Primary nodal hemangiosarcoma in four dogs

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CASE DESCRIPTION
4 dogs with a slow-growing mass in the cervical region were evaluated.

CLINICAL FINDINGS
All dogs had no clinical signs at the time of the evaluation. There was no apparent evidence of visceral metastases or other primary tumor based on available CT or MRI data for any dog.

TREATMENT AND OUTCOME
For each dog, surgery to remove the mass was performed. Histologic examination of the excised tissue revealed a completely excised grade 1 or 2 lymph node hemangiosarcoma. All dogs received adjuvant chemotherapy; 2 dogs underwent curative intent chemotherapy, 1 dog underwent metronomic treatment with cyclophosphamide, and 1 dog underwent metronomic treatment with chlorambucil. The survival time was 259 days in 1 dog; 3 dogs were still alive 615, 399, and 365 days after surgery.

CLINICAL RELEVANCE
Primary nodal hemangiosarcoma in dogs is a rare and, to the authors' knowledge, previously undescribed disease that appears to develop in the cervical lymph nodes as a slow-growing mass or masses. Surgical excision and adjunct treatment resulted in long survival times for 3 of the 4 dogs of the present report. Given the aggressive biologic behavior of hemangiosarcomas in other body locations, adjunct chemotherapy should be considered for affected dogs, although its role in the cases described in this report was unclear. Additional clinical information is required to further characterize the biologic behavior of this tumor type and determine the expected survival times and associated risk factors in dogs. (*J Am Vet Med Assoc* 2016;249:1053–1060)

A 7-year-old neutered male Schnauzer (dog 1) weighing 11.5 kg (25.3 lb) was evaluated because of an 8-week history of a slow-growing mass in the left cervical region. The mass measured 4.5 X 2.5 X 2 cm at this time. The dog appeared otherwise clinically normal. Hematologic and serum biochemical analyses and urinalysis were performed but revealed no notable abnormalities. Three-view thoracic radiography revealed no radiographically detectable evidence of pulmonary metastases. Gross abnormalities were not identified via abdominal ultrasonography. There were no echocardiographic signs of an atrial mass, and cardiac function was considered normal.

Surgery was performed to remove the mass (day 0). Histologic examination of the excised tissue was performed, and the following characteristics were assessed: overall differentiation, nuclear pleomorphism, amount of necrosis, number of mitotic figures/10 hpf (X400 [mitotic count][1]), plexiform vascularization, retention of lymph node architecture, completeness of margins, and other features. A tumor grade was assigned to the mass on the basis of a published scoring system.[2] A score was determined for the tumor with regard to overall differentiation (1 = a well-differentiated tumor with numerous, irregular vascular channels; 2 = a moderately differentiated tumor with well-defined vascular channels in ≥ 50% of the tissue; and 3 = a poorly differentiated tumor composed mostly of solid sheets of cells with few vascular channels), nuclear pleomorphism (0 = none [no difference in size and shape of nuclei], 1 = mild [minimal variation in size and shape of nuclei], 2 = moderate [moderate degree of variation in size and shape of nuclei with less than a 2-fold difference in nuclear size], and 3 = marked pleomorphism [substantial or marked degree of variation, often with a ≥ 2-fold difference in nuclear size]), amount of necrosis (0 = none; 1 = < 25%; 2 = 25% to 50%; and 3 = > 50%), and mitotic count (0 = 5 to 10 mitoses; 1 = 11 to 20 mitoses; 2 = 21 to 30 mitoses; and 3 = > 30 mitoses). A total score for the tumor was calculated by summation of the scores for each of the aforementioned criteria and used to assign a grade to the tumor. A total score of 0 to 5 was designated as grade 1, a total score of 6 to 9 was designated as grade 2, and a total score of 10 to 12 was designated as grade 3. For dog 1, histologic assessment revealed a completely excised (< 0.2-mm-wide margins) grade 2 nodal hemangiosarcoma; lymph node architecture was evident in approximately 20% of the specimen with extensive areas of the node affected by plexiform vascularization **(Table 1; Figure 1)**.

Thirty-three days after surgery, findings of a physical examination were unremarkable. The surgery site was healed with no evidence of tumor recurrence upon palpation. With the dog positioned in sternal recumbency, CT images of the neck, thorax, and abdomen were

ABBREVIATIONS
VCOG Veterinary Cooperative Oncology Group

Table 1—Summary of histopathologic features of primary nodal hemangiosarcomas excised from 4 dogs that were initially evaluated because of a slow-growing mass in the cervical region.

Dog	Overall differentiation	Nuclear pleomorphism	Mitotic count	Necrosis (%)	Total score	Tumor grade	Plexiform vascularization	Retention of lymph node architecture (%)	Depth of complete margins (mm)	Other features
1	Moderate	Marked	13	< 25	7	2	Yes, extensive	20	< 0.2	Extensive thrombosis
2	Poor	Moderate	21	< 25	8	2	Yes, small foci	10	< 0.2	Extensive hemorrhage
3	Poor	Moderate	5	< 25	6	2	Yes, some	60	< 0.2	Patches of hemorrhage
4	Well	Mild to moderate	3	< 25	4 to 5	1	Yes, some	10	0.5	Some areas of plexiform vascularization had progressed into a well-differentiated hemangiosarcoma

On the basis of a published scheme,[2] each tumor was assessed for the following characteristics: overall differentiation, nuclear pleomorphism, amount of necrosis, number of mitotic figures/10 hpf (X400 [mitotic count][1]), plexiform vascularization, retention of lymph node architecture, completeness of margins, and other features. A tumor grade was assigned to the mass on the basis of a published scoring system. A score was determined for the tumor with regard to overall differentiation (1 = a well-differentiated tumor with numerous, irregular vascular channels; 2 = a moderately differentiated tumor with well-defined vascular channels in ≥ 50% of the tissue; and 3 = a poorly differentiated tumor composed mostly of solid sheets of cells with few vascular channels), nuclear pleomorphism (0 = none [no difference in size and shape of nuclei], 1 = mild [minimal variation in size and shape of nuclei], 2 = moderate [moderate degree of variation in size and shape of nuclei with less than a 2-fold difference in nuclear size], and 3 = marked pleomorphism [substantial or marked degree of variation, often with a 2-fold difference {or greater} in nuclear size]), amount of necrosis (0 = none, 1 = < 25%, 2 = 25% to 50%, and 3 = > 50%), and mitotic count (0 = 5 to 10 mitoses, 1 = 11 to 20 mitoses, 2 = 21 to 30 mitoses, and 3 = > 30 mitoses). A total score for the tumor was calculated by summation of the scores for each of the aforementioned criteria and used to assign a grade to the tumor.

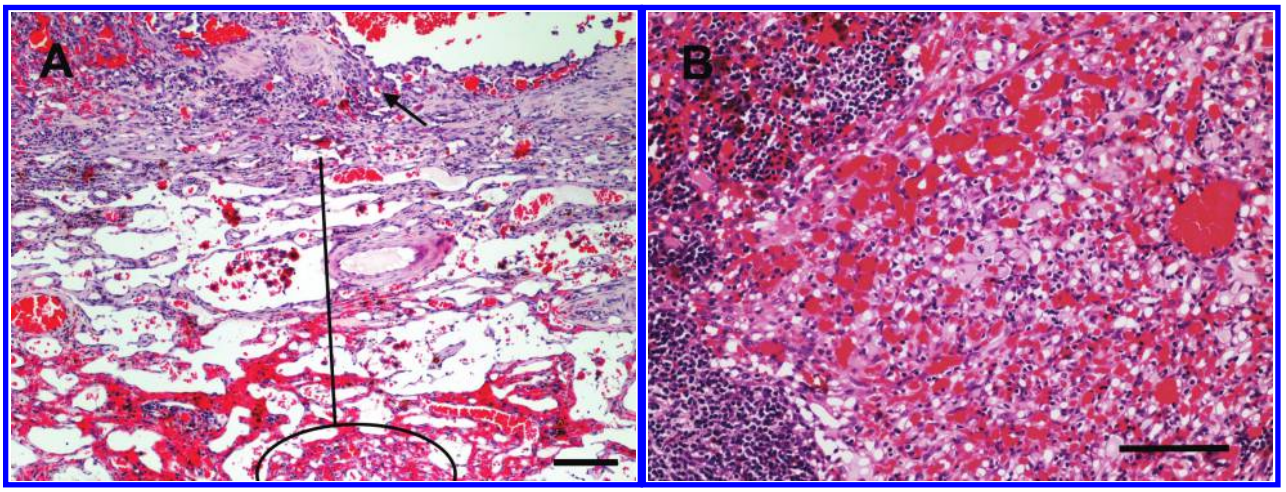

Figure 1—Photomicrographs of sections of the left cervical lymph node excised from a Schnauzer (dog 1) that was evaluated because of an 8-week history of a slow-growing mass in the left cervical region. A—In this section, plexiform vascularization is apparent as a network of capillary-like vascular channels (outlined) that transition to a hemangiosarcoma (arrow); between those areas is a loose irregular network of occasionally anastomosing vascular channels (solid line). H&E stain; bar = 250 µm. B—In this section, plexiform vascularization is apparent as a network of capillary-like vascular channels that expands the cortex of the lymph node (left side). H&E stain; bar = 250 µm.

obtained before and after administration of contrast medium. Contrast tomography revealed no evidence of residual local, pulmonary, or abdominal disease.

On day 56, adjuvant chemotherapy and concurrent antiangiogenic treatment were commenced. Chemotherapy consisted of doxorubicin (30 mg/m^2, IV) alternated every 3 weeks with lomustine (50 mg/m^2, PO). Antiangiogenic treatment consisted of piroxicam (0.3 mg/kg [0.136 mg/lb], PO, q 24 h), doxycycline (5 mg/kg [2.27 mg/lb], PO, q 12 h), and tamoxifen (1 mg/kg [0.45 mg/lb], PO, q 24 h). Prophylactic treatment with sulfadiazine-trimethoprim was administered at a dosage of 15 mg/kg (6.8 mg/lb), PO, twice daily for 14 days with each cycle of doxorubicin chemotherapy and after the first cycle of lomustine chemotherapy only. S-adenosyl methionine administration was recommended with lomustine chemotherapy but declined by the owners. Dog 1 tolerated chemotherapy well with only VCOG grade 1 hematologic toxicosis after lomustine chemotherapy.[3] There were no dose reductions or dose delays, and a single episode of emesis occurred immediately after the first dose of piroxicam. Misoprostol (5 µg/kg, PO, q 12 h) was thereafter administered concurrently with piroxicam, and no further gastrointestinal toxic effects developed.

Dog 1 was scheduled for 5 cycles of alternating doxorubicin chemotherapy and lomustine chemotherapy every 3 weeks; however, it received a total of 3 cycles of doxorubicin chemotherapy and 2 cycles of lomustine chemotherapy because 3 days after receiving the third scheduled doxorubicin treatment (day 149), the dog became acutely weak with pale mucous membranes. Abdominal ultrasonography revealed a large heteroechoic splenic lesion. Three-view thoracic radiography did not reveal any evidence of pulmonary metastases. During exploratory laparotomy, a 15-cm-diameter bleeding splenic mass was identified. The remainder of the abdominal viscera, including the liver, appeared normal. Splenectomy was performed, and histologic examina-

tion of the affected tissue revealed splenic hemangiosarcoma (moderate pleomorphism and mitotic count of 11). Additional administration of chemotherapeutic agents was declined by the owners, but antiangiogenic treatment was continued. On day 259, the dog became acutely weak with pale mucous membranes. Abdominal ultrasonography revealed free peritoneal fluid, which was presumed to be blood. There were no obvious mass lesions in the abdomen. The dog was euthanized with pentobarbital sodium solution (500 mg/kg, IV) at the owners' request. Necropsy was not performed.

A 12-year-old spayed female Maltese (dog 2) weighing 6.8 kg (14.96 lb) was evaluated for removal of a cutaneous lesion. At the time of surgery, an approximately 3-cm-diameter mass was palpated in the right cervical region. An incisional wedge biopsy was performed; histologic examination of the specimen revealed nodal hemangiosarcoma. Three-view thoracic radiography revealed no radiographic detectable evidence of pulmonary metastases. Abdominal ultrasonography revealed mild hepatomegaly with diffuse hyperechoic and heterogeneous echotexture throughout the liver parenchyma. Fine-needle aspirate specimens of the liver were obtained; microscopic examination of the specimens revealed hepatocytes of normal appearance with no evidence of neoplasia. No notable abnormalities were identified by hematologic and serum biochemical analyses. During the following 8 weeks, the neck mass continued to slowly grow. The dog appeared otherwise normal with no clinical signs.

Dog 2 was referred for further evaluation. Physical examination findings were unremarkable except for a 4.0 X 2.5 X 1.5-cm mass in the right cervical region **(Figure 2)** and a grade 2/6 left systolic heart murmur. With the dog positioned in sternal recumbency, CT images of the neck and thorax were obtained before and after administration of contrast medium. There was no macroscopic evidence of metastatic disease. In the right cranial cervical region (in the expected location of the right retropharyngeal lymph node), there was a 3.3 X 2.3 X 2.1-cm soft tissue attenuating mass with irregular shape and rounded contours that displaced the trachea and the larynx medially to the left, the mandibular salivary gland laterally to the right, and the right thyroid gland lobe and right common carotid artery ventrally. Following contrast medium administration, the mass was heterogeneously enhanced **(Figure 3)**. Surgery was performed to remove the mass (day 0). Histologic

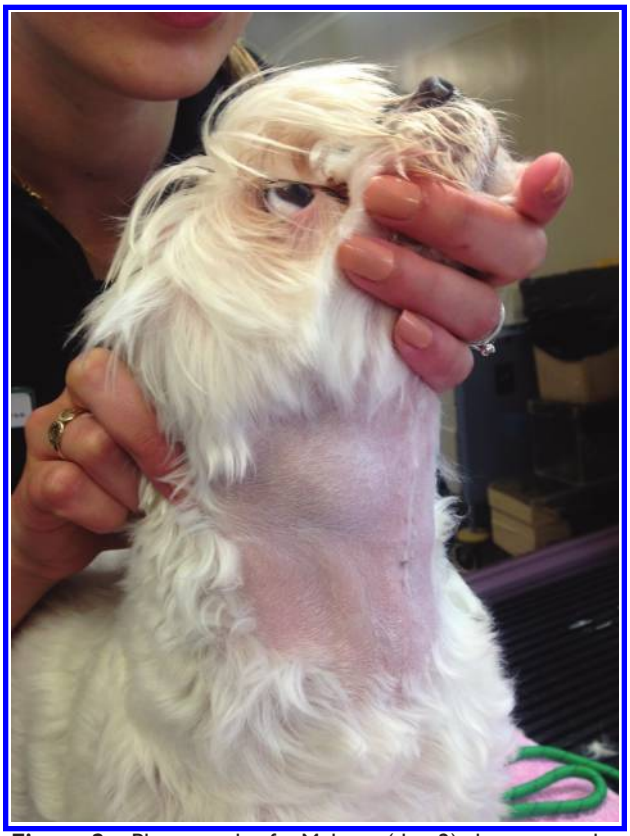

Figure 2—Photograph of a Maltese (dog 2) that was evaluated for removal of a cutaneous lesion. A 4 X 2.5 X 1.5-cm mass is present in the right cervical region. The surgical scar located cranial to the mass is the site of a wedge biopsy performed previously.

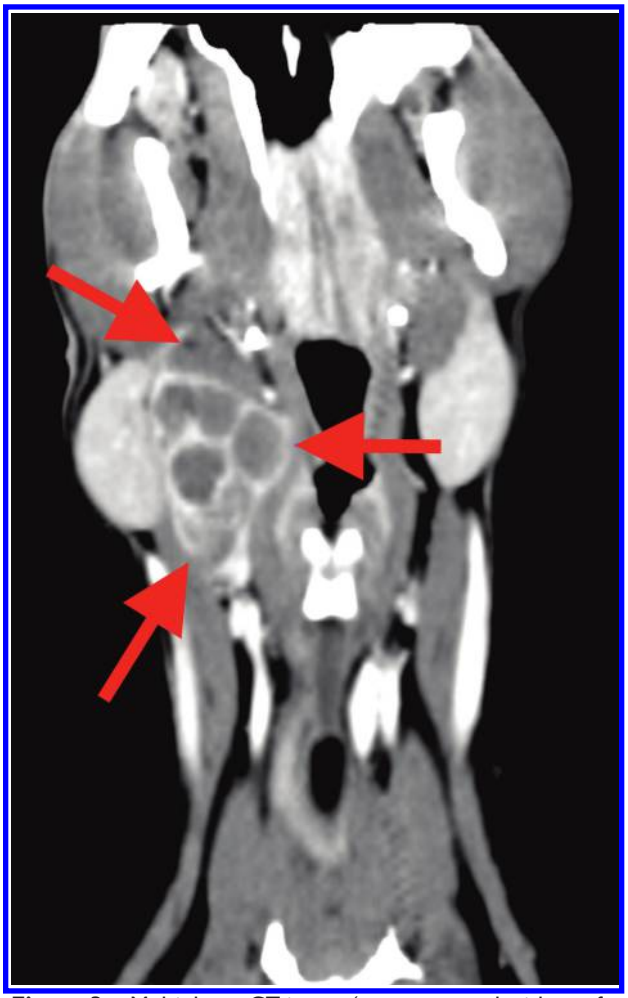

Figure 3—Multiplanar CT image (reconstructed with a soft-tissue algorithm in the dorsal plane) of the neck and thorax of dog 2 obtained after administration of contrast medium. Notice the large heterogeneously enhanced soft tissue mass within the right retropharyngeal region (arrows). The right mandibular salivary gland is displaced laterally by the mass.

examination and grading (by use of the scheme described for dog 1) of the excised tissue revealed a completely excised (< 0.2-mm-wide margins) grade 2 nodal hemangiosarcoma; lymph node architecture was evident in approximately 10% of the specimen with small foci of the node affected by plexiform vascularization (Table 1).

On day 43, adjuvant chemotherapy and concurrent antiangiogenic treatment were commenced. Dog 2 was scheduled for 5 cycles of alternating mitoxantrone hydrochloride chemotherapy (5.5 mg/m^2, IV [treatment selected because of a perceived risk of exacerbating subclinical cardiac disease]) and lomustine (50 mg/m^2, PO) chemotherapy every 3 weeks. After 3 cycles of mitoxantrone chemotherapy and lomustine chemotherapy alternated at 3-week intervals, the dog's serum alanine aminotransferase activity was more than 3 times the upper reference limit; the dog received another 2 cycles of mitoxantrone chemotherapy but no additional lomustine chemotherapy. Antiangiogenic treatment involved administration of doxycycline (5 mg/kg, PO, q 12 h) and tamoxifen (1 mg/kg, PO, q 24 h). Treatment with piroxicam was suggested but declined by the owners for unknown reasons. Prophylactic treatment with sulfadiazine-trimethoprim was administered at a dosage of 15 mg/kg, PO, twice daily for 14 days after the first mitoxantrone cycle and then again after the first lomustine cycle. S-adenosyl methionine (30 mg/kg [13.6 mg/lb], PO) was administered daily for 14 days after each lomustine chemotherapy cycle. The dog tolerated both adjuvant chemotherapy and concurrent antiangiogenic treatment, with no documented hematologic or gastrointestinal toxic effects.

Following completion of adjuvant chemotherapy, metronomic administration of cyclophosphamide and continuation of antiangiogenic treatment (doxycycline and tamoxifen) were recommended, but the owners elected to discontinue all treatments owing to inconveniences with administering oral medications at home. At 210 days after surgery, 3-view thoracic radiography revealed no evidence of pulmonary metastases. On day 615, dog 2 was still alive with no clinical signs and there was no evidence of tumor recurrence or metastasis on physical examination.

A 9-year-old spayed female pit bull–type cross (dog 3) weighing 17.5 kg (38.5 lb) was evaluated because of a 4-month history of stertorous breathing and snoring. On physical examination, the dog had a 3.5-cm-diameter mass in the left retropharyngeal region and a grade 2/6 left systolic heart murmur. Ultrasonography of the mass revealed a vascularized mass, which was presumed to originate from the thyroid gland. A CBC, serum biochemical analysis, and assessment of blood electrolyte concentrations were performed and revealed no notable abnormalities. Three-view thoracic radiography revealed no radiographic detectable evidence of pulmonary metastases. Echocardiography revealed mild myxomatous degeneration of the mitral, aortic, and tricuspid valves but no evidence of an atrial mass lesion. With the dog positioned in dorsal recumbency, MRI images of the head and neck were obtained before and after administration of contrast medium. In the region of the left retropharyngeal lymph node and medial to the left carotid artery, there was a large (4.6 × 3.2 × 3.3-cm) mass with a heterogeneous signal intensity mass **(Figure 4)**. The mass was predominantly hyperintense, compared with muscle, and isointense, compared with the mandibular salivary gland, on T1-weighted, proton density–weighted images; it had heterogeneous signal intensity on T2-weighted images. The mass was associated with a susceptibility artifact on the gradient echo images, which was consistent with the paramagnetic effects of blood within the lesion. Fine-needle aspirate specimens of the mass were obtained; microscopic examination of the specimens revealed pleomorphic round to ovoid cells (neuroendocrine appearance) thought to be consistent with thyroid gland neoplasia. A planar scintigraphic scan (with technetium Tc 99m pertechnetate) of the thyroid gland was performed and revealed bilateral and slightly asymmetric radionuclide uptake (left more than right) in normal-sized thyroid lobes. There was a subtle diffuse and poorly marginated increase in radionuclide distribution within the left retropharyngeal region indicative of increased vascularity. These findings suggested that the left retropharyngeal mass was unlikely to be a thyroid gland cancer.

Surgery was performed (day 0), and 2 closely associated masses were removed from the left retropharyngeal region. Histologic examination revealed that the larger mass was an incompletely resected chemo-

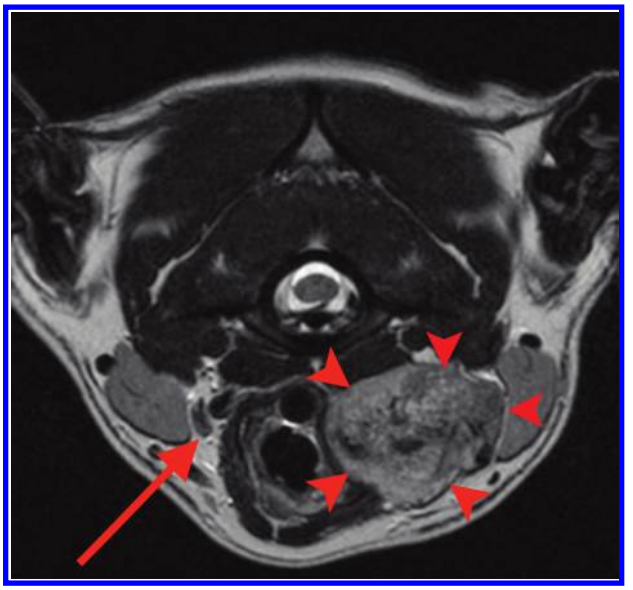

Figure 4—Transverse T2-weighted MRI image of the head and neck of a pit bull–type cross (dog 3) that was evaluated because of a 4-month history of stertorous breathing and snoring. Notice that the right retropharyngeal lymph node is of normal size (arrow) and there is a heterogeneously intense mass lesion in the expected location of the left retropharyngeal lymph node (arrowheads).

dectoma. The smaller mass was a completely excised (< 0.2 mm-wide margins) grade 2 nodal hemangiosarcoma (graded by use of the scheme described for dog 1); lymph node architecture was evident in approximately 60% of the specimen with some areas of the node affected by plexiform vascularization (Table 1; **Figure 5**).

The day following surgery, dog 3 developed a fever and increased respiratory effort. Thoracic radiography revealed evidence of megaesophagus and aspiration pneumonia in the right caudal lung lobe. The dog also developed Horner syndrome in the left eye. The dog was examined on day 14 and, with the exception of mild weight loss and a few episodes of regurgitation and inappetence, was doing well. Metronomic treatment with cyclophosphamide (15 mg/m^2, PO, q 24 h), furosemide (1 mg/kg, PO, q 24 h), and doxycycline (5 mg/kg, PO, q 24 h) were started. Two weeks later, the dog was reexamined because of persistent regurgitation, weight loss, and poor appetite. The decision was then made to place a percutaneous endoscopic gastrostomy tube. One month later, the dog resumed metronomic treatment with cyclophosphamide, furosemide, and doxycycline. Once the dog's clinical signs revolved 2 months after surgery, piroxicam (0.3 mg/kg, PO, q 24 h) was added to the treatment regimen. The percutaneous endoscopic gastrostomy tube was removed 4 months (day 120) after surgery.

For dog 3, initial monitoring involved monthly CBCs, and findings were unremarkable. Hematologic and serum biochemical analyses were performed every 3 months, and results were unremarkable. The dog underwent 3-view thoracic radiography and abdominal ultrasonography on day 336, and there was no evidence of metastases. On day 399, the dog was still alive with no clinical signs and there was no evidence of tumor recurrence or spread on physical examination.

A 5-year-old spayed female Bernese Mountain Dog (dog 4) weighing 49.5 kg (108.9 lb) was evaluated because of a 3-month history of a slow-growing mass in the region of the right mandibular lymph node. The mass measured 5.5 cm (length) × 4.5 cm (width). The dog was otherwise clinically normal. Fine-needle aspirate specimens of the mass were obtained; microscopic examination findings were nondiagnostic (RBCs only). Hematologic and serum biochemical analyses and urinalysis revealed no notable abnormalities.

With the dog positioned in sternal recumbency, CT images of the head, thorax, and abdomen were obtained before and after administration of contrast medium. In the region of the right mandibular lymph node, there was a 6.0 × 4.4 × 2.4-cm heterogeneous, hypoattenuating, mildly contrast-enhancing soft tissue mass. Incidentally, a 3 × 8 × 5-mm mass in the right ear canal and enlarged retropharyngeal and cranial mediastinal lymph nodes (measuring 0.9 × 0.4 × 0.2 cm and 1.0 × 0.9 × 1.6 cm, respectively) were identified. There were no oral cavity lesions and no evidence of visceral metastases.

Surgery to remove the cervical masses (mandibular and superficial retropharyngeal lymph nodes) was performed (day 0). For both sites, histologic examination, grading (by use of the scheme described for dog 1), and immunohistochemical analysis (for CD31) of the excised tissues revealed completely excised (0.5-mm margins) grade 1 nodal hemangiosarcomas; lymph node architecture was evident in approximately 10% of each specimen, with some areas of the node affected by plexiform vascularization (Table 1).

Because no other primary tumor was identified in dog 4, a diagnosis of nodal hemangiosarcoma of the right cervical (mandibular and superficial retropharyngeal) lymph nodes was suspected, with possible involvement of other deeper retropharyngeal and

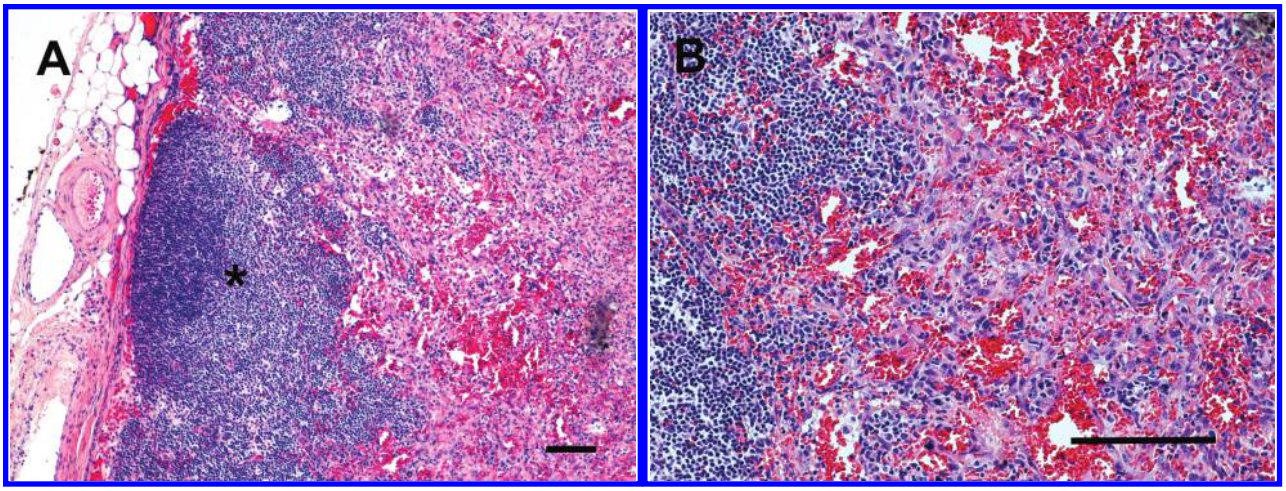

Figure 5—Photomicrographs of sections of the left retropharyngeal lymph node excised from dog 3. A—The lymph node cortex and medulla are effaced by invasive streams of pleomorphic spindle cells forming irregular, anastomosing vascular channels (right side). The lymphoid follicles are pushed to the periphery of the node (asterisk). H&E stain; bar = 250 μm. B—At higher magnification, notice the irregular streams of pleomorphic spindle cells that infiltrate through lymph node and form irregular vascular spaces, many of which are filled with erythrocytes. H&E stain; bar = 250 μm.

cranial mediastinal lymph nodes. The right ear canal mass was a ceruminous plug. Metronomic treatment with cyclophosphamide (15 mg/m^2, PO, q 24 h), furosemide (1 mg/kg, PO, q 24 h), and piroxicam (0.3 mg/kg, PO, q 24 h) was commenced on day 45. However, the dog developed high (VCOG grade 1) serum creatinine concentration on day 95 that resolved following discontinuation of the orally administered drugs.

On day 178, repeated CT (with and without contrast medium administration) of the head and thorax revealed a > 20% increase in the sum of longest diameters of the previously noted deeper retropharyngeal and multiple cranial lymph nodes, consistent with progressive disease according to the VCOG response evaluation criteria in solid tumors (RECIST [version 1.0]) criteria.[4]

Dog 4 received metronomic chlorambucil monotherapy (4 mg/m^2, PO, q 24 h) beginning day 192 and tolerated this treatment regimen well. Monitoring involved a CBC monthly for 3 months and then every 2 to 3 months thereafter; results were consistently unremarkable. At day 365, the dog was still alive with no clinical signs of illness.

Discussion

Hemangiosarcoma is an aggressive malignant cancer derived from vascular endothelium. The disease is common in dogs, representing approximately 7% of all neoplasms in that species.[5] The most common primary sites include the spleen, right atrium, subcutis, and liver.[5,6] It has also been reported to develop in other organs and tissues such as bones, kidneys, urinary bladder, skin, oral cavity, lungs, peritoneum, aorta, pulmonary artery, and CNS.[5] Hemangiosarcoma generally affects middle-aged dogs,[5,6] with German Shepherd Dogs, Golden Retrievers, and Labrador Retrievers being overrepresented.[5–9]

For humans, there are only 2 reported cases of primary nodal angiosarcoma, to our knowledge.[10,11] The first case report[10] involved a 38-year-old woman with a 2-month history of a mass that was growing in the cervical region. On examination, a firm, nonpainful, round (3-cm-diameter) mass was palpated in the left cervical region. Results of oral and indirect laryngoscopy, nasal endoscopy, thoracic radiography, CT examination of the neck, and laboratory analyses were normal and did not reveal any evidence of metastases. Surgery alone was performed and revealed a primary low-grade angiosarcoma in a cervical lymph node. Eight years after surgery, the patient was still alive and in good health with no evidence of disease. The second case report[11] described a primary high-grade poorly differentiated angiosarcoma in the intraparotid lymph node in a 47-year-old man; the mass was not associated with pain and had been growing for 6 months. A positron emission tomography scan revealed no evidence of another primary tumor or metastases. The patient was treated with surgery alone and was still alive without symptoms at 32 months after surgery.

The histologic and clinical features of primary lymph node hemangiosarcomas in 12 cats have been described.[12] All cats underwent tumor excision (8 marginally and 4 incompletely). One cat received adjuvant doxorubicin chemotherapy after marginal excision and was still alive 13 months after diagnosis of the tumor. Four cats with incompletely excised tumors developed recurrence or progressive disease at a median interval after surgery of 7 months (range, 2 to 10 months). Details regarding disease progression or recurrence for the other 7 cats with marginally excised nodal hemangiosarcomas were not reported. The overall median survival time after diagnosis for these 12 cats was 7 months (range, < 1 month to 17 months). Six cats were euthanized or died as a result of their disease (1 cat with confirmed progressive disease, 1 cat with suspected progressive disease, and 4 cats with recurrent or persistent hemangiosarcoma). To our knowledge, primary nodal hemangiosarcoma in dogs has not been previously reported.

In this series of 4 cases, all histologic slides were reviewed by 1 board-certified pathologist to determine tumor type and confirm that the lymph node was the tissue of origin, assess tumor grade, and evaluate completeness of excision. Tumors were graded on the basis of the degree of overall differentiation, nuclear pleomorphism, amount of necrosis, and number of mitotic figures/10 hpf (mitotic count),[1] as previously described[2] (Table 1).

On the basis of the report[12] of 12 cats with primary nodal hemangiosarcomas, the 2 primary nodal angiosarcoma cases in people, and the 4 primary nodal hemangiosarcomas in the dogs of the present report, there appear to be some clinical similarities among species. Primary nodal hemangiosarcoma appears to be a slow-growing mass that predominately originates in the cervical lymph nodes.[10–12] The 12 cats with confirmed nodal hemangiosarcomas were evaluated because of single (n = 10) or multiple (2) palpable subcutaneous mass lesions in the cervical (5), mandibular (4), or prescapular (1) lymph nodes. In 2 cats, the tumor location was not reported.[12] In the 2 people with angiosarcomas, the tumors were located in the cervical and intraparotid lymph nodes, respectively.[10,11] In the 4 dogs of the present report, all tumors originated within the cervical lymph nodes.

In addition, primary nodal hemangiosarcoma is usually detected incidentally because it is not associated with obvious clinical signs. The 4 dogs of the present report resided in 3 countries (Australia [dogs 1 and 2], United States of America [dog 3], and Canada [dog 4]), and all had no clinical signs attributed to the tumors. In all but 1 of the 12 feline cases reported,[12] the cats had no clinical signs and the owners found the masses incidentally; in the 2 human cases reported,[10,11] both tumors were found incidentally. Furthermore, the affected cats[12] and humans[10,11] had no other lesions suggestive of primary or metastatic disease identified by means of advanced imaging. In the series of 4 dogs of the present report, 1 (dog 4) had suspected regional lymph node involvement. Al-

though tumor staging was reasonably thorough for the affected dogs, 2 dogs (dogs 2 and 3) did not undergo abdominal imaging immediately before or after surgery. Thus, it would have been possible that a small primary tumor or a primary tumor that had regressed after metastasizing remained undetected.

Regardless of species, the primary treatment recommended for primary nodal hemangiosarcoma is complete excision. In the 2 reported human cases, complete excision of the tumor was achieved; the 2 patients received no other treatment and were still alive 8 years and 2.7 years later.[10,11] The overall median survival time after excision (4 incompletely and 8 marginally) of primary nodal hemangiosarcomas among the 12 cats in the previous report[12] was 7 months, with only 1 cat receiving adjuvant doxorubicin chemotherapy after surgery. Half of those 12 cats died or were euthanized because of their disease (1 cat had confirmed progressive disease, 1 cat had suspected progressive disease, and 4 cats had recurrent or persistent hemangiosarcoma). Of those 6 cats, 4 had marginal tumor excision and 2 had incomplete tumor excision,[12] suggesting that complete excision may help prevent recurrence or disease progression in affected animals. In all 4 dogs of the present report, histologically complete tumor excision was achieved followed by administration of some form of adjuvant chemotherapy. Dog 1 received adjuvant conventional chemotherapy and concurrent antiangiogenic treatment after removal of a splenic hemangiosarcoma but died (either as a result of metastasis to the spleen or an unrelated primary tumor); this dog's survival time was 259 days. Dogs 2, 3, and 4 were still alive at 615, 399, and 365 days after surgery, respectively. Those 3 dogs received conventional chemotherapy and concurrent antiangiogenic treatment (dog 2), metronomic administration of cyclophosphamide (dog 3), and metronomic administration of chlorambucil (dog 4). The choice of adjuvant therapy was based in part on published literature but was also clinician dependent. However, given the small number of dogs and different chemotherapy protocols used, the contribution of chemotherapy to survival times of the 4 dogs of this report cannot be critically assessed.

It is possible that nodal hemangiosarcoma develops from nonneoplastic lesions within the lymph node. Plexiform vascularization is characterized by nonmalignant capillary vasoproliferation with lymphoid atrophy, often accompanied by fibrosis. This is similar to what has been described in the human medical literature as vascular transformation of lymph node sinuses.[12–15] The underlying mechanism is poorly understood; however, it is thought to be associated with venous or lymphatic obstruction. The transformation process is histologically characterized by nodal sinuses forming complex, capillary-like (vascular) channels.[12,13] Plexiform vascularization in the lymph nodes of 14 cats has been described as slow-growing single (n = 12) or multiple (2) palpable subcutaneous mass lesions in the cervical (8), inguinal (4), retropharyngeal (1), and axillary (1) lymph nodes.[12,14,16] In 10 of the 14 cats, the masses were incidental findings and the cats had no associate clinical signs. However, in 1 report,[12] 2 cats with plexiform vascularization had abnormal proliferations that extended beyond the lymph node capsule and evidence of early progression to hemangiosarcoma, which led the authors to speculate that there may be a continuum from benign disease to malignancy.

In all 4 dogs of the present report, the nodal hemangiosarcomas had areas of plexiform vascularization, although the proportion of the node involved varied from extensive in dog 1 (Figure 1) to small foci in dog 2 (Table 1). In dog 4, the plexiform vascularization appeared to have progressed to a well-differentiated hemangiosarcoma. Whether plexiform vascularization occurs before or because of hemangiosarcoma development is uncertain.

In dogs, primary nodal hemangiosarcoma is a rare disease that appears to develop in the cervical lymph nodes as a slow-growing mass or masses. All dogs of the present report had no associated clinical signs at the initial evaluation and had no apparent evidence of visceral metastases or other primary tumors on diagnostic images. Complete tumor excision followed by adjuvant chemotherapy was performed in all cases. It is unclear from this small number of dogs whether adjunct chemotherapy is indicated after surgery; however, until a larger number of dogs are evaluated, given the aggressive biologic behavior of hemangiosarcomas in other body locations, adjunct chemotherapy should be considered for the treatment of affected dogs. Assessment of more cases is required to further characterize the biologic behavior of this tumor type and determine the expected survival times and associated risk factors in dogs. In addition, further investigation of the cause of vascular transformation and whether primary nodal hemangiosarcoma is part of a spectrum of disease from benign (plexiform vascularization) to malignant hemangiosarcoma is needed.

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Preliminary data has not been presented elsewhere.

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From this month's *AJVR*

Population pharmacokinetics of enrofloxacin in purple sea stars (*Pisaster ochraceus*) following an intracoelomic injection or extended immersion

Justin F. Rosenberg et al

OBJECTIVE
To determine population pharmacokinetics of enrofloxacin in purple sea stars (*Pisaster ochraceus*) administered an intracoelomic injection of enrofloxacin (5 mg/kg) or immersed in an enrofloxacin solution (5 mg/L) for 6 hours.

ANIMALS
28 sea stars of undetermined age and sex.

PROCEDURES
The study had 2 phases. Twelve sea stars received an intracoelomic injection of enrofloxacin (5 mg/kg) or were immersed in an enrofloxacin solution (5 mg/L) for 6 hours during the injection and immersion phases, respectively. Two untreated sea stars were housed with the treated animals following enrofloxacin administration during both phases. Water vascular system fluid samples were collected from 4 sea stars and all controls at predetermined times during and after enrofloxacin administration. The enrofloxacin concentration in those samples was determined by high-performance liquid chromatography. For each phase, noncompartmental analysis of naïve averaged pooled samples was used to obtain initial parameter estimates; then, population pharmacokinetic analysis was performed that accounted for the sparse sampling technique used.

RESULTS
Injection phase data were best fit with a 2-compartment model; elimination half-life, peak concentration, area under the curve, and volume of distribution were 42.8 hours, 18.9 μg/mL, 353.8 μg•h/mL, and 0.25 L/kg, respectively. Immersion phase data were best fit with a 1-compartment model; elimination half-life, peak concentration, and area under the curve were 56 hours, 36.3 μg•h/mL, and 0.39 μg/mL, respectively.

CONCLUSIONS AND CLINICAL RELEVANCE
Results suggested that the described enrofloxacin administration resulted in water vascular system fluid drug concentrations expected to exceed the minimum inhibitory concentration for many bacterial pathogens. (*Am J Vet Res* 2016;77:1266–1275)

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