clarify the location of the mass and provide evidence of metastasis for surgical planning. A 2x1.8 cm soft tissue mass in the retropharyngeal space was visible on radiographic findings of the skull and neck (Fig.1). This mass compressed the underlying nasopharynx and obstructed the upper airway. Both the nasal cavity and frontal sinus were normal. Thoracic radiography was normal of heart size and shape. The trachea and lung were normal (Fig. 1). The cat was sedated for computed tomography (CT). The computed tomography reports found soft tissue opacity mass at the nasopharyngeal area, size 2.1 x 3.2 x 1.3 cm, with low contrast enhancement and slight rim enhancement. It occupies the nasopharynx from the dorsal wall to the soft palate. There is a focal hyperattenuating material size of 0.46 cm occupying the mass. The mass also extended to the left medial retropharyngeal lymph nodes via the left longus capitis muscle. Both ventral nasal cavities have increased attenuation with blurring of nasal turbinate bone. The frontal sinus and cribriform plate are intact with normal alignment. Both tympanic bullae are filled with non-contrast enhancement fluid accumulation with smooth and thin walls. The submandibular lymph nodes have a normal appearance. The teeth are in normal alignment of the mandible and temporomandibular joints. The lung parenchyma has mild increase attenuation and pulmonary band signs at the right cranial and middle lung lobes, mainly at ventral distribution. The intrathoracic lymph nodes are in normal size and attenuation. Rhinoscopy was performed after CT scanning to visualize mass morphology, thoroughly examine the nasal cavity as well as collect tissue samples. Both nasal cavities were marked as chronic rhinitis without occupying mass. The soft tissue mass was smooth and located at the nasopharyngeal area down to the left soft palate. An incisional biopsy was performed with a rigid scope guide through the oral cavity. The soft tissue mass was then evaluated by histopathology, hematoxylin and eosin (H&E) staining, and specifically indicated by immunohistochemistry (IHC) using S100 and melan-A.

Table 1 The hematology and blood chemistry profiles.

Parameter	Result	Reference range
Hematology		
RBC (x 10^6 per µl)	8.91	4.95 - 10.53
Hemoglobin (g/dL)	13.9	8.5 - 14.4
Hematocrit (%)	42.7	25.8 - 41.8
Platelet (x 10^3 per µl)	215	160 - 660
WBC (x10^3 per µl)	8.06	3.8 - 19
Neutrophil (x 10^3 µl)	6.49	2.5 - 12.5
Eosinophil (x 10^3 per µl)	0.32	0 - 1.5
Basophil (x 10^3 per µl)	-	Rare
Lymphocyte (x 10^3 per µl)	1.12	1.5 - 7.0
Monocytes (x 10^3 per µl)	0.12	0 - 0.85
Blood chemistry		
ALT (units)	31	13 - 75
ALP (units)	24	3 - 61
BUN (mg%)	28.5	10 - 30
Creatinine (mg/dL)	1.8	0.8 - 2.0
Total protein (g%)	8.7	6.1 - 8.8
Albumin (g%)	3	2.6 - 4.3

RBC = red blood cells; WBC = white blood cells; ALT = alanine aminotransferase; ALP = alkaline phosphate; BUN = blood urea nitrogen

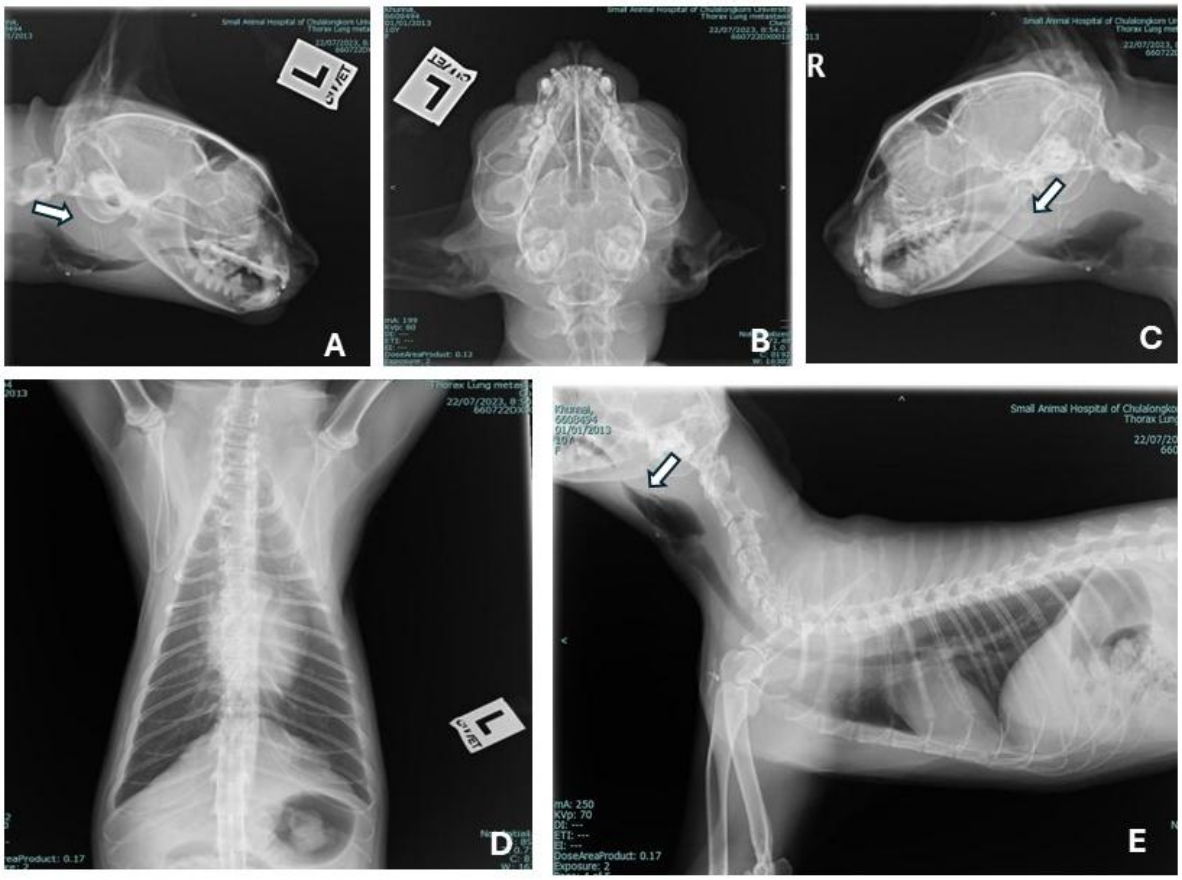

Figure 1 Radiographic finding: The left lateral skull(A), dorsoventral skull view(B), right lateral skull view(C), ventrodorsal thoracic view (D) and right lateral thoracic view(E). A, C, and E radiographs reveal a soft tissue density mass in the retropharyngeal space (white arrow). The ventrodorsal thoracic view (D) and Right lateral (E) demonstrated normal lung patterns without metastatic lesions.

Result and Discussion

The most common cause of nasopharyngeal disease in cats is neoplasia (Allen *et al.*, 1999). Typical presenting signs include stertor, nasal discharge (including epistaxis), facial deformities, and possibly neurological signs (Reed and Gunn-Moore, 2012). In comparison, this case presented only stertor.

Based on the results of the CT scan in Fig. 2, metastasis was considered. The CT scan revealed that the mass had spread via the left longus capitis muscle to the left medial retropharyngeal lymph node. The

sampling from the left retropharyngeal lymph node cannot be evaluated. The majority of regional lymphocentrums of the oral and maxillofacial region are the mandibular, medial retropharyngeal, and parotid lymph nodes in dogs and cats. As the metastasis to the lymph node has been associated with a poor prognosis, the lymph node metastasis should be investigated for prognosis and surgical planning. Currently, there are many techniques for investigating metastases, such as Sentinel lymph node (SLN) mapping, which is used to assess metastases in cats, and Gallium citrate scintigraphy, which is used for oral melanoma in dogs. (Liuti *et al.*, 2009; Chiti *et al.*, 2022). Identification of metastases is necessary for selective lymphadenectomy to avoid indiscriminate extirpation of multiple lymph nodes, as this represents a less extensive surgical dissection and reduces the risk of postoperative complications.

Incisional biopsy sections consisted of densely cellular, well-demarcated, unencapsulated neoplasm composed of sheets of pleomorphic spindle cells within a scant fibrovascular stroma. Neoplastic cells were spindle to polygonal with variable distinct cell borders and moderate amounts of eosinophilic cytoplasm. Nuclei were round to oval, centrally located with finely stippled chromatin and up to four prominent magenta nucleoli. Mitoses were occasionally seen. There were multifocal areas of necrosis with infiltrates of neutrophils. Amelanotic melanoma was diagnosed.

Amelanotic melanoma was a lack of melanin pigments. To further investigate the tumor, an IHC was used for a tentative diagnosis. In dogs, an antibody combination consisting of melan-A, PNL2, TRP1, and TRP2 has been shown to have the highest sensitivity and specificity for accurately identifying amelanotic melanocytic neoplasms (Ramos-Vara *et al.*, 2002; Smedley *et al.*, 2011; Chamel *et al.*, 2017; Saverino *et al.*, 2021). Only melan-A, PNL2, and S100 have been previously investigated as melanocytic markers in cats. (Pittaway *et al.*, 2019a). In this study, IHC demonstrated positive staining for S-100 and negative staining for Melan-A (Fig. 5). S100 protein has been the most widely utilized immunohistochemical marker in both human and animal melanomas and was capable of staining up to 100% of feline melanomas (Van der Linde-Sipman *et al.*, 1997a). Melan-A, specific melanocytic differentiation antigens, showed more specific but less sensitive marker compared with S100 (Ramos-Vara *et al.*, 2002). However, a previous study reported negative or equivocal staining of melan-A in amelanotic tumors in cats (Ramos-Vara *et al.*, 2002; Briggs *et al.*, 2023). Due to characteristic histopathologic features of amelanotic melanoma, which lack pigmentation of neoplastic cells, round to spindle cell morphology, and variable junctional activity, the final amelanotic melanoma diagnosis was not possible to exclude. However, for a tentative diagnosis, PNL2 should be further investigated.

From the retrospective study of NOMs, the data show that middle-aged to older cats have the largest population. (Patnaik and Mooney, 1988), the same as the previous study (Luna *et al.*, 2000). Sex was not a significant association of this tumor, but coat color was unclear. The most common localization of feline NOMs is the pinna, the skin of the head and the oral cavity, and truncal skin, whereas the nasopharynx has not been reported. The grading criteria for NOMs at the lip, oral, nasal mucosa, and planum were based on histological findings such as mitotic count >4 per 10 HPF and the presence of intratumoral necrosis. If the histology met one or both criteria, high grade feline NOMs were considered. The grading system predicted tumor-related death with 80% sensitivity and 92% specificity. MST of the high-grade melanoma was 90 days and 83 days in cases of lips, nose, and oral cavity. In this study, amelanotic tumors died from melanocytic disease, with a degree of pigmentation significantly associated with the outcome (Pittaway *et al.*, 2019b).

According to this report, the owner decided to treat the cat palliatively with robenacoxib (Onsior®) and chlorambucil (Lukeran®) due to financial problems. After a phone follow-up, the cat died on the 27th day after the biopsy. Metronomic treatment utilizing cyclophosphamide and celecoxib has also been documented in cases of oral melanoma in dogs and cats (Marchetti *et al.*, 2012; Leo *et al.*, 2014; Milevoj *et al.*, 2022). However, the surviving time was not mentioned. One potential clinical therapy avenue that has been minimally reported on to date in canine and feline melanoma is the use of cyclooxygenase (COX)-2 inhibitor. Two studies suggested COX-2 expression was elevated in malignant melanoma. Therefore, COX-2 inhibitors could be used as a prognostic biomarker and a target treatment for melanocytic neoplasms (Pires *et al.*, 2010; Martínez *et al.*, 2011). In humans, selective COX-2 inhibitors can inhibit cell growth in various types of human cancer, including malignant melanoma. From two studies, *in vitro* data suggests that NSAIDs, selective COX-2 inhibitors, might be effective against malignant melanoma in dogs (Seo *et al.*, 2014; Yoshitake *et al.*, 2017). However, chemotherapy is not typically the primary treatment for melanoma in dogs and cats. A combination of surgical excision and radiation has been suggested.

In case of oral and local melanoma, wide and extension surgical excision is the treatment of choice (Raleigh *et al.*, 2021). For benign cutaneous tumors, the surgical margin guiding width is 1 cm for the skin margin, one fascial plan for deep margins, and 2-3 cm for wide margins in the case of malignancy. However, oral melanoma is not possible for wide margin excision. The radiotherapy needs to be combined with the surgery for adequate tumor control.

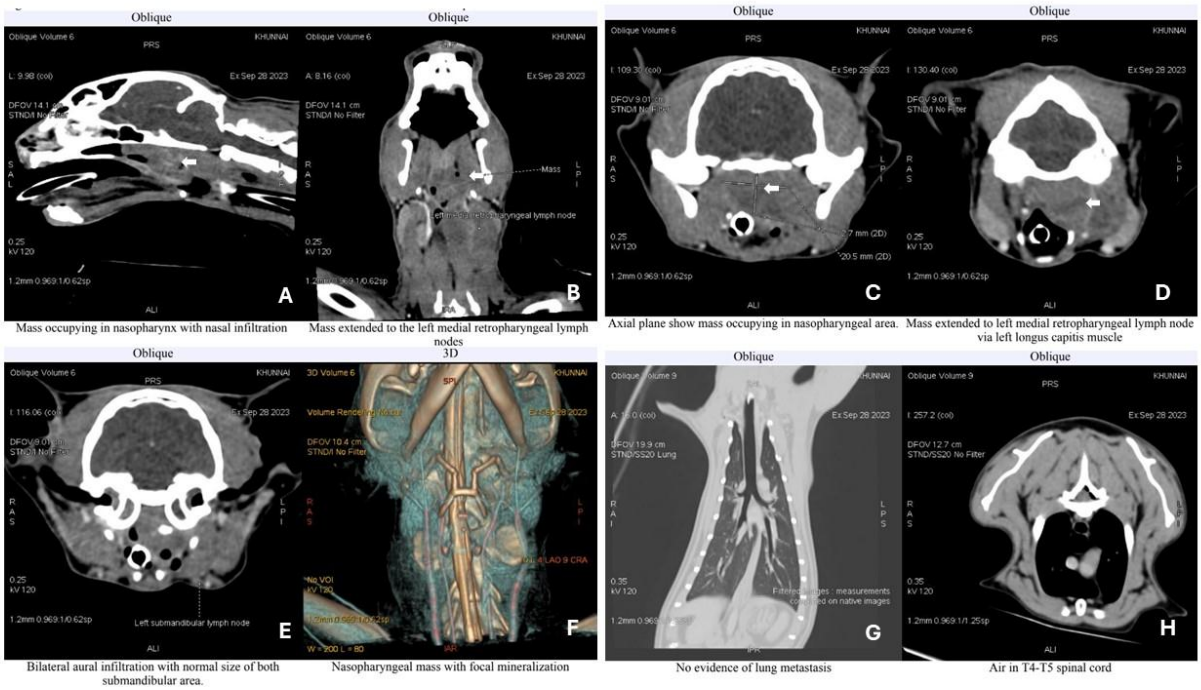

Figure 2 The computerized tomography scan of the skull in sagittal (A), dorsal (B), and transverse (C, D, E) plan reveal nasopharyngeal mass (white arrow). The computerized tomography scan of thorax in dorsal(G) and transverse(H) had no metastasis.

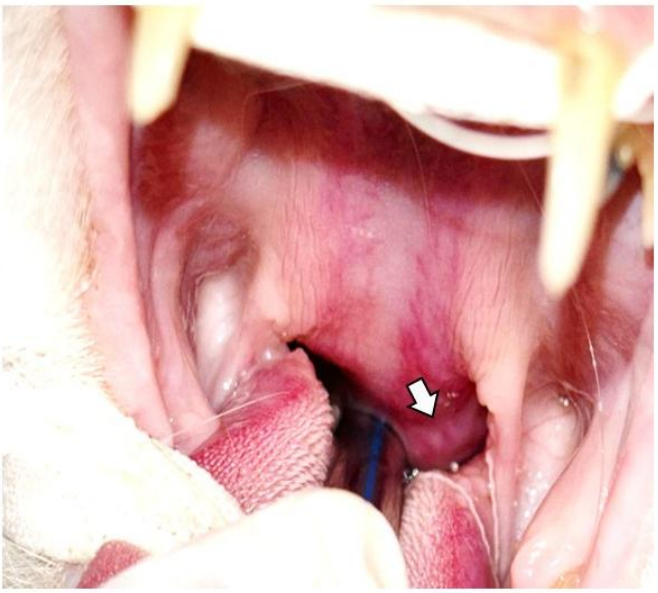

Figure 3 The oral cavity of this cat found nasopharyngeal mass (white arrow).

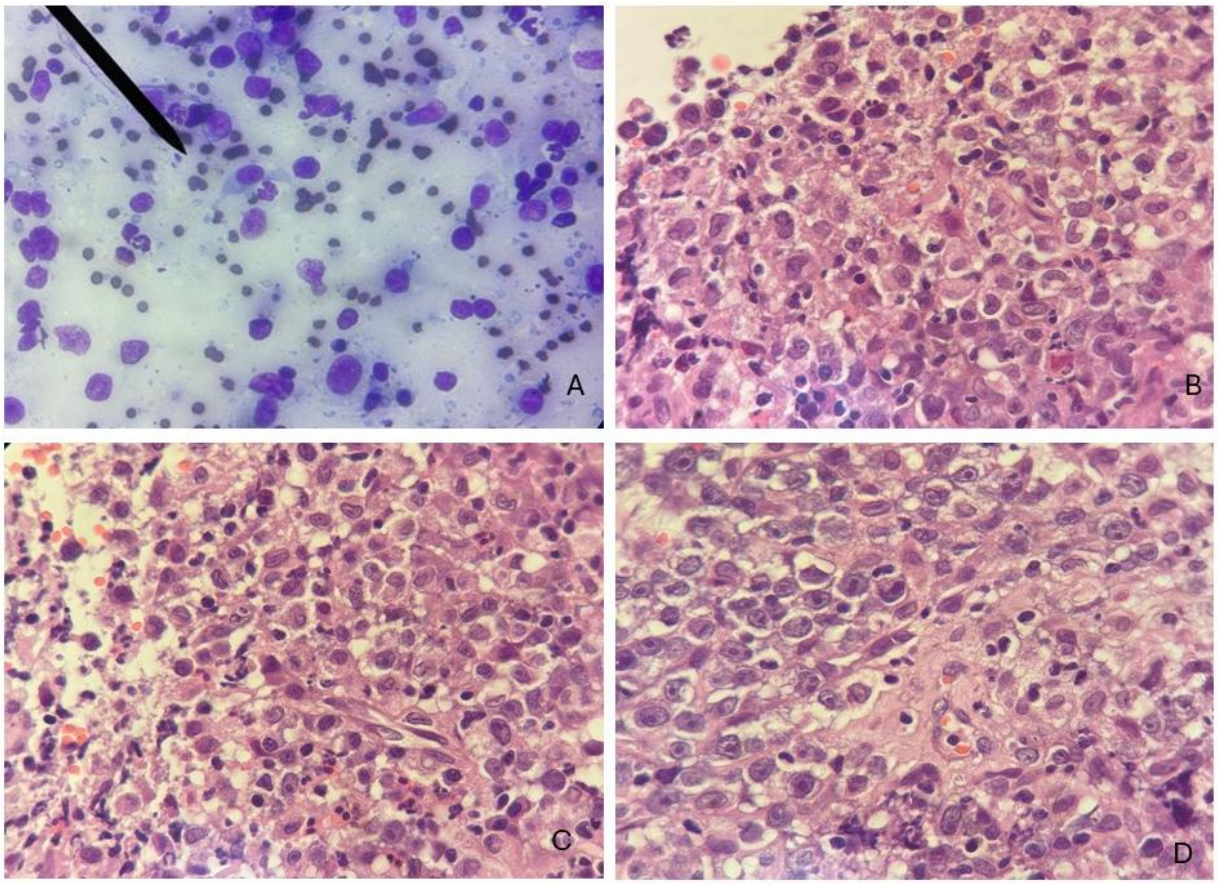

Figure 4 The cytology reveals pleomorphic ovoid to spindle-shaped cells with round to oval nuclei, coarsely stippled chromatin, and a high N: C ratio (A). Histology of nasopharyngeal mass (B, C, D) reveals anisocytotic and anisokaryotic spindle to polygonal cells with round to oval nuclei, with up to four prominent magenta nucleoli and mild multifocal areas of necrosis. Hematoxylin and Eosin (H&E), 400x magnification.

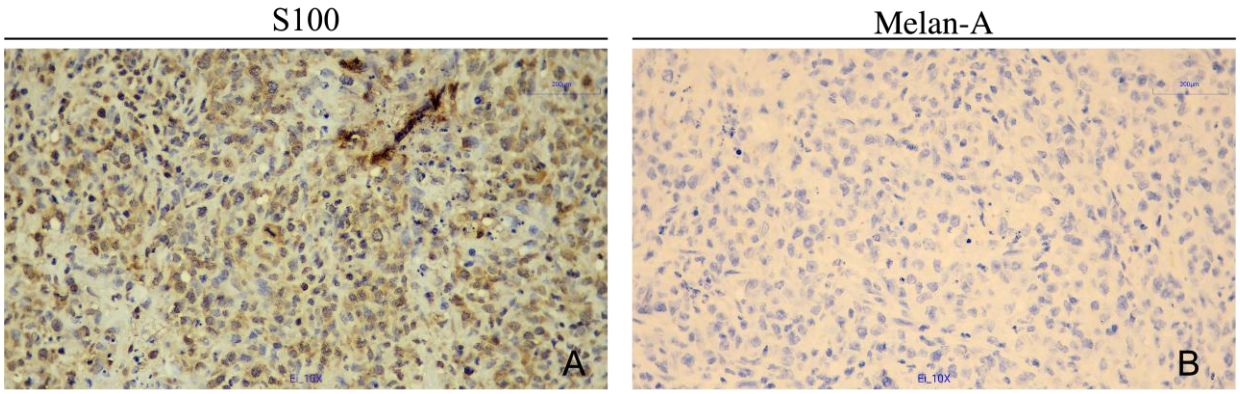

Figure 5 Immunohistochemical staining of melanoma-related indicators. Sections of the main mass illustrated intracytoplasmic positive immunolabelling for S-100 (A) and negative staining for melan-A (B), immunohistochemical images, 400x magnification.

Radiation therapy plays an important role in the treatment of canine and feline oral melanoma to achieve locoregional tumor control. The retrospective study evaluated the effectiveness of hypofractionated radiation therapy in five oral melanoma cats. Three cats received only radiation therapy; one cat was completely responsive, but two were not. Two cats treated with radiation and chemotherapy were partially responsive. One in two cats was also treated with an experimental DNA melanoma vaccine. However, all five cats were euthanized due to evidence of metastasis (Farrelly *et al*., 2004). Only radiation therapy is not a good choice for melanoma treatment. In addition, radiation therapy with chemotherapy cannot control the metastasis of oral melanoma, and from several studies, using chemotherapy combined with radiation therapy or surgery did not improve the outcome (Proulx *et al*., 2003; Murphy *et al*., 2005; Brockley *et al*., 2013; Tuohy *et al*., 2014).

Chemotherapy is a systemic therapy that is indicated in dogs with a moderate to high metastatic risk. Several studies suggest chemotherapy may play a role in the treatment of oral melanoma with radiation treatment (Rassnick *et al*., 2001; Dank *et al*., 2014). However, there is no study in cats.

The xenogeneic DNA vaccine, encoded with human tyrosinase, is currently available and labeled for use in dogs for the treatment of oral melanoma. The use of vaccines is recommended in cases where the primary tumor is controlled through surgery and radiation. It appears to improve survival by inducing tumor specific antibodies, cytotoxic T cells, and antitumor responses (Grosenbaugh *et al*., 2011). Administration of the vaccine typically involves an initial administration of 4 intradermal injections biweekly, followed by boosters every 6 months thereafter (Bergman *et al*., 2006). Currently, this vaccine has been reported to be used off-label in cats (Farrelly *et al*., 2004; Sarbu *et al*., 2017). From this study, it was concluded that the vaccine was safe for the feline patient. However, the study did not evaluate response to therapy or survival times (Sarbu *et al*., 2017).

Focusing on MST, retrospective studies of feline oral melanoma including oropharynx, lip, buccal mucosa, palatal mucosa, and maxillary alveolar mucosa, revealed that MST of palliative treatment was 52.5 days whereas surgical excision was 205 days. In cases of clear margin excision, MST was up to 421 days. Moreover, cats getting a complete surgical excision with xenogeneic vaccine administration had a survival period of more than 630 days (Briggs *et al*., 2023). However, nasopharyngeal melanoma has not been investigated for MST.

In conclusion, this report describes an unusual nasopharyngeal tumor. Amelanotic melanoma raises awareness as a potential differential diagnosis within the nasopharyngeal region in cats with chronic noisy breathing sound and upper airway obstruction.

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