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Successful Combination Chemotherapy for Nasal Carcinoma in a Dog

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Abstract ; A Miniature Schnauzer presented with bilateral mucopurulent nasal discharge and sneezing. Computed tomography of the skull revealed exudates in the nasal cavity and frontal gyrus. Nasal swab cytology showed features of an epithelial-origin tumor. Histopathologic evaluation of the biopsy specimen revealed irregular proliferation of epithelial cells and necrotized tissue. Positive immunohistochemical staining confirmed the epithelial origin of the cells. The dog was diagnosed with nasal carcinoma and was treated with a chemotherapy protocol of carboplatin and piroxicam. This report confirms the effectiveness of combination chemotherapy only without radiotherapy in a dog with nasal carcinoma and provides a guideline for providing alternative treatment.

Key words **:** carboplatin, combination chemotherapy, nasal carcinoma, piroxicam.

Introduction

Nasal tumors in dogs are rare, accounting for less than 2% of all reported neoplasms (2,15,19,21). They are usually diagnosed in middle-aged or older dogs (2). Locally invasive carcinomas, with low rates of metastases, comprise approximately 70% of diagnosed canine nasal tumors (13,14,16,19). The etiology of nasal neoplasia remains unknown, but evidence suggests a relationship with environmental pollutants (5). Treatment for nasal tumors includes radiotherapy, surgery, chemotherapy, and combination treatments (8-12). Despite treatment, the long-term prognosis remains poor. The mean survival time of patients without treatment is 3-6 months (11,23).

Cytoreductive surgery using rhinotomy has been performed and is well documented for other tumors (2,14). However, since most nasal tumors are locally invasive, the prognosis with surgery alone is often poor (4,7,15,18). To prolong the survival time in dogs with nasal tumors, a combination of radiotherapy and systemic chemotherapy has been suggested (6). Nasal tumor is the fifth type of neoplasia treated with external beam irradiation (17). In contrast, chemotherapy alone has not been efficacious in the treatment of nasal tumors (9,10,20). Chemotherapy with cisplatin alone for the treatment of nasal adenocarcinoma improved clinical signs of the disease, thereby improving the patients' quality of life (9). Therefore, combination therapy of carboplatin and piroxicam was used in this case. Both drugs have antitumor effects and are safe for use in combination (3).

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Case Report

An 8-year old spayed female Miniature Schnauzer presented to a local animal hospital. The chief complaint was bilateral mucopurulent nasal discharge and sneezing since 4 weeks ago. On physical examination, bilateral mucopurulent nasal discharge, more prominent on the left side, was identified. The nasal discharge made it difficult for the dog to breath without opening its mouth. Intermittent sneezing was also observed. Submandibular and popliteal lymphadenopathy was detected by palpation.

Complete blood cell count was within the normal reference range. Serum chemistry evaluation showed a mild elevation in alanine aminotransferase levels (109 U/L; Normal: 19-70) and a prominent elevation in alkaline phosphatase

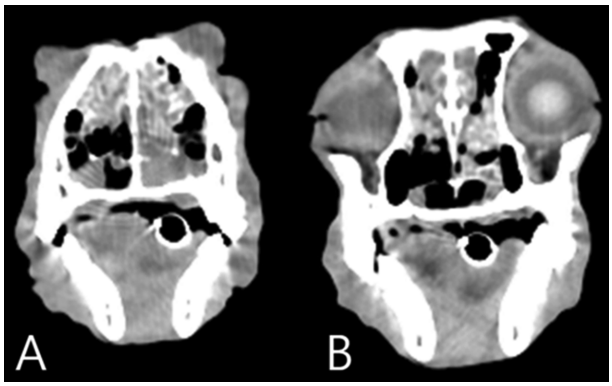

Fig 1. Computed tomography of the skull. Computed tomography images show exudates filling the nasal cavity and frontal gyrus. The nasal septum structure is intact but the nasal concha is not clearly identified. Images from the middle of the nasal cavity (A) and the rostral frontal sinuses (B).

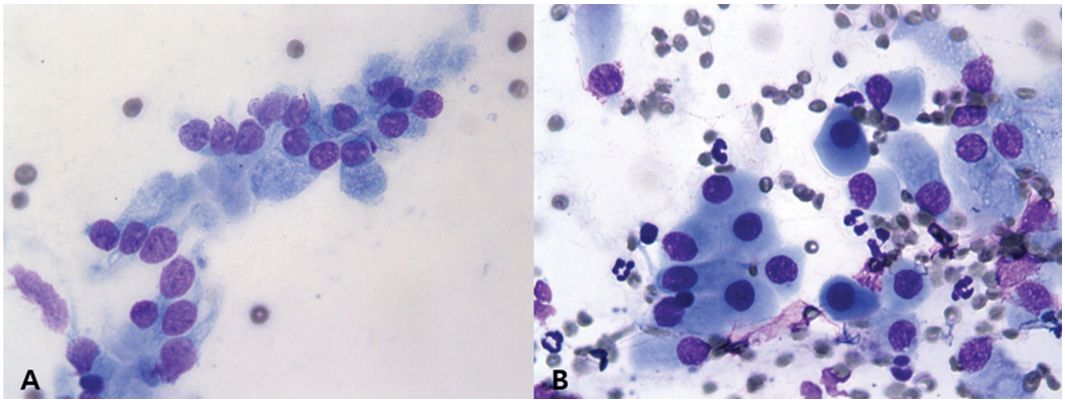

Fig 2. Cytobrush sample cytology. Cytologic evaluation shows malignant changes of the epithelium, including coarse nucleolus and predominant nucleoli in both left (A) and right nasal samples (B). A number of neutrophilic inflammatory cells and erythrocytes can be identified, especially from the right nasal sample.

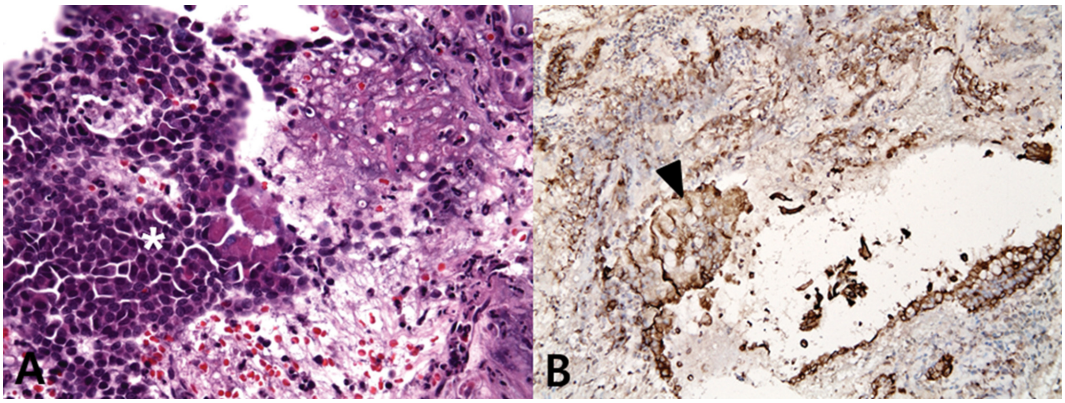

Fig 3. Histopathologic and immunohistochemical staining. Histological evaluation shows prominent epithelial proliferation (*) in a nodular pattern with infiltration of neutrophils and red blood cells (A). Cytokeratin AE1/AE3 immunohistochemistry identifies the nasal epithelial cells (B). Nasal epithelial cells are stained brown, proliferated epithelial cells (arrowhead) could be detected prominently.

(956 U/L; Normal: 15-127) and gamma-glutamyl transferase levels (12.4 mg/dl; Normal: 0-6).

Radiographic evaluation of the thorax and abdomen showed a generalized bronchointerstitial pattern with perihilar lymphadenopathy. Mild hepatomegaly and splenomegaly were detected. Abdominal ultrasonographic examination revealed irregularity of the urinary bladder wall and crystals and sludge in the urinary bladder. The gallbladder was enlarged and contained sludge. The liver showed a mild increase in echogenicity. Computed tomography of the skull showed that the nasal cavity was filled with exudates that reached into the frontal gyrus (Fig 1). There was no evidence of mass formation of the tumor. And also, any abnormalities of other visceral organs couldn't be detected in CT findings.

Nasal swab cytology was conducted to determine the cause of the nasal discharge. Cells of epithelial origin were observed with evidence of malignancy, including coarse nuclei and predominant nucleoli. Neutrophils were also identified (Fig 2). Bacteria were not found. The results of cytology suggested nasal carcinoma or autoimmune inflammation.

Rhinoscopy revealed significant exudates in the nasal cavity. To evaluate abnormalities of the nasopharyngeal space, nasal flushing was performed, followed by biopsy for a definitive diagnosis. Histopathologic examination showed irregular proliferation of epithelial cells in the form of a nodule (Fig 3). Immunohistochemical staining for cytokeratin AE1/AE3 was performed to determine if the proliferated cells originated from the epithelium. Positive staining demonstrated that the abnormal cells were derived from epithelial tissue (Fig 3). As a result of histologic evaluation, the patient was diagnosed with nasal cell carcinoma.

Surgery was not a treatment option due to the characteristics and amorphous structure of the tumor. Radiotherapy was not used in this case because it was not available at our institution, and the patient was treated with chemotherapy. Carboplatin (300 mg/m^2) was injected intravenously once every 3 weeks. The nonsteroidal drug piroxicam (0.3 mg/kg orally once daily), used as an adjunct for chemotherapy, was administered. Amoxicillin clavulanate (12.5 mg/kg orally twice daily), enrofloxacin (5 mg/kg orally twice daily), lysozyme (0.5 T/dog orally twice daily), misoprostol (5 μg/kg orally twice daily), and ursodeoxycholic acid (7.5 mg/kg orally twice daily) were prescribed. Once chemotherapy was initiated, clinical signs improved, with marked improvement in nasal discharge, respiratory stabilization, and increased vitality and appetite. Common side effects of chemotherapy, such

as digestive problems, were not detected. But signs associated with respiratory difficulty reappeared 2 weeks after the cease of chemotherapy. At first, Chemotherapy was carried out as scheduled and there were no clinical signs of respiratory distress then. However, the signs recurred when the dosing interval was extended due to issues of the owner. Although chemotherapy was conducted consistently for 11 months, follow-up treatment was not completed due to financial constraints. Despite irregular chemotherapy, evidence of metastasis has not been detected.

Discussion

Canine nasal tumors are rare and generally reported as malignant. Despite the low incidence, nasal tumors comprise a large fraction of tumors treated by veterinary oncologists (17). Forty percent of dogs with nasal tumor show evidence of metastasis to the lungs or regional lymph nodes at death. However, most patients die due to local enlargement of the tumor, rather than metastasis. Patients with metastatic disease have few signs of the disease (19). At diagnosis, 0-12% of patients show metastatic disease (1,8,10,22). Canine nasal carcinoma is generally locally invasive with early destruction of the bones (15). Treatment is mainly focused on controlling the disease associated with local invasion (1,8,10,22).

Orthovoltage radiation combined with aggressive debulking surgery of the nasal tumor has been shown to achieve survival durations of 8-23 months (23). However, domestic veterinary hospitals may not have access to radiotherapy. Furthermore, some dogs can be in the status that is impossible to undergo multiple anesthetic episodes, or cannot be suitable for treatment with radiation therapy. An alternative to radiation is therefore often necessary. Combination of systemic cisplatin chemotherapy and radiotherapy has been shown to increase the survival time in dogs with nasal tumors (6). However, in our case, we used chemotherapy alone, without radiotherapy.

Cisplatin has been used for treating nasal carcinomas (6,9). However, it has side effects related to renal toxicity (12). In this case, there was evidence of urolithiasis on ultrasonographic evaluation. So, we should consider the adverse effects of cisplatin. Recently, carboplatin, a second-generation platinum drug, was developed in order to overcome the nephrotoxicity of cisplatin. Carboplatin has a decreased potential of causing nephrotoxicity and other side effects. The antitumor effects and spectrum of carboplatin are lower and narrower than cisplatin; however, considering its safety, we used carboplatin for better quality of life of our patient. In the same reason, due to toxicity, other anti-tumor agents such as doxorubicin were not included in our chemotherapy protocol.

Piroxicam, originally used as an analgesic drug, is prescribed with carboplatin for its antitumor activity. It has been used safely with carboplatin in a combination chemotherapy protocol (3). Treatment of tumors with combination protocols results in better recovery compared to that with single agent chemotherapy. In order to eliminate the significant side effects of radiotherapy, and considering patient status, combination of carboplatin and piroxicam was selected for treatment in our patient.

In this case, combination chemotherapy of carboplatin and piroxicam resulted in improvement of clinical signs. Decreased nasal discharge, stabilization of respiration, and improvement of vitality were observed throughout the treatment, suggesting that this combination chemotherapy was efficacious in the treatment of the nasal tumor. But, the chemotherapy protocol was not completed due to the owner's financial constraints. Irregular dosing intervals and unexpected suspension of treatment made evaluation of the protocol difficult. Also, this chemotherapy was applied to only one case of nasal carcinoma. Thus, it could be too early to make conclusion or comment on potential prognosis of our chemotherapy protocol. However, this paper must be valuable in that it offers a counterplan in the treatment of nasal carcinoma without radiotherapy.

Conclusions

Radiotherapy is the most effective treatment option for nasal tumors. However, its use is complicated for several reasons. To overcome these limitations, research has been conducted on the effectiveness of other treatments for nasal carcinoma in the absence of radiotherapy. The effectiveness of using combination chemotherapy alone in the treatment of nasal carcinoma has not been previously reported. The combination chemotherapy protocol may suggest a reasonable option for veterinarians to treat nasal tumors. Therefore, through this report, our combination chemotherapy protocols provide veterinary clinicians as one of the alternative treatment options of malignant nasal tumors.

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