Extramedullary Plasmacytoma in the Canine Trachea: Case Report and Literature Review

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ABSTRACT: An English mastiff with an intratracheal mass identified as an extramedullary plasmacytoma was treated successfully with surgical excision. This article describes the classification of plasma cell tumors and their relationship to multiple myelomas as well as the diagnosis, treatment, and prognosis of extramedullary plasmacytoma.

Extramedullary plasmacytomas (EMPs) are neoplasms of B lymphocytes that usually occur as a single entity at cutaneous and mucocutaneous sites but rarely in the gastrointestinal (GI) tract of dogs. Studies in dogs and humans indicate that EMPs are linked to the future development of multiple myeloma (MM).\textsuperscript{1–6} MM is rare in dogs; however, solitary and multiple EMPs have been diagnosed more frequently over the past decade.\textsuperscript{2,6–9} Approximately 80% of EMPs in humans occur in the head and neck region; 16% to 25% of these develop into MM.\textsuperscript{2,3,5,10–13} Subcutaneous EMPs are often solitary and eliminated by surgical excision. However, EMP tends to metastasize if originally found in the GI tract. Only one other report of a solitary EMP in the trachea of a dog has been published.\textsuperscript{14} This article documents the diagnosis and treatment of an EMP in the thoracic trachea of a dog and examines the relationship between EMP and MM.

CASE REPORT
A 7-year-old male English mastiff weighing 177 lb (80.45 kg) was treated for
progressive dyspnea and stridor and diagnosed with pneumonia. Treatment included oral antibiotics, antitussives, and corticosteroids for 3 weeks. Thoracic radiographs at that time were unremarkable. The dog had no other signs of systemic disease; was current on vaccinations; and tested negative for heartworms, although it was not on preventive medication. Lack of response to therapy prompted referral to the University of Tennessee Veterinary Teaching Hospital.

**Initial Examination and Diagnostic Tests**

The dog was examined at the University of Tennessee Veterinary Teaching Hospital and found to be bright, alert, and in good physical condition. The most significant physical examination finding was severe respiratory dyspnea with a loud inspiratory wheeze that radiated throughout all lung fields. The dog appeared anxious and distressed and its head was outstretched, but there was no tachypnea and respiration was normal at 36 breaths/minute. No coughing was elicited on tracheal palpation. Temperature was 99°F, and heart rate was 100 beats/minute with no murmur or arrhythmia. Femoral pulses were strong, and mucous membranes were slightly hyperemic. The dog had a clear, serous discharge from each nostril, and the oral cavity appeared normal with no sign of obstruction. Diagnostic differentials for stridor include tracheal collapse, airway obstruction (e.g., foreign body, laryngeal paralysis), elongated soft palate, everted laryngeal saccules, parasitic granuloma (e.g., *Oslerus osleri* in the trachea or bronchi), and neoplasia. Lung sounds were consistent with pneumonia, infectious or allergic bronchitis, or neoplasia.

The dog was placed on oxygen in the intensive care unit (ICU). Diagnostic tests included a complete blood cell count, serum chemistry profile, and thoracic and cervical radiography. Hematologic abnormalities included a leukocytosis with a mature neutrophilia and lymphopenia. Platelets were adequate, and total protein was slightly elevated. Other abnormalities included a slightly elevated alkaline phosphatase level, low phosphorus level, and hypercholesterolemia. These findings were consistent with a steroid hepatopathy and/or an infectious process or metabolic disorder (e.g., hypothyroidism). Thoracic radiographs revealed a 2-cm discrete, soft tissue mass within the lumen of the trachea appearing to arise from the dorsal border of the trachea at the level of the third intercostal space (Figure 1). The mass could not be definitively identified on the ventrodorsal projection. Other findings included a moderately severe, diffuse, peribronchial infiltrate throughout all lung lobes and multiple sites of spondylosis deformans in the caudal thoracic spine. Diagnostic differentials included neoplasms, abscess, and granuloma. The dog was placed in the ICU for therapy and observation, and three 50-µg/hour fentanyl patches were applied to the dorsum of its neck. Exploratory surgery was scheduled for the next day.

**Surgery**

The dog was premedicated with intramuscular acetylprocaine (0.1 mg/kg), butorphanol (0.2 mg/kg), and atropine (0.04 mg/kg). Anesthesia was induced with intravenous propofol (4 mg/kg) and maintained at 12 breaths/minute with isoflurane. Fluid therapy consisted of 885 ml/hour of a balanced electrolyte solution through a cephelic catheter. Intravenous prednisolone sodium succinate (25 mg/kg) was given for 30 minutes on induction, and intravenous cefazolin (22 mg/kg) was given every 4 hours. Such physiologic parameters as heart rate and rhythm, indirect blood pressure, pulse oximetry, and expiratory CO₂ were monitored throughout the procedure. The dog was clipped, prepared for surgery, and placed in left lateral recumbency.

The thorax was entered via a right thoracotomy into the third intercostal space. The right cranial lung lobe was retracted caudally, and the cranial border of the heart, trachea, esophagus, azygous vein, and cranial vena cava were exposed. The azygous vein was isolated and double ligated with 2-0 polydioxanone. Using blunt dissection, the trachea was freed from the overlying fascia at the level of the third rib. The mass was visible within the trachea, and two Penrose drains were placed around and on both sides of the trachea. A stay suture of 2-0 polydioxanone was placed on the dorso-lateral surface of the trachea to roll it laterally to expose the dorsal ligament (Figure 2). The dorsal ligament was incised just distal to the mass, and a sterile endotracheal tube was inserted into the distal portion of the tracheal opening to maintain positive-pressure ventilation. It was then well circumscribed within the trachea and attached to the dorsal tracheal ligament. The mass was excised from the dorsal ligament and adjacent tracheal...
rings. There was no gross evidence of deep infiltration of the mass.

A transient oxygen desaturation occurred during excision of the mass, possibly because of bronchus intubation or failure of inflation and/or an inadequate seal of the cuff of the tube. Therefore, the sterile endotracheal tube was removed from the distal tracheal opening and another endotracheal tube was inserted into the trachea via the oral cavity. The endotracheal tube extended distally past the tracheal incision, and the cuff was inflated just distal to the tracheal opening to reestablish positive-pressure ventilation. The tracheal incision was closed using 3-0 polypropylene in a simple continuous pattern. The tracheal closure was checked for leakage by filling the thoracic cavity with sterile saline and applying positive-pressure ventilation.

The pleura was closed over the trachea using 2-0 polydioxanone in a simple interrupted pattern. A thoracic drain was placed in the seventh intercostal space. The intercostal nerves were blocked with bupivacaine, and the ribs were approximated using #1 polydioxanone sutures in a circumcostal pattern. The musculature, fascia, and skin were closed routinely and the pleural space was evacuated.

Recovery

The dog remained in the ICU on oxygen for 3 days and was given intravenous cefazolin sodium (22 mg/kg) three times daily; morphine was given as needed for analgesia. For the first 24 hours after surgery, small amounts of serosanguineous fluid and air were drawn from the thoracic drain, which was then removed. The day after surgery the dog was showing signs of bradycardia and runs of five to seven multifocal, premature heartbeats. The bradycardia was treated with atropine when the heart rate dropped below 50 beats/minute. Echocardiography revealed normal contractility and chamber size.

Morphine was discontinued 24 hours after surgery, and the fentanyl patches were removed 72 hours after surgery. The incision site was clean and dry, and the dyspnea and stridor were markedly improved. The dog continued to improve and was discharged 4 days after surgery on oral antibiotics.

Cytology and Histopathology

Impression smears of the mass showed an extremely cellular, monomorphic layer of homogenous round to oval cells indicative of a tumor of plasma cell origin (Figure 3). The cells had eccentrically located nuclei and moderate to marked anisocytosis and anisokaryosis, with an increased nuclear:cytoplasm ratio. Many binucleate tumor cells and occasional mitotic figures were observed (Figure 4).

The excised 2 × 1.5–cm tumor was firm, gray, multilobular, and nonencapsulated and had a smoothly contoured surface. The mass was fixed in 10% neutral buffered formalin, routinely processed, embedded in paraffin, and sectioned at 5 µm. The sections were stained with hematoxylin and eosin, methyl green pyronin, and Congo red. The mucosal surface of the mass was ulcerated, and the submucosa was infiltrated by leukocytes (predominately neutrophils). The neoplasm consisted of dense, broad sheets of round cells separated by thin, fibrovascular septa. The round cells extended to the margin of the tissue. In some areas broader bands of connective tissue and small focal areas of necrosis segregated the tumor into irregular lobules. The neoplastic cells had indistinct borders; moderate amounts of eosinophilic, granular cytoplasm; and medium-sized, round to oval nuclei with many fine indents. The nuclei of the cells had finely stippled chromatin with one to two small basophilic nucleoli. The cells were variable in size, with two to five mitotic figures visible per high-power field, moderate numbers of binucleate cells, and an occasional multinucleated giant cell (Figure 5).
neoplastic cells were positive for methyl green pyronin, which is specific for plasma cells (Figure 6). Congo red stains were negative for the presence of amyloid within the mass.

Follow-Up

Eight weeks after surgery, the dog was anesthetized with isoflurane and a tracheoscopy was performed. The trachea appeared normal with no evidence of tumor regrowth (Figure 7). Other diagnostic tests included a bone marrow aspiration from the proximal humerus that showed normal cellularity, maturation, and morphology of its constituents. A urine sample was negative for Bence Jones proteins. Total serum protein was 5.7 µg/dl, and serum electrophoresis showed no evidence of a monoclonal gammopathy. The dog remained symptom-free for 18 months after the original surgery.

DISCUSSION

Primary Tumors of the Trachea

Primary tumors of the trachea are rare in dogs.\(^{15-17}\) Chondromas, osteosarcomas, mast cell tumors, squamous cell carcinomas, adenocarcinomas, and leiomyomas are known to occur.\(^{15,17,18}\) Prognosis for most benign tracheal tumors is excellent because resection and anastomosis is usually curative.\(^{15,18}\) A solitary EMP of the trachea has been reported twice in the veterinary literature.\(^{14}\) There have also been reports of tracheal involvement in cases of multiple tumors in patients with MM.\(^{6,19}\) EMPs are neoplasms of mature B lymphocytes that have undergone an early stem cell change, which usually occurs without other bone marrow involvement.\(^{1,11,20-25}\)

Classification of Neoplasms of B-Lymphocyte Proliferation

Neoplasms of B-lymphocyte proliferation are classified into three broad categories based on their distribution and clinical signs. The most common category in humans is MM, which is characterized by diffuse plasma cell proliferation with bone marrow involvement and affects several organ systems. Although less common, plasma cell proliferation can occur alone either in the bone marrow or as primary tumors in outside sites (EMP).\(^{1,11,13,20-22,24}\) EMPs tend to stay localized and rarely metastasize to bone. Solitary bony plasma cell tumors tend to spread rapidly and ultimately result in the generalized disease associated with MM.\(^{3,5,19,22}\)

Characteristics of Extramedullary Plasmacytomas

In small animals, EMPs arise most frequently from such cutaneous and mucocutaneous sites as the mouth, feet, trunk, or ears and appear less commonly in the esophagus, stomach, rectum, and oral mucosa.\(^{5,9,11,12,21,25,26}\) EMPs rarely occur in the lungs, spleen, kidneys, spinal canal, or sinonasal cavity and its orbit.\(^{21,27-29}\) Clinical signs depend on the region affected: Cutaneous EMP is rarely associated with systemic signs, but GI EMP can cause vomiting, rectal prolapse, tenesmus, and hematochezia.\(^{21,26,27}\) Unlike MM, EMP is rarely associated with paraneoplastic syndromes.\(^{2}\) The incidence of EMP is unknown because it may be misdiagnosed as another type of poorly differentiated neoplasm, such as a reticulum cell sarcoma, cutaneous lymphoma, or neuroendocrine tumor.\(^{2,6,8,9}\) Reticulum cell sarcoma is a dated term; originally used when the cell of origin was unknown, it was often used to refer to a mucocutaneous tumor as a variant of cutaneous lymphosarcoma.\(^{6}\)

Extramedullary plasmacytomas found in such cutaneous sites as the oral cavity and digits are often eliminated by excision alone, and metastasis is uncommon.\(^{2,3,30,31}\) One study of 56 dogs showed that 70% of mucocutaneous plasmacytomas had not recurred 1 year after excision.\(^{6}\) EMPs appear to be more common in 9- and 10-year-old dogs with no sex predilection, but
some reports indicate an increased incidence in cocker spaniels and Airedale terriers.\textsuperscript{5,6,7,30} In dogs, metastasis is more likely to occur in GI EMP and spread to regional lymph nodes.\textsuperscript{12,20,21,27,32} In humans, 80\% to 82\% of EMPs occur in the subepithelial tissue of the paranasal sinuses, oropharynx, and upper airways.\textsuperscript{5,8,11,13,19} They have also been reported in the lungs, spleen, urethra, vagina, thyroid, tonsils, pulmonary bronchi, breasts, testes, parotid gland, small intestine, dura mater, tentorium, and sinonasal cavity.\textsuperscript{13,20,21,28} Men are three times more likely to develop EMP than are women, and the majority of patients are diagnosed at 40 to 70 years of age.\textsuperscript{13,19} Metastasis in humans can occur in the spleen, liver, and lymph nodes, and subcutaneous sites may occasionally represent metastatic lesions with an unknown primary site.\textsuperscript{5,13}

Extramedullary Plasmacytoma and Multiple Myeloma

Multiple myeloma reportedly develops in 18\% of humans with EMP.\textsuperscript{5} MM has developed in dogs after the diagnosis of a solitary EMP.\textsuperscript{4,6} The incidence of recurrence in animals is much lower than in humans, of whom 12\% to 25\% develop MM up to 10 years after the initial diagnosis of solitary EMP.\textsuperscript{1,3,7,10,13} Whether EMP is a separate disease process or an early sign of MM has been debated.\textsuperscript{1,3,6} The majority of EMPs of the skin and mucocutaneous junction of dogs are benign neoplasms, but there are reports of MM developing concurrently or later. Dogs occasionally have multiple EMPs, which can also develop into MM.\textsuperscript{5,6,8}

In the case reported here, it was concluded that the plasmacytoma was a single, primary tumor because of a lack of clinical signs and hematologic abnormalities commonly associated with MM. Clinical signs of MM include general lethargy and anorexia; ocular changes associated with hyperviscosity, including retinal hemorrhages and detachment; neurologic abnormalities, including paresis; and musculoskeletal signs, including bone pain, lameness, and pathologic fracture. Clinical pathology often reveals hypercalcemia, hyperproteinemia, hyperviscosity, anemia, renal failure, and thrombocytopenia.\textsuperscript{20–23,33}

The relationship between EMP and MM is unclear. A diagnosis of MM is made when two or more of the following criteria exist: lytic bone lesions and associated symptoms; Bence Jones (light chain) proteinuria; hyperproteinemia with a monoclonal gammopathy; or the discovery of neoplastic cells during bone marrow examination.\textsuperscript{1,20–23,29,33} The dog in this case showed no signs of these abnormalities. A low or normal total protein level without a monoclonal spike can occur in primary EMP before MM is clinically evident. EMP has been known to cause a monoclonal spike, which resolved when the tumor was excised.\textsuperscript{11} Therefore, it is possible that the dog in this case could have had a gammopathy before tumor excision; however, it is thought that localized EMPs rarely generate a measurable amount of myeloma protein.\textsuperscript{6,8}

Figure 6—The cytoplasm of the neoplastic cells in this plasmacytoma was moderately to strongly positive for pyronin. Occasional positive cells have a perinuclear clear zone (arrow) consistent with the Golgi apparatus (methyl green pyronin, original magnification ×660).

Figure 7—Tracheoscopy of the tumor site 2 months after surgery. The blue streaks are the polypropylene sutures used to close the dorsal incision. There was no tumor recurrence at the excision site (arrow).

Classification

Canine EMP is often graded according to the extent of cellular differentiation. Grades help to indicate the biologic behavior of the tumor. Grade I tumors have over 70\% well-differentiated plasma cells, grade II tumors have 30\% to 70\% poorly differentiated plasma cells, and grade III tumors have more than 70\% poorly differentiated plasma cells.\textsuperscript{7,24} Binucleate and multinucleate neoplastic cells are common in tumors of each histologic grade. Grade II is the most common at any anatomic site previously reported.\textsuperscript{7} In this case, the tumor would be classified as a high grade II. Another proposed classification system for EMP consists of five types characterized by differentiation of the plasma cells as well as nuclear morphology.\textsuperscript{34}

Diagnosis

Although previously misdiagnosed as reticulum cell sar-
coma and cutaneous lymphoma, EMP is currently more likely to be misdiagnosed as a neuroendocrine tumor. In cases of poorly differentiated plasmacytic tumors, special stains, such as thioflavine T, and immunohistochemistry, which detects immunoglobulin light and heavy chains, may help differentiate EMPs from other round cell tumors. "The cytologic and histopathologic findings are consistent with a round cell tumor, and the special staining techniques (e.g., methyl green pyronin) identify the tumor as plasma cell in origin."

The cytologic and histopathologic findings are consistent with a round cell tumor, and the special staining techniques (e.g., methyl green pyronin) identify the tumor as plasma cell in origin. Myeloma cells contain high levels of RNA—approximately six times more than unstimulated lymphocytes contain. Normal plasma cell characteristics found in the tumor in the case reported here, such as the light gray-blue cytoplasm with a perinuclear clear zone indicative of the Golgi apparatus, are indicative of a tumor of plasma cell origin.

Amyloid is found in approximately 10% of canine EMPs, and canine EMPs with amyloid recur more commonly at the site of surgical excision than do those without amyloid. Amyloid fibrils often contain portions of immunoglobulin light chains. It has been proposed that amyloid in EMP is caused by the enzymatic degradation of Bence Jones proteins. The expression of mainly light chain monoclonality in plasma cell infiltrates indicates their neoplastic nature, although production of intracellular immunoglobulin is not always found.

Treatment

Treatment of EMPs and other plasma cell dyscrasias often requires various combinations of immunosuppressive and cytotoxic drugs, including corticosteroids, chlorambucil, melphalan, and cyclophosphamide. The efficacy of chemotherapy is questionable because of reports of additional EMP development during treatment. Some dogs with MM have gone into complete remission after treatment with a combination of these drugs. In two studies, dogs with both diffuse and solitary EMPs were free of clinical signs 30 and 33 months after therapy, respectively. Although not always curative, chemotherapy significantly prolongs survival time in dogs.

Plasmacytomas are highly radiosensitive, and radiation has been curative in a high percentage of human patients with tumors of the upper respiratory and digestive tracts, especially when combined with complete excision. Unlike MM, EMPs have responded to a single course of radiotherapy. Solitary plasmacytomas respond well to moderate doses of radiation therapy. A dose of 4000 cGy has been found to control 95% of these tumors in humans. Radiation volume should include the entire bone and tissue involved, with a 2- to 3-cm margin of normal tissue. Primary draining lymph nodes should be examined and radiated if diseased.
Surgical excision is often curative for tracheal masses. In the case reported here, a right thoracotomy was performed to maximize exposure of the section of trachea containing the mass. If a left thoracotomy had been performed, the ascending aorta would have obstructed the site. A medial sternotomy could have been attempted, but exposure would have been limited by the cranial vena cava. The preoperative plan of complete tracheal resection became impossible because of limited exposure at the site due to the dog’s size, the depth of the surgical site, and the declining oxygen saturation. Local recurrences of EMP have been encountered when the initial surgical margins are not free of neoplastic cells. In these instances, follow-up treatment with chemotherapeutic agents is sometimes effective but recurrent tumors are occasionally more locally invasive and difficult to treat than are initial tumors. Distal recurrences have been observed, and there have been reports of spontaneous regression. In the case reported here, tracheoscopy showed no evidence of regrowth at 2 months and the dog remained asymptomatic 1 year later.

**CONCLUSION**

This case demonstrates the rare occurrence of an EMP in the trachea of a dog. Canine EMP is a round cell tumor that is usually a benign neoplasm cured by surgical excision. Although a definitive correlation has been reported in the literature, the relationship between EMP and MM is still questioned. Local recurrence of EMP and involvement of distant sites can occur and are more common when the EMP is in the GI tract. Because only one other case of solitary EMP of the trachea has been published, a prognosis for long-term survival is difficult to make. The prognosis was favorable in the case reported here because amyloid was absent in the tumor, tracheoscopy at 8 weeks showed no evidence of tumor regrowth, and clinical signs had not recurred 1 year later.

**REFERENCES**


1. EMP can be characterized as a
   a. multicentric form of lymphoma.
   b. single neoplasm of B-lymphocyte origin.
   c. single neoplasm of T-lymphocyte origin.
   d. solitary, malignant lymphoma.

2. Which of the following is not a typical neoplasm of the trachea?
   a. chondroma
   b. epithelioma
   c. osteosarcoma
   d. leiomyoma

3. EMPs are most likely to metastasize if found in the
   a. eyes.
   b. skin.
   c. GI tract.
   d. trachea.

4. ________ is a clinical sign of EMP of the trachea.
   a. Moist rales
   b. Expiratory crackles
   c. Inspiratory stridor
   d. all of the above

5. EMP can be histopathologically differentiated from other round cell tumors by
   a. methyl green pyronin.
   b. immunocytochemistry.
   c. thioflavine T.
   d. all of the above

6. Amyloid in the presence of EMP signifies
   a. concurrent renal disease.
   b. a possible link to MM.
   c. an increased incidence of local immunologic reaction at the tumor site.
   d. an increased association with a monoclonal gammopathy.

7. MM can be definitively diagnosed via
   a. physical signs and ocular examination.
   b. Bence Jones proteinuria, radiographs, and bone marrow aspirate.
   c. radiographs and physical examination.
   d. hyperproteinemia with polyclonal gammopathy.

8. The most effective adjunctive treatment for EMP is
   a. cryotherapy.
   b. radiation therapy.
   c. melphalan and cyclophosphamide.
   d. immunotherapy.

9. Round cell tumors that have been known to progress to MM include
   a. EMP and solitary plasma cell tumors of the bone.
   b. T-cell lymphomas.
   c. plasma cell sarcomas.
   d. b and c

10. Which of the following statements regarding EMP is false?
    a. Cutaneous EMP is associated with local pain, pruritus, and excoriation.
    b. EMP commonly arises from mucocutaneous sites.
    c. GI EMP can be associated with vomiting, tenesmus, and hematochezia.
    d. EMP is rarely associated with paraneoplastic syndromes.