Sunlight-Induced Skin Cancer in Companion Animals

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Key Points

- Animals with pale skin and thin hair coats are at increased risk of suffering solar injury.
- The two most prevalent neoplastic lesions induced by ultraviolet irradiation are cutaneous squamous cell carcinomas (cSCC), in dogs and cats, and cutaneous hemangiosarcoma (cHSA), primarily seen in dogs.
- Squamous cell carcinomas account for 1.25–15 % of all cutaneous tumors in dogs and for approximately 15–50 % of all cutaneous tumors in cats.
- The classic multistep colorectal carcinogenesis model is useful for understanding the progression of sunlight-induced skin lesions from the premalignant actinic keratosis (AK) stage to fully manifested cSCC.
- Alterations in the *p53* gene product comprise the most common genetic abnormalities found in actinic keratosis (AK), in situ SCC (ISSCC) and cSCC. In addition, immunocompromised status and viral pathogenesis may play a contributory role in cSCC development.
- Prognostic factors for cSCC in veterinary medicine related to recurrence and metastasis are unknown. Cutaneous SCC lesions in dogs and cats are considered to be slow to metastasize. In humans, prognostic factors include size and location of the primary tumor, tumor differentiation, and histologic features such as involvement of the reticular dermis or underlying tissues.
- Most veterinary patients with primary sunlight-induced cSCC have a good-to-excellent prognosis when lesions are detected and addressed early in the course of disease.
- Squamous cell carcinoma lesions occurring on sun-exposed skin have better prognosis than those occurring in unexposed skin.
- Local modalities of treatment include complete surgical excision as the most cost-effective and successful means of local control for cSCC.
- Molecular understanding of the pathogenesis of HSA is primarily focused on visceral disease and seems to be consistent with the biology of human angiosarcoma lesions.

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A. Baldi et al. (eds.), *Skin Cancer*, Current Clinical Pathology,
DOI 10.1007/978-1-4614-7357-2_33,

- Heterozygosity of chromosome 22, chromosomal deletions of the tumor suppressor gene PTEN, and amplifications or rearrangements of various genes are genomic abnormalities frequently found in cHSA in humans.
- Cutaneous HSA is commonly observed in predisposed breeds such as American Staffordshire terriers, pit bulls, beagles, Dalmatians, Italian greyhounds, whippets, and bull terriers.
- Identified prognostic factors included breed, tumor location, and the presence of solar actinic changes.
- Locoregional recurrence is very common in predisposed thin-coated breeds with the solar-induced form of this disease.
- Metastasis was documented or suspected in 34 % of dogs with cHSA and occurred at a median of 326 days from diagnosis. Progression to the visceral form of HSA was observed in 62 % of dogs with metastatic disease.
- Overall, the median survival for dogs treated by surgical excision with no adjuvant chemotherapy was reported to range from 780 to 987 days, with 1-, 2-, and 3-year survival rates of 79, 60, and 44, respectively. Median survival was 1,095 days in surgically treated cats with cHSA.
- Cutaneous HSA lesions are most often treated with curative-intent surgical excision.
- Biopsy margin status documenting complete surgical excision, absence of metastasis, and no subcutaneous invasion were surprisingly unassociated with incidence of local recurrence.
- The dearth of prospective studies defining the clinical behavior of cHSA results in uncertainty and controversy regarding the role of complete surgical excision of the lesion as a predictor of clinical outcome in dogs and cats.
- Use of chemotherapy in management of dogs and cats affected by cHSA is largely recommended only if there is evidence of invasion of the subcutaneous tissue or of distant metastasis.
- Doxorubicin-based protocols provide several more months of survival time for these cats, when compared to no therapy.
- Metronomic therapy may be feasible as a first-line therapy option for patients with cHSA that cannot undergo surgery protocols.

Background and Pathogenesis of Dermal Injury by UV Light

As the skin is the largest organ in the body, it is perhaps unsurprising that skin tumors represent one third of the tumors diagnosed in dogs [1]. The incidence rate of skin tumors has been increasing throughout the past decades (1960–2000), representing 1.9–3.6 % of tumors diagnosed in dogs examined at veterinary teaching hospitals in North America, as compiled by the Veterinary Medical Database [2].

Companion animals are largely protected from the carcinogenic effects of ultraviolet light by having adequate pelage and dermal pigmentation. However, animals with pale skin and thin hair coats are at increased risk of suffering solar injury. The two most prevalent neoplastic lesions induced by ultraviolet irradiation are cutaneous squamous cell carcinomas (cSCC), in dogs and cats, and cutaneous hemangiosarcoma (cHSA), primarily seen in dogs.

Squamous cell carcinoma arises from epidermal stem cells that have the potential for self-renewal and multi-lineage differentiation. These stem precursors are located in the hair follicle bulge and the basal layer of the interfollicular epidermis. There is also evidence that bone marrow-derived cells may home to the bulge region of the epidermis in response to skin wounding and there differentiate into keratinocyte stem

cells [3]. The classic multistep colorectal carcinogenesis model described by Fearon and Vogelstein et al., in 1990, is useful for understanding the progression of sunlight-induced skin lesions from the premalignant actinic keratosis (AK) stage to fully manifested cSCC [4].

The spectrum of electromagnetic solar radiation interfacing the Earth's atmosphere is comprised of five regions based upon light wavelengths. Light in the ultraviolet spectrum (UV-A, UV-B, and UV-C) is in an invisible wavelength form that comprises 3 of the 5 spectra. The UV spectrum of radiation is of medical interest because these wavelengths have both carcinogenic and germicidal properties [5]. In fact, the high incidence of cSCC is caused by the mutagenic effects of ultraviolet light (UV) which is intensified by geographic latitude [6, 7]. The mechanism leading to genomic instability in keratinocytes likely results from ultraviolet-β (UV-B)-induced inactivation of the p53 gene product, which acts as a tumor suppressor gene in skin cancer. In humans, it is estimated that approximately 58 % of cSCCs harbor UV-B signature mutations such as CC:GG to TT:AA and C:G to T:A transitions [8]. The precise mutational events in cutaneous carcinogenesis in dogs and cats are less well established, although missense mutations in highly conserved regions of the p53 gene have been reported in the veterinary literature [9, 10]. Alterations in the *p53* gene product comprise the most common genetic abnormalities found in actinic keratosis (AK), in situ SCC (ISSCC) and cSCC, demonstrating that dysplastic lesions have acquired an initiating genetic mutation prior to becoming cSCC. This is evidenced by the fact that p53 dysfunction generally occurs prior to tumor invasion [11]. Additionally, aberrant activation of epidermal growth factor receptor (EGFR) and Fyn, a Src-family tyrosine kinase, is seen in human cSCCs. These kinases downregulate p53 mRNA and protein levels, revealing another mechanism for controlling p53 function [12].

Loss of heterozygosity has also been observed in human cSCCs at chromosome 9p21. This region contains several tumor suppressor genes, including p16INK4A (CDKN2A), p15INK4B, and MTAP. These genes are hypothesized to be associated with progression from AKs to cSCCs [13, 14].

Activating mutations of the Ras oncogene have been found in cSCCs and AKs [15]. Ras family members are proto-oncogenes that transduce cellular growth and proliferation signals downstream of cell-membrane-bound receptor tyrosine kinases (RTKs). Ras can be activated by gene amplification, activating mutations, or overexpression of upstream RTKs [16].

Epigenetic effects refer to the molecular mechanisms that regulate gene expression in the absence of changes in the DNA sequence itself. Epigenetic alterations include DNA promoter methylation and histone protein modifications, which consist among others of methylation, acetylation, or phosphorylation of histone cores [17]. Epigenetic dysregulation is thought to be involved in tumor biology and cancer progression. In fact, a higher level of expression of FOXE1, a promoter of hypermethylation, was found in cSCC compared to normal skin, indicating that FOXE1 may be a direct target for the aberrant methylation noted in cSCC lesions [18]. In a similar manner, it has been shown that a distinct microRNA profile is modulated by UV radiation [19].

Cutaneous HSA has been also associated with ultraviolet light exposure in dogs [20, 21]. Molecular understanding of the pathogenesis of cHSA is primarily focused on visceral disease and seems to be consistent with the biology of human angiosarcoma lesions. In human dermatology, cHSA lesions are predominantly seen in older men who work in outdoor occupations that result in excessive sunlight exposure to the scalp, face, and ears [22]. Tumor-derived HSA cell lines express hematopoietic stem cell markers, suggesting that they arise from bone marrow-derived pluripotent stem cells [23, 24]. Genomic abnormalities have been noted in cHSA lesions in people. These include large chromosomal abnormalities such as loss of heterozygosity of chromosome 22, chromosomal deletions such as at the C-terminal domain of the tumor suppressor gene PTEN, and amplifications or rearrangements of various genes. However, the importance of these mutations or

gene amplifications for tumorigenesis in canine and feline cHSA is still unknown [25].

Loss of vascular endothelial cadherin (VE-cadherin) may be involved in cancer gene regulation, facilitating angiogenesis, tumor cell invasion, and metastasis [26]. Mutations of tumor suppressor gene p53, Kras, VEGFR2, and VEGFR3 have been associated with angiosarcoma pathogenesis in humans [27–29]. A progression from cutaneous hemangioma to cHSA may occur, reflecting phenotypic development of more malignant tumor as a result of repeated genetic damage. Subcutaneous hemangiomas do not seem to have this progression [20].

Viral pathogenesis may play a contributory role in cSCC development. Viruses associated with SCC lesions include papillomavirus (PV) and retroviruses such as FIV which cause immunosuppression in cats. Papillomavirus is commonly present in normal skin, and it is possible that this virus is an innocent bystander. Papillomavirus DNA has been detected within cutaneous in situ SCCs of cats and dogs, but evidence that PVs increase the development and progression of these lesions is less conclusive in animals [30–32]. However, the frequent and rapid progression of endophytic papillomas to in situ SCCs observed in severe combined immunodeficiency (SCID) dogs suggests that CfPV-2 infection can cause neoplastic transformation [33, 34]. Three theories have been suggested for the mechanism of human PV (HPV) carcinogenesis. First, UV radiation-induced immunosuppression may explain enhanced interaction between HPV and UV radiation [35]. Second, viral expression of E6 and E7 oncoproteins can inactivate p53 and Rb tumor suppressor genes, leading to an unregulated system of cell proliferation and apoptosis [36]. Finally, integration of HPV DNA may disrupt genomic stability [37].

An immunocompromised status is associated with marked escalation of cSCC, with up to 64–250 times greater incidence noted than that seen in the general human population. Immunosuppression significantly impacts the biology of cSCC. In solid organ transplant patients, cSCC tumors, mostly associated with papillomaviruses, tend to be numerous, exhibit a strong propensity to recur, and metastasize at a high rate regardless of lesion size [38].

Feline immunodeficiency virus (FIV) causes immune dysfunction, and it is also associated with an increased incidence of cancers [39–41]. Reported incidence of FIV-associated tumors, predominantly lymphomas, ranges from 1 to 21 % of FIV-positive cats. Infection with this chronic retrovirus has also been described in cats with cutaneous tumors [42].

The general epidemiologic information referenced here reflects the geographic diversity of the reported studies cited (Australia, Greece, the United Kingdom, the United States of America, and Zimbabwe). Also, the diagnostic methodology employed in these studies was varied. Therefore, epidemiologic information must always be interpreted cautiously rather than as broadly applicable discrete facts.

Squamous Cell Carcinoma of the Skin

Incidence and Risk Factors

Squamous cell carcinomas account for 1.25–15 % of all cutaneous tumors in dogs. Squamous cell carcinomas reportedly range between the second and the sixteenth most common canine skin tumor type, depending on the referenced study [2, 43]. In cats, SCC accounts for approximately 15–50 % of all cutaneous tumors, making this among the four most common feline skin tumors, along with basal cell tumors, mast cell tumors, and fibrosarcomas [44, 45]. Common locations for SCC in dogs are the oral cavity, nasal planum, and nail bed (Fig. 33.1). This is as opposed to locations associated with ultraviolet sunlight exposure, such as on the flank, medial thighs, or abdomen in the skin of short-coated, lightly pigmented dogs [46, 47]. The most common location of cSCC in cats is the head, where 57–65 % may be observed on the ear pinna. Other common sites of feline cSCC include the nasal planum, eyelids, preauricular area, and lips (Fig. 33.2) [44, 45]. Cutaneous SCC commonly affects older dogs and cats, with a mean of 8 and 12 years of age, respectively, and there appears to be no gender predilection [47]. Overall, cSCC is most common in

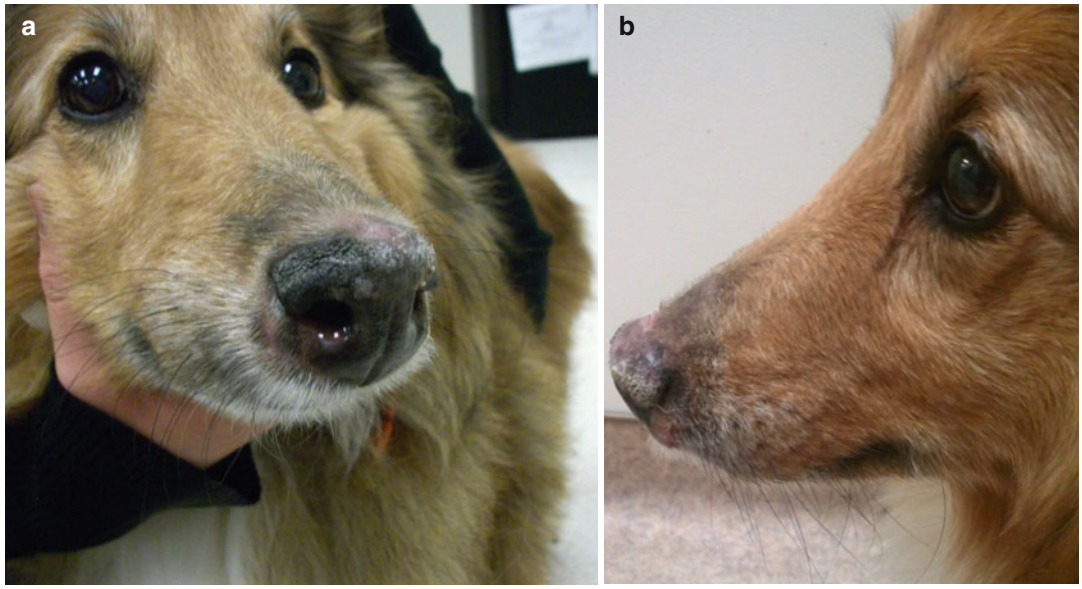

Fig. 33.1 Frontal (**a**) and lateral (**b**) view in a dog with diffuse and infiltrative SCC of the nasal planum. Please note marked depigmentation and asymmetry associated with the lesions

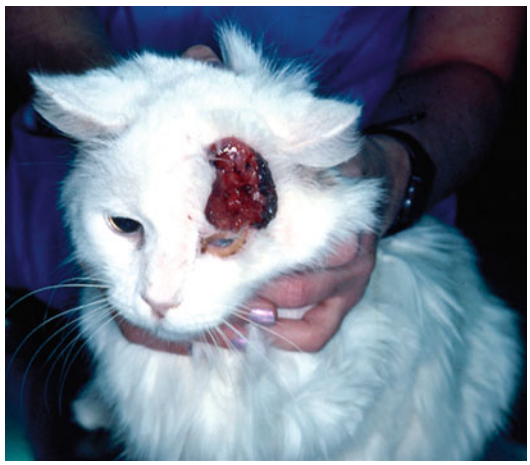

Fig. 33.2 White-coated cat with advanced, aggressive cutaneous SCC lesion and progressing to the periorbital area

animals without pigmentation in areas of sparse hair coat, and there is a reported 5–13 times higher incidence in white-coated than in pigmented cats [47, 48]. Similarly, cSCC are overrepresented in Dalmatian dogs (6.94 odds ratio compared to dogs with no cutaneous neoplasias) and Basset hounds (3.97 odds ratio vs. dogs with no cutaneous neoplasias). Not surprisingly, cSCC lesions are underrepresented in colorpoint breeds, such as Siamese cats [2, 45].

Biologic Behavior

Canine SCC of the oral cavity has site-associated metastatic behavior, with tumors of the rostral aspect of the mouth less prone to metastasis than those of the caudal tongue, oropharynx, and tonsil [49]. However, this site-associated metastatic behavior has not been reported for cSCC. Prognostic factors for cSCC in veterinary medicine related to recurrence and metastasis are unknown. In humans, the most important factors affecting risk of recurrence and metastasis are the size and location of the primary tumor. Large lesions, considered to be those greater than 2 cm in diameter, recur at a rate of 15 %, which is twice that of smaller lesions. These larger lesions also metastasize at a rate of 30 %, three times that of smaller lesions [50]. Squamous cell carcinomas of the human lip and ear are also aggressive lesions, with rates of recurrence and metastasis ranging from 10 to 25 % [50, 51]. Other sites associated with a high risk of recurrence and metastasis in humans are eyelid, nose, and mucous membranes [52, 53]. Locally recurrent squamous cell carcinomas metastasize at rates that range from 25 % for most cutaneous lesions to 30–45 % for ear and lip tumors [50, 52]. Squamous cell carcinomas arising in injured,

chronically diseased or chronically inflamed skin can also demonstrate more aggressive clinical behavior and a greater propensity to metastasize, with an overall metastatic rate of 40 % [50, 54]. Clinical features associated with recurrence and metastases include rapid growth and local recurrence of the tumor as well as immunosuppression [52]. Histologic features that are predictive of recurrence or metastasis include a depth of more than 4 mm, involvement of the reticular dermis or underlying tissues. Poorly differentiated cSCC in humans recurred at a rate of 28.6 %; in contrast, well-differentiated tumors had a local recurrence rate of 13.6 % [50].

However, despite the fact that the majority of these tumors present at early stages, cSCC accounts for the majority of non-melanotic skin cancer deaths and 20 % of all skin-cancer-related deaths in humans [50, 55]. For those with metastatic disease, however, the long-term prognosis is extremely poor [56]. In humans, if metastasis does occur, regional lymph nodes are involved in approximately 85 % of cases; approximately 15 % of cases involve distant sites, including the lungs, liver, brain, skin, and bone [56, 57].

Most veterinary patients with primary sunlight-induced cSCC have a good-to-excellent prognosis when lesions are detected and addressed early in the course of disease. Lesions occurring on sun-exposed skin have better prognosis than those occurring in unexposed skin. In North America, dogs and cats affected by sunlight-induced cSCC are often kept outdoors, and lesions may not be detected in early stages. Also, owners may be less willing or financially unable to seek veterinary care for their outdoor pets, when the lesions are most manageable. Fortunately, cSCC lesions in dogs and cats are slow to metastasize. Small and superficial lesions may never progress, whereas more deeply invasive lesions can become metastatic by the lymphatic route primarily. Ultimate visceral metastasis can be seen in end-stage cases [47].

Diagnosis

Cytology may allow differentiation of neoplastic from inflammatory lesions and of epithelial from spindle cell tumors. Cytologic diagnosis of ulcerative lesions may be problematic, as inflammation can induce secondary proliferative changes in epithelial cells even in benign lesions. Moreover, ulcerative lesions may be associated with lymphadenopathy, which may be reactive or may represent metastasis to regional nodes in cases with cSCC. Cytologic examination of enlarged regional lymph nodes should be performed before definitive therapy. Histologic examination of the tumor is important for further treatment planning and identifies possible prognostic factors associated with the suspected malignancy such as grade or level of cellular differentiation. In addition, histopathology allows determination of invasion and whether surgical excision was adequate. Cutaneous lesions are rarely metastatic to visceral organs; however, systemic staging for pulmonary metastasis is indicated for patients with advanced local disease or nodal metastasis. Advance local staging with CT scanning may be helpful for surgical and radiation therapy planning [47].

Treatment

Cutaneous SCC lesions may be locally aggressive but are slow to metastasize. Thus, adequate local control may be curative for these tumors, particularly when they are addressed early in the clinical course of disease. Local modalities of treatment include complete surgical excision as the most cost-effective and successful means of local control. Complete excision with 1–3 cm surgical margins may be curative for most lesions. This might necessitate ear pinna amputation in cats, or nasal planum resection, which owners may consider unacceptably disfiguring. For lesions not amenable to resection due to size or location, radiation therapy, cryosurgery, electrochemotherapy, photodynamic therapy, or intralesional chemotherapy may be helpful.

Cryosurgery

Cryosurgery is a minimally invasive procedure that destroys malignant tissue through inducing cell death by formation of intracellular and extracellular ice crystals. Liquid nitrogen, argon, and

dimethyl ether-propane are frequently used as cryotherapy agents. The agent is directly applied to the skin or introduced by cryoneedles for delivery. Most canine and feline cSCC treated with cryosurgery achieve good-to-excellent overall remission rates (80 %), although many required multiple treatments and development of recurrence is observed in up to 73 % of cases. Recurrence of the malignancy is mostly associated with degree of infiltration (deep vs. superficial) and volume size (>0.5 cm in diameter) of the mass [48, 58, 59].

Most of the adverse effects associated with this low-cost therapy, including erythema, bleeding, blisters, and minimal pain, are localized and well tolerated by the patient.

Electrochemotherapy

Electrochemotherapy is a form of localized treatment for tumors that involves administration of a chemotherapeutic agent combined with delivery of appropriate energy waveforms. The ultimate goal of those waveforms is to induce an increased uptake of the drug by cancer cells. One published manuscript for treatment of cSCC describes the local administration of bleomycin (1–1.5 mg/cm^3 of lesion) followed in 5 min by permeabilizing biphasic electric pulses. Eight pulses of 50 + 50 μ (microns) at 1,300 V/cm^3 are delivered by a pair of electrodes. Total treatment consists of two sessions of electrochemotherapy 1 week apart. Toxicity reported was described as mild erythema localized to tumor lesion and was transient and well tolerated by cats. Almost 80 % (7/9 cases) of the patients had a complete response (CR), and 55 % (5/9) had durable control lasting more than 1 year [60, 61].

Intralesional Chemotherapy

This treatment modality involves the direct intratumoral delivery of chemotherapeutic agents. Site-directed administration of the drug is intended to achieve local control of malignancy by providing a higher tumor-to-plasma ratio of the drug over a prolonged period of time. An additional advantage of this therapy is reduced to absent systemic adverse effects.

Cisplatin (1 mg/cm^3 of tissue target in oily emulsion) and bleomycin (1 mg/cm^3 of tissue) four times a week on a 2-week interval has proven efficacious in treatment of cSCC in horses. The local control rate at 1 year for lesions treated with cisplatin was approximately 93 % and with bleomycin was approximately 78 % [62, 63]. Cisplatin in cats at standard IV doses (50–70 mg/m^2) is lethal through induction of severe pulmonary edema. However, local injection as repositol implants, consisting of purified cosmetic-grade bovine collagen matrix (20 mg/ml), epinephrine (0.1 mg/ml), and the chemotherapy agent (cisplatin 3.3 mg/ml), resulted in 86 % CR and 4 % partial response (PR) after 2 weekly treatments on average for a study population of 17 cats with a total of 51 cSCC lesions. Average disease-free interval (DFI) was 10.5 months with a local recurrence rate of 30 % in these cats (B. Kitchell 1994, personal communication).

The antimetabolite chemotherapeutic agent fluorouracil (5-FU) inhibits both RNA and DNA synthesis and targets dividing cells. Fluorouracil in cats at standard IV human doses (400–600 mg/m^2) induces rapidly lethal neurotoxicity. In fact, it is possible to see fatal neurotoxicosis in cats with the use of 5 % topical fluorouracil cream to the ear tips [64].

One study described the use of collagen implants as described above, substituting fluorouracil (5-FU 30 mg/ml) for cisplatin in the formulation. Using a regimen of 3 weekly implants, 58 % CR and 17 % PR were noted for a study population of six cats with a total of 16 lesions. Average DFI was 5 months with local recurrence rate of 14 %. Mild-to-moderate local adverse effects such as erythema and desquamation were noticed (B. Kitchell 1994, personal communication).

Intralesional delivery of chemotherapy in purified bovine collagen with fluorouracil as described above was applied to 13 dogs with sunlight-induced cSCC with 100 % overall response rate (54 % CR, 46 % PR). Cisplatin (3.3 mg/ml) in the collagen gel implant was given sequentially when CR was not achieved with fluorouracil, and no further reduction in area of the tumor was apparent after 2 weekly injections of fluorouracil implants. Cisplatin implants achieved CR that provided DFI of 44 months in two cases that achieved initial PR

after treatment with fluorouracil implants. Partial remission allowed complete surgical excision to achieve cure in 3/6 dogs. The average DFI was almost 50 months. Further, weekly fluorouracil or cisplatin collagen implant treatments were well tolerated with minimal local erythema and no systemic adverse effects [65, 66].

Photodynamic Therapy (PDT)

This treatment modality consists of intravenous injection of an inert photosensitizer that is activated by light at the appropriate wavelength (600–900 nm "therapeutic windows"). Upon activation, the photosensitizer can undergo type I reaction, reacting directly with substrates such as DNA. Alternately, the photosensitizer can undergo type II reaction, directly producing free radicals or interacting with molecular oxygen to generate cytotoxic reactive oxygen species.

In a previous study, six feline cSCC were treated, resulting in two partial responses and four long-term complete responses with DFI that ranged from 276 to 576 days. Toxicity was described as tolerable and mostly localized to the skin. Erythema was noted and ulceration was occasionally observed, especially when PDT was applied for lesions of the eyelid. Systemic toxicity included nausea associated with the photosensitizer injection and elevated body temperatures 2 days after PDT. In one cat, anorexia and peripheral neuropathy of undetermined cause noted 2 weeks after PDT resolved without treatment [67]. Another study described the use of a novel liposomal photosensitizer for PDT in 18 cats. Local toxicity consisting of erythema and edema was reported in 15 % of the patients, and the CR rate was100 %. The overall 1-year control rate was 75 %. The tumor recurrence rate in this cohort of patients was 20 % with a median time to recurrence of 172 days [68]. Similar response rates (overall response rate 96 %; CR 84 % and PR 11 %) to a single treatment with topical photosensitizer (5-ALA) were observed by Bexfield et al. [69] in a population of 56 cats with nasal planum cSCC. Recurrence was noticed in 51 % of the cases, with a median time to recurrence of 157 days. At a median follow-up of 1,146 days, 45 % of cats were alive and disease-free but 33 % had to be euthanized due to local tumor recurrence. In this study, erythema and edema were observed in all cats after treatment, but these adverse effects were localized, mild, and transient. The lesions appeared to cause some discomfort, as manifested by occasional rubbing of the nasal planum [69].

Topical Therapy

Imiquimod is an antiproliferative agent and immune system stimulator. Imiquimod acts as a Toll-like receptor 7 agonist. Activation of this receptor protein plays a fundamental role in pathogen recognition and activation of innate immunity. Imiquimod is available as a topical cream and has been used to treat in situ cSCC presented as multiple lesions not invading the basal layer of the skin [70]. Imiquimod 5 %, used once daily on an alternate-day dosing regimen was associated with 100 % (40 % CR, 60 % PR) response rate in 12 cats affected by in ISSSC. Because of multifocal nature of the disease, appearance of new masses was observed in 75 % of the cats included in the study, and treatment duration extended to approximately 300 days on average. New lesions also responded to treatment in all cats. Toxicity was reported in 40 % of the cats. The toxicity observed included local erythema, mildly increased liver enzymes, mild neutropenia, anorexia, and vomiting [71–73].

Radiation Therapy

Most of the published data is focused on radiation therapy for cSCC of the nasal planum in cats. The volume of cSCC lesion treated was inversely associated with DFI and survival time [74]. Orthovoltage fractionated radiotherapy given as a total dose of 40 Gy provided a 1-year progression-free survival rate of 60 % in 90 cats with nasal planum SCC [74]. Proton therapy achieved similar control rates to orthovoltage radiotherapy with an overall response rate of 93 % in 15 cats with nasal planum SCC [75]. Plesiotherapy is a direct application of a strontium-90 radiation source to superficial cutaneous lesions. In this therapy, 50 Gy of radiation is delivered to a depth of 2 mm and administered in five fractions over a 10-day period to small (2–5 cm diameter)

superficial lesions. This treatment achieved 87 % complete remission with no local recurrence noted for 2 years in 15 cats with cSCC [76]. Radiotherapy was not as effective in controlling residual cSCC in seven dogs that failed surgical curative-intent resection. Radiation therapy alone in three dogs only provided control of the disease for no longer than 8 weeks as an average [77].

The retinoic acid drugs called retinoids are derivatives of vitamin A, which is an essential factor for epithelial cell differentiation. Retinoids have been demonstrated to induce growth inhibition of premalignant lesions such as actinic keratoses, by induction of terminal differentiation, apoptosis, and cell cycle arrest [78]. Administration of etretinate to ten dogs at 1 mg/kg twice daily for a minimum of 90 days induced complete resolution of preneoplastic lesions in two dogs and partial responses in three dogs. Treatment toxicity included reversible hypertriglyceridemia and transient serum liver enzyme elevations in three dogs [79].

Systemic chemotherapy is not typically used to treat cSCC, as these lesions are rarely systemically disseminated. Agents such as carboplatin, bleomycin, fluorouracil, and doxorubicin have been administered with limited effect. The use of nonsteroidal anti-inflammatory agents such as piroxicam has been used in adjunctive protocols, as there is some evidence of tumor regression in oral SCC in the dog. Pain control afforded by NSAIDS may have a palliative effect for the patients, even if direct anticancer effect is not noted [80].

Future Treatment Strategies

The signal transducing G-coupled peptide Hras upregulates *Fyn* mRNA, and this suggests the potential for an interesting biologic relationship between Ras and Fyn in cutaneous neoplasms such as cSCC. Ratushny et al. [4] proposed the topical application of small-molecule kinase inhibitors (SMKIs) that have the physical properties required to penetrate the skin. The ideal SMKIs would target Fyn and related tyrosine kinases or would target kinases in the Ras pathway. The tyrosine kinase inhibitor dasatinib is smaller than 500 Da in molecular size and targets multiple tyrosine kinase receptors, including Fyn. Topical dasatinib has been proposed as a possible therapeutic agent in this context [81]. Metronomic chemotherapy protocols involving the use of the oral receptor tyrosine kinase inhibitors toceranib and masitinib have some modest evidence of efficacy against oral SCC lesions, which might prove helpful in cSCC management as well [82].

Cutaneous Hemangiosarcoma

Incidence and Risk Factors

Hemangiosarcoma is a malignancy of vascular- or vessel-forming cells. The median of age range of dogs at the time of diagnosis of hemangiosarcomas affecting the cutis (cHSA) is approximately 10 years; in cats the median age at diagnosis is approximately 12 years [20, 83–85]. There is no known sex predilection, but most cutaneous vascular tumors (hemangiomas and hemangiosarcomas) in cats have been reported in males [20, 45, 83–85]. Hemangiosarcomas of the skin have predilection for cutaneous over subcutaneous tissue and for glabrous, lightly pigmented skin when compared with haired skin. Dogs with short hair coats and lightly pigmented skin have more hemangiomas and hemangiosarcomas of the cutis than do dogs with variable length hair coats and pigmentation [20]. Cutaneous HSA is commonly observed in predisposed breeds such as American Staffordshire terriers, pit bulls, beagles, Dalmatians, Italian greyhounds, whippets, and bull terriers [20, 83, 85]. Outdoor cats with unpigmented skin may be predisposed to cutaneous tumor development in areas without adequate pelage, particularly on the pinna and head [84].

Cutaneous HSA usually presents as solitary or multiple small cutaneous lesions, often less than 1 cm in diameter. In a recent report of 94 dogs with suspected or confirmed diagnosis of cHSA, 71 % of the cases at initial diagnosis had one solitary dermal lesion, and 29 % had multiple cutaneous lesions [20, 83]. Whether the presence of multiple sites of cHSA is a result of metastasis or whether

the lesions arise de novo as multiple primary tumors is unclear.

Biologic Behavior

Recently, Szivek et al. [83] were able to identify prognostic factors that predict outcome for cHSA in dogs. Identified prognostic factors included breed, tumor location, and the presence of solar actinic changes. Predisposed breeds were found to have a median survival of 1,570 days compared with 593 days in non-predisposed or atypical breeds. Predisposed breeds had a lower metastatic relative risk of 0.45 when compared with non-predisposed breeds. Tumor location predicted survival of dogs with cHSA. Dogs with lesions arising in typical sun-exposed ventral abdominal locations had a median survival of 1,085 days compared with 539 days for dogs with tumors seen in other body locations. Tumor location also predicted locoregional recurrence. The solar-induced form associated with actinic changes has a reported median survival of 1,549 days compared with 545 days in dogs without actinic lesions [83]. The prognostic significance of association of solar elastosis or actinic changes with outcome of cHSA is controversial in the literature, however [83, 85]. Dogs of non-predisposed breeds with tumors in areas other than the ventrum, and that also lack actinic changes, or those with subcutaneous involvement appear to have a more aggressive form of HSA with higher risk of developing visceral HSA. Dogs with subcutaneous invasion have an associated metastatic relative risk of 2.04 when compared to dogs with only cutaneous involvement [83].

Lesions confined to the dermis are correlated with better prognostic outcome and lower recurrence rates, possibly because of ease of surgical excision [85]. Cutaneous HSA lesions may be easier to excise completely, and recurrence is much less frequent than for tumors involving deeper tissues. Locoregional recurrence is very common in predisposed thin-coated breeds with the solar-induced form of this disease. The incidence of metastasis is considered to be low in cHSA in dogs and cats, but some patients may ultimately develop metastatic disease. Metastasis was documented or suspected in 34 % of dogs with cHSA and occurred at a median of 326 days from diagnosis. Progression to the visceral form of HSA was observed in 62 % of dogs with metastatic disease. These dogs are frequently diagnosed by the presence of hemoabdomen that occurs in more than the 95 % of the cases with visceral metastasis. Overall, the median survival for dogs treated by surgical excision with no adjuvant chemotherapy was reported to range from 780 to 987 days, with 1-, 2-, and 3-year survival rates of 79, 60, and 44 %, respectively. Median survival was 1,095 days in surgically treated cats with cHSA [20, 83, 84].

Diagnosis

Cutaneous HSA lesions closely resemble benign hemangiomas of the dermis, in both gross and cytologic appearance. Therefore, a cytologic approach may not be adequate for accurate diagnosis. Histologic examination allows determination of invasion and whether surgical excision was adequate. Systemic staging for pulmonary and visceral metastasis is indicated based on potential for spread to distant organs. Advanced local staging with computed tomography scanning may be helpful for surgical and radiation therapy planning.

Treatment

Surgery

Cutaneous HSA lesions are most often treated with curative-intent surgical excision. When patients have cHSA present in multiple sites, multiple surgeries are required. Locoregional recurrence was documented in 77 % of the cases at a median time of 211 days after initial diagnosis. Locoregional recurrence only occurred in skin anatomically close to the previously resected tumor. Predisposed breeds were found to be more affected by the development of locoregional recurrence, particularly when

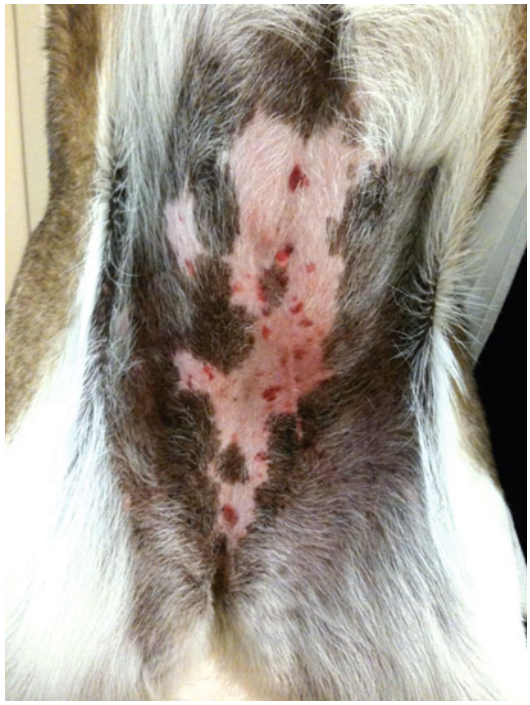

Fig. 33.3 Multiple small cutaneous HSA lesions located in the unpigmented skin of the ventral abdomen of a dog

masses were located on the ventrum, and also for dogs with multiple masses at initial presentation (Fig. 33.3). Biopsy margin status documenting complete surgical excision, absence of metastasis, and no subcutaneous invasion were surprisingly unassociated with incidence of local recurrence [83]. This may represent the effect of solar field cancerization, in which case all cells in the solar-exposed field have increased risk of carcinogenesis [86]. The dearth of prospective studies defining the clinical behavior of cHSA results in uncertainty and controversy regarding the role of complete surgical excision of the lesion as a predictor of clinical outcome in dogs and cats [83, 85].

Chemotherapy

Use of chemotherapy in the management of dogs and cats affected by cHSA is largely recommended only if there is an evidence of invasion of the subcutaneous tissue or of distant metastasis. Recent studies have documented a possibly higher metastatic potential than previously believed in cats with cHSA [20, 83, 87]. Doxorubicin-based protocols provide several more months of survival time for these cats, when compared to no therapy. The most common chemotherapeutic agent used to treat systemic HSA is doxorubicin. Doxorubicin may be administered as a single agent every 2 or 3 weeks at 30 mg/m^2 for dogs, and 20–25 mg/m^2 or 1 mg/kg for dog <10 kg or for cats affected by cHSA with poor prognostic features. Doxorubicin may be used as described above in combination with cyclophosphamide 200–250 mg/m^2 IV, or 50 mg/m^2 PO for 4 days during week 1, and vincristine 0.5–0.7 mg/m^2 on days 8 and 15 of a 21-day cycle (VAC protocol). The DAV protocol substitutes the alkylating agent dacarbazine (DTIC) for cyclophosphamide in the VAC protocol. In the DAV protocol, dacarbazine is delivered at 800 mg/m^2 as an 8-h infusion diluted in 0.9 % NaCl at maintenance rate on day 1, with doxorubicin and vincristine delivered as scheduled for the VAC protocol. The DAV protocol has been used for treatment of visceral HSA. However, no chemotherapy protocol has been proven superior when compared to single-agent doxorubicin. More intense protocols such as VAC and DAV are associated with more toxicity [88–90].

Other therapies used to treat visceral HSA include ifosfamide delivered at a dose of 350–375 mg/m^2 IV every 3 weeks as a single agent. Complete response with tolerable toxicity was observed in a dog with metastatic cHSA [91].

Targeting tumor-associated neovasculature is the object of many anticancer therapeutics strategies. These investigations have been conducted in dogs with HSA and include studies of the efficacy of doxorubicin nanoconjugates that target transmembrane proteins expressed in the neovasculature of cHSA and other solid tumors. In vitro and in vivo studies using nanoconjugates showed measurable anticancer activity in cHSA cell lines and in xenograft mouse models implanted with canine cancer cells. These promising preliminary results warrant further investigation on macroscopic solid tumors [92].

Radiation Therapy

The use of radiation therapy for treatment of cHSA has not been extensively explored in dogs and cats. Palliative radiation therapy has been reported to have relative success in controlling nonsurgical cutaneous bleeding masses. The treatment protocol consisted of 3–4 Gy fractions to achieve a 24 Gy total radiation dose [90]. Other investigators have suggested the use of radiation therapy for control of cutaneous cHSAs with incomplete surgical resection. These studies reported poor responses in two cats with large, unresectable cHSA lesions [93].

Future Treatment Strategies

A newer concept in chemotherapy drug delivery is referred to as metronomic chemotherapy. Metronomic therapy is based on continuous drug exposure to susceptible cancer cells that results in direct inhibition of tumor cell replication, as well as inhibition of angiogenesis and alteration of immune function. The metronomic strategy is attractive as a cost-effective and well-tolerated treatment alternative for veterinary patients with malignancy.

Most of the metronomic treatment protocols in common veterinary use consist of combinations of NSAIDS and oral alkylating agents. Oral alkylating agents such as cyclophosphamide at 15–25 mg/m^2 or chlorambucil at 4 mg/m^2 may be given daily or on alternate days in combination with the oral administration of an NSAID such as piroxicam at the dose of 0.3 mg/kg daily. Increased benefit also appears to occur when metronomic chemotherapy is used in combination tyrosine kinase inhibitor drugs, such as toceranib and masitinib [94].

In human medicine, metronomic therapy has been used to treat patients with cutaneous angiosarcomas using a similar protocol to those employed for veterinary patients. This metronomic protocol consisted of low-dose trofosfamide in combination with the peroxisome proliferator-activated receptor gamma agonist pioglitazone and the selective cyclooxygenase-2 inhibitor rofecoxib. Response was observed in four out of the six patients and stabilization of the disease in the other two cases for a period of almost 8 months on average. This treatment protocol was well tolerated with minimal adverse effects [95]. Similarly in veterinary medicine, canine splenic hemangiosarcoma was treated with metronomic therapy using daily cyclophosphamide at 12.5–25 mg/m^2 on an alternating 3-week schedule with orally administered etoposide at 50 mg/m^2. The protocol's performance was similar to that seen in historical controls treated with conventional intravenous biweekly doxorubicin at 30 mg/m^2 IV for 5 doses [96, 97]. Metronomic therapy may be feasible as a first-line therapy option for patients with cHSA that cannot undergo surgery. However, further study is needed to determine the ultimate value of metronomic chemotherapy for treatment of canine and feline cHSA.

Glossary

Actinic keratosis Solar-induced premalignant condition of the skin characterized by abnormal maturation of keratinocytes, thickening of the epidermis, and inflammatory infiltrate of the dermis.

Cryosurgery Treatment modality for localized tumors that induces cell death by formation of intracellular and extracellular ice crystals.

Electrochemotherapy Treatment modality for localized tumors that involves administration of a chemotherapeutic agent combined with delivery of appropriate energy waveforms that induces increased cell drug uptake.

Epigenetic effects Molecular mechanisms that regulate gene expression in the absence of changes in the DNA sequence itself.

Hemangiosarcoma Malignant neoplastic condition of vascular- or vessel-forming cells.

Intralesional chemotherapy Treatment modality for localized tumors that involves the direct intratumoral delivery of chemotherapeutic agents.

Metronomic therapy Treatment modality based on continuous drug exposure that results in direct inhibition of tumor cell replication, as well as inhibition of angiogenesis and stimulation of immune function.

MicroRNAs (miRNA) Small RNA fragments of no more than 25–50 nucleotides that act as post-transcriptional regulators by hybridizing complementary bases in strands of messenger RNA.

Missense mutation Single-point nucleotide change, mutation that results in substituted amino acids or mRNA chain termination.

Nanoconjugates Nano-sized particles compounded to incorporate a polymer and an anticancer drug.

Oncogene Altered or mutated gene associated with unregulated cell replication that results in cancer.

Peroxisome proliferator-activated receptor Nuclear receptors that modulate expression of growth regulatory genes and enzymes involved in oxidative stress leading to DNA damage.

Photodynamic therapy Treatment modality for localized tumors that consists of intravenous injection of an inert photosensitizer that is activated by light at the appropriate wavelength, resulting in a reactive agent that ultimately induces DNA damage.

Retrovirus Single-strain RNA viruses that require the host transcriptase enzyme to create the DNA-viral genome.

Solar elastosis Elastic fiber proliferation in the dermis of chronically sun-exposed skin.

Squamous cell carcinoma Epithelial tumor that arises from epidermal stem cells located in the hair follicle bulge and the basal layer of the interfollicular epidermis.

Stem cells Cell lineage precursors with the potential for self-renewal and multi-lineage differentiation.

Topical therapy Treatment modality that consists in the delivery of drug in target site lesion of the skin.

Tyrosine kinases Enzymes that induce changes in cell communication pathways that regulate cellular activity by phosphorylation of other proteins.

Ultraviolet light Invisible wavelength forms of the electromagnetic solar radiation spectrum with carcinogenic, germicidal, and other multiple properties.

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