

Neoplasia of the Skin and Associated Tissues

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The skin, including the subcutis, is the largest and most accessible organ of the body. Cutaneous neoplasms are diagnosed more frequently than tumors of other organs, and skin tumors represent approximately 30% of all canine and 20% of all feline tumors.

DEFINITION

The skin and subcutis are composed of many different types of tissue that may be affected by a vast array of different tumors. Such tumors can be broadly divided into the following categories:

- **Primary tumors**—those that arise within the dermis, subcutis, and adjacent connective tissues. Primary tumors can be either malignant or benign and can occur as solitary or multiple lesions.
- **Secondary tumors**—those that arise at a distant site and metastasize to the skin. These tumors are part of a systemic malignant neoplastic condition and can present as solitary or multiple lesions.

Thus tumors of the skin may be benign or malignant and primary or secondary and may present as solitary or multiple lesions. The classification of primary tumors of the skin is listed in the box on p. 28. Skin tumors must also be differentiated from a diverse array of nonneoplastic tumor-like conditions including hyperplastic, granulomatous, inflammatory, and developmental lesions.

CLINICAL APPROACH TO CUTANEOUS NEOPLASMS

A prerequisite to the successful management of any

neoplastic condition is an accurate definition of the nature and extent of the disease. There are inherent problems in the management of cases if the clinician concentrates on the skin mass without appropriate consideration of the patient as a whole. The clinician's primary tasks are to:

- Achieve a definitive diagnosis.
- Determine the extent of the primary tumor(s).
- Investigate the presence of local or disseminated metastases.
- Investigate any concurrent disease.

Only when the full extent of the disease and any attendant problems have been identified is the clinician able to give a rational prognosis and select an appropriate therapy.

DIAGNOSIS

Diagnosis of a skin tumor requires a detailed history and an appropriate clinical examination. The aim of the clinician is to define the tissue type of the mass. This can be achieved in two complementary ways: cytology and histology.

Cytology

It is easy to obtain samples from lesions of the skin and subcutis for cytologic examination. Exfoliative cytology may be performed by fine-needle aspiration, tissue imprint, or exudate smear. Cytologic examination provides information regarding the appearance of neoplastic cells and can show whether they are epithelial, round cell, or spindle cell in type. In some cases (e.g., the mast cell tumor) this information may allow a definitive diagnosis. The importance of cytology as a diagnostic tool in the early diagnosis of cutaneous tumors cannot be overemphasized.

Histology

Definitive diagnosis of a neoplasm invariably depends on microscopic examination of tumor architecture, cell type, mitotic rate, and relationship of the neoplastic cells to the adjacent normal tissues. These can only be accomplished via histologic examination of excised tissue.

Histologic diagnosis, clinical staging of a tumor, and a knowledge of the likely biologic behavior of the tumor provide the information upon which to base prognosis and to select treatment.

CLASSIFICATION OF CUTANEOUS NEOPLASMS IN DOMESTIC ANIMALS

Epithelial Tumors

- Basal cell tumor
- Squamous cell carcinoma
- Papilloma
- Adnexal tumors
 - Sebaceous gland tumors
 - Sebaceous adenoma
 - Sebaceous epithelioma
 - Sebaceous adenocarcinoma
 - Tumors of perianal glands
 - Hepatoid gland adenoma
 - Hepatoid gland adenocarcinoma
 - Sweat gland tumors
 - Adenoma/adenocarcinoma
 - Tumors of hair follicles
 - Pilomatricoma
 - Trichoepithelioma
 - Intracutaneous cornifying epithelioma

Melanocytic Tumors

- Benign melanoma
- Malignant melanoma

Mesenchymal Tumors

- Fibrous tissue
 - Fibroma
 - Fibrosarcoma
 - Canine hemangiopericytoma
 - Adipose tissue
 - Lipoma
 - Liposarcoma
 - Vascular tissue
 - Hemangioma
 - Hemangiosarcoma
- (Also myxoma, myxosarcoma, leiomyoma, leiomyosarcoma, etc.)

Canine Cutaneous Histiocytoma

Mast Cell Tumors

SPECIFIC TUMOR TYPES

Neoplasms that usually present as solitary cutaneous lesions include the epithelial tumors (basal cell, squamous cell, and adnexal tumors), melanocytic tumors, and tumors of mesenchymal origin (fibroma, lipoma, fibrosarcoma). Approximately 25% to 35% of canine skin tumors and 75% of feline skin tumors are malignant. The general principles of diagnosis and management previously described apply to all such tumors

Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) is one of the most

common malignant cutaneous tumors in the dog and accounts for 4% to 18% of all canine cutaneous tumors. Sites of occurrence include the limbs (particularly the digits) and the head (lips and nose). In the majority of cases the etiology is unknown; however, long-term exposure of nonpigmented skin to ultraviolet light can result in development of SCC, the classic examples being SCCs of the pinna, eyelids, and rhinarium that develop in cats with unpigmented skin in sunny climates. Squamous cell carcinoma of the eyelid in cats and other species may have a similar etiology. In dogs the development of SCC on nonpigmented or lightly pigmented areas has also been attributed to ultraviolet light.

Squamous cell carcinomas arise from the squamous epithelial cells of the epidermis and infiltrate into the underlying dermal and subcutaneous tissues. The tumor may be “productive” (i.e., forming a papillary growth with a cauliflower-like appearance) or “erosive” (i.e., forming a shallow ulcer with raised edges). In both instances the lesion is frequently ulcerated, infected, and associated with a chronic inflammatory infiltrate. **It is not uncommon for these tumors to be incorrectly dismissed as infective/inflammatory lesions on initial presentation.**

The majority of SCCs are well differentiated, and the prognosis is good if adequate surgical resection can be achieved. A good example of this is total resection of the pinna in cats to remove a squamous cell carcinoma affecting the tip of the ear. Such surgery is usually curative, whereas partial resection is cosmetically less satisfactory and there is the very real potential that inadequate margins will be obtained.

The most malignant cutaneous SCC in the dog is that which arises in the nail bed region of the digit. This is an aggressive tumor, and invasion and destruction of the distal phalanx are frequent. Amputation of the affected digit(s) is the treatment of choice, but these tumors may metastasize to regional lymph nodes; therefore the prognosis is guarded. Anaplastic squamous cell tumors at other sites may also metastasize via the lymphatic route, and disseminated metastases have been observed.

Squamous cell carcinomas arising on the nasal rhinarium present a particular problem. These tumors have a tendency to infiltrate the alar cartilage and are often more extensive than may be appreciated. Radical surgical resection of some SCCs affecting the rhinarium and the alar cartilage can now be performed with appropriate reconstruction of the area using rotational skin flaps to close the defect. Squamous cell carcinomas are considered to be radiosensitive, and such tumors of the nose or at sites where surgery is

not feasible may respond favorably to radiation therapy. One year control rates of 34% to 46% have been reported for radiation therapy of all SCCs, but there is considerable variation depending on tumor site and the fractionation schedule employed. It is our experience that the tumor response rate may be enhanced by the combination of radiation with hyperthermia.

Soft Tissue Sarcomas

The term *soft tissue sarcoma* describes malignant neoplasms that arise from mesenchymal tissues, including dermal and subcutaneous connective tissues. Tumors of fibrous, adipose, muscular, and vascular tissues and tumors arising from peripheral nervous tissue are included in this definition. In total these tumors represent 9% to 14% of all canine skin neoplasms. Irrespective of tissue type, soft tissue sarcomas may be considered as a group since they are characterized by common morphologic and behavioral features. However, these tumors do vary in their degree of malignancy, and a definitive diagnosis is necessary to determine a prognosis.

The most common soft tissue sarcomas in both the dog and the cat are the tumors of fibrous tissue, traditionally classified as fibrosarcoma and canine hemangiopericytoma. Some soft tissue sarcomas lack sufficient differentiation for definitive classification and may be described as spindle cell sarcoma or anaplastic sarcoma. A group of tumors that contain mixtures of spindle (fibroblast-like), rounded (histiocyte-like), and pleomorphic giant cells is also recognized, some of which resemble the fibrohistiocytic tumors in humans (e.g., the malignant fibrous histiocytoma). As a group soft tissue sarcomas display a spectrum of biologic behavior and therapeutic response.

Soft tissue sarcomas usually develop in older animals (mean age = 9 years in dogs and cats), although fibrosarcomas have occasionally been found in dogs as young as 6 months of age. In the cat there is a particularly aggressive, multicentric fibrosarcoma that is associated with the feline sarcoma virus and occurs predominantly in cats less than 5 years of age.

The distribution of soft tissue sarcomas is widespread, and sites include the head, limbs, and trunk. The rate of growth is variable; hemangiopericytoma and solitary fibrosarcoma may be slow growing, whereas the anaplastic tumors often grow at an alarming rate. As a group these tumors are characterized by an infiltrative pattern of growth. The tumors may appear to be encapsulated because of the formation of a pseudocapsule from compressed normal tissues. The tumor invariably extends into and beyond this structure. The treatment of choice is radical surgical exci-

sion; in most cases it is necessary to resect the entire anatomic compartment if all neoplastic cells are to be eradicated. Failure to achieve this aim accounts for the high rate of local recurrence. It is therefore essential to identify the tumor and to carefully plan the surgical procedure prior to attempting therapy. Although sarcomas are often considered to be radioresistant tumors, radiation therapy may play a role in their management, especially as an adjunct to surgical excision. The response to chemotherapy is usually disappointing.

The potential for metastatic spread from soft tissue sarcomas is variable. Hemangiopericytoma is notorious for local recurrence but rarely metastasizes. Approximately 25% of fibrosarcomas metastasize; although metastasis is frequently stated as being via hematogenous dissemination to the lung, in our experience lymph node involvement is quite common. The incidence of metastases is higher in the anaplastic tumors, where hematogenous spread is more common.

Other soft tissue sarcomas such as liposarcoma, hemangiosarcoma, and the like display similar behavior to the tumors already described. Hemangiosarcoma is a particularly malignant tumor that may arise at any site, and metastatic rates as high as 90% are documented.

Melanocytic Tumors

Melanomas arise from melanocytes situated in the basal layer of the epidermis or the epithelium of the gingiva. Cutaneous melanomas that arise on the distal extremities (nail bed) or mucocutaneous junctions (e.g., the lip and eyelid) are highly malignant. Generally, those arising in the skin are usually benign.

Benign melanomas of the dermis are classically small pigmented nodules. Instances of spontaneous regression of such lesions are documented. Malignant melanomas may be pigmented, but amelanotic forms are recognized. Ulceration and secondary infection are common features. Regional lymph node metastasis and widespread distant metastases frequently occur early in the course of the disease. It is essential that clinical staging includes a thorough physical evaluation of drainage lymph nodes and radiographic evaluation of thoracic and abdominal cavities.

Therapy for primary malignant tumors requires radical surgical excision; surgical margins of up to 3 cm are necessary to ensure complete resection. Melanoma of an extremity requires at least amputation of the affected digit, and limb amputation may be necessary to achieve an adequate margin.

Canine melanomas are radiosensitive but require large individual fractions to achieve response. The combination of irradiation with hyperthermia may

provide an alternative means of local control of the primary tumor. Prophylactic irradiation of lymph nodes is indicated if this form of therapy is undertaken. Various chemotherapeutic regimens have been advocated for treatment of malignant, disseminated melanoma, but efficacy is unproven.

Canine Cutaneous Histiocytoma

The canine cutaneous histiocytoma (CCH) is a tumor that is unique to the skin of the dog. It is relatively common, representing up to 10% of all canine cutaneous neoplasms. There are several characteristic features: CCH is more often seen in young dogs than older animals—50% of tumors occur in dogs under 2 years of age. The tumors are most commonly found on the head (especially the pinna), the hindlimbs, feet, and trunk. The boxer and dachshund appear to be predisposed to development of CCH.

CCH presents as a rapidly growing, circular, intra-dermal lesion. The surface may be alopecic and is often ulcerated, but rarely does the lesion cause any discomfort to the animal.

Histologic sections show infiltration of the epidermis and dermis by histiocytic tumor cells with round to oval nuclei. Numerous mitotic figures give the lesion the appearance of a highly malignant neoplasm. This appearance may result in a misdiagnosis on the part of nonveterinary pathologists who are unfamiliar with the condition because the tumor resembles the human malignant cutaneous histiocytoma, a tumor that carries a poor prognosis. Despite the histologic appearance and rapid growth rate, CCH is a benign tumor that may even regress spontaneously; local surgical excision is usually curative.

Mast Cell Tumors

Mast cell tumors (MCTs) are important cutaneous tumors, representing 9% to 21% of all canine skin tumors. They also occur in the cat and other species. The terms “mast cell tumor,” “mastocytoma,” “mastocytosis,” and “mast cell sarcoma” are often used interchangeably, although the latter two terms tend to be reserved for cases with systemic involvement. MCTs present a considerable challenge to the clinician, and a knowledge of their unique biologic aspects is essential in their management.

Mast cells are found throughout the body in loose connective tissues and are involved in a wide variety of physiologic reactions. They are widely known for their importance in type I hypersensitivity reactions, but their primary function is related to the induction of acute inflammatory reactions in response to injury. The cytoplasm of mast cells contains granules with

numerous biologically active vasoactive peptides, which include histamine, heparin, proteolytic enzymes, and many other amines. It is these granules that stain metachromatically to give the mast cell its characteristic appearance under light microscopy.

MCTs have many presentations and have been described as “the great imitator” and probably should be included in the list of differential diagnoses for any cutaneous mass regardless of its appearance. MCTs may arise in the dermis or in subcutaneous tissues and may be solitary or multiple; internal organs (particularly the spleen and liver) may be involved. MCTs have been reported in all age groups (mean age for dogs = 8.5 years). The brachiocephalic breeds, notably the boxer, are reported to have the highest incidence of MCTs, but all breeds of dog may be affected.

There is no typical appearance of an MCT, but some features are characteristic. Cutaneous tumors range from well-circumscribed, firm, raised plaques within the dermis, the surface of which is often erythematous or ulcerated, to poorly circumscribed subcutaneous lesions. The tumor may be associated with inflammatory swelling, and fluctuating edema may be a presenting feature.

Many attempts have been made to categorize the clinical behavior of MCTs and to correlate this with histologic criteria. Histologic grading systems have been proposed that recognize three grades: anaplastic/undifferentiated, poorly differentiated, and well differentiated/mature. These grades do bear some correlation to patient survival but are by no means absolute, and in this respect the classification of MCTs remains a gray area. Clinically, one can recognize two basic types of MCTs: solitary, slow-growing tumors and rapid-growing tumors that invariably metastasize to regional lymph nodes. However, it is not unknown for a slow-growing, apparently benign tumor to suddenly change into the aggressive variety; therefore the distinction is not definitive. It is imperative that any MCT be treated with careful respect.

A proportion of MCTs may be “physiologically” active. The release of histamine, heparin, other vasoactive amines, and enzymes from the cytoplasmic granules may have local and systemic effects that are important in both the diagnosis and management of the tumor. Locally, release of histamine may result in acute inflammation, erythema, edema, ulceration, and irritation. In some circumstances these reactions may confuse the diagnosis, but a history of fluctuating swelling and erythema should alert the clinician to the possibility of an MCT. Prolonged bleeding times may result from heparin released by tumor cells, which may occur spontaneously in ulcerated lesions or may

be noted subsequent to surgical interference. Delayed wound healing may result from release of proteolytic enzymes at the time of surgery. It is because of this activity that I consider MCTs to fall into two categories: those that are physiologically active and those that are not.

Any interference—be it physical manipulation, surgical incision, or cryosurgery—with an MCT, particularly where there has been a history that suggests that the mass has been releasing the vasoactive amines, may precipitate histamine release from the tumor. Cases of anaphylaxis have been reported, and premedication with antihistamine (H_1) agents is a wise precaution. Other systemic effects include gastrointestinal ulceration due to chronic stimulation of H_2 histamine receptors on gastric parietal cells that results in increased acid secretion and gastric hypermotility. Gastrointestinal ulceration must not be overlooked: It is debilitating and distressing to the patient, and, in severe cases, duodenal perforation will occur and the associated peritonitis can be fatal.

The management of MCTs depends on the stage of the disease at presentation, the histologic grade of the tumor, and whether there are systemic effects associated with the release of heparin and other vasoactive amines. Surgical excision is the treatment of choice for solitary lesions without local lymph node involvement. Excision margins of at least 2 to 3 cm should be achieved as neoplastic cells may extend into peripheral and deep tissues much farther than expected. Where the grade of the tumor is known, the margin of excision should be adjusted accordingly. In those instances where the histopathology shows that it is a highly malignant MCT, adjunct chemotherapy must be used postoperatively to delay the development of metastatic disease. In those cases where it is a moderately well-differentiated MCT, it is strongly advised that radiation therapy of the surgery field and regional lymph node and/or chemotherapy be given. Surgical removal of a well-differentiated MCT is often curative.

Where lymph nodes are involved and/or the primary lesion is too extensive to allow adequate surgical excision, radiotherapy or chemotherapy (or both) may be appropriate, but the prognosis is guarded to poor. Any treatment that damages the tumor cells in situ may provoke a marked inflammatory response that will result in swelling and erythema, giving the impression that the lesion is progressing. Oncologists have expended considerable effort to evaluate chemotherapeutic agents for the management of MCTs. Despite this effort little progress has been made, and it still appears that prednisolone is probably the most useful

agent for systemic therapy. Significant tumor regression may be achieved and maintained using the regimen based on this drug.

As discussed above, an important systemic effect of MCTs is duodenal ulceration. This is seen in those patients with MCTs that release significant amounts of the vasoactive amines mentioned previously. The use of cimetidine to block the H_2 receptor has proven invaluable in the long-term management of these cases and prevents the development of duodenal ulceration.

Cutaneous MCTs in the cat differ from those in the dog. Classically they present as small white foci in the skin, are invariably multiple, and in the initial phases are not ulcerated and do not cause the cat problems. There is a tendency for this tumor to spread within the skin, to disseminate into the circulation, and to involve the liver, spleen, and bone marrow. However, there is a great variability in the rate at which the MCTs progress, and it is very difficult to give an accurate prognosis. Few MCTs are amenable to surgery. This is due largely to the diffuse number of lesions seen on presentation. Thus the mainstay of treatment is chemotherapy and does not differ significantly from that described for the dog.

Cutaneous Lymphomas

Lymphoproliferative disease is well characterized in the dog, and there is a wealth of information on the various common types. It has long been recognized that the skin can be involved, but the true incidence of cutaneous lymphomas in the dog remains unknown. This is largely due to the fact that the definition of the various forms of lymphomatous infiltrate into the skin is still unclear and needs to be carefully examined. The classification in this article is not definitive but is designed to be clinically helpful.

The two major forms of cutaneous lymphoma in the dog—primary cutaneous T-cell lymphoma and secondary cutaneous lymphoma—are discussed separately.

Primary Cutaneous T-Cell Lymphoma

In primary cutaneous T-cell lymphoma the lymphocyte that becomes malignant (a T-cell) is one that normally recirculates through the skin. There are two forms of primary cutaneous T-cell lymphoma: primary cutaneous lymphoma and mycosis fungoides.

Primary Cutaneous Lymphoma

The clinical presentation of cutaneous lymphoma is varied. In the majority of cases multiple lesions including nodules, plaques, erythroderma, and exfoliative dermatitis are present. There is a rapid progression of the neoplasm following the initial appearance

of the lesion. In the early stages dogs do not appear systemically ill, but once the disease has progressed the systemic signs associated with lymphomas, particularly hypercalcemia, are a characteristic feature. The aggressive nature of this form of the disease is remarkable, and it is my experience that the response to treatment is poor in comparison to that of other forms of lymphoma.

The clinical diagnosis of primary cutaneous lymphoma can sometimes be difficult but is readily confirmed on cytologic and histologic examination of tissue samples. There is a diffuse infiltrate of the dermis with lymphoblasts, which can extend into the epidermis.

The treatment of this form of lymphoma is similar to the treatment of other systemic lymphomas. It is folly to think that the treatment can be less aggressive because the tumor is "simply in the skin." There are a number of regimens available for the treatment of lymphoma, and each clinician has a personal preference.

Mycosis Fungoides

Mycosis fungoides is the epitheliotropic form of cutaneous lymphoma that is characterized by a lymphoid infiltrate into the epidermis rather than the dermis. There is a long clinical course to this disease, and it is fair to say that there is no classic presentation. There are three stages to the disease: premycotic, mycotic or plaque, and the tumor stage. The first two can be present for many months or years before there is progression to the tumor stage. In the premycotic stage there is generally a history of either an erythroderma or a generalized exfoliative, pruritic dermatitis. In this particular stage the clinical presentation can be very similar to exfoliative seborrheic condition. The premycotic lesions may have had a very protracted course before some of them progress to the plaque stage, which is characterized by firm, elevated plaques. In an individual animal the premycotic and mycotic stages can occur concurrently and present a very confusing clinical presentation. The final progression is to the tumor stage, which is characterized by the development of multiple raised plaques in the skin. Once the disease has progressed to this stage, there is usually a rapid clinical course with dissemination to the regional lymph nodes and then systemic spread of the lymphoma. At this stage clinical signs are those associated with a disseminated lymphoma.

Diagnosis of mycosis fungoides can only be achieved by a biopsy of the affected site(s). There is a characteristic lymphocytic infiltrate into the epidermis and the associated Pautrier's microabscesses. The epidermal changes also include hyperkeratosis and acanthosis, but there is great variation in the severity of these changes.

Secondary Cutaneous Lymphoma

In secondary cutaneous lymphoma the skin becomes involved because of dissemination from a lymphoma at another site, be it multicentric, alimentary, or thymic. The lymphocytes in this case are not all T-cells but reflect the phenotype of the original tumor. Because the skin infiltrate is secondary to an underlying lymphoma, the clinical presentation is usually one of lymphoma rather than skin disease. There are usually multiple lesions, which are often ulcerated.

Canine Histiocytic Lymphoma

It is well recognized by histopathologists that there can be a diffuse infiltrate of mononuclear cells that have a histiocytic appearance in the dermis. These histiocytic-like cells have the morphologic characteristics that one would expect of a malignant cell population. However, it is clear that there is considerable variation in the characteristics of this histiocytic infiltration and it is more than likely that there are a number of neoplastic diseases that hide under the guise of histiocytic lymphoma. Clarification requires that the exact phenotype and lineage of the cells be defined.

The variation that is noted on histopathology is echoed by the clinical course of the histiocytic lymphoma. In my experience there is a predilection for young to middle-aged dogs to be affected, with spaniels and collies overrepresented in this hospital population. The course of the disease is generally not as aggressive as primary cutaneous lymphoma, and it is my impression that this group appears to be more sensitive to combination chemotherapy than other forms of cutaneous lymphoma, although this does need to be substantiated.

A breed predilection for systemic histiocytosis has been reported in the Bernese mountain dog. As part of this complex, multiple histiocytic infiltrates are found widely disseminated in the skin with involvement of the peripheral lymph nodes. In addition, however, there can be infiltrates found in all organs. The precise nature of this particular disease remains a mystery, and it is open to debate whether this is a lymphoproliferative disease or a malignant proliferation of the histiocytic cell series. Only when sufficient cell markers become available will this be resolved.

Feline Cutaneous Lymphoma

There are very few reported cases of cutaneous lymphoma in the cat. As a result it has not been possible to identify whether there are various forms of this disease nor to define the relationship with feline leukemia virus infection. The clinical presentation can either be multiple nodules within the skin or ulcerated

nonhealing areas. Depending on the stage of the disease, there may or may not be systemic involvement. In the limited number of cases seen there has been a disappointing response to therapy.

ADDITIONAL READING

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