NOTE

Surgery

Hypertrophic Osteopathy Associated with Pulmonary Adenosquamous Carcinoma in a Dog

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ABSTRACT. A six-year-old intact female Maltese dog weighing 3.8 kg presented with a history of mild lameness and swelling on both forelimbs. Radiographic and computed tomographic views revealed an extensive periosteal reaction in all four limbs and a large round mass on the right middle lung lobe. A total lobectomy was performed and pulmonary adenosquamous carcinoma was histologically confirmed. A diagnosis of hypertrophic osteopathy (HO) secondary to a lung tumor was made. Periosteal proliferation decreased significantly after surgery; however, there was evidence of dyspnea, mass recurrence, and periosteal reaction three months post-operatively. This is the first case report of pulmonary adenosquamous carcinoma with HO in a dog in which we describe clinical, imaging, surgical, and histological findings.

KEY WORDS: canine, hypertrophic osteopathy, pulmonary adenosquamous carcinoma.


Canine pulmonary tumors, especially adenosquamous carcinoma, are rarely reported [9, 11, 13]. Pulmonary adenosquamous carcinomas coexist with adenocarcinoma and squamous cell carcinoma, and have been reported to have a poorer prognosis than single tumor types in humans [6]. The clinical signs associated with pulmonary tumors are dry cough, hemoptysis, fever, exercise intolerance, weight loss, dysphagia, and anorexia. Lameness may occur with development of hypertrophic osteopathy (HO) [7, 11, 12, 14–16]. HO is characterized by swelling of the distal long bones with a periosteal reaction and is most frequently associated with lung tumors [1, 5]. To the author’s knowledge, pulmonary adenosquamous carcinoma with HO has not been previously documented. This report describes the clinical signs, diagnosis, histologic findings, treatment, and follow-up of pulmonary adenosquamous carcinoma with HO.

A six-year-old intact female Maltese dog weighing 3.8 kg presented with a history of lameness and swelling in both forelimbs. On physical examination, the dog was depressed, reluctant to walk, and had pain on palpation of the forelimbs. The radial, carpal, metacarpal, tibial, tarsal, and metatarsal regions were firm, swollen, and thickened. A complete blood count revealed moderate leukocytosis (20.24 × 10³/µl; reference range, 6–17 × 10³/µl) and thrombocytosis (588 × 10³/µl; reference range, 200–500 × 10³/µl). Serum chemistry revealed high concentrations of alkaline phosphatase (ALP) and amylase (481 U/l and 1268 U/l, respectively, reference range; 15–127 U/l and 185–700 U/l, respectively). On thoracic radiographs, a well-defined round mass was found in the right middle lung lobe (Fig. 1A). Radiographs of all extremities revealed a periosteal reaction from the humerus and femur to phalanges, mainly on the radius and ulna (Fig. 1B and 1C). On echocardiography, a mass with a mixed echogenic pattern was located near the heart, compressing the right atrium. Computed tomography (CT) revealed a right middle lung lobe mass (30.19 × 35.05 × 35.99 mm) well circumscribed and adhered to the right thoracic wall and heart base (Fig. 2A–2C). Calcified pleural nodules were also detected in the left cranial and right caudal lung lobes (Fig. 2D and 2E). Based on these findings, a diagnosis of HO secondary to a lung tumor was made. The following day, a total lobectomy of the right middle lung lobe was performed through the fifth intercostal space. A capsulated, dark reddish, round mass was identified in the cranial portion of the right middle lung lobe (Fig. 3A) which was adhered to the right pleura, heart base, and right phrenic nerve. The mass was bluntly dissected from the thoracic wall, the cardium, and the phrenic nerve and resected; however, complete removal was not possible due to severe infiltration into the phrenic nerve. There was no evidence of pleural effusion. Histopathology revealed the resected mass to be an adenosquamous carcinoma originating from pulmonary epithelial cells composed of adenocarcinoma and squamous cell carcinoma. The area of adenocarcinoma contained irregular acinar, cuboidal, and glandular structures (Fig. 3B). The area of squamous cell carcinoma contained solid squamous epithelial tumor cells formed into well-differentiated sheets (Fig. 3C). Intravascular tumor cells were observed and blood clot was...
also identified in vessels. Immunohistochemistry for thyroid transcription factor-1 (TTF-1; M3575, clone 8G7G3/1, DakoCytomation, Glostrup, Denmark) was performed, which revealed a positive staining in the nucleus of epithelial neoplastic cells (Fig. 3D).

The day after surgery, swelling of the forelimbs decreased and pain disappeared. At 14 days after surgery, thoracic radiographs revealed that the pulmonary tumor previously occupying the right middle lung lobe had been removed (Fig. 4A) and radiographs of the distal extremities showed a significant decrease in periosteal reaction (Fig. 4B and 4C). At 48 days after surgery, a continuous decrease in periosteal reaction was evident in all four limbs and metastatic lesions were not founded. At three months after surgery, the dog presented with respiratory distress. A hyper-opaque mass was radiologically detected at the right middle and caudal lung lobes (Fig. 4D) and HO had developed in all extremities (Fig. 4E and 4F). On CT views, a recurrence

Fig. 1. Pre-operative radiologic images of the thorax (A), forelimbs (B), and hindlimbs (C). The dog’s right is on the left of all images. (A) Well-defined round mass with soft tissue opacity identified in the right middle lung lobe on ventrodorsal view. (B) Periosteal reactions are identified on the forelimbs (B) and hindlimbs (C) on anterior-posterior view.

Fig. 2. Thoracic CT scan images of the transverse view (A, D, E), sagittal view (B), and the reconstructed 3-dimentional image (C) before surgery. The dog’s right is on the left of all images. (A-C) Right middle lung lobe mass (30.19 × 35.05 × 35.99 mm) adhered to the right thoracic wall and heart base. Calcified pleural nodules (arrows) identified in the left cranial lobe (D) and right caudal lobe (E). Abbreviation; M=mass
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of a pulmonary tumor (33.7 × 42.2 × 48.04 mm) and an additional lung mass (20.2 × 20.0 × 23.98 mm) were identified in the right middle lung lobe and left caudal lobe, respectively (Fig. 5A and B). Calcified pleural nodules in the right caudal lobe and left cranial lobe had grown twice as large as before (Fig. 5C and 5D). The owner did not consent to additional surgery and the dog has since been treated conservatively with analgesics, diuretics, and antibiotics.

Adenocarcinoma is the most common histologic type of canine lung tumor, followed by squamous cell carcinoma, chondroma, fibroma, and plasmacytoma [14]. Adenosquamous carcinoma is uncommon in animals and humans [9, 13]. One study reported that histologic findings of adenosquamous carcinoma in dogs were similar to those in humans [13]. Coexistence of acinar or gland-like adenocarcinoma and nests of differentiated squamous cell carcinoma are ultrastructural features typical of adenosquamous carcinoma [13]. In humans, pulmonary adenosquamous carcinoma is classified into three types depending on the ratios of adenocarcinoma and squamous cell carcinoma [6]. In the mixed type, components are present in the same amount; in the glandular type, the adenocarcinoma component is dominant; and in the squamous type, the squamous component is dominant [6]. In this case, both the glandular and squamous components had malignant characteristics and presented in the same ratio.

HO can be a paraneoplastic syndrome and is most frequently associated with lung tumors. In a previous report, 53 of 60 dogs with HO had related pulmonary tumors [1]. Other causes of HO are pulmonary infection, congenital or acquired cardiac disease, megaesophagus, renal neoplasia, urinary bladder rhabdomyosarcoma, and prostate neoplasia [2, 4]. To the author’s knowledge, there has been no case report of HO associated with adenosquamous carcinoma in dogs.

A previous study reported that 30% of dogs with pulmonary tumors did not have clinical signs relative to the tumor [10]. In this case, the dog had clinical signs associated with HO, but no respiratory signs. Another study described an improvement in clinical signs such as swelling of the extremities and lameness within a week, and periosteal reactions disappearing within three weeks to seven months after surgery [5]. In this case, the aforementioned clinical signs improved earlier than in the previous study. Swelling of the extremities disappeared the day after surgery and periosteal reactions of all limbs improved significantly two
weeks postoperatively.

In the previous retrospective report of HO, 12 of 36 female dogs with HO had metastatic lung tumors from mammary gland tumors [2]. In this case, the possibility of pulmonary metastasis of a mammary gland tumor could not be completely excluded since the dog had had a history of surgical resection of a mammary gland tumor at a local animal clinic one year previously. However, the pulmonary mass was considered to be the primary origin because the mass showed positive staining for TTF-1 immunohistochemically. TTF-1 is expressed in follicular cells of pneumocytes and the thyroid gland [1]. In humans, TTF-1 immunohistochemistry is a sensitive and specific method in the differential diagnosis of primary and metastatic lung adenocarcinomas [1]. According to a previous report of TTF-1 immunochemical staining in canine primary or metastatic pulmonary tumors, 17 of 20 primary pulmonary carcinomas exhibited strongly positive whereas all metastatic pulmonary tumors were negative [1].

The mechanisms involved in HO have not been completely determined. Three hypotheses suggest vagal nerve stimulation, circulation shunting, and hormonal substances as being involved. Affected animals show an increase in blood flow to the extremities, resulting in new periosteal bone formation [1, 5, 8]. In this case, the tumor was not associated with the vagus nerve but had invaded into the right phrenic nerve. Anatomically, the right vagus nerve running ventral to the subclavian artery and continuing caudally along the trachea is adjacent to the right phrenic nerve [3]. At the level of the subclavian artery, the vagus nerve receives branches from the cervicothoracic ganglion which may also supply a branch to the phrenic nerve [3].
In this case, HO might have been caused by vagus nerve stimulation from the affected phrenic nerve. The tumor was separated as close as possible to the phrenic nerve during surgery; however, a small amount of the tumor remained surrounding the phrenic nerve. This small amount of mass was considered to be the reason for the recurrence of the pulmonary tumor and HO three months post-operatively.

Tumor staging is the most important predictor of survival and is determined by prognostic factors including the extent of primary tumor involvement, regional lymph node involvement, distant metastasis, histological grade, tumor size, and the presence of clinical signs [10, 12]. Depending on the tumor stage, median survival time of T1, T2, and T3 tumors are 26, 7, and 3 months, respectively [10, 12]. In this case report, the tumor was classified as T3 since it had invaded into the surrounding phrenic nerves. There was evidence of a recurrent pulmonary tumor and HO three months post-operatively. At present, the dog is alive and the survival time is currently five months.

In conclusion, this is the first case report of pulmonary adenosquamous carcinoma with HO in a dog in which we describe clinical, imaging, surgical, and histological findings.

REFERENCES


