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Objective—To characterize the biological behavior and prognostic factors associated with hemangiosarcoma in cats.

Design—Retrospective case series.

Animals—53 cats with hemangiosarcoma.

Procedures—Data were retrieved from a state veterinary diagnostic laboratory, 3 veterinary colleges, and a private practice.

Results—Cutaneous and subcutaneous tumor locations were more common than visceral (abdominal and thoracic) and oral locations. Surgical excision was the primary treatment in 47 cats. Tumor-free surgical margins were more likely in cutaneous than subcutaneous lesions and were associated with longer survival times. Local recurrence was observed in 6 of 12 cats with subcutaneous lesions for which follow-up was available. Metastatic disease was detected in 5 of 13 cats with adequate staging at initial diagnosis. A sixth cat had pulmonary metastases at the time of euthanasia. In 4 of 10 cats with visceral hemangiosarcoma, the diagnosis was made at necropsy or they were euthanized at the time of diagnosis. Adjunct therapy was uncommonly used. Eighteen of the 21 known deaths or euthanasias were tumor-related. Higher mitotic counts (>3 in 10 hpfs) were associated with shorter survival times.

Conclusions and Clinical Relevance—Subcutaneous hemangiosarcoma was more biologically aggressive than the cutaneous form and was more likely to recur locally and result in euthanasia or death of the cat. Metastatic potential of the cutaneous and subcutaneous forms may be greater than previously reported. Visceral hemangiosarcoma is associated with a grave prognosis. (J Am Vet Med Assoc 2007;231:1851–1856)

Hemangiosarcomas, malignant neoplasms arising from the vascular endothelium, are rare in cats and account for <1.5% to 2% of nonhematopoietic neoplasms.1,2 Feline hemangiosarcoma is commonly classified as dermal or visceral, with no distinction made between cutaneous and subcutaneous origins for dermal tumors. Early reports indicated that cutaneous-subcutaneous and visceral forms of hemangiosarcoma occur with similar frequency in cats,3 with those originating within the abdominal cavity having a higher rate of metastasis and a poorer prognosis than those arising from the subcutis.4,5 More recent reports indicate that cutaneous-subcutaneous hemangiosarcoma also has substantial metastatic potential, in addition to the recognized propensity for local recurrence.5,6 Although canine subcutaneous hemangiosarcoma is more likely to metastasize than that of dermal origin,4 data in cats regarding this issue are sparse. The low number of recognized cases of feline hemangiosarcoma has made large studies regarding biological behavior, treatment outcomes, and prognostic factors difficult.

The purpose of the study reported here was to characterize feline hemangiosarcoma and determine the signalment, clinical signs, biological behavior, treatment outcomes, and prognostic indicators associated with this neoplasm. In the present study, hemangiosarcoma tumors were grouped as cutaneous, subcutaneous, visceral (abdominal or thoracic), or other (ie, gingival).

Criteria for Selection of Cases

Cases were selected on the basis of a diagnosis of hemangiosarcoma in a cat. The database of a state veterinary diagnostic laboratory (University of Missouri Veterinary Medical Diagnostic Laboratory) was searched to identify cases of feline hemangiosarcoma diagnosed between December 1992 and March 2002. Additional case records were submitted from 3 veterinary college teaching hospitals (University of Missouri, Auburn University, and Kansas State University) and a private referral practice (Veterinary Referral Clinic, Bedford Heights, Ohio).

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ABBREVIATION

VDC Vincristine, doxorubicin, and cyclophosphamide
Procedures

Histologic slides were reviewed by a pathologist (SET), and mitotic counts were determined by evaluating the number of mitoses observed per 10 high-power (400X) fields. Data from 2 cases were obtained from an additional diagnostic service, although histologic slides and specimens were unavailable for review. Necropsy specimens were also reviewed histologically when available.

Data regarding signalment, initial complaint, tumor staging, treatment modalities, and outcome were collected for all confirmed cases by review of medical records, laboratory submission forms, and telephone interview of referring veterinarians and clients, when applicable.

Distributions of postulated categoric risk factors were determined. Categoric risk factors included sex, breed (domestic shorthair, domestic longhair, or other), tumor site (cutaneous, subcutaneous, visceral, or other), surgical margins (no surgery, complete [tumor-free] margins, or incomplete [non-tumor-free] margins). For continuous variables that were postulated to be risk factors, mean, SD, median, and range were calculated.

The association of postulated risk factors with survival time was determined in a series of Kaplan-Meier product-limit survival analyses. In each analysis, only those records for which data on survival time, cause of death, and the postulated risk factor were available were used. Cats in strata with ≤ 5 observations in the initial dataset were likewise removed from consideration. In the analysis that examined the effect of surgical margins on survival time, 2 analyses were performed. In the first analysis, 3 groups (no surgery, complete margins, and incomplete margins) were considered. In the second analysis, only the complete and incomplete margin groups were considered. Consequently, the number of cases considered varied among analyses. In all analyses, cats that were lost to follow-up or died as the result of a disease unrelated to hemangiosarcoma were censored. Risk factors that had continuous data were stratified by use of a cutpoint that approximated the mean for that variable. For survival analysis determined by use of the log-rank method, P < 0.05 was considered significant.

Results

Case records were reviewed for 53 cats with a histopathologic diagnosis of hemangiosarcoma. One case was identified at Kansas State University, 1 at Auburn University, 4 at the Veterinary Referral Clinic, and the remainder at the University of Missouri. Histologic slides were reviewed, and the diagnosis was confirmed for 51 of these cases; slides were unavailable for 2 cases. Immunohistochemical testing for factor VIII–related antigen had been performed on 7 of the specimens at the time of diagnosis for confirmation of endothelial origin. The study population included 29 neutered males, 3 sexually intact males, 15 spayed females, 4 sexually intact females, and 2 cats of unknown sex. There were 39 domestic shorthair cats, 9 domestic longhair cats, and 5 cats of other breeds. Weight at time of admission was available for 35 cats. Mean ± SD weight was 5.9 ± 2.3 kg (13 ± 5.1 lb). Weight ranged from 2.7 to 14.0 kg (6 to 30.9 lb). Age was available for 52 cats and ranged from 4 to 19 years. Mean ± SD and median ages were 10 ± 3.2 years and 11 years, respectively. Age, breed, sex, and weight were not significantly associated with survival time (Table 1).

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*Median survival time not reported because excessive censoring precluded calculation of survival time. P values were calculated by use of the log-rank method.

DSH = Domestic shorthair. DLH = Domestic longhair.

To convert kilograms to pounds, multiply by 2.2.
Data regarding clinical signs at the time of evaluation were not consistently available to an extent that allowed statistical evaluation. Complete blood counts were available for 12 cats, and 3 cats were anemic (PCV ≤ 23%). Platelet counts were available for 8 cats, and 1 cat was thrombocytopenic (86,000 platelets/µL). Statistical analysis of laboratory data was not possible because of the limited data available.

Twenty-four cutaneous, 17 subcutaneous, and 10 visceral tumors were identified. Two tumors occurred at primary locations (gingival) not within these 3 categories. Primary sites for cutaneous masses included head-face-nose (n = 6 cats), pinna (6), paw-digit (5), thorax (3), flank (2), lumbar region (1), and limb (1). Sites of occurrence for subcutaneous masses included flank (n = 6 cats), ventral abdominal-inguinal region (4), neck (3), thorax-axilla (2), thigh (1), and tail (1). Together, the cutaneous and subcutaneous lesions accounted for 77% of all cases. Primary visceral sites included the liver (n = 3 cats); spleen (2); kidney (2); and 1 each in the colon, mesentery, and mediastinum.

Of the 33 cases, only 13 were known to have had complete staging (thoracic radiography, abdominal radiography, or ultrasonography; or necropsy) at the time of diagnosis. Five of those 13 had documented metastatic disease: 1 mesenteric and 1 liver mass with pulmonary metastases (thoracic radiographic detection); 2 splenic masses with hepatic metastases (surgical detection); and 1 cutaneous flank mass with pulmonary metastases (necropsy detection). One cat with a subcutaneous flank hemangiosarcoma had documented pulmonary metastatic disease at the time of euthanasia (necropsy detection), 475 days following initial diagnosis. Four additional cats (3 with subcutaneous lesions and 1 with a colonic lesion) had suspected metastatic disease at the time of death or euthanasia; however, necropsies were not performed.

Surgical excision was the most common primary treatment modality; only 6 cats received no surgery. Complete surgical resection was accomplished in 19 cats (17/23 cutaneous tumors, 1/16 subcutaneous tumors, and 1/6 visceral tumors). Twenty-eight resections resulted in incomplete surgical margins (6/23 cutaneous tumors, 13/16 subcutaneous tumors, 5/6 visceral tumors, and 2/2 gingival tumors). Local recurrence was documented in 6 of 12 subcutaneous lesions for which adequate follow-up was available. Of the 6 cats with local recurrence, all originally had incomplete surgical excision; locations included flank (n = 4), inguinal (1), and axillary (1) regions. Median time to recurrence was 208 days. Four of the 6 cats had multiple surgical excisions because of recurrence (2 excisions [n = 2] or 3 excisions [2]). The cat with a completely excised subcutaneous flank hemangiosarcoma had no local recurrence at last available follow-up (650 days) without adjunctive treatment. Local recurrence was not reported in any of the 12 cats with cutaneous hemangiosarcoma, including 2 with tumors with incomplete surgical margins, for which follow-up was available (median, 660 days).

Mitotic counts (No. of mitoses observed/10 hpfs) were available for 51 tumors and ranged from 0 to 205. Mean ± SD and median mitotic counts were 10.2 ± 3.4 and 5.0, respectively. Follow-up information, including cause of death and survival time, was unavailable for 19 cats. Eighteen cats died or were euthanized as a direct result of hemangiosarcoma. Sixteen cats were censored. Two of the censored cats died as a result of unrelated disease, and 14 were lost to follow-up after various periods of observation. Survival time was available for 34 cats and ranged from 0 to 1,280 days. Mean ± SD and median survival times were 378 ± 34 days and 283 days, respectively. Tumor site, tumor margins, and mitotic count were significantly associated with survival (Table 1). Subcutaneous tumors were associated with longer survival than visceral tumors, and cutaneous tumors were associated with longer survival than subcutaneous tumors. Completely excised tumors were associated with longer survival than incompletely excised tumors, and cats with incompletely excised tumors had longer survival times than those for which surgical resection was not attempted. The difference between completely and incompletely excised tumors persisted when nonresected tumors were excluded from consideration. Higher mitotic counts (>3/10 hpfs) were associated with shorter survival times.

Adjunctive therapy for cutaneous lesions was limited to 1 cat (dorsal area of the nose, incomplete margins) that was treated with a VDC-c combination chemotherapy protocol (doses and intervals unavailable; survival > 3.5 years). Two cats with incompletely excised subcutaneous masses received chemotherapy following surgery: 1 cat with a tumor in the ventral abdominal region received cyclophosphamide and mitoxantrone (doses and intervals unavailable; survival 440 days, with euthanasia because of an unrelated cause); and 1 cat with a tumor in the axillary region received doxorubicin at 25 mg/m², IV, once every 3 weeks for 4 treatments (survival, 290 days with local recurrence and death suspected to have been caused by thoracic metastatic disease [unconfirmed]). One cat with a recurrent subcutaneous flank mass was treated with cobalt radiation therapy (4 Gy for 13 fractions) following the second surgical excision with incomplete margins (survival, 400 days; 225 days following second surgery, with suspected metastatic disease at euthanasia). Two cats with visceral lesions were treated with adjunctive chemotherapy. One cat with colonic hemangiosarcoma and complete surgical margins received doxorubicin at 25 mg/m², IV, once every 3 weeks for 4 treatments (survival, 150 days with suspected abdominal metastatic disease at euthanasia). Another cat with a mesenteric hemangiosarcoma and incomplete surgical resection received carboplatin (dose and interval unavailable; survival, 60 days with progressive disease). No adjunctive therapy was administered in either cat with gingival hemangiosarcoma.

Discussion

Feline hemangiosarcoma is a rare neoplasm of cats and was diagnosed in only 18 of 3,145 necropsies performed over an 11-year period. Results of a previous study indicated that subcutaneous (without clear distinction between cutaneous and subcutaneous location) and visceral hemangiosarcoma occurred with similar
frequency, with the visceral form being much more locally aggressive and likely to metastasize. More recent reports indicate that hemangiosarcoma is a common skin neoplasm in cats and that the cutaneous-subcutaneous form may have much more aggressive biological behavior and metastatic potential than previously thought. Additional case reports include a cat with an inguinal subcutaneous hemangiosarcoma that developed cerebral metastatic lesions despite chemotherapy (VDC) and 4 cats with primary intestinal hemangiosarcoma (2 with intra-abdominal metastases). Large retrospective studies regarding feline hemangiosarcoma are rare in the literature, and prospective studies evaluating treatment and survival outcomes were not identified.

As in prior reports, no breed or sex predilection was detected in the present study, and most cats were middle-aged to older animals at the time of initial diagnosis. Statistical analysis of laboratory data could not be performed because of the limited data available. In contrast to an earlier report, our results indicated that primary cutaneous and subcutaneous hemangiosarcoma was more commonly diagnosed in cats than visceral hemangiosarcoma, and this finding is supported by results of a recent study. It is unclear whether this is attributable strictly to the biological behavior of hemangiosarcoma in cats or is, in part, the result of the ease of recognition of cutaneous and subcutaneous masses, compared with visceral masses. This is also in contrast to canine hemangiosarcoma, in which splenic and right atrial primary sites predominate, with dermal and subcutaneous sites accounting for only 17% of primary tumors.

Although the specific etiology of hemangiosarcoma is not well understood, the prevalence of cutaneous lesions on the head (including conjunctiva), muzzle, and ears make exposure to UV radiation and local pigmentation characteristics potential predisposing factors. The fact that human angiosarcoma occurs primarily on the scalp and more frequently at sites of previous radiation therapy also lends support to the concept that the effects of radiation are associated with the development of hemangiosarcoma. Other factors implicated in the etiology of angiosarcoma in humans include chronic lymphedema and vascular stasis. Irradiation exposure to the areas where masses developed, as well as pigmentation characteristics at the site of mass removal, could not be determined in the present study given the historical information available. With shoulders and thigh regions being uncommon sites for feline hemangiosarcoma lesions in this study, vaccination-related inflammation was an unlikely factor in tumor development. The reported predisposition for development of feline hemangiosarcoma in the subcutaneous tissue of the flank or inguinal region was confirmed in this study as well.

Surgical excision was the primary treatment modality used for cutaneous and subcutaneous hemangiosarcoma in the present study. Another report of cats with nonvisceral hemangiosarcoma has documented the benefits of surgical resection, revealing a significantly longer median survival time in cats treated with surgical resection, compared with those that did not receive surgery. Our data confirmed that finding and also indicated that completely excised tumors were associated with longer survival than were incompletely excised tumors. Surgical margins in the present study were much more likely to be complete with cutaneous lesions than with subcutaneous masses. Additionally, a high rate of local recurrence (6/12 cases in cases with follow-up) was detected for subcutaneous hemangiosarcoma, compared with cutaneous masses (no recurrence reported). This recurrence rate is similar to that reported previously for feline subcutaneous hemangiosarcoma (60%). The higher rate of local recurrence may indicate more aggressive biological behavior, as is reported for canine hemangiosarcoma. However, the high rate of local recurrence could also be affected by the low rate of complete excision for subcutaneous masses. Results of another recent study also indicated that completeness of excision is the most important factor for predicting clinical outcome in cases of nonvisceral hemangiosarcoma. Regardless, on the basis of the potential for local recurrence, wide surgical margins are indicated when removing a cutaneous or subcutaneous mass that is suspicious for hemangiosarcoma.

Visceral hemangiosarcoma masses were the most aggressive clinically, with more than a third of cats being euthanized at the time of diagnosis or having that diagnosis at necropsy. Four of 10 cats also had metastases at the time of diagnosis, and 1 cat was suspected to have developed metastatic disease by the time of euthanasia. Surgical excision was the primary treatment modality in only 6 of 10 cats with visceral hemangiosarcoma because of the typically widespread nature of the disease, metastases present at the time of diagnosis, or both. These findings are consistent with previous reports.

Unfortunately, complete staging was performed at the time of diagnosis in only a fourth of cats in the present study, which limited detailed information regarding metastatic potential. Although only 2 of the 5 cats with documented metastatic disease at diagnosis had metastases detected via imaging modalities, thoracic radiography and abdominal ultrasonography as well as a minimum data base (CBC, serum biochemical profile, and urinalysis) should be considered in all cats with hemangiosarcoma, regardless of location. A previous report regarding the unusual metastatic behavior of several cases of hemangiosarcoma of cutaneous and subcutaneous origin further supports this recommendation. Because 4 additional cats in the present study were suspected (not documented) of having metastatic disease at the time of death or euthanasia, long-term follow-up imaging after surgery and during adjunctive therapy should be considered. In cats with cutaneous or subcutaneous lesions, staging may also be important to determine whether these masses are primary tumor sites or distant metastases from visceral hemangiosarcoma, as has been reported in human angiosarcoma. Unlike the situation in dogs, echocardiography does not appear to be routinely indicated in cases of feline hemangiosarcoma. Cardiac or pericardial hemangiosarcoma is extremely uncommon in cats, having been rarely reported. The potential benefit of adjunctive therapy following surgical excision of hemangiosarcoma in cats is not well established. Reported adjunctive therapies for feline
hemangiosarcoma include an inguinal subcutaneous hemangiosarcoma treated with a VDC protocol after surgery (450-day survival, CNS metastasis) and a metastatic hemangiosarcoma treated with multiple cycles of vincristine (77-day survival). In the present study, 6 cats received adjunctive therapy after surgical excision. Of cats with visceral hemangiosarcoma, the longest survival time (150 days) was in a cat that received doxorubicin chemotherapy after complete surgical excision of a colonic mass. The cat with cutaneous hemangiosarcoma that had the longest known survival time in the present study (>3.5 years), on the basis of available follow-up information, was treated with a VDC protocol. The cat with subcutaneous hemangiosarcoma that received local radiation therapy had no signs of local recurrence when it was euthanized 225 days after diagnosis because of suspected metastatic disease. The number of cats that received adjunctive therapy was too small to allow statistical comparison of median survival times with those treated with surgical excision alone.

Although our results were limited to a few cases and are potentially biased by the fact that those cats that received adjunctive therapy had more complete follow-up, the results suggest that a multimodality treatment approach may be indicated. On the basis of the high metastatic potential of visceral hemangiosarcoma in cats, chemotherapy would be a valid recommendation, especially in cats in which no signs of metastatic disease are detected at the time of diagnosis. Given the strong tendency for local recurrence and the metastatic potential of subcutaneous hemangiosarcoma, combination adjuvant chemotherapy and local radiation therapy may be indicated after surgery, especially when surgical margins are incomplete. Humans with angiosarcoma who undergo both radical surgery and adjuvant radiotherapy with or without chemotherapy have improved 5-year survival rates, compared with those who undergo either chemotherapy plus radiotherapy or surgery alone. For cutaneous hemangiosarcoma, appropriate treatment recommendations are less clear; however, multimodality therapy may be considered. As evidenced by the fact that 18 of the 21 known deaths or euthanasias were related to hemangiosarcoma, this neoplasm must be regarded with caution.

Even in humans with angiosarcoma, optimum treatment options are frequently unclear. With the most common sites of angiosarcoma in humans being the skin and soft tissue of the head and neck region, treatment primarily centers around wide local excision (when possible) and radiotherapy. Several investigators have reported that surgery with radiotherapy provides the best clinical outcome. For unresectable tumors, chemotherapy has been suggested but has not proven beneficial overall. A more recent study found multimodal treatment, including wide local excision followed by chemotherapy with or without radiotherapy, to be an independent favorable factor in angiosarcoma. The prognosis for humans with angiosarcoma is generally poor, regardless of treatment. One retrospective study revealed 2- and 5-year disease-free survival rates of 44% and 24%, respectively. Of potential prognostic importance is the observation from the present study that high mitotic counts (>3/10 hpfs) determined from histologic specimens were associated with shorter survival times, compared with low mitotic counts. This indicated that the mitotic count may serve as a crude index of biological aggressiveness for feline hemangiosarcomas. This is consistent with findings in human angiosarcoma indicating that mitotic count is the most prognostically important factor for histologic grading of angiosarcoma.

The choice of the type of analysis used in this study, multiple univariate survival analysis, is a subject that deserves further discussion. Each independent analysis carries an inherent risk of a type I error, that is, the incorrect finding of a significant difference among groups when no such difference is actually present. As the number of univariate analyses increases, the potential for type I errors is compounded. Multivariate analyses would have eliminated this concern. An additional benefit of a multivariate analysis would have been the ability to identify and eliminate potential confounding relationships among independent variables. For example, tumor site, tumor margins, and mitotic counts were all significantly associated with survival time in the present study. If tumors at different sites had different mitotic counts, differences in survival time could erroneously be attributed to tumor site when these differences were actually related to mitotic count. Multivariate analyses have the potential to isolate the effect of related independent variables on the dependent variable. Unfortunately, the dataset available for this study precluded a multivariate analysis. No more than 17 cases were available for any univariate analysis, and in many instances, as few as 14 cases were available for analysis. Even a bivariate analysis in which 2 risk factors were simultaneously considered as predictors of survival time would likely have been inappropriate because unique combinations of 2 risk factors would only have been represented 3 or 4 times within the dataset. More extensive multivariate approaches in which all 8 potential independent variables were considered would have generated a large number of combinations of risk factors with 0 relevant observations. Although clearly a compromise, the multiple univariate analysis used in this study was deemed the logical and appropriate approach.

Results of the present study indicated that in cats cutaneous and subcutaneous hemangiosarcoma may occur more commonly than visceral hemangiosarcoma. Similar to canine hemangiosarcomas, feline subcutaneous hemangiosarcomas are more likely to be incompletely excised, recur locally, and have more aggressive biological behavior than cutaneous masses. Thus, subcutaneous hemangiosarcoma may warrant more aggressive surgical excision, multimodality therapy, and a more guarded prognosis. Mitotic count may serve as a prognostic indicator, with a poorer prognosis warranted when mitotic count exceeds 3 in 10 hpfs. As in dogs, visceral hemangiosarcoma in cats warrants a poor to grave prognosis despite therapeutic interventions. As additional cats with hemangiosarcoma are treated with adjunctive therapy, more detailed information regarding the best treatment options and response to specific therapy will hopefully become available.

a. Oncovin, Eli Lilly, Indianapolis, Ind.
c. Cytoxan, Bristol-Myers Squibb, Princeton, NJ.
References