



Figure 1—Photograph of an ulcerated mass on the rostral aspect of the mandible of an approximately 9-year-old mixed-breed dog. The mass was 2 × 1.5 × 2 cm, soft, and mottled dark red to black; it had recurred rapidly following 2 previous debulking procedures.

History

An approximately 9-year-old neutered male mixed-breed dog was evaluated at the Michigan State University Veterinary Teaching Hospital because of an ulcerated mass on the rostral aspect of the mandible. The mass was first noted approximately 3 months prior and had been surgically debulked twice. Recurrence of the mass was rapid after each surgery. Three years before the evaluation, the dog had a hepatocellular carcinoma (mixed solid and pelioid) that was incompletely resected. At that time, the dog underwent 4 cycles of chemotherapy (gemcitabine and carboplatin administered IV). At the evaluation, the dog did not have any clinical signs that suggested local recurrence of the hepatocellular carcinoma. Thoracic radiography, at this time, revealed multiple pulmonary nodules. The dog was euthanized because of poor quality of life as a result of the oral mass, and the body was submitted for postmortem examination.

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Clinical and Gross Findings

At necropsy, the lesion on the rostral aspect of the mandible measured 2 × 1.5 × 2 cm; it was soft, mottled dark red, and ulcerated (Figure 1). The mass extended from the right side of the mandible toward the left side and invaded into the underlying bone. The incisors along the right mandible were missing, and those along the left were loose and displaced laterally. Submandibular lymph nodes were prominent. Within the abdominal cavity, the gallbladder was adhered to the diaphragm, and the left lateral and medial lobes of the liver were not present. All remaining lobes of the liver contained masses that ranged from 1.5 to 7 cm in diameter and were friable to firm and tan or brown to dark red or black. Many of the masses were multilobulated, and some had an umbilicated surface. Multiple masses contained large central areas of necrosis. Masses spanned the right medial and right lateral liver lobes. The omentum was regionally adhered to a fractured 4-cm-diameter mass in the right lateral liver lobe. The lungs contained multiple similar masses (0.2 to 7 cm in diameter) as well as multifocal areas of consolidation. Two additional tan smooth masses that measured 0.2 and 0.5 cm in diameter were located in the intestinal wall of the jejunum and ileum, respectively.

Formulate differential diagnoses from the history, clinical findings, and Figure 1—then turn the page →

Histopathologic Findings

Samples of tissue containing the oral mass and tissues from the submandibular lymph nodes, liver, jejunum, and ileum were processed for histologic examination. Effacing the normal submucosa of the oral cavity, there was a fairly well-demarcated, expansile, nonencapsulated, multinodular mass composed of densely cellular neoplastic cells arranged in packets and trabeculae

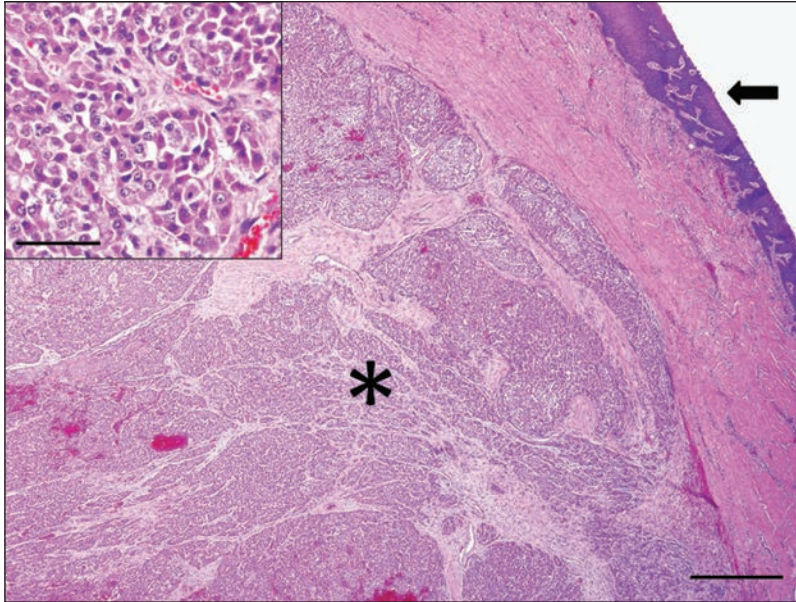


Figure 2—Photomicrographs of a section of the oral mass from the dog in Figure 1. Underlying the oral mucosa (arrow), there is a multinodular mass of polygonal neoplastic cells arranged in packets and trabeculae that replace the normal subepithelial stroma (asterisk). Junctional activity among the neoplastic cells is not evident. H&E stain; bar = 500 μ m. Inset—Neoplastic cells contain abundant granular eosinophilic cytoplasm with centrally placed small round nuclei and 1 to 2 nucleoli. H&E stain; bar = 35 μ m.

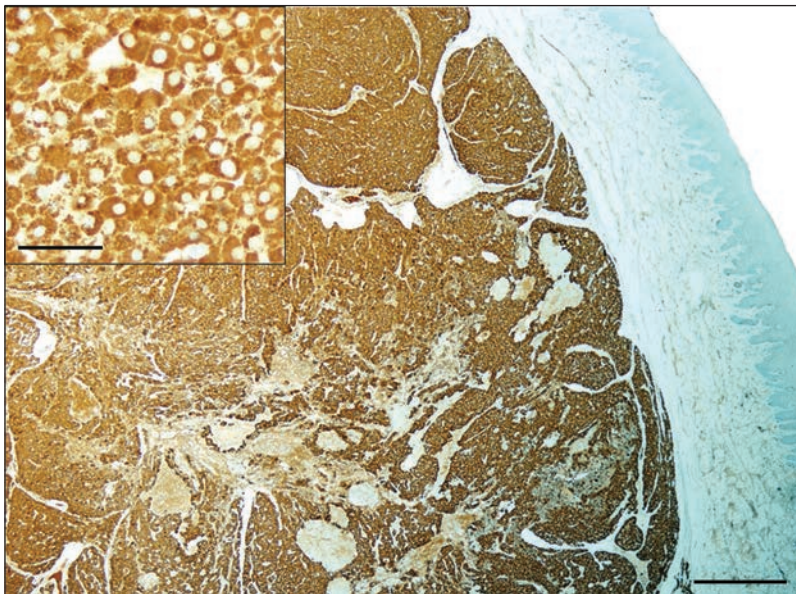


Figure 3—Photomicrographs of a section of the oral mass from the dog in Figure 1 following immunohistochemical staining for the hepatocyte paraffin 1 (Hep Par 1) marker. Notice the strong diffuse immunohistochemical labeling for Hep Par 1 among the neoplastic cells in the oral mass. 3,3'-diaminobenzidine stain; bar = 500 μ m. Inset—The labeling of the neoplastic cells was cytoplasmic and appeared granular. 3,3'-diaminobenzidine stain; bar = 35 μ m.

ulae supported by fine fibrovascular stroma. The neoplastic cells were polygonal, contained abundant granular eosinophilic cytoplasm, and had a central small round nucleus with 1 to 2 small nucleoli (Figure 2). Nuclei had finely stippled chromatin and low mitotic index (0 to 1 mitoses/hpf). Anisocytosis and anisokaryosis were minimal. There were multifocal areas of coagulative necrosis and neoplastic trabeculae that formed cavernous blood-filled spaces. Similar neoplastic cells replaced the lymphoid parenchyma of the submandibular lymph nodes.

Within sections of liver, multiple masses that were composed of similar neoplastic cells had replaced the normal hepatic parenchyma. Multifocally, vessels contained neoplastic emboli. In the surrounding parenchyma, there was mild fibrosis, compression of hepatocytes, and accumulations of lymphocytes, plasma cells, and low numbers of neutrophils. The masses in the lungs, jejunum, and ileum were composed of a similar population of neoplastic cells.

Immunohistochemical labeling for the hepatocyte paraffin 1 (Hep Par 1) marker was performed on sections of the oral mass (Figure 3), a liver mass, and a lung mass. Approximately 95% of the neoplastic cells in each mass had diffuse intense granular cytoplasmic labeling of Hep Par 1.

Morphologic Diagnosis and Case Summary

Morphologic diagnosis: hepatocellular carcinoma with metastasis to the rostral aspect of the mandible, submandibular lymph nodes, lungs, and small intestine.

Case summary: metastatic hepatocellular carcinoma in a dog.

Comments

The dog of the present report had an ulcerated mass on the rostral aspect of the mandible that had recurred rapidly following debulking procedures. In general, differential diagnoses for oral tumors in dogs include squamous cell carcinoma, fibrosarcoma, melanoma, and odontogenic neoplasia.

After the first debulking of the oral mass, tissue from the mass was submitted for histologic evaluation, but this dog's history of hepatocellular carcinoma was not provided at that time. The histologic features of the original biopsy specimen were similar to those detected in samples collected at necropsy. On the basis of the histomorphologic characteristics, differential diagnoses for the mass originally included neuroendocrine car-

cinoma (because of the arrangement of the neoplastic cells in packets separated by fine fibrovascular stroma), undifferentiated carcinoma, and amelanotic melanoma. Fontana-Masson staining of sections of the mass did not highlight any melanin pigment, and neoplastic cells did not have junctional activity or form intraepithelial nests; thus, melanoma was considered the least likely of the 3 differential diagnoses at that time. Immunohistochemical staining to further classify the neoplasm was recommended but declined by the owners.

After the dog was euthanized and necropsy and microscopic postmortem examination of the tissues were performed, a metastatic neuroendocrine carcinoma was still considered; however, once the history of a previous hepatocellular carcinoma was made known, metastatic hepatocellular carcinoma was a concern. Hepatocyte paraffin 1 is a marker that has been shown to be highly sensitive and specific for diagnosis of hepatocellular tumors in dogs.¹ Thus, immunohistochemical labeling for Hep Par 1 was performed on sections of the oral mass, a liver mass, and a lung mass; the neoplastic cells in each mass had diffuse label uptake, consistent with neoplasms of hepatocellular origin.

Hepatocellular carcinomas are uncommon neoplasms of dogs. In fact, primary liver tumors account for only approximately 0.6% to 1.3% of all neoplasms in dogs; of those primary liver tumors, hepatocellular carcinoma is the most common malignancy.² Other primary malignant tumors of the liver include bile duct carcinoma, neuroendocrine carcinoma, and sarcoma. Hepatocellular carcinomas appear to occur more frequently in males.³

The clinical signs for dogs with primary hepatic tumors are variable and nonspecific, including anorexia, lethargy, vomiting, and weight loss.²⁻⁵ Other clinical signs may be dyspnea, polyuria, polydipsia, abdominal distention, hepatomegaly, diarrhea, hematochezia, melena, jaundice, seizures, and myelopathy.^{2,4,5} In affected dogs, hematologic and biochemical abnormalities are common but are also nonspecific for liver neoplasia.^{2,4,5} Reported hematologic disturbances include anemia, leukocytosis with neutrophilia, and thrombocytosis.^{2,4,5} Additionally, high liver enzyme activities, hypoalbuminemia, hyperglobulinemia, hypocholesterolemia, hypoglycemia, high bile acids concentration, and coagulation profile abnormalities have also been reported.^{2,4,5} When the dog of the present report was first examined because of the primary hepatic tumor, serum biochemical abnormalities included hyperphosphatemia, hyperamylasemia, hypocholesterolemia, and moderately high alkaline phosphatase, aspartate transaminase, and creatine kinase activities; a CBC revealed anemia and neutrophilia. Coagulation profile variables

and serum bile acids concentration were within reference intervals at that time. Prior to necropsy, however, hematologic evaluation was not performed.

Hepatocellular carcinomas can be classified on the basis of gross morphology as nodular, diffuse, or massive.^{2,3,6} Among hepatocellular carcinomas in dogs, approximately 29% are nodular, characterized by discrete nodules in several liver lobes.⁴ Diffuse hepatocellular carcinomas account for only 10% of all hepatocellular carcinomas in dogs; these tumors are characterized by indistinct nodules throughout the entire liver. The most common hepatocellular carcinomas in dogs is the massive form, which accounts for 61% of all hepatocellular carcinomas in this species.⁴ This form is defined as a large tumor that affects a single liver lobe, most frequently the left lateral lobe. In dogs, massive hepatocellular carcinomas are surgically treatable, with liver lobectomy being the procedure of choice,² whereas nodular and diffuse hepatocellular carcinomas are not.⁴ The median survival time for dogs that underwent complete excision of a massive hepatocellular carcinoma via liver lobectomy exceeded 4 years in 1 study.^{2,4} Dogs that did not undergo surgical excision had a median survival time of only 270 days.⁴ Chemotherapy is considered to be ineffective for the treatment of primary liver tumors.² In the case described in the present report, the original liver tumor was determined to be a massive hepatocellular carcinoma and had been diagnosed approximately 3 years prior to euthanasia. The most common sites of metastasis for hepatocellular carcinomas are lymph nodes, lungs, and peritoneum; other less commonly reported sites of metastasis include kidneys, adrenal glands, spinal cord, pancreas, heart, spleen, gastrointestinal tract, and bone marrow.^{3,5,6} Thus, metastasis to the oral cavity of this dog was considered highly unusual.

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