Pathology in Practice

In collaboration with the American College of Veterinary Pathologists

Figure 1—Necropsy images of the thoracic and abdominal cavities of a 12-year-old 4.8-kg spayed female black Miniature Poodle euthanized for a decline in quality of life after treatment for 18 months for a chronic, progressive illness. There are multifocal black to gray variably sized nodules (arrows) widespread through the viscera. A large mass (4 cm) located near the pelvic inlet involves mesentery and distal jejunum. Cranial is toward the right of the image. He = Heart. Lu = Lung. Li = Liver. Ki = Kidney.

History

A 12-year-old 4.8-kg spayed female black Miniature Poodle was submitted for necropsy following euthanasia because of a diminished quality of life after treatment of a chronic progressive disease for 18 months. During the weeks before euthanasia, clinical signs noted by the owner included shaking, decreased appetite, and occasional vomiting.

Clinical and Gross Findings

Mild dehydration, a 3.5-cm necrotic mass in the area of the right caudal mandible, a 1.5-cm firm right submandibular lymph node, and a tense, mildly painful abdomen were noted on ante mortem examination of the dog. The remaining findings on physical examination were unremarkable.

On postmortem examination, the dog was in good nutritional status with mild autolytic changes. Multiple black to gray firm masses of various diameters were present on the caudal aspect of the right mandible (3 cm), distal jejunum and mesentery (4 cm), interventricular septum (0.5 cm), subcutis of the ventrum (2 cm), and all lung lobes (0.1 to 3 cm; **Figure 1**). Additional black to gray masses were in both adrenal glands (2 to 3 mm), hilar lymph nodes (2 cm), and the left occipital lobe of the brain. White to tan, firm, oval masses were found in the right medial lobe of the liver (0.5 cm) and spleen (1 cm). There were no additional clinically meaningful gross findings.

Formulate differential diagnoses, then continue reading.

Histopathologic Findings

In the oral cavity, an expansive and infiltrative melanocytic neoplasm, with moderate anaplasia, multifocal hemorrhage and necrosis, and tumor emboli, had effaced large portions of the buccal mucosa and submucosa of the vestibule (cheek) of the left mandible. The neoplasm consisted of moderately pleomorphic spindled and epithelioid cells arranged into closely apposed nests within a fine fibrovascular stroma that contained occasional melanomacrophages. Spindled and epithelioid cells had moderate amounts of eosinophilic cytoplasm with distinct cell borders and occasional fine black to brown granules. The normo- to hyperchromatic nuclei were round to oval, with mild to moderate anisokaryosis and distinct, often multiple nucleoli. Multinucleated neoplastic cells were frequent, there were 47 mitotic figures in 2.4 mm² (10 contiguous hpfs [400X]), and vascular invasion was observed.

In the heart, an infiltrative melanocytic neoplasm, with hemorrhage and necrosis, had obliterated the wall of the left ventricle transmurally (**Figure 2**). Metastases of similar neoplastic cells were recognized in the lungs and tracheobronchial hilar lymph node as well as in the cerebral leptomeninges of the left occipital lobe. Additional metastases were recognized in the prescapular lymph node, liver, adrenal gland, small and large intestines, and fatty mesentery. No evidence of metastasis was detected in the spleen, kidneys, and urinary bladder.

Patricia Gualtieri, DVM¹; Uriel Blas-Machado, DVM, PhD¹; Wilson Yau, DVM²; Dawn M. Clarke, DVM^{1*}

¹University of Georgia College of Veterinary Medicine, Athens, GA

²Antech Diagnostics, Fountain Valley, CA

*Corresponding author: Dr. Clarke (dmclarke@uga.edu)

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Figure 2—Photomicrographs of sections of the left ventricle from the dog described in Figure 1. **A**—Multinodular malignant melanoma (arrows) extends transmurally, and there is an area of hemorrhage and necrosis (asterisk). H&E stain; bar = 2.5 mm. **B**—Neoplastic cells extend between and compress individual cardiomyocytes (arrows). H&E stain; bar = 50 μ m. **C**—Higher magnification of the malignant melanoma in the heart. The neoplasm consists of moderately pleomorphic spindled and epithelioid cells arranged into nests within a fine fibrovascular stroma. Spindled and epithelioid cells have moderate amounts of eosinophilic cytoplasm with distinct cell borders and occasional fine black to brown granules. The normo- to hyperchromatic nuclei are round to oval, with mild to moderate anisokaryosis and distinct, often multiple nucleoli. Two mitotic figures (arrows) are evident in the image. H&E stain; bar = 10 μ m.

Morphological Diagnosis and Case Summary

Oral malignant melanoma with metastasis to the heart, lungs, lymph nodes, liver, adrenal gland, intestines, mesentery, and cerebral leptomeninges in a dog.

Comments

Malignant melanoma is the most common oral tumor in dogs, representing 30% to 40% of all oral tumors, followed by squamous cell carcinoma (17% to 25%) and fibrosarcoma (8% to 25%).¹ It tends to occur in smaller breed dogs; the average age at presentation is 11.4 years.²

Oral malignant melanoma is a locally infiltrative tumor, with a high metastatic rate (up to 80% of dogs).¹ It generally metastasizes via hematogenous and lymphatic routes.^{3,4} Common metastatic sites include the local lymph nodes and lungs.^{1-3,5,6} Late in the disease course, metastasis can be widespread and include liver, brain, adrenal glands, heart, and osseous structures.^{3,7,8} Diagnosis of melanoma can be challenging due to the variability in degree of pigmentation

of some tumors.^{2,9} In fact, the variety of histologic appearances of canine amelanotic melanocytic neoplasms (epithelioid, spindled, round) makes them challenging to distinguish from other common oral tumors such as squamous cell carcinomas, fibrosarcomas, or round cell tumors. Positivity for immunohistochemical stains such as Melan A, S100, tyrosinase, and PNL2 are helpful to differentiate melanoma from other poorly differentiated oral tumors.^{1,2,4,9-12} PNL2 was shown to be the most specific marker for the identification of canine melanoma, and the sensitivity is close to 100% when used in conjunction with the previously mentioned markers.¹²

Canine and human melanomas share many features, such as clinical presentation, aggressive biologic behavior, pathologic features, and molecular mechanisms. In humans, cardiac metastases are found in approximately 15% of patients dying from malignant neoplasms, with melanoma and breast and bronchial carcinomas being the most common primary cancers.¹³⁻¹⁷ Because of absent or nonspecific signs of cardiac involvement, most metastases are diagnosed post mortem in humans. In the majority of cases, cardiac metastases occur in patients

with advanced tumor burden and diffuse metastatic involvement. Metastatic melanoma of the heart in people is typically a lobular mass that may be intracavitary or may involve the myocardium or pericardium and the right side of the heart is more commonly involved.^{3,13-17}

Similarly, in dogs, secondary neoplasms of the heart are uncommon, with a reported incidence between 0.12% and 4.33% of tumors in all dogs subjected to necropsy.^{8,18} Reportedly, an unexpectedly high number of metastases (36%) were found in the heart of dogs with malignant neoplasms who underwent thorough necropsy.¹⁸ Secondary heart tumors occur more frequently than primary and include carcinomas, lymphoma, and hemangiosarcoma. They are often clinically silent, not detectable on physical examination or by echocardiogram.^{8,18}

Cardiac or pericardial locations are rarely the first sites of metastatic disease in either species. In human medicine, echocardiography is often the initial imaging modality used to diagnose cardiac metastases. Additionally, CT, MRI, and fluorodeoxyglucose positron emission tomography may be used to detect and define cardiac involvement.^{3,13-16} In veterinary medicine, an echocardiogram is not a routine cancer staging test due to its low sensitivity in diagnosing primary or secondary heart masses.^{8,18} Furthermore, due to the uncommon use of full-body advanced imaging for staging and the absence of clinical signs related to the metastasis, it is likely that metastatic disease to the heart remains underdiagnosed in canine cancer patients, unless the body is submitted for necropsy.

In this case, the primary oral tumor had been surgically excised with an incomplete margin. Histopathology of the mass diagnosed an oral malignant melanoma, which prompted referral to the University of Georgia Veterinary Teaching Hospital for treatment consultation. Initially, owners opted for treatment with Oncept melanoma vaccine, radiation therapy (5 X 6.5 Gy), palliative debulking surgery at the time of disease recurrence, and finally, metronomic chemotherapy. Only thoracic radiographs were performed to monitor the progression of the disease; pulmonary metastases were detected 9 months after diagnosis. The dog had an extended survival of 18 months in total before nonspecific clinical signs led to euthanasia.

In conclusion, although most are clinically silent, cardiac metastasis appears relatively common in both species and should be considered in any patient with a malignancy, including melanoma, particularly when distant metastases or thoracic involvement are present. Furthermore, in cases where secondary cardiac involvement is detected, thorough evaluation for other metastatic sites should be performed because cardiac involvement often indicates an advanced stage of disease. Because canine and human melanomas share several clinical and pathological similarities,^{9,19-21} canine oral malignant melanoma represents a good spontaneous model for the investigation of

novel diagnostic and therapeutic options for advanced metastatic disease in people.

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