Nasal Cavity Masses Resembling Chondro-osseous Respiratory Epithelial Adenomatoid Hamartomas in 3 Dogs

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Abstract
Chondro-osseous respiratory epithelial adenomatoid hamartomas (COREAHs) are rare tumors in the nasal cavity of people, which have not been described in other species. COREAHs in people are minimally invasive and rarely recur following excision. Histologically, these tumors are composed of disorganized, mature, nasal turbinate tissue that is organized into polypoid growths. These growths are lined by respiratory epithelium, contain glandular elements, and are organized around central cores of chondro-osseous matrix. This report describes 3 cases of dogs with nasal tumors that have histomorphology similar to that of COREAH in people. The tumors were all identified within the nasal cavity and were associated with regional bony lysis of the turbinates and surrounding skull bones, a feature that has not been reported in COREAH in people. There was no evidence of metastasis or extension beyond the nasal cavity in any of the 3 cases.

Keywords
dog, epistaxis, exophthalmos, hamartoma, histology, nasal sinus, pathology, respiratory

A hamartoma is defined as a focal, disordered growth of mature tissue indigenous to the organ involved.5 Respiratory epithelial adenomatoid hamartoma (REAH) is an uncommon mass in the upper respiratory tract that was first described in people in 1995.8 To date, REAH has been reported in <400 people and in a single dog.6,8 It occurs most commonly in men (roughly 7:1 male-to-female ratio) in the third to ninth decades of life and rarely in children.8 Clinically, REAH causes nasal discharge, facial pain, facial pressure, headaches, and olfactory impairment or loss.8 Although REAH is generally considered a benign hamartoma and there are no reports of metastasis, recent reviews indicate that the pathogenesis is controversial and that REAH may be the result of an inflammatory/reactive or a neoplastic process.7,8

In human patients, REAH occurs in the nasal cavity, paranasal sinuses, and nasopharynx.3,8 Grossly, REAH masses tend to have a polypoid organization. The polyps are soft to firm and yellow to white, sometimes with an edematous appearance.3 The diagnosis of REAH is relatively straightforward with microscopic examination.8 Histologic features include (1) a glandular component that consists of respiratory epithelium originating from the surface epithelium and (2) polypoid growth that is the result of respiratory epithelium-lined adenomatoid proliferation.8 In people, sinonasal masses with histologic features of REAH that are organized around central cores of chondro-osseous matrix are considered a subset of REAH called chondro-osseous respiratory epithelial adenomatoid hamartoma (COREAH).2 There are only 4 reported cases of COREAH in people, 2 of which were in children (7-year-old girl and 11-year-old boy) and 2 in adults (34-year-old woman and 38-year-old woman).1,2,4,7 COREAH has not been previously reported in other species. The clinical behavior and prognosis of COREAH in people are believed to be similar to that of REAH, although rapid recurrence following excision was reported in 1 case of COREAH.7 Grossly, COREAH masses are similar to REAH; they are smooth, soft to firm, pale tan, and polypoid with solid-cut surfaces and occasional mucus-filled cysts.2,4,7 Here we report 3 cases of dogs with nasal cavity masses that are consistent with the histologic diagnostic criteria for COREAH.

Cases included an 8-year-old spayed female Golden Retriever (case No. 1), a 10-year-old castrated male Bouvier des
Flandres (case No. 2), and a 2-year-old intact female Fox Terrier (case No. 3). Case Nos. 1 and 2 presented to the School of Veterinary Medicine at the University of California–Davis (UCD; Davis, CA) and case No. 3 to Universidad de Chile (Santiago, Chile) for clinical signs of 6, 18, and 2 months, respectively. Clinical signs included exophthalmia (case Nos. 1, 2), epistaxis (case Nos. 1, 3), difficulty inspiring (case Nos. 1, 3), reverse sneezing (case No. 2), hyporexia (case No. 2), and lethargy (case No. 2). One of the cases (No. 2) had an enucleation performed 9 months prior to presentation to UCD due to exophthalmos. Nasal masses were identified through a computed tomography (CT) scan at presentation to UCD in case No. 1, on CT scan 18 months prior to presentation to UCD in case No. 2, and on radiographs at presentation to Universidad de Chile in case No. 3. Physical examination findings pertinent to the nasal masses included unilateral exophthalmos (case Nos. 1, 2), stertor (case Nos. 2, 3), unilateral mucopurulent nasal discharge (case No. 1), and unilaterally decreased airflow (case No. 1). Thoracic radiographs and CT scan of the chest were performed in 2 cases (Nos. 1, 2) and did not reveal evidence of metastasis.

CT scans in case Nos. 1 and 2 revealed large, primarily unilateral soft tissue masses within the caudal aspect of the nasal cavity that extended into the frontal sinuses bilaterally and invaded but did not bridge the cribriform plate (Fig. 1). Frequent, thin scrolls of mineralized tissue were identified throughout the masses. In both cases, the nasal turbinates, cribriform plate, and nasal septum were osteolytic or absent in regions of the mass. Patchy osteolysis and periosteal new bone were noted, affecting the maxillary, frontal, and ethmoid bones in both cases, as well as the palatine and sphenoid bones in case No. 1 and the lacrimal bone in case No. 2. The primary differential diagnosis after CT scan was an aggressive osteolytic mass, such as a carcinoma (squamous cell or adenocarcinoma) or sarcoma (osteosarcoma or chondrosarcoma). After CT scan, case No. 1 was euthanized due to perceived poor prognosis. Case No. 2 exhibited lethargy and hyporexia and was euthanized 9 months after CT scan due to quality-of-life concerns. A full necropsy with histologic examination was performed on case Nos. 1 and 2 at UCD; significant lesions were limited to the nasal cavity.

Skull radiographs were performed on case No. 3 and revealed a unilateral soft tissue opacity within the left nasal cavity. The opacity was associated with bony lysis of the vomer and nasal bones with periosteal new bone formation. An excisional biopsy was performed. The dog was alive with no clinical signs related to the mass at 5 months postsurgery.

On gross examination, each mass unilaterally occupied the majority of 1 of the nasal cavities (left nasal cavity in case Nos. 2, 3; right nasal cavity in case No. 1) and effaced the ipsilateral nasal turbinates. All masses were associated with deviation and partial destruction of the nasal septum and extended from approximately 2 to 4 cm from the nares caudally to abut the cribriform plate. Macroscopically, all masses were polypoid and pale pink to tan with red mottling (Fig. 2); on cut surface, masses were gritty and soft (case Nos. 1, 3) or hard (case No. 2). Microscopically, all masses were composed of tightly clustered, polypoid proliferations that had an outer lining of respiratory epithelium (ie, pseudostratified, columnar, ciliated epithelium) and a central core of fibrous stroma surrounding thin, variably mineralized, branching plates of chondro-osseous matrix, variably ectatic adenomatoid proliferations lined by respiratory epithelium, and small acini of seromucinous glands (Figs. 3, 4). Adenomatoid proliferations often contained abundant mucinous or proteinaceous fluid with small numbers of neutrophils. Fibrous stroma was variably edematous and of moderate cellularity with regions of hypercellularity immediately surrounding the chondro-osseous matrix. In all cases, the majority of the matrix was osseous and composed of woven to lamellar bone with regularly spaced lacunae encircling a single osteocyte; this matrix was variably lined by a rim of osteoblasts with multifocal osteoclasts. Lacunae had mild variation in diameter. The woven and lamellar bone was organized into branching and anastomosing plate-like structures. Osseous matrix occasionally had multifocal clefts that contained fibrovascular stroma and adipocytes and were lined by osteoblasts (early bone marrow formation). Blood cell precursors, including erythroid and myeloid precursor cells, as well as megakaryocytes, rarely populated bone marrow spaces (case No. 2). Chondroid portions of the matrix had lacunae surrounded by a deeply basophilic rim that encircled a single chondrocyte (Fig. 5). Small numbers of scattered, mixed inflammatory cells (neutrophils, lymphocytes, plasma cells) and hemosiderophages were identified throughout the mass. The adjacent skull bone had increased numbers of cementing lines, as well as small numbers of osteoclasts in resorption bays.

Cases of REAH in humans are considered to have an excellent prognosis, as complete surgical resection is often curative.\(^3\) In the 4 published human cases of COREAH, however, 1 had recurrence at 1-year postresection; 2 did not have postresection follow-up information; and 1 was free of recurrence at 6-month postresection.\(^1,2,4,7\) None of the human COREAH cases were directly associated with mortality or severe morbidity, but it has been suggested that COREAH and possibly REAH masses may have a more aggressive behavior than previously assumed.\(^7,8\) The paucity of human and canine cases of COREAH that have been described makes prognostication difficult; the only canine case of COREAH in this series that was diagnosed antemortem had no evidence of recurrence at 5 months postsurgery. Although metastasis was not observed in the canine cases reported here, bone loss was associated with the masses in these cases and in the reported canine case of REAH. The cause for the bone loss was likely compression atrophy, as there was no evidence of bone invasion. Invasion of bone is not an expected feature of benign hamartomas, but compression atrophy may be possible with sufficient chronicity.\(^5,6\) Although the designation of these masses as “hamartomas” would seem to be histologically appropriate, the osseous destruction seen in canine cases, adult onset in most human cases, and rare recurrence following excision make it unclear whether this entity truly represents a hamartoma, inflammatory lesion, or neoplasm.
or is of another cause. Inflammation in the canine cases was mild, and a predisposition from chronic rhinitis cannot be excluded.

An idiopathic lesion with some histologic similarities to COREAH is the equine sinonasal cyst (SNC). SNC has a good prognosis, and surgical excision is often curative with complete resolution of clinical signs, such as facial swelling, nasal discharge, and airflow obstruction. Histologically, SNCs are composed of a cyst wall lined by respiratory-like epithelium with a central core of fibrous stroma, embedded within which are bony trabeculae. Occasionally, the fibrous layer has multifocal cysts that contain proteinaceous fluid, similar to the adenomatoid proliferations seen in canine cases presented here. At present, COREAH and SNC both have an unknown pathogenesis.

Significant osseous destruction is not a reported feature of COREAH in humans. Inflammation in the canine cases was mild, and a predisposition from chronic rhinitis cannot be excluded.

Figures 1–5. Chondro-osseous respiratory epithelial adenomatoid hamartoma, nasal cavity, dog, case No. 1. Figure 1. The right nasal cavity is filled with a partially mineralized soft tissue mass that extends across the midline. There is destruction of the nasal turbinates, mostly on the right, and leftward deviation and destruction of the nasal septum. Permeative osteolysis and periosteal new bone affect the frontal and palatine bones. Computed tomography scan. Figure 2. There is a soft, pink to pale tan mass (asterisk) within the right nasal cavity that partially invades the frontal and palatine bones, causing periosteal new bone formation. The mass multifocally effaces and deviates the nasal septum (arrows). Figure 3. Tumors are composed of disorganized, mature, nasal turbinate tissue—specifically, polypoid growths lined by respiratory epithelium with central cores of chondro-osseous matrix (arrows) and embedded adenomatoid proliferations, some of which are ectatic and filled with mucinous secretions (asterisks). Hematoxylin and eosin (HE). Figure 4. Adenomatoid proliferations are lined by pseudostratified, ciliated epithelium (respiratory epithelium). Luminal contents are mucinous. Fibrous stroma is infiltrated by small numbers of inflammatory cells and studded with acini of seromucinous glands. Osseous trabeculae are lined by osteoblasts and rare osteoclasts. HE. Figure 5. Chondro-osseous matrix varies from regions that are chondroid with deeply basophilic rims surrounding chondrocyte lacunae to lamellar bone with osteocyte lacunae. HE.
or an early resection in people prior to the development of significant bone loss. With regard to the latter, the diagnosis and surgical excision of COREAH and REAH in people presumably occur early in the course of the disease because diagnosis is typically made after mild or subjective clinical signs, such as hyposmia (reduced ability to smell) and rhinorrhea. In dogs, the diagnosis of COREAH and REAH is presumably made after disease is more advanced and overt clinical signs are present (e.g., exophthalmia and/or epistaxis) that cause owners to bring their pets to a veterinarian. Other reported signs of REAH in people that were observed in these dogs and the previously reported canine case of REAH include epistaxis, nasal airflow obstruction, and deviated septum.6,8

REAH occurs most commonly in middle-aged to older people, and COREAH has been reported in 2 adults and 2 children.4,7 The previously reported canine REAH case was in a 6-month-old dog.6 This wide age range is similar to the canine cases here, as 2 were geriatric animals and 1 was a young adult. The CT appearance of these canine masses is similar to reported descriptions of COREAH in people—specifically, a soft tissue mass causing septal deviation with a unilateral distribution and multifocal mineralization.2,3 However, the canine masses described here were associated with destruction of the nasal turbinates and mild to moderate osteolysis of the surrounding skull bones, which led to the radiologist’s preliminary diagnosis of an aggressive osteolytic neoplasm.

The gross and microscopic features of the sinonasal masses described here closely resemble that described for COREAH in people. In addition to the diagnostic criteria previously described, several histologic features were present in the canine masses that are common but not consistently present in REAH in people, including prominent glandular dilation with abundant mucinous and eosinophilic luminal contents, as well as seromucinous gland proliferation.3 This study presents the first descriptions of COREAH-like masses in dogs. These findings present an additional differential for nasal cavity masses in dogs.

Acknowledgements
We wish to thank VCA Loomis Basin Veterinary Clinic (Loomis, CA), Dr Christian Torres, Dr Patricia Pesavento, and Dr Verena Affolter for contributing to case material. We also thank Felicia DonRussello, Christopher Kwong, and Kurt Takahashi for their histopathologic technical expertise.

Declaration of Conflicting Interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) received no financial support for the research, authorship, and/or publication of this article.

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