Malignant collision tumors in two dogs

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CASE DESCRIPTION

A 13-year-old Labrador Retriever with a 4-cm-diameter ulcerated perianal mass and a 12-year-old Golden Retriever with a 5-cm-diameter ulcerated caudolateral abdominal mass were brought to a referral oncology practice for evaluation of the dermal masses. Both masses were resected with wide margins without reported postoperative complications. For both dogs, a diagnosis of collision tumor was made. The database of the Veterinary Diagnostic Laboratories at Colorado State University was searched for other examples of collision tumors in dogs.

CLINICAL FINDINGS

Histologic assessment of the masses revealed collision tumors in both patients. The perianal mass was diagnosed as a perianal gland carcinoma with adjacent hemangiosarcoma. The flank mass was diagnosed as a fibrosarcoma with an adjacent mast cell tumor. The university database search of sample submissions in 2008 through 2014 for the keywords collision, admixed, or adjacent yielded 37 additional cases of dogs with malignant nontesticular collision tumors.

TREATMENT AND OUTCOME

Both dogs were treated with surgery alone and received no adjunctive treatments. Both tumors were completely excised. There was no evidence of either local tumor recurrence or metastasis in the Labrador Retriever and the Golden Retriever at 1,009 and 433 days after surgery, respectively.

CLINICAL RELEVANCE

Collision tumors are rare, and there is minimal information regarding treatment recommendations and outcome for animals with collision tumors. On the basis of the 2 cases described in this report, the outcome associated with treatment of collision tumors may be similar to the expected outcome for treatment of any of the individual tumor types in dogs. (*J Am Vet Med Assoc* 2017;251:941–945)

A 38-kg (83.6-lb) 13-year-old neutered male Labrador Retriever (dog 1) was evaluated because of an open wound following biopsy of a left-sided perianal mass by a referring veterinarian. Histologic examination of the biopsy specimen was consistent with a perianal adenoma. Physical examination revealed ulceration of the previous biopsy site and a 4-cm-diameter left-sided perianal mass. The remaining physical examination findings were unremarkable, and results of preoperative clinicopathologic analyses were within the reference ranges. Sublumbar lymph nodes were not palpable. The perianal mass was resected with 1-cm-wide lateral margins.

Histologic examination of the perianal mass revealed 2 distinctly different tumors: a perianal gland carcinoma with an adjacent infiltrative hemangiosarcoma **(Figure 1)**. Excision was complete with 3- to 4-mm-wide margins of unaffected tissue. The hemangiosarcoma appeared to infiltrate the perianal gland carcinoma as irregular vascular channels filled with blood. However, this infiltration was limited to the interface between the 2 tumors. The diagnosis was a mixed tumor known as a collision tumor. A mixed tumor is defined as a neoplasm that macroscopically represents 1 tumor, but histologically or immunohistologically contains ≥ 2 components.[1] Collision tumors represent 2 independent foci of neoplasia that develop adjacent to one another and yet remain separate.

Dog 1 recovered from the procedure uneventfully. Further diagnostic assessments (eg, 3-view thoracic radiography and abdominal ultrasonography) and adjunctive chemotherapy for the dermal hemangiosarcoma component of the collision tumor were declined by the owner.

The dog was again evaluated at 785 days after perianal mass removal because of a grade II soft tissue sarcoma over the lateral aspect of the left elbow. Clinical staging tests were again declined. Marginal excision of the mass was performed, and the dog recovered uneventfully. The mass was histologically confirmed as a grade II soft tissue sarcoma and had been completely excised with 1- to 2-mm-wide margins. Dog 1 was clinically disease free 224 days after the second surgery and 1,009 days after the first surgery.

A 32.3-kg (71.1-lb) 12-year-old spayed female Golden Retriever (dog 2) underwent assessment of a left caudolateral abdominal mass that was noticed by the owner 3 months prior. Physical examination revealed a mobile ulcerated left caudolateral abdominal mass, adjacent to the proximal portion of the thigh, measuring 5.8 × 5.1 cm. The remainder of the physical examination findings were unremarkable. Pre-

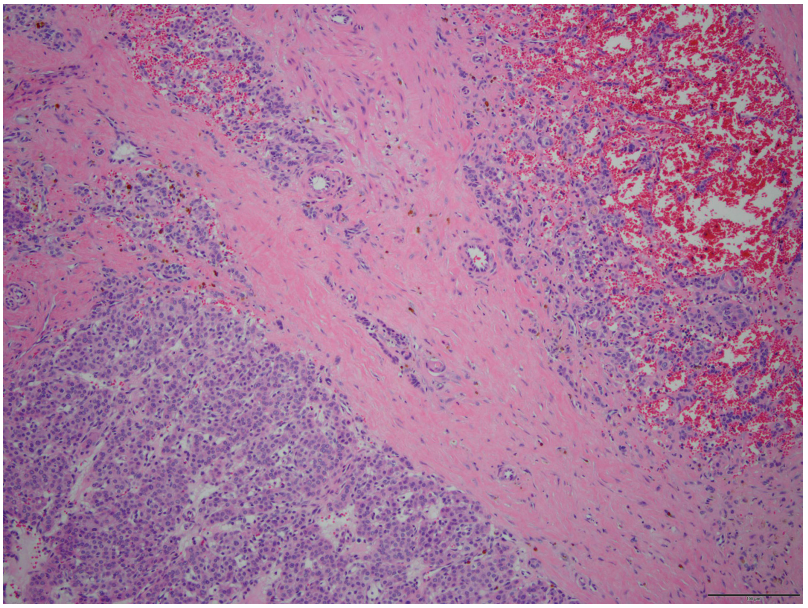

Figure 1—Photomicrograph of a section of a perianal mass excised from a 13-year-old neutered male Labrador Retriever (dog 1). Notice a perianal gland carcinoma (left) adjacent to a hemangiosarcoma (right), between which is a small amount of fibrous tissue. H&E stain; bar = 100 µm.

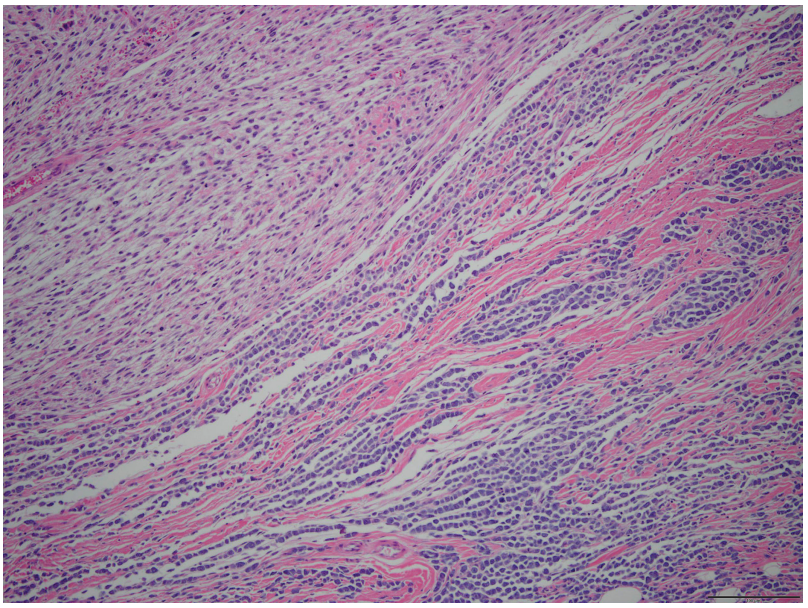

Figure 2—Photomicrograph of a section of a mass excised from the left flank region of a 12-year-old spayed female Golden Retriever (dog 2). Notice the soft tissue sarcoma (upper portion) abutting a mast cell tumor (lower portion) with some intermixing of the 2 tumor types at the intertumor junction. H&E stain; bar = 100 µm.

operative clinicopathologic analyses revealed mildly high creatine kinase activity (213 U/L; reference range, 4 to 170 U/L). There was no evidence of pulmonary metastasis on 3-view thoracic radiographs. The mass was resected with 3-cm-wide margins and a deep margin of 1 fascial plane.

Histologic examination of the excised mass revealed 2 distinctly different tumors: a grade III fibrosarcoma with an adjacent low grade II mast cell tumor (classified by use of the Patnaik grading scheme[2]). The mast cell tumor appeared to be wrapped around and intimately associated with the fibrosarcoma with a thin epithelial layer separating the tumors **(Figure 2)**. Surgical excision of the collision tumor was considered complete with 8- to 25-mm-wide margins. Dog 2 recovered from the procedure uneventfully and was disease free 433 days after surgery.

The database of the Veterinary Diagnostic Laboratories at Colorado State University was searched for canine patients with histology reports that included the words collision, admixed, or adjacent in 2008 through 2014. The search yielded 7,052 reports (including those of dogs 1 and 2 of the present report). Filtering of the reports was performed to exclude repeated entries and benign, mammary, and testicular tumors. Testicular tumors were excluded because it is not uncommon for dogs to have 2 or more testicular tumors within a testis, and those tumors are usually benign.[3] Testicular tumors may be adjacent to each other, although they are often separated by a considerable amount of nonneoplastic testicular tissue. Mammary tumors were likewise excluded because most mixed mammary tumors are benign and also common. Some mixed mammary tumors are malignant. However, in both the benign and malignant forms, the different components are typically highly intermixed; therefore, these are not collision tumors.[4] By use of these filter criteria, 41 cases (including dogs 1 and 2 of the present report) of canine malignant mixed tumors were identified, 39 of which were classified as collision tumors **(Table 1)**.

Of the 39 collision tumors, 27 were dermal; for 10 of those 27 cases, tumor location was not recorded. Eight of the 17 dermal tumors for which location was recorded were on the trunk, including the axillary and inguinal regions. The most common type of collision tumor on the trunk was soft tissue sarcoma with an adjacent mast cell tumor (Table 1). Among the noncutaneous collision tumors, a hepatic location was most common with 4 cases of primary hepatocellular carcinoma and adjacent hemangiosarcoma. The most common type of individual tumors involved in collision tumors were soft tissue sarcomas (n = 18) and

Table 1—Cases of mixed tumors in dogs identified through a search of the database of the Veterinary Diagnostic Laboratories at Colorado State University for canine patients with histology reports that included the words collision, admixed, or adjacent in 2008 through 2014.

Histologic description	Tumor 1	Tumor 2	Complete excision	Location
Collision	Adenocarcinoma	Pheochromocytoma	Yes	Adrenal gland
		Osteosarcoma	Yes	Kidney
	Anal sac apocrine gland adenocarcinoma	Infiltrative lipoma	Yes	Perianal region
	Carcinoma	Chondrosarcoma	Marginal	Ear
	Fibrosarcoma, grade III*	Mast cell tumor, grade II*	Yes*	Left flank region*
		Melanoma	Yes	Cutaneous location
		Melanoma	No	Hip region
		Adenocarcinoma, grade III	Unknown	Lungs
	Hemangiosarcoma	Fibrosarcoma, grade II	Yes	Tarsal region
	Hemangiosarcoma, grade II	Melanoma	Yes	Prepuce
	Hepatocellular carcinoma	Hemangiosarcoma	Unknown	Liver
		Hemangiosarcoma	Unknown	Liver
		Hemangiosarcoma	No	Liver
		Hemangiosarcoma, grade III	No	Liver
	Mast cell tumor	Malignant lymphoma	Yes	Axilla
	Mast cell tumor, grade II	Plasma cell tumor	No	Cutaneous location
		Myxosarcoma, grade I	No	Body wall
		Malignant melanoma	Marginal	Cutaneous location
		Soft tissue sarcoma, grade I	Marginal	Cutaneous location
	Mast cell tumor, grade III	Melanoma	Unknown	Eyelid
		Hemangiosarcoma, grade I	Yes	Thigh region
	Melanoma	Mast cell tumor, grade II	Yes	Cutaneous location
	Metastatic osteosarcoma	Adenocarcinoma	Necropsy	Lungs
	Soft tissue sarcoma	Hemangiosarcoma	Yes	Spleen
	Soft tissue sarcoma, grade I	Mast cell tumor grade II	Yes	Ischium
		Mast cell tumor, grade II	Marginal	Thorax
		Mast cell tumor, grade II	Yes	Cutaneous location
		Extraskeletal osteosarcoma	Yes	Cutaneous location
	Soft tissue sarcoma, grade I (peripheral nerve origin)	Mast cell tumor, grade II	No	Cutaneous location
	Soft tissue sarcoma, grade II	Mast cell tumor, grade II	Marginal	Shoulder region
		Mast cell tumor, grade II	No	Cutaneous location
	Squamous cell carcinoma	Soft tissue sarcoma (smooth muscle)	Unknown	Nasal region
		Lymphoma	No	Mammary gland
		Hemangiosarcoma, grade II	No	Inguinal region
		Malignant melanoma	No	Tail
		Hemangiosarcoma	Yes	Inguinal
	Thyroid carcinoma	Undifferentiated sarcoma	Marginal	Thyroid gland
Collision and colonized	Apocrine sweat gland adenocarcinoma	Chondrosarcoma	Yes	Cutaneous location
	Perianal gland carcinoma*	Hemangiosarcoma, grade I*	Yes*	Perianal region*
Combination	Chondrosarcoma, grade II	Liposarcoma, grade I	Yes	Thoracic wall
Composite	Adenocarcinoma	Squamous cell carcinoma and osteosarcoma	Yes	Cutaneous location

The search yielded 7,052 reports (including dogs 1 and 2 of the present report). Filtering of the reports was performed to exclude repeated entries and benign, mammary, and testicular tumors. Collision tumors are a type of mixed tumor with 2 independent foci of neoplasia that develop adjacent to one another, yet remain separate. Colonization is a term used to describe a mixed tumor in which a secondary tumor permeates an underlying primary tumor in situ. A combination tumor has a cell population that originates from the same germ layer, whereas composite tumors contain cell populations that are from 2 germ layers.

*This case represents dog 1 or 2 of the present report.

mast cell tumors (15). The most commonly paired tumors within a collision tumor were soft tissue sarcoma and mast cell tumor.

Discussion

A mixed tumor, such as a collision tumor, is a neoplasm that macroscopically represents 1 tumor, but histologically or immunohistologically contains 2 or more components.[1] In a collision tumor, 2 adjacent foci of neoplasia develop independently and separately. There are several other types of mixed tumors, including combination, composite, and biphenotypic tumors. These tumors contain an intermingling of 2 populations of malignant cells.[1,5] Colonization is a term used to describe a mixed tumor in which a secondary tumor permeates an underlying primary tumor in situ.[5] Intermixed or intermingling tumors, especially those in canine benign mammary masses, are relatively common[4]; however, true collision tumors in people and other animals are rare, with little known about treatment and outcomes.

In dogs, collision tumors are rare and represent a subgroup of mixed tumors in which 2 different tumors are closely associated but microscopically separate within a single macroscopic mass.[1,5–9] There is confusion in the medical literature as to the classification of collision tumors, with some authors suggesting collision tumors are a combination of 2 individual neoplastic cell populations intermingled within a single mass with no defining separation[10,11]; however, these intermingling or intermixed tumors are best categorized as combined, composite, or biphenotypic tumors.[1,5–8,12,13]

The differentiation between combined, composite, and biphenotypic tumors lies in the origin of the cell populations. Combination tumor cell lineage originates from the same germ layer, whereas composite tumors contain cell populations that are from 2 germ layers.[1] Biphenotypic tumors originate from a common stem cell precursor, with overlapping immunohistochemical and molecular properties.[5] To further complicate the nomenclature, there is a discrepancy with this differentiation, and some reports[6,7] define composite tumors as the differentiation of 1 type of cell into 2 lineages.

Of the 2 cases described in the present report, dog 2 had a classic example of a collision tumor with an easily identifiable epithelial layer separating the fibrosarcoma and mast cell tumor. For dog 1, it may be more appropriate to classify the perianal mass as a blend of a collision tumor and a colonized tumor because of the thin fibrous layer between the tumors and hemangiosarcoma infiltration into the perianal gland carcinoma at the interface of these 2 tumors.[5] Colonized tumors are characterized by a primary tumor with a secondary tumor in situ that extends into and colonizes the primary tumor.[5,14,15]

The veterinary medical literature is almost exclusively limited to examples of collision tumors in the testes of dogs. To the authors' knowledge, in the English-language literature, there is a single case report[1] of a nontesticular collision tumor in a dog. That case involved a Tibetan Spaniel with a dermal mass composed of a high-grade sarcoma and a malignant melanoma in the upper lip. At 2 years after complete surgical excision of the mass, the dog had no evidence of either local tumor recurrence or metastasis.[1]

Although rare, the most commonly reported collision tumors in humans are skin tumors composed of basal or squamous cell carcinoma with adjacent malignant melanoma.[1,5,12,16] These frequently develop on the head or neck, and males appear to be overrepresented among affected individuals.[12]

The origin and importance of collision tumors are unknown, and several theories as to their etiopathogenesis exist. It has been postulated that collision tumors result from a pluripotent stem cell line that differentiates into 2 phenotypically diverse cell lines. It has also been proposed that recurrent skin damage (eg, UV radiation or thermal burns) of the primary tumor alters the surrounding tissues and influences neoplastic changes; however, this skin damage theory does not account for the occurrence of collision tumors within the thoracic or abdominal viscera.[8,9,11,12] An alternative theory is that a collision tumor is a coincidental occurrence.[12] Regardless of the cause, it is difficult to assess the prognosis for dogs with collision tumors because of the limited number of reported cases. In humans, it appears that collision tumors are either less biologically aggressive than or as biologically aggressive as their individual component tumor types.[11]

Dog 1 had a 4-cm-diameter perianal gland carcinoma with an adjacent infiltrative hemangiosarcoma and was clinically in remission at 1,009 days following complete mass resection. With regard to perianal gland carcinomas in dogs, tumor size has shown to be associated with outcome; tumors < 5 cm in diameter are associated with a 2-year tumor control rate of > 60% and with an 80% survival rate at 20 months.[17] In dogs, cutaneous hemangiosarcomas confined to the dermis have a metastatic rate of 30% and a median survival time of 780 days.[18] The outcome for dog 1 was within the expected tumor control rate for perianal gland carcinomas (ie, the dog was alive without locally recurrent or metastatic disease at 1,009 days) and had exceeded the expected median survival time for stage I cutaneous hemangiosarcoma in this species.

Dog 2 had a collision tumor composed of a grade III fibrosarcoma with an adjacent low-grade grade II mast cell tumor. No evidence of local tumor recurrence or metastatic disease was evident at 433 days after surgery. The median survival time for dogs with soft tissue sarcoma following surgical excision alone is 1,416 days.[19] This dog had a high-grade fibrosarcoma (according to the described histologic grading system for canine soft tissue sarcomas[19]) with highly pleomorphic oval nuclei and prominent nucleoli, large areas of necrosis, and a mitotic index > 50 mitoses/10 hpfs (100X). In dogs, fibrosarcomas with a mitotic index of < 10, 10 to 20, and > 20 mitoses/10 hpfs are associated with a median survival time of 1,444 days, 532 days, and 236 days, respectively.[18,19] For mast cell tumors, 75% of those classified as grade II by use of the Patnaik histologic grading scheme[2] can be cured via resection alone if margins are complete. However, the biological behavior of grade II mast cell tumors can be unpredictable and, until the more recent description of the 2-tier Kuipel histologic grading system,[20] grade II mast cell tumors were commonly subclassified as low and high grade II on the basis of their mitotic index. For dogs, grade II mast cell tumors with a mitotic index of ≤ 5 mitoses/hpf were considered low grade II, with a median survival time of 70 months following surgical excision; grade II mast cell tumors with a mitotic index of > 5 mitoses/hpf were considered high grade II, with a median survival time of 5 months following surgical excision.[21,22] In dog 2 of the present report, a low grade II mast cell tumor with a mitotic index of ≤ 5 mitoses/hpf was diagnosed. In accordance with the human medical literature,[11] the outcome for this dog did not appear to differ from the expected outcomes for the individual tumor types.

Collision tumors in dogs, while rare, represent a subset of mixed tumors with an unknown prognosis. A search of the database of the Veterinary Diagnostic Laboratories at Colorado State University revealed 41 cases (including dogs 1 and 2 of the present report) of malignant mixed tumors (not of testicular or mammary origin) in dogs. For each case, there was 1 collision tumor/dog. Thirty-nine cases could be defined as collision tumors, with 2 of those cases also having evidence of colonization. Of the other 2 of the 41 cas-

es, 1 was considered to involve a combination (same cell lineage) tumor, and 1 was considered to involve a composite tumor. Although a specific anatomic location was not recorded for 11 dogs (ie, tumor location classified only as cutaneous), there was no obvious preferential body location for development of collision tumors.

Among the 39 collision tumors (including those of dogs 1 and 2 of the present report), the most common combination of tumors was a mast cell tumor and a soft tissue sarcoma (n = 10). The second most frequent collision tumor was composed of a hemangiosarcoma and a carcinoma, with 6 cases recorded, of which 4 were dermal in origin. Four dogs with hepatic collision tumors were identified; each collision tumor involved a primary hepatocellular carcinoma and adjacent hemangiosarcoma.

The relatively high rate of mast cell tumors and soft tissue sarcomas in combination may reflect the frequency of development of these tumors in the dog population rather than their predisposition to collision tumor formation. This pattern may also be true for the human population, in which basal and squamous cell carcinomas with adjacent malignant melanoma are the most commonly reported collision tumors.[12,16]

The 2 cases described in the present report are examples of malignant nontesticular, nonmammary collision tumors in dogs. To date, there is minimal information regarding treatment recommendations and outcome of animals with collision tumors in the veterinary medical literature. The outcomes following complete surgical excision of the collision tumors for the dogs of the present report were similar to outcomes expected following complete surgical excision of any of the individual tumor types in dogs. Wide surgical excision of a collision tumor should be the initial treatment; however, surgical planning may be difficult owing to the inability to identify collision tumors on the basis of gross appearance or cytologic findings alone. Adjunctive treatments, such as chemotherapy or radiation therapy, should be considered depending on the histopathologic diagnosis and other histologic criteria such as tumor grade, if appropriate, and completeness of tumor excision.

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References

1. Jakab C, Balka G. First report of a malignant collision skin tumour with malignant melanoma and anaplastic sarcoma components in a dog. *Acta Vet Hung* 2012;60:245–255.
2. Patnaik AK, Ehler WJ, MacEwen EG. Canine cutaneous mast cell tumor: morphologic grading and survival time in 83 dogs. *Vet Pathol* 1984;21:469–474.
3. Maclachlan NJ, Kennedy PC. Tumors of the genital systems. In: Meuten DJ, eds. *Tumors in domestic animals*. 2nd ed. Ames, Iowa: Iowa State Press, 2002;547–573.
4. Sorenmo KU, Worley DR, Goldschmidt MH. Tumors of the mammary gland. In: Withrow SJ, Vail DM, Page RL, eds. *Withrow and MacEwen's small animal clinical oncology*. 5th ed. St Louis: Elsevier, 2013;538–556.
5. Satter EK, Metcalf J, Lountzis N, et al. Tumours composed of malignant epithelial and melanocytic populations: a case series and review of the literature. *J Cutan Pathol* 2009;36:211–219.
6. Golbar HM, Izawa T, Kuwamura M, et al. A collision tumor consisting of granular cell tumor and adenocarcinoma in the uterus of an aged Djungarian hamster. *J Toxicol Pathol* 2011;24:233–237.
7. Golbar HM, Izawa T, Kuwamura M, et al. A collision tumour consisting of malignant trichoblastoma and melanosarcoma in a rabbit. *J Comp Pathol* 2014;151:63–66.
8. Niu GM, Jin DY, Ji Y, et al. Survival analysis of pancreatic and periampullary collision cancers. *J Dig Dis* 2010;11:231–236.
9. Young J, Potdevin L, Davidov T, et al. Prostate adenocarcinoma metastasis and papillary thyroid carcinoma: a case report of coexisting thyroid tumors. *J Curr Surg* 2012;2:141–143.
10. Inoshita T, Laurain AR, Youngberg GA, et al. Metastasis of bronchogenic carcinoma to the skin involved by melanoma. *Arch Pathol Lab Med* 1984;108:595–598.
11. Papa G, Grandi G, Pascone M. Collision tumor of malignant skin cancers: a case of melanoma in basal cell carcinoma. *Pathol Res Pract* 2006;202:691–694.
12. Cornejo KM, Deng AC. Malignant melanoma within squamous cell carcinoma and basal cell carcinoma: is it a combined or collision tumor?—a case report and review of the literature. *Am J Dermatopathol* 2013;35:226–234.
13. Piérard GE, Fazaa B, Henry F, et al. Collision of primary malignant neoplasms on the skin: the connection between malignant melanoma and basal cell carcinoma. *Dermatology* 1997;194:378–379.
14. Burkhalter A, White WL. Malignant melanoma in situ colonizing basal cell carcinoma: a simulator of invasive melanoma. *Am J Dermatopathol* 1997;19:303–307.
15. Busam KJ, Halpern A, Marghoob AA. Malignant melanoma metastatic to a basal cell carcinoma simulating the pattern of a basomelanocytic tumor. *Am J Surg Pathol* 2006;30:133–136.
16. Boyd AS, Rapini RP. Cutaneous collision tumors: an analysis of 69 cases and review of the literature. *Am J Dermatopathol* 1994;16:253–257.
17. Turek MM, Withrow SJ. Cancer of the gastrointestinal tract. Section H. Perianal tumors. In: Withrow SJ, Vail DM, Page RL, eds. *Withrow and MacEwen's small animal clinical oncology*. 5th ed. St Louis: Elsevier, 2013;423–431.
18. Liptak JM, Forrest LJ. Soft tissue sarcomas. In: Withrow SJ, Vail DM, Page RL, eds. *Withrow and MacEwen's small animal clinical oncology*. 5th ed. St Louis: Elsevier, 2013;356–380.
19. Kuntz CA, Dernell WS, Powers BE, et al. Prognostic factors for surgical treatment of soft-tissue sarcomas in dogs: 75 cases (1986–1996). *J Am Vet Med Assoc* 1997;211:1147–1151.
20. Kiupel M, Webster JD, Bailey KL, et al. Proposal of a 2-tier histologic grading system for canine cutaneous mast cell tumors to more accurately predict biological behavior. *Vet Pathol* 2011;48:147–155.
21. London CA, Thamm DH. Mast cell tumors. In: Withrow SJ, Vail DM, Page RL, eds. *Withrow and MacEwen's small animal clinical oncology*. 5th ed. St Louis: Elsevier, 2013;335–355.
22. Romansik EM, Reilly CM, Kass PH, et al. Mitotic index is predictive of survival for canine cutaneous mast cell tumors. *Vet Pathol* 2007;44:335–341.