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CHAPTER 9

Neoplasia

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With the exception of routine vaccinations, neoplasms and accompanying paraneoplastic syndromes are the most common reason ferrets are seen for veterinary care. The probability is good that most ferrets will develop a neoplasm of the endocrine system during the "golden age" for tumors (4 to 6 years) and excellent that some type of neoplasm will become evident over the course of a lifetime. In ferrets from American bloodlines, the incidence of three neoplasms—adrenocortical neoplasia, insulinoma, and malignant lymphoma—exceeds the incidence of all other neoplasms combined.

The increasing popularity of ferrets as both pets and laboratory animals over the past decade has facilitated the compilation of impressive data on neoplasms that provide a fairly accurate look at the distribution of neoplasia in this species* and establish that neoplasia is much more common in ferrets than previously indicated. Our review focuses primarily on the occurrence, diagnosis, treatment, and prognosis of clinically significant neoplasms in the ferret, with emphasis on nonendocrine neoplasms. Incidence data for this review were taken from an archive of 1525 neoplasms (Table 9-1) compiled over a 10-year period at the Armed Forces Institute of Pathology (Washington, DC) and a commercial pathology laboratory with a high prevalence of ferret submissions (Accupath, Potomac, MD).

One tenet should be considered by all veterinarians dealing with ferrets and their neoplasms—a ferret is not a cat or a dog. The clinical behavior, prognosis, and paraneoplastic syndromes in ferrets are often far different than those seen with similar neoplasms in dogs or cats. Insulinoma in the ferret is a neoplasm that rarely metastasizes to distant organs and may be associated with prolonged survival, as opposed to the same neoplasm in dogs and cats, which metastasizes widely and results in short survival times. Adrenocortical carcinoma, a neoplasm that is prone to metastasize widely in the dog, metastasizes only late in the course of disease in ferrets and, with early removal, warrants a good prognosis. Mast cell tumors, often malignant (and fatal) in the dog, are invariably benign and associated with a good prognosis in ferrets. Practitioners who extrapolate diagnostic and therapeutic options from comparable syndromes in more traditional pet species may find themselves in difficult and unexpected situations.

*References 2, 5, 10, 24, 26, 35, 36.

ETIOLOGY

Although the last decade has brought us tremendous information on the frequency and distribution of neoplasia, there is still little definitive information on the cause of neoplasm formation in ferrets. Many theories abound, but few have supportive evidence. The most common theories are as follows:

1. Genetic (familial) predisposition. Genetic or chromosomal aberrations have yet to be studied in domestic ferrets, but the tremendous incidence of neoplasia in American bloodlines of ferrets compared with their European counterparts certainly lends credence to this widely held belief. Fox et al.[16] document a syndrome of multiple neoplasms in an adult ferret that closely resembles multiple endocrine neoplasia type 2 in humans, a condition caused by a genetic mutation.
2. Infectious agents. Suspicious cluster outbreaks of malignant lymphoma in laboratory colonies and rescue operations[1,12] have sparked the investigation of a possible viral cause for

TABLE 9-1
Distribution of Neoplasia in Ferrets Based on 1525 Cases Submitted to the Armed Forces Institute of Pathology (1990-2000)

System	Tumor Type	Site	No.
Endocrine	Islet cell tumor	Pancreas	382
	Adrenocortical adenoma	Adrenal cortex	129
	Adrenocortical carcinoma	Adrenal cortex	251
	Adrenocortical carcinoma	Liver	11
	(metastatic)	Spleen	3
		Mesenteric node	1
		Mesentery	1
	Leiomyosarcoma, low-grade	Adrenal gland	20
	Teratoma	Adrenal gland	4
	Malignant lymphoma	Adrenal gland	1
	Pituitary adenoma	Pituitary gland	1
Hematolymphatic	Malignant lymphoma	Multicentric	50
		Peripheral node	37
		Mesenteric node	17
		Spleen	16
		Peripheral blood	14
		Skin	9
		Intestine	9
		Abdominal	4
		Thymus	4
		Stomach	3
		Liver	3
		Colon	2
		Lung	2
		Bladder	2
		Eye	1
		Palate	1
		Uterus	1
		Kidney	1
	Round cell tumor, NOS	Spleen	2
	Metastatic adenocarcinoma		
	Rectal	Lymph node	1
	Salivary	Lymph node	1
	Gastric	Lymph node	1
	Ceruminous	Lymph node	1
	Myelolipoma	Spleen	1
	Thymoma	Thymus	1
Integumentary	Sebaceous epithelioma/adenoma	Skin, site unspecified	68
		Tail	10
		Leg	8
		Ear	5
		Back	5
		Neck	3
		Head	3
		Face	3
		Abdomen	2
		Chin	1
		Digit	1
	Mast cell tumor	Site unspecified	63
		Leg	7
		Digit	3

TABLE 9-1
Distribution of Neoplasia in Ferrets Based on 1525 Cases Submitted to the Armed Forces Institute of Pathology (1990-2000)—cont'd

System	Tumor Type	Site	No.
		Back	2
		Neck	2
		Chin	2
		Face	1
		Head	1
		Abdomen	1
		Trunk	1
	Apocrine		
	Adenocarcinoma	Prepuce	19
		Vulva	3
		Perianal	3
		Site unspecified	3
		Lymph node	2
		Hip	1
		Thigh	1
		Face	1
		Tail	1
	Adenoma	Prepuce	5
	Cystadenoma	Site unspecified	4
	Squamous cell carcinoma	Site unspecified	4
		Head	2
		Mandible	2
		Abdomen	1
		Mandibular node	1
		Lip	1
	Leiomyosarcoma	Neck	6
		Back	3
		Leg	1
	Lipoma	Site unspecified	5
	Simple mammary adenoma	Mammary	4
	Anal sac carcinoma	Anal sac	2
	Ceruminous gland adenocarcinoma	Pinna	2
	Fibrosarcoma	Site unspecified	2
	Complex mammary adenoma	Mammary	2
	Squamous papilloma	Skin	1
	Eccrine adenoma	Footpad	1
Gastrointestinal	Pancreatic adenocarcinoma	Pancreas	11
	Biliary cystadenoma	Liver	10
	Metastatic adenocarcinoma	Liver	10
	Cholangioma	Liver	7
	Hepatocellular carcinoma	Liver	4
	Cholangiocarcinoma	Liver	2
	Hepatoma	Liver	2
	Malignant neoplasm, NOS	Liver	2
	Round cell tumor, NOS	Liver	2
	Signet ring adenocarcinoma	Stomach, intestine	2
	Tubular adenocarcinoma	Stomach, intestine	2
	Mucinous adenocarcinoma	Stomach, intestine	2
	Pancreatic exocrine adenocarcinoma (metastatic)	Liver	1

Continued

TABLE 9-1
Distribution of Neoplasia in Ferrets Based on 1525 Cases Submitted to the Armed Forces Institute of Pathology (1990-2000)—cont'd

System	Tumor Type	Site	No.
	Carcinoma, NOS	Liver	1
	Pyloric adenocarcinoma	Stomach, intestine	1
	Squamous papilloma	Esophagus	1
Vascular	Hemangiosarcoma	Skin	8
		Subcutis	2
		Spleen	2
		Liver	2
		Peritoneum	1
		Mesenteric node	1
	Hemangioma	Skin	7
		Ear	1
		Pancreas	1
		Spleen	1
		Site unspecified	1
Reproductive	Leiomyosarcoma, low-grade	Ovary	10
		Uterus	3
	Leiomyoma	Uterus	4
		Ovary	1
	Leydig cell tumor	Testis	7
		Ovary	3
	Seminoma	Testis	5
	Granulosa cell tumor	Ovary	4
	Teratoma	Ovary	4
	Sertoli cell tumor	Testis	4
	Sex cord stromal tumor	Ovary	2
	Uterine adenocarcinoma	Uterus	2
	Deciduoma	Uterus	1
	Carcinoma of rete testis	Testis	1
Musculoskeletal	Chordoma	Tail	51
		Cervical	3
		Sacral	1
		Skin	1
	Osteoma	Flat bone	10
	Osteosarcoma	Bone	4
	Rhabdomyosarcoma	Skeletal muscle	1
Nervous	Astrocytoma	Brain	3
	Malignant peripheral nerve sheath tumor	Skin	3
		Eyelid	1
	Schwannoma	Eyelid	2
		Muzzle	1
	Primitive neuroepithelial tumor	Brain	1
	Granular cell tumor	Brain	1
	Meningioma	Brain	1
	Ganglioneuroma	Adrenal gland	1
Urinary	Transitional cell carcinoma	Kidney	4
Special senses	Melanoma	Eye	2
Miscellaneous	Carcinoma, NOS	Site unspecified	2
		Mesentery	1
	Sarcoma, NOS	Skin	6
		Oral cavity	2
		Muscle	4

TABLE 9-1
Distribution of Neoplasia in Ferrets Based on 1525 Cases Submitted to the Armed Forces Institute of Pathology (1990-2000)—cont'd

System	Tumor Type	Site	No.
		Kidney	1
		Mesentery	1
		Lung	2
		Multicentric	1
		Humerus	1
		Mammary gland	1
	Round cell tumor, NOS	Site unspecified	2
		Multicentric	1
		Mesentery	1
		Thorax	1
	Mesothelioma	Abdomen	4
	Malignant mast cell tumor	Multicentric	1

NOS, Not otherwise specified.

this neoplasm in ferrets. Transforming retroviruses are known to be responsible for the development of lymphoma in other species, including humans, cats, and rabbits. Erdman et al.[14] in 1995 demonstrated the transmissibility of this neoplasm between ferrets by using cell-free inocula, furthering this theory, although a prolonged incubation time was required. *Helicobacter mustelae*, a ubiquitous inhabitant of the stomach of ferrets, has been circumstantially incriminated in the development of gastric adenocarcinoma,[15,17,21] which is enhanced when coupled with ingestion of chemical carcinogens as promoters, as well as in the development of gastric B-cell lymphomas.[11]

3. Early neutering. There is widespread speculation that early neutering at 4 to 6 weeks of age, a common practice in the United States, may be responsible for the high incidence of adrenal neoplasia in this country. In Europe and Australia, where this is not practiced, adrenal neoplasia is rarely seen. A recent publication in The Netherlands[31] indicated a link between age at neutering and age at the onset of hyperadrenocorticism; however, it did not show an increased incidence of hyperadrenocorticism in ferrets neutered at an early age.
4. Light cycles. It has been suggested that the ferret's innate sensitivity to light may be upset by Americans' predilection for housing ferrets indoors with artificial lighting. In Europe, where most ferrets are housed outdoors and exposed to natural lighting cycles, the incidence of neoplasia, especially adrenocortical, is greatly decreased.[4]
5. Diet. Theories abound concerning the impact of commercially prepared diets on the development of neoplasms in ferrets. The higher concentration of carbohydrates in commercially available food in the United States has been suggested as a primary cause for the increased incidence of insulinoma compared with rates seen in other countries, where raw whole prey (e.g., rats, mice) are fed as the dietary staple.[4]

INCIDENCE AND BEHAVIOR

Our knowledge of ferret neoplasia grows year by year; however, a few general comments about neoplasia in ferrets are warranted. The data presented here (1525 cases), as well as that reported by others,[2,4,6,8,24] are only an approximation of the distribution of neoplasia in North American ferrets. A number of factors affect the reporting of neoplasms for this species, including the economic status of the owner, proximity to veterinarians experienced in ferret diseases, opportunity for qualified histologic examination, and methods of reporting and retrieval. In spite of these factors, we believe that certain generalizations about the incidence of neoplasia in this species can be made.

Overall, the endocrine system appears to be the most common site of neoplasia in ferrets (see Table 9-1 and reports by Li et al.[24] and Brown[4]). Pancreatic islet cell tumors (insulinomas) are the most common neoplasms overall, with adrenocortical neoplasms the second most common. In these studies, lymphoma was both the most common hematopoietic neoplasm and the most common malignancy. Between 12% and 20% of cases in each study had multiple tumor types, with insulinoma and adrenocortical carcinoma most often seen concurrently.[4,24] However, the presence of multiple tumor types in an individual animal should not be interpreted as a neoplastic syndrome arising from a common tumorigenic mechanism. In a study of 66 cases in which ferrets had multiple concurrent neoplasms,[24] there was no evidence of an association between tumor type and multiplicity. Because endocrine neoplasia is extremely common today in ferret bloodlines in North America, it seems reasonable that multiple tumors would develop over time in middle-aged or geriatric ferrets.

TUMORS OF THE ENDOCRINE SYSTEM

Most neoplasms in domestic ferrets in North America arise in the endocrine system, chiefly as islet cell tumors and adrenocortical tumors. In the neoplasms we reviewed (Table 9-1), endocrine neoplasms accounted for 53% (805 of 1525) of the total. Although these are extremely common neoplasms in ferrets, these neoplasms may be slightly overrepresented because of their relatively obvious symptomatology and their response to surgical excision. Although we briefly discuss these neoplasms, detailed information is presented in Chapter 8.

Insulinoma

Islet cell tumors, known as insulinomas because of their secretion of this glucose-regulating hormone, are the most common neoplasm in our review (25% [382 of 1525]; see Table 9-1) as well as in reports by Li et al.[24] (21%) and Brown[4] (38%). In these studies, the average age of ferrets with islet cell tumors was 5 years; there is no sex predilection.

Insulinoma in the ferret progresses differently than in the dog and cat, in which it is highly malignant with marked metastatic potential and a short survival time. In ferrets, surgical removal may result in a prolonged disease-free state.

Therapeutic approaches for the treatment of insulinoma in ferrets are reviewed in Chapter 8. Surgical excision is the preferred course of treatment for symptomatic animals with hypoglycemia. In a recent clinical study,[36] partial pancreatectomy resulted in the longest disease-free intervals and survival times (365 and 668 days, respectively), followed by simple nodulectomy (234 and 456 days, respectively). Medical treatment alone resulted in a mean disease-free interval of 22 days and a mean survival time of 186 days. Owners should be informed of the potential for recurrence of clinical signs of the disease, even with surgery.

Adrenocortical Neoplasms

The second most common neoplasm in ferrets occurs in the adrenal cortex (see Table 9-1). Our review included 380 "true" neoplasms of the adrenal cortex (129 adenomas, 251 carcinomas; 25% of overall neoplasms). Furthermore, 439 cases of adrenocortical hyperplasia, which present with identical symptoms, were also identified. The average age of ferrets with adrenal disease was 4.8 years, which is consistent with reports by Brown[4] and Weiss et al.[35] The cause of the high incidence of adrenal disease in ferrets is currently unknown and a subject of great speculation; however, recent reports[4,30,31,34] suggest that anterior pituitary hyperfunction may have a key role in the development of these lesions.

The combination of cutaneous, behavioral, and reproductive signs exhibited by most ferrets with adrenal disease contributes significantly to the frequency of their presentation for treatment (see Chapter 8). The differentiation of hyperplasia, adenoma, and carcinoma is difficult to make on the basis of clinical signs or laboratory findings and is usually based on histologic examination. Although early literature reports suggested an increased incidence of neoplasia in the left adrenal cortex (perhaps because its comparative ease of removal), results of our survey indicate that the distribution of adrenocortical neoplasms approaches 50% (1:1.06, left vs right). A total of 16% (60 of 380) of adrenal neoplasms in this review were bilateral, either at presentation or over time, including those cases in which a hyperplastic lesion was seen in one gland and a neoplasm in the other.

Although a wide range of medical and surgical approaches exists for removal of adrenal neoplasms (see Chapter 8), some personal observations are warranted at this point. Surgical excision of proliferative adrenocortical lesions (to include neoplasia and the more common finding of cortical hyperplasia) is the treatment of choice. Medical treatment at this time should be restricted to the amelioration of clinical signs in nonsurgical candidates. There is currently no evidence that medical treatment inhibits the progression of these lesions or diminishes the risk of metastatic disease or hemoperitoneum associated with large neoplasms.

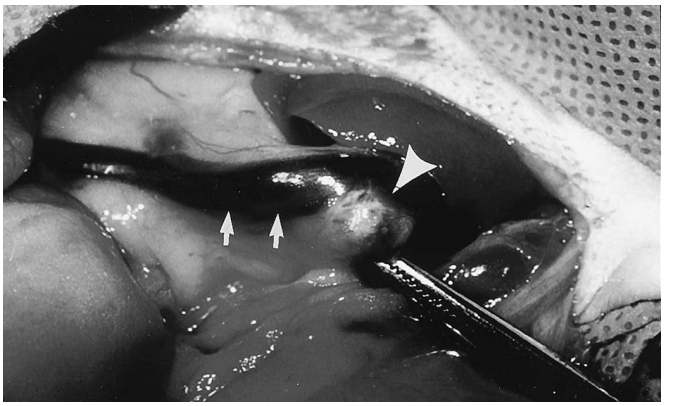

Figure 9-1 Carcinoma of the right adrenal gland (*arrowhead*) in a ferret, demonstrating the proximity between these neoplasms and the caudal vena cava (*arrows*).

Because of its proximity to the vena cava (Fig. 9-1), surgical excision of the right adrenal gland is often a significant challenge for most practitioners. In my practice (C.A.W.), we have achieved excellent results with a wide array of techniques, including liquid nitrogen cryosurgery (584 cases) and carbon dioxide laser (48 cases). In ferrets in which the neoplasm occludes the vena cava by 50% or more, en bloc excision of the neoplasm and the affected section of vena cava may also be performed. This procedure should be approached with care because postsurgical death may occur in ferrets with rapidly growing invasive malignancies that have not yet developed adequate collateral venous return. In such cases, obstruction of venous return leads to hypoxic damage and infarction in multiple organs.

Although common, adrenal carcinoma in the ferret, as opposed to the dog and cat, has low metastatic potential. In this review, only 6% (15 of 267) of ferrets with adrenal carcinoma had evidence of metastasis, primarily to the liver (69% [11 of 16]).

TUMORS OF THE HEMATOLYMPHATIC SYSTEM

Lymphoma (malignant lymphoma, lymphosarcoma) is the most common malignancy in the domestic ferret and the third most common neoplasm overall, following islet cell tumors and adrenocortical neoplasia. Lymphomas most commonly arise spontaneously; however, horizontal transmission of malignant lymphoma in ferrets with cell or cell-free inoculum has been documented.[14] This finding, coupled with the occasional clustering of lymphomas in a single facility, has prompted speculation that lymphosarcoma in the ferret may be the result of a retroviral infection.[12] A viral agent has not yet been isolated from cases of lymphosarcoma in the ferret.

Several variants of lymphoma exist in the ferret. Although various classification schemes for lymphoma exist, including those based on human lymphoma,[1,10,13] the following classification scheme based on broad cell type and distribution is both reproducible and relevant to practitioners.

The most commonly seen form of lymphoma, occurring primarily in older ferrets, is the lymphocytic form. In this variant, the neoplastic cell is a mature, well-differentiated lymphocyte; the lymph nodes are the most affected sites, resulting in peripheral lymphadenopathy, with visceral spread and organ failure occurring late in the course of disease. A second form, the lymphoblastic form, is seen primarily in young ferrets less than 2 years of age. Visceral neoplasms early in the course of disease characterize this form, in which the neoplastic cell is a large, immature lymphocyte. In most cases, the thymus, spleen, and liver are involved, resulting in profound organomegaly. An enlarging thymic neoplasm often results in compression of the lung lobes, dyspnea, and pleural effusion and may often be misdiagnosed as pneumonia or heart disease. A third relatively uncommon form, which is characterized by combinations of peripheral lymphadenopathy, visceral tumors, and the predominant cell type, is a lymphoblast with occasional bizarre karyomegalic or multinucleate forms known as the immunoblastic polymorphous variant.

Terminology involving lymphoma classification can be confusing. *Lymphosarcoma* (malignant lymphoma or lymphoma) denotes solid tissue tumors in organs or lymph nodes throughout the body. However, if neoplastic cells are seen in both the bone marrow and the peripheral blood, a diagnosis of *lymphocytic leukemia* can be made. *Chronic lymphocytic leukemia* indicates a more mature form and the distribution of lymphocytes in the peripheral blood, with total leukocyte counts rarely exceeding normal. *Acute lymphocytic leukemia* suggests lymphoblasts in the bone marrow as well as in the peripheral blood, with leukocyte counts well in excess of normal. True lymphomas are far more commonly seen than leukemias (a ratio of 11:1 in this review).

Clinical Signs and Gross Lesions

Adult (lymphocytic) form Overall, the adult form is the most common variant in ferrets because of its predilection to affect animals over the widest age range (2 to 9 years). Because the neoplastic process is associated with mature lymphocytes, the course of disease is prolonged and longer survival times are seen. Owners often notice clinical signs well before the disease state reaches a critical point. Many cases are associated with cycles of illness and apparent recovery, which may be precipitated by treatment with antibiotics or steroids. In most ferrets with lymphocytic lymphoma, generalized lymph node enlargement is the most common sign (Fig. 9-2), but at times animals are seen simply for chronic lethargy, inappetence, and weight loss. Occasionally only a single node may be enlarged at presentation. In the absence of visibly or palpably enlarged nodes, clinical signs are generally vague and nonspecific. In addition to general malaise, gastric ulcers may be seen as a reaction to the stress of chronic disease.

When evaluating node size, practitioners are cautioned not to be misled by the large accumulations of fat that often surround peripheral nodes (especially the popliteal and axillary nodes) of older ferrets, which may be grossly mistaken for generalized lymphadenopathy. The gross appearance of a neoplastic node is a hard lump often described as a marble, whereas fat-encased normal nodes of geriatric animals are usually soft and pliable. A quick needle aspiration of suspect nodes generally yields an answer. If the aspirate is acellular with abundant greasy fat on the slide, the possibility of lymphoma is greatly lessened.

Figure 9-2 Presentation of cervical lymph node enlargement characteristic of adult-onset (lymphocytic) lymphoma.

Juvenile (lymphoblastic) form The infiltration of visceral organs by blastic lymphocytes in the juvenile form results in clinical signs referable to the affected organs. The most common presentation is diffuse enlargement of the liver, spleen, and thymus (Fig. 9-3). Organomegaly of the spleen and liver can be tolerated to a much greater extent in the relatively distensible abdomen than can expansion of the thymus in the bony cage of the thorax. Neoplastic enlargement of the thymus quickly impinges on the ability of the lungs to expand, resulting in exer-

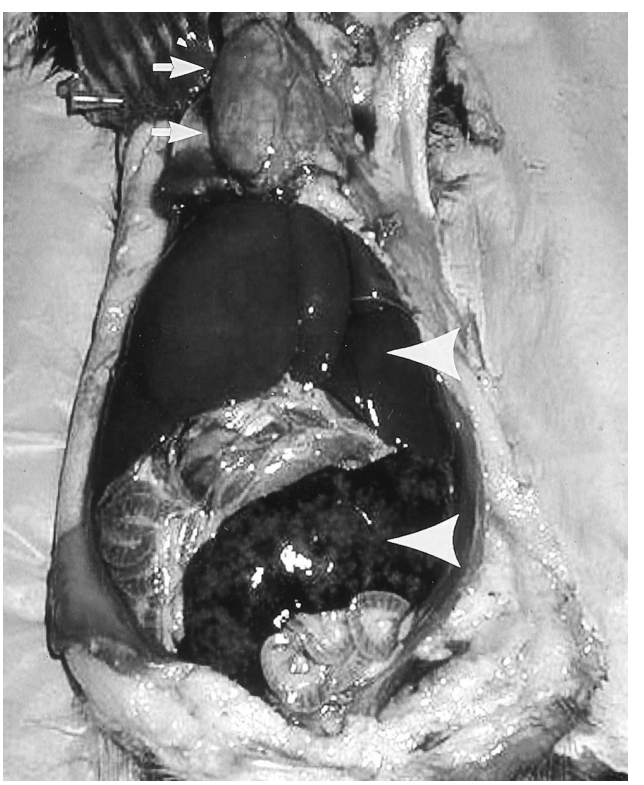

Figure 9-3 Juvenile lymphoma in a 1-year-old ferret. Note thymic mass (*arrows*) and marked hepatosplenomegaly (*arrowheads*) as a result of massive infiltration by this neoplasm.

cise intolerance, increased respiratory rate, dyspnea, and possibly pleural effusion. In such cases, the onset of clinical signs is abrupt because owners may not notice significant impairment until the disease has reached life-threatening proportions. Neoplastic cells may be seen in any organ, including the bone marrow. The incidence of bone marrow infiltration and leukemia is highest in this form of disease. Infiltration of the gastrointestinal tract by neoplastic cells may present vague gastrointestinal signs suggestive of a number of diseases, including a gastric foreign body.

Immunoblastic polymorphous form The progression of the immunoblastic polymorphous form of this disease parallels that of the juvenile form; however, ferrets of all ages can be affected. The combination of immunoblasts, large atypical lymphocytes, Reed-Sternberg–like cells, lymphoblasts, and small lymphocytes has been associated with certain retroviral-associated lymphomas in humans and has given an early clue that ferret lymphomas may be associated with viral infection.[13] This form of lymphoma primarily affects visceral organs, has a short survival time after diagnosis, and is most commonly found in the midwestern United States.

Other forms Cutaneous (epitheliotropic) lymphoma (Fig. 9-4) is of T-cell origin and possesses a mature lymphocytic phenotype and a profound affinity for infiltrate epithelial structures, such as the epidermis and hair follicles. It alone among the ferret lymphomas does not warrant a poor prognosis at onset because prolonged survival times (possibly up to 3 to 4 years) are associated with it, especially in cases in which cutaneous lesions are rapidly surgically excised. Cutaneous lymphoma in ferrets does not necessarily progress to systemic involvement. Epitheliotropic lymphoma is commonly seen in the feet and extremities of ferrets, resulting in grossly swollen, hyperemic, alopecic feet. If untreated, lesions grow in size and multiply. Complete surgical excision of cutaneous lesions may result in prolonged disease-free intervals; chemotherapeutic attempts, both topical and systemic, have generally proved to be unsatisfactory.[22,29]

Mucosa-associated lymphoid tissue lymphomas also have been reported in four ferrets.[11] Considered akin to lymphomas associated with *H. pylori* infection in humans, these neoplasms arise in the stomach of ferrets infected with *H. mustelae*.

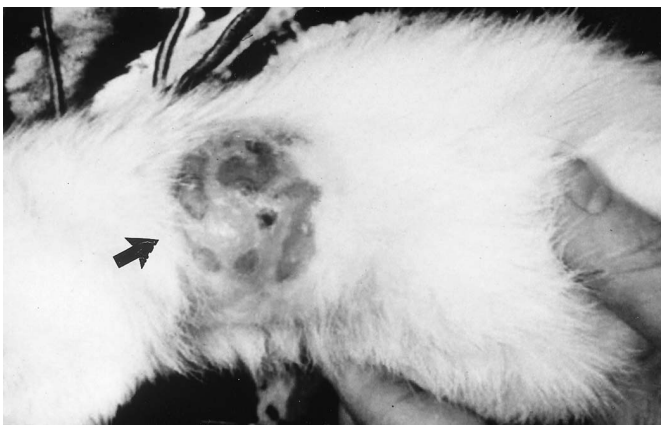

Figure 9-4 Cutaneous lymphoma in a ferret. Surgical excision of this ulcerated neoplasm (*arrow*) was accomplished; despite several recurrences, the ferret was still alive 3 years later.

Diagnosis

Diagnosis of all forms of lymphoma involves direct visualization of neoplastic cells. Excisional biopsy of affected nodes or visceral tumors is best because it allows evaluation of cellular morphology as well as architectural effacement, which may be required in cases composed of well-differentiated lymphocytes. Needle biopsy samples of visceral organs (thymus, liver, spleen) in young animals with suspected juvenile-onset lymphoma may be acceptable for diagnosis. Needle biopsy samples of lymph nodes generally do not yield significant architectural information to confirm a diagnosis of lymphoma.

Avoid biopsy of intraabdominal nodes whenever possible; severe reactive hyperplasia to chronic bowel inflammation may be marked in older ferrets and indistinguishable from lymphoma. Peripheral nodes, such as popliteal and prescapular nodes, are less likely to be affected by local inflammation, and excisional biopsy of these nodes is easily accomplished; complications of this procedure are extremely rare. Definitive diagnosis of lymphoma is best accomplished by a pathologist experienced in the evaluation of ferret lymph nodes because there is often great overlap between the histologic picture of lymphoma and other nonneoplastic causes of lymphadenomegaly.

Aspiration is frequently performed as part of an initial examination, especially when clinical signs point strongly to lymphoma. False readings because of sample preparation, reactive changes, and well-differentiated neoplasms may occur. The possibility of false-negative results is increased when aspirates of visceral organs are obtained.

The cytologic hallmarks of lymphoma are a monotonous population of lymphocytes and the absence of peripheral blood elements. A range of cell size and type, or the presence of other types of white blood cells in aspirated nodes, is not consistent with a diagnosis of lymphoma. In forms of leukemia, bone marrow aspiration may be performed by the proximal femur with an 18- to 20-gauge spinal needle. In most cases of leukemia, the bone marrow is hypercellular and often monomorphic, with a significant decrease or total absence of normal marrow elements.

Pathologists are commonly asked to evaluate splenic aspirates from animals with enlarged spleens. In our experience, at least 95% of these cases are the result of extramedullary hematopoiesis (see Chapter 38). Evidence of erythrocytic precursors and megakaryocytes and abundant peripheral blood should lead to a diagnosis of extramedullary hematopoiesis. Splenic lymphosarcoma is characterized by the presence of a monomorphic population of cells with large nuclei, prominent nucleoli, an absence of erythrocytic precursors, and minimal blood elements. Additionally, mitotic figures should be present.

Results of a CBC and cytologic examination of peripheral blood smears may yield valuable information but are rarely diagnostic for lymphoma. Affected animals may show mild to marked anemia and variable leukocyte counts. Lymphocyte counts may vary widely; levels as high as 90,000/mm^3 may be seen in leukemic cases.[4] Alternatively, older ferrets with chronic disease may become lymphopenic after months or years.[10] Persistently elevated lymphocyte counts should not be used as evidence of lymphoma. As in other species, chronic smoldering infection is the most common cause of lymphocytosis in the

ferret. The ubiquitous nature of *Helicobacter* and coronavirus infection in the U.S. ferret population has tremendous potential for inciting this nonspecific change in ferrets. Atypical circulating lymphocytes may occasionally be seen in ferrets with lymphoblastic lymphoma and are more likely to be seen in animals exhibiting lymphopenia.[1,4,10]

Clinical chemistry findings are not considered diagnostic in cases of lymphoma. Abnormalities often reflect only significant replacement of organs by neoplastic infiltrates. Hepatic enzyme concentrations may be elevated in cases of lymphoma. Hypercalcemia has been documented in cases of T-cell lymphomas in ferrets.[1,4,10]

Other clinical tests may yield diagnostic information. Radiographs can be especially valuable, especially in cases of juvenile lymphoma. A large density cranial to the heart, with or without pleural effusion, should immediately raise suspicion of lymphoma in a ferret of any age. Pleural effusion may also be identified by thoracic radiographs; however, effusions may be seen in younger ferrets with other diseases (most commonly cardiomyopathy). Microscopic examination of fluids obtained by thoracocentesis may yield clues to the cause of the effusion. Mature lymphocytes are usually the most prominent cell type in cardiac effusions, and centrifugation of these may yield a cytologic picture identical to that seen with lymphoma. Removal of effusion in some cases may reveal thymic neoplasms (or enlarged hearts) that were previously obscured. Ultrasonography, frequently accompanied by fine-needle aspiration, may also be a useful tool.

Treatment

Ferrets generally tolerate the use of common chemotherapeutic agents in lymphoma protocols well; however, only about 10% experience remission. Several factors may contribute to this apparent lack of success:

1. Concurrent disease. Animals with concurrent adrenal disease or insulinoma, two very common diseases that strike the same age group as most cases of lymphoma, may significantly complicate chemotherapeutic protocols.[4]
2. Inappropriate use of chemotherapeutic agents. Successful chemotherapy often relies on the complex interaction of agents given at specific intervals. The choice of agents based on expense, availability, or ease of administration will affect success rates.
3. Resistance to chemotherapeutic agents. It is well documented that ferrets previously treated with prednisone for other conditions (insulinoma, inflammatory bowel disease, pemphigus) have a diminished response to prednisone when it is subsequently used as part of a chemotherapeutic protocol.[4,38]

It is best to give lymphoma patients a poor prognosis at the outset of chemotherapy. Longer periods of remission have generally been reported in animals with lymphocytic (adult-onset) forms of lymphoma.[4] Because of the variable and generally slow progression of adult-onset lymphomas, it is often difficult to assess the true benefits of chemotherapy. In fact, one group of ferrets survived 2 years (considered the upper limit of remission) with no treatment.[10]

Treatment of lymphoma in ferrets should follow a careful evaluation of the patient's age, concurrent disease and therapy, type of lymphoma, and distribution and staging of tumors. Ferrets with tumors of the stomach, intestine, bone marrow, or liver generally have the poorest response to therapy.[4] Removal of focal lesions (single nodes, spleen, and so on) may be of benefit before initiating chemotherapy.[1,4,10]

Multiple chemotherapeutic protocols have been used in ferrets and are presented in Tables 9-2 and 9-3. The following generalizations and cautionary statements should be noted before chemotherapeutic agents are used in ferrets:

TABLE 9-2
Chemotherapy Protocol I for Lymphoma*

Week	Day	Drug	Dose
1	1	Prednisone	1-2 mg/kg PO q12h and continued throughout therapy
	1	Vincristine	0.2 mg/kg IV
	3	Cyclophosphamide	10 mg/kg PO or SC
2	8	Vincristine	0.2 mg/kg IV
3	15	Vincristine	0.2 mg/kg IV
4	22	Vincristine	0.2 mg/kg IV
	24	Cyclophosphamide	10 mg/kg PO or SC
7	46	Cyclophosphamide	10 mg/kg PO or SC
9	63	Prednisone	Start decreasing the dose gradually to 0 over the next 4 wk

Modified from Brown SA: Ferrets. *In* Jenkins JR, Brown SA, eds. A practitioner's Guide to Rabbits and Ferrets. Lakewood, CO: American Animal Hospital Association, 1993, pp 87-89.
*A CBC should be obtained weekly during therapy (spare the cephalic veins). Stop vincristine if WBCs are <2000 or PCV is <25% and begin antibiotics. Check CBC the following week and resume therapy if rebounding. After therapy is discontinued, continue to monitor CBC results and perform physical examinations at 3-month intervals.

TABLE 9-3
Chemotherapy Protocol II for Lymphoma*

Week	Drug	Dosage
1	Vincristine	0.2 mg/kg IV
	L-Asparaginase	400 IU/kg IP
	Prednisone	1 mg/kg PO q24h and continued throughout therapy
2	Cyclophosphamide	10 mg/kg SC
3	Doxorubicin	1 mg/kg IV
4–6	As weeks 1–3 but discontinue asparaginase	
8	Vincristine	0.2 mg/kg IV
10	Cyclophosphamide	10 mg/kg SC
12	Vincristine	0.2 mg/kg IV
14	Methotrexate	0.5 mg/kg IV

From Rosenthal KE: Ferrets. Vet Clin North Am 1994; 24:19-20.
*Protocol is continued in sequence biweekly after week 14.

1. Chemotherapeutic agents should be used carefully to minimize risks to the patient, technician, and veterinarian. Intravenous chemotherapeutic agents should be administered through a vascular access port[27] or a well-maintained catheter to an anesthetized or sedated ferret. Extravasation of most chemotherapeutic drugs often results in extensive tissue damage and loss of the vein for the remainder of the treatment period.
2. Consultation with a veterinary oncologist and referral should be considered for veterinarians whose experience with these agents is limited.
3. Careful and frequent monitoring of the clinical status and blood values, to include a weekly platelet count and a CBC, should be part of every chemotherapy protocol.

Other chemotherapy agents have been used in the treatment of ferrets with lymphoma in addition to those listed in Tables 9-2 and 9-3. For example, doxorubicin (alone and in conjunction with radiation) has been attempted for treatment of lymphoma in ferrets (2 mg/kg IV q21d for 3-5 treatments).[20]

If traditional multiagent chemotherapy is not an option, palliative therapy often results in a significant decrease in tumor burden for several months. All forms of lymphoma tend to be initially responsive to steroids. Adult-onset forms may show a less significant response to the mature lymphocyte's innate steroid resistance; however, all neoplasms tend to recur over a period of months. When tumors recur, they are steroid resistant. Ferrets that have been receiving prednisone therapy for other diseases (insulinoma, chronic bowel disease) tend to be resistant to definitive and palliative forms of chemotherapy and have shorter mean survival rates.[4,38] A minimum oral dose of prednisone (2.2 mg/kg q24h) should be used and increased as needed to decrease tumor burden and alleviate clinical signs. Fortunately, steroid-induced gastric ulceration is not common in ferrets, even with high-dose regimens.

Adjunct therapy is an important component of lymphoma treatment. Dietary supplementation with a number of high-calorie, high-protein supplements is often necessary for supporting cancer patients. Gerber Second Foods Chicken (Gerber, Inc., Fremont, MI) is well tolerated by most ferrets, may be fed by hand rather than by syringe, and makes an excellent vehicle for the administration of unpalatable medications.[38] Hill's a/d (Hills Pet Products, Topeka, KS) is also widely used, as are a variety of supplements with high-calorie human supplements as a core ingredient, such as Ensure (Abbott Labs, Abbott Park, IL) or Deliver 2.0 (Mead-Johnson Pharmaceuticals, Evansville, IN) combined with any number of additives. Vitamin and mineral supplementation may be required in animals maintained exclusively receiving these types of supplements.[4,38]

If nutritional supplements are administered by syringe, use a rate of 2 to 5 mL q2-3h. Ideally, ill ferrets can be trained to drink gruel from a saucer or bowl, at which time they can be fed every 4 hours.[38] If these products are used for more than 30 days, the ferret's normal ration should be ground up and added to the mixture. This will ensure that all trace mineral and vitamin requirements are met and facilitate the animal's eventual return to normal rations. Ferrets eating a high-quality feline or ferret maintenance diet generally do not need additional mineral or vitamin supplements.[38]

A key to the proper fluid and nutritional support of the ferret patient is the delegation of this activity to the owner to the greatest extent possible. Many ferret owners are capable of giving subcutaneous fluids and hand-feeding ferrets when such activity is required on an around-the-clock basis. Therefore encourage owners to take an active role in nursing as early in the treatment cycle as possible.

Other types of hematopoietic neoplasms, generally arising from cells of leukocytic lineage, are rarely seen. The spleen is the most common site of origin for these neoplasms. Myelolipoma, a benign neoplasm of immature leukocytes admixed with well-differentiated adipocytes, may occasionally present as a space-occupying mass in the spleen but is of no clinical significance.[23] Thymoma, a neoplasm involving the epithelial and mature lymphocytic elements of the thymus, may present as a mass lesion of the anterior thorax and be easily confused with thymic lymphoma. A report of thymoma in two 5-year-old ferrets[33] noted vomiting, lethargy, and dyspnea in both cases. The antemortem diagnosis and treatment of thymomas are challenging, at best.

TUMORS OF THE INTEGUMENTARY SYSTEM

The skin and subcutis are also common sites of neoplasia in ferrets. In this review (see Table 9-1), 275 primary neoplasms of the skin and subcutis were seen, accounting for an overall incidence of 18%. The classification and distribution of cutaneous neoplasia in this collection are consistent with previous reports.[4,24,26] Of the 275 skin neoplasms reviewed, 77 (28%) were malignant, with 67 (87%) of these representing primary malignancy of the skin or subcutis.

Benign tumors of basal cell origin, including sebaceous adenoma and sebaceous epitheliomas (Fig. 9-5), were most prevalent. These warty exophytic neoplasms, which may attain a large size and ominous appearance (largely as a result of self-trauma), are almost invariably benign. In two long-standing cases, squamous cell carcinomas appeared to have arisen in pre-existing sebaceous epitheliomas. These neoplasms occasionally caused irritation to the ferret, and self-trauma may result in local inflammation and infection. Surgical excision is curative and should be performed early.

Mast cell tumors are the second most common skin tumor in ferrets. In contrast to the dog and cat, mast cell tumors in ferrets are universally benign and warrant a good prognosis. In the 83

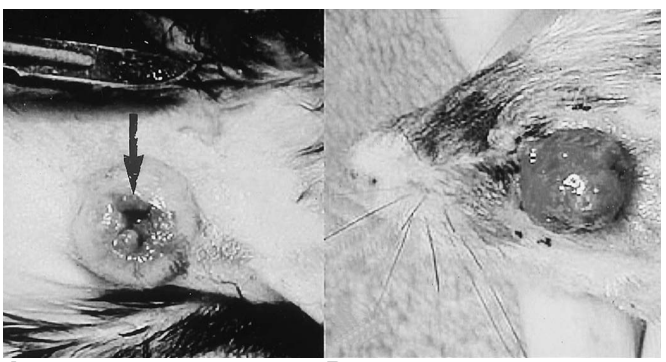

Figure 9-5 Multiple sebaceous adenomas in a ferret on the thorax (**A**) and face (**B**). The neoplasm on the face did not involve the orbit. The center of these neoplasms may occasionally be cavitated because of necrosis (*arrow*). Although impressive in appearance, surgical removal was curative.

cases reviewed, none were considered malignant or showed metastatic potential. These neoplasms are flat, discrete, and have a crusty yellow appearance. Most mast cell tumors in ferrets show minimal infiltration into the dermis and are easily excised; surgical excision is curative. A number of ferrets, however, may show multicentric development of mast cell tumors over time and require additional surgery, but this finding has no prognostic significance.

Neoplasms of apocrine scent glands are the third most common neoplasm seen in the skin and subcutis. These neoplasms are largely restricted to the deeper layers of the skin and subcutis and are often malignant. Apocrine neoplasms are most often seen in areas where scent glands are concentrated (head, neck, prepuce, and vulva). Neoplasms of the prepuce in males are almost exclusively of apocrine scent gland origin. In this review, 19 (79%) of 24 preputial neoplasms (as well as 100% of the less common perianal and perivulvar tumors) were malignant, exhibiting aggressive infiltration of local tissues, metastasis to local nodes, and, occasionally, visceral metastasis. Complete surgical excision of apocrine malignancies is difficult because of their rapid and aggressive growth and the possibility of presurgical metastasis. For this reason, wide excision of all suspected apocrine neoplasms is warranted. In cases of apocrine carcinoma of the prepuce, appropriate surgical treatment may entail amputating the prepuce and a perineal urethrostomy.

Vascular neoplasms of the skin and subcutis occasionally occur in the ferret. In this review, malignant vascular neoplasms (10 cases) of the skin and subcutis were slightly more common than their benign counterparts (eight cases), but all neoplasms were cured after complete surgical excision. Coat color and pigmentation had no prognostic significance for the development of vascular neoplasms because sable animals predominated in both subsets.

Low-grade subcutaneous sarcomas are also occasionally seen in the subcutaneous tissues of the ferret. Although predominantly of smooth muscle origin (10 of 12 in this review), two cutaneous fibrosarcomas were also identified. Most subcutaneous sarcomas are generally low-grade malignancies, with slow rates of growth, low metastatic potential, and a good response to surgical excision. Wide surgical margins should be achieved to ensure complete removal of these infiltrative neoplasms.

Mammary gland neoplasms are rare in domestic ferrets. Six mammary neoplasms were seen in this review, and all were benign (four simple, two complex). Three cases of simple mammary hyperplasia were also observed; similar to that reported previously,[25] two cases were seen in conjunction with adrenal carcinoma.

In this review, other benign neoplasms seen in the skin of ferrets include lipoma (five cases), squamous papilloma (one case), and an adenoma of the eccrine sweat glands of the footpad (one case). Malignant neoplasms include epitheliotropic lymphoma (nine cases), squamous cell carcinoma (six cases), ceruminous gland adenocarcinoma of the ear (two cases), and anal sac carcinoma (two cases).

General guidelines for treatment of cutaneous neoplasms are similar to those prescribed for more traditional pet species. Early surgical intervention is the rule with cutaneous neoplasms; most neoplasms are benign, and most malignancies are low grade and can be successfully treated with early surgical excision with wide margins. Submit sample of all neoplasms for histopathologic evaluation to provide an accurate prognosis. Surgically excise all preputial or perivulvar/perianal neoplasms as early as possible, after careful palpation and radiography, to minimize the opportunity for metastasis.

TUMORS OF THE GASTROINTESTINAL TRACT

Neoplasms of the gastrointestinal tract are common in ferrets and represented 60 primary neoplasms and 83 metastatic neoplasms in this review. The liver, a particularly common site for metastasis, was involved in a total of 71 metastatic neoplasms (including 48 cases of malignant lymphoma, 11 cases of metastatic adrenocortical carcinoma, 10 cases of metastatic adenocarcinoma of unspecified origin, 1 malignant mast cell tumor, and 1 metastatic pancreatic exocrine adenocarcinoma). In contrast to a previous study,[4] metastatic islet cell tumors were not identified.

The liver is also a relatively common site for the development of primary neoplasms. A total of 25 primary neoplasms of the liver were identified, including 17 biliary cystadenoma/cholangiomas, 2 cholangiocarcinomas, 4 hepatocellular carcinomas, and 2 hepatomas. The differentiation of biliary cystadenoma from biliary cyst (a common incidental finding in this species) is made on the basis of one or more of the following factors: presence of clinical symptoms, abnormalities in liver-specific clinical pathology, or expansive growth over time documented by abdominal ultrasound. In several cases, histologically benign biliary cystadenomas (Fig. 9-6) pursued an aggressive course similar to their malignant counterparts, replacing one or more lobes of the liver and ultimately resulting in hepatic failure. Hepatic carcinoma and cholangiocarcinoma in this study consistently resulted in increased concentrations of hepatic enzymes, eventual hepatic failure, and other signs such as profound anemia, hemoperitoneum, and ascites.

In most cases, animals with hepatic neoplasia are seen for nonspecific weight loss, anorexia, and lethargy. A cranial abdominal mass is generally identified by palpation or radiography; clinicopathologic abnormalities are usually mild and nonspecific. Biopsy all hepatic neoplasms, especially those involving

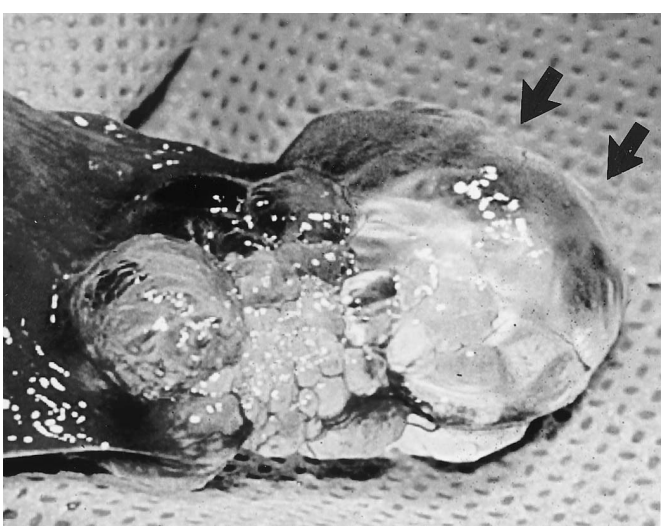

Figure 9-6 Biliary cystadenoma in a ferret. Because of their aggressive nature, these histologically benign tumors *(arrows)* are best treated with lobectomy or, at a minimum, excision with wide surgical margins.

multiple lobes. If the neoplasm is confined to one lobe of the liver, lobectomy is recommended. Because of the aggressive nature of biliary cystadenoma in ferrets, remove any cystic lesion of the liver with wide surgical margins or lobectomy. Neoplasms involving multiple lobes have a poor long-term prognosis; however, survival times of several months or more may be seen with hepatocellular carcinoma. Animals possessing malignancies of the biliary system generally succumb within a short time frame.

The most common neoplasm affecting the gastrointestinal tract is malignant lymphoma (18 primary, 48 secondary in this review). Of the cases in which the gastrointestinal tract was considered the primary site, the intestine was the most common site of origin (9 of 18; 50%), followed by the stomach (3 cases), liver (3 cases), colon (2 cases), and 1 case involving the oral cavity. Lymphoma of the intestine is considered to carry an extremely poor prognosis, is often refractory to treatment, and is associated with the shortest survival times.[4]

Neoplasms of the exocrine pancreas (11 cases in this review) are occasionally seen in the ferret. Most neoplasms exhibit aggressive growth into the surrounding pancreas, but metastasis to distant organs is rare (and only seen in one case in this review). Complete surgical excision may be useful if the neoplasms are discovered early.

Primary neoplasms of the gastrointestinal tract tend to be malignant, with adenocarcinomas arising in the stomach (three cases), intestine (three cases), and rectum (one case). These neoplasms are locally aggressive, often involving multiple layers of the wall with metastasis to local lymph nodes. The predilection of these neoplasms to incite a prominent scirrhous response often results in obstruction and clinical symptoms. This same scirrhous response, however, tends to achieve a type of containment to the neoplasm, allows visualization of the tumor's margins, and facilitates complete excision. The prognosis at this point is affected heavily by the presence or absence of presurgical metastasis.

Tumors of the oral cavity are occasionally seen in ferrets and are usually associated with a poor prognosis. Squamous cell carcinoma appears as an aggressive neoplasm of the gums that invades underlying bone, resulting in tooth loss, disfigurement, and inappetence (Fig. 9-7). One report described treatment of a mandibular squamous cell carcinoma with bleomycin at a dose of 20 U/m^2, which reduced tumor mass.[19] Surgical excision, if attempted, should be attempted early and with wide surgical margins. Various sarcomas, including fibrosarcoma,[4] have been reported in the oral cavity and respond poorly to all forms of treatment.

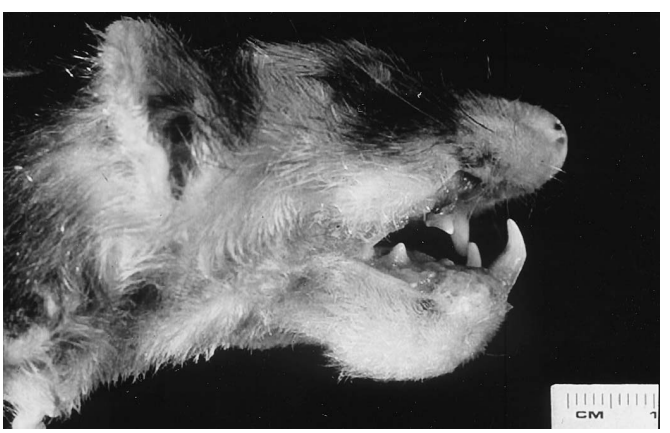

Figure 9-7 Mandibular squamous cell carcinoma in a ferret. There is marked invasion of alveolar bone with tooth loss.

TUMORS OF THE REPRODUCTIVE TRACT

Because of the prevalence of neutering in North American pet ferrets, tumors of the reproductive system are rarely seen in clinical practice. Earlier reports indicated a high prevalence of these neoplasms,[2,8] but the rarity of intact animals in today's pet and laboratory populations has significantly reduced the numbers of the tumors seen. Clinical signs of reproductive neoplasia in ferrets are variable and often nonspecific. Ovarian tumors often result in no overt signs; in a few cases, a failure to breed is noticed. Testicular neoplasms, which commonly arise in retained testes, may result in signs of hyperestrogenism (intact sexual behavior, aggression, prominent musky odor, and poor, greasy hair coat) in affected males. However, with rare exceptions, surgical excision of affected gonads is curative.

In this review, most neoplasms of the ovary and uterine tube were of smooth muscle origin. Although 13 (72%) of 18 were considered malignant based on histologic appearance, evidence of metastasis was not seen and surgical excision was curative.

A total of 13 primary gonadal tumors of the ovary were identified (3 Leydig cell tumors, 4 granulosa cell tumors, 4 teratomas, and 2 sex cord stromal tumors). Ovarian neoplasms are most commonly identified as incidental findings during routine spays. Teratomas may attain a size that is obvious on routine palpation or may be identified by survey radiographs as a result of the presence of bone within the tumor mass. One Leydig cell tumor metastasized to a regional lymph node.

Testicular neoplasms occurred most commonly in cryptorchid testes in this review. Multiple neoplasms may be seen in retained testes, and in one case four distinct neoplasms (interstitial cell, seminoma, Sertoli cell, and a carcinoma of the rete testis) were seen. A total of 17 testicular neoplasms were identified (7 Leydig [interstitial] cell tumors, 5 seminomas, 4 Sertoli cell tumors, and 1 carcinoma of the rete testis). One Sertoli cell tumor metastasized to the liver.

Nonmuscular tumors of the uterine tube are extremely rare in ferrets. One uterine adenocarcinoma and one deciduoma were seen. Implantation sites in female ferrets or even uterine biopsy samples from pseudopregnant animals may be mistaken for uterine carcinoma on histologic examination as a result of the profound atypia of symplasmal cells.

TUMORS OF THE MUSCULOSKELETAL SYSTEM

Neoplasms of the skeletal system are not uncommon in ferrets and generally result in a clinical appearance that is obvious to both owner and practitioner. Tumors of the skeletal muscles, however, are extremely rare; only one example, a rhabdomyosarcoma, was identified (1 of 1524 [<0.07%]).

Chordomas (56 cases in this review) are the most common neoplasm of the musculoskeletal system in the ferret (comprising 79% of the musculoskeletal neoplasms reviewed). They most commonly appear as irregularly round, white-gray, firm, clublike swellings of the tail tip. This low-grade malignancy arising from

primitive notochord is most commonly seen at the tip of the tail but may arise in vertebrae in any region of the spinal column.[9] These neoplasms are locally aggressive, destroying the vertebral body in which they arise,[9] but have minimal metastatic potential (with only one report of metastasis after surgical intervention).[39] Radiographs of affected vertebrae reveal a focally extensive vertebral lesion that is both lytic and proliferative.

Chordomas of the tail tip are easily treated by amputation but carry a poor prognosis when affecting other parts of the spinal column. Because of their aggressive nature, extirpation from affected vertebrae is currently not feasible, and eventual loss of function and pathologic fracture will inevitably result. Previous reports of chondrosarcoma of the tail tip, as well as reports that may be obtained from histologic examination of current cases, should be viewed with skepticism.

True tumors of bone (osteomas and osteosarcomas) are occasionally seen in ferrets. Osteomas most commonly arise on flat bones, including the skull and ribs, and progress slowly. Surgical removal may occasionally be accomplished; however, many osteomas regrow when excision is incomplete. Osteosarcomas are rarely reported in ferrets[37] but may arise either on flat or long bones. These malignancies are locally destructive and are best treated by amputation, if possible. Surgeons are cautioned that noncore biopsy samples of malignant bone tumors may result in an errant diagnosis because of the presence of pronounced periosteal reactions overlying the osteosarcomas.

Chondromas and chondrosarcomas, neoplasms of chondrocytic cells, are rare tumors of flat bones that have been occasionally reported but not described in detail.[4,24] Pathologists unfamiliar with the histologic interpretation of ferret tissue sections may confuse this neoplasm with chordoma.

Tumors of skeletal muscle are extremely rare in ferrets. Rhabdomyosarcomas, malignant tumors of skeletal muscle, have been reported[6,24] and one was present in this review. These neoplasms are treatable by radical excision, if possible.

TUMORS OF THE NERVOUS SYSTEM

Neoplasms of the nervous system are rare in ferrets. These tumors can be divided into those of the central nervous system, affecting the brain, and those of the peripheral nervous system, affecting the peripheral nerves and ganglia. Tumors of the central nervous system generally result in neurologic signs, whereas those of the peripheral nervous system result in space-occupying lesions, usually in the subcutis. In this review, neural tumors were seen in only 12 (0.8%) of 1525 neoplasms, with 5 neoplasms in the brain and 7 in the peripheral nerves of the skin and subcutis (see Table 9-1).

Central nervous system tumors are the third most common cause of neurologic signs in ferrets, after insulinoma and bacterial meningitis/encephalitis. Central nervous system neoplasia should only be considered when these two syndromes are conclusively ruled out. Clinical signs associated with these tumors are quite variable and often nonspecific. Lateralizing signs (such as turning toward the side of the lesion), ataxia, cranial nerve deficits, normocellular cerebrospinal fluid, and uncontrolled seizure activity in the presence of a normal blood glucose level are suggestive of, though not specific for, a central nervous system neoplasm.

In this survey, astrocytomas (three cases) were the most common primary brain tumor. These glial neoplasms are generally diagnosed after euthanasia for severe neurologic deficits. They are locally aggressive within the neuropil and resection is not considered feasible.

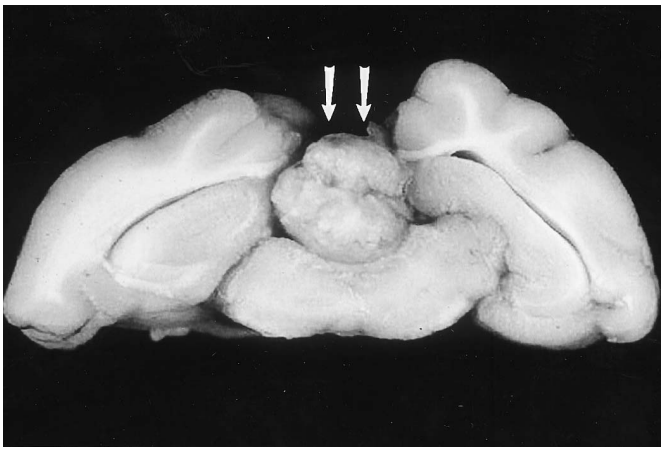

Figure 9-8 Meningioma *(arrows)* in the diencephalon of a ferret. This discrete neoplasm compresses the adjacent cerebrum and brainstem. *(Courtesy Dr. Michael Garner, Northwest ZooPath, Monroe, WA.)*

One granular cell tumor was present in this review. Similar to the only reported case in the literature,[32] this neoplasm presented as a space-occupying mass within the cerebrum and brainstem, which was diagnosed at necropsy in an animal with severe neural deficits, including blindness and seizures. The origin of granular cell tumors in ferrets is currently unknown. Another nonresectable tumor seen in this review that has not been previously reported is a primitive neuroepithelial tumor.

A single meningioma was also observed (Fig. 9-8). This neoplasm was a discrete tumor extending downward from the meninges of the cranium and caused compression and atrophy of the cerebrum and brainstem as well as profound neurologic deficits. This neoplasm has previously been reported only once.[24] Of all of the primary brain tumors, meningiomas show the most promise for surgical excision because they are discrete neoplasms arising from the meninges and, in this limited number of cases, do not infiltrate the neuropil. Antemortem diagnosis is challenging, however.

Neoplasms of the peripheral nervous system carry a significantly improved prognosis over those in the central nervous system because they tend to be restricted to the skin and subcutis. Prognosis is based on the degree of malignancy and infiltration of local tissue. In this review, both benign and malignant peripheral nerve sheath neoplasms were identified. Malignant peripheral nerve sheath tumors as a general rule exhibit rapid growth and tend to infiltrate adjacent tissue to a higher degree than their benign counterparts, rendering complete excision more difficult. In many cases, repeat surgeries are required for a cure. Although these neoplasms may be seen at any site in the body, the tissues of the head (and, interestingly, the eyelid) appear to be a common site of origin (Fig. 9-9). Tumors of nerve sheath origin may be misdiagnosed as fibrosarcoma or leiomyosarcoma when immunohistochemical procedures are not used; however, the prognosis of these three low-grade malignancies is not appreciably different. Schwannoma is a similar neoplasm of perineural cells that generally has a benign course. These tumors should be surgically excised as quickly as possible

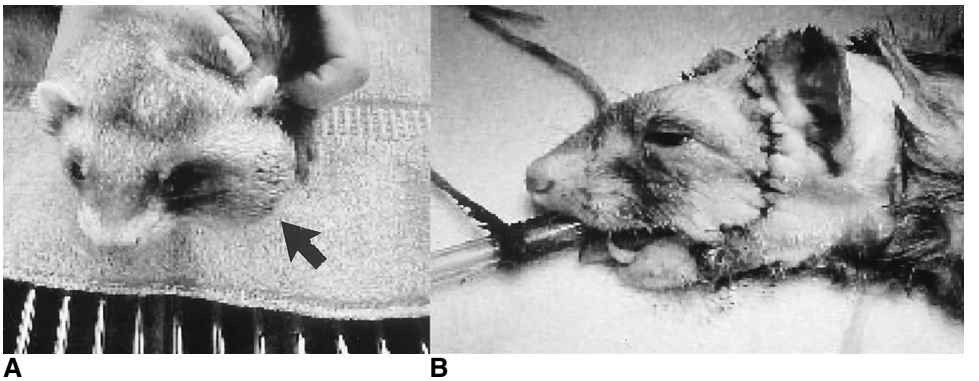

Figure 9-9 Preoperative (**A**) and postoperative images (**B**) of a malignant peripheral nerve sheath tumor (*arrow*) in a ferret. The tumor was removed by cryosurgery; however, facial nerve paralysis was encountered after surgery. Recurrence resulted in eventual euthanasia of this patient. *(Courtesy Dr. Darrell Kraft, Woodinville, WA.)*

after diagnosis because growth in areas with high skin tension may result in large defects that are difficult to close.

Ganglioneuromas are rare neoplasms of the peripheral nerve ganglia. The single case reported in this review bears a marked similarity to previously reported cases[24] in which a well-differentiated neoplasm with neurons and glia in a matrix of neural tissue was present in close proximity to the right adrenal gland. Close examination is required to differentiate these nodules from normal ganglia on a histologic basis; however, these tumors tend to be much larger than ganglia—ranging up to 1.5 cm in diameter. Ganglioneuromas have no apparent clinical signs and are often misjudged to be adrenal tumors on gross inspection.

TUMORS OF THE URINARY SYSTEM

Neoplasms involving the urinary system are rare in ferrets. Transitional cell carcinoma of the kidney is the most common; these neoplasms have also been reported in the urinary bladder.[4] In the kidney, transitional cell carcinomas arise in the renal pelvis,[3] eventually causing outflow obstruction and hydronephrosis. Metastasis has not been reported from this site, and unilateral nephrectomy may be curative if early diagnosis is achieved.

In the bladder, transitional cell carcinoma generally results in a poor prognosis. Because the presenting signs are vague, diagnosis is generally achieved only after extensive local invasion has occurred.[4] Dysuria and incontinence may be presenting signs and initially ascribed to cystic prostatic disease or crystalluria. Urinalysis, including the examination of urinary sediment, and contrast radiographic techniques may be helpful to identify this neoplasm; definitive diagnosis is made by surgical biopsy.[4] It is likely that these tumors, once identified, would prove a surgical challenge, especially in the area of the trigone. For unresectable tumors, chemotherapeutic agents that inhibit cyclooxygenase-2 (COX-2) enzymes have shown promise in dogs and may ameliorate clinical signs and prolong life in ferrets; other more traditional agents such as doxorubicin, cisplatin, and cyclophosphamide may also be useful. However, appropriate dosages of all of these agents for the treatment of this and other types of invasive carcinomas have not been defined.

Renal carcinomas and renal adenomas have also been reported in ferrets.[4,24] These unilateral neoplasms of the kidney are most often encountered at necropsy because the majority tend to be slow growing with low metastatic potential. Renal neoplasms generally present as cystic areas on ultrasound examination; however, the high incidence of renal cysts in domestic ferrets would likely preclude further diagnostic workup on the basis of this finding. Renal carcinoma may occasionally result in hemoperitoneum and require emergency nephrectomy.

TUMORS OF THE RESPIRATORY SYSTEM

Neoplasms involving the lung are generally of metastatic origin, although one undescribed primary neoplasm of the lung has been reported.[24] In this review, two cases of malignant lymphoma, one case of metastatic adenocarcinoma, and one poorly differentiated sarcoma of uncertain cause were identified at necropsy. In most cases, pulmonary metastasis of these neoplasms would likely go unnoticed; chemotherapy, however, might be of benefit in metastatic lymphoma.

OTHER MISCELLANEOUS NEOPLASMS

Two neoplasms of structural elements that may be seen in any organ are neoplasms of endothelium and smooth muscle.

Hemangiomas and hemangiosarcomas are occasionally seen in ferrets. In this study, 27 (2%) of 1525 vascular neoplasms were identified, with most arising in the skin or subcutis (18 of 27; 67%). Endothelial neoplasms, however, also were seen in the liver, spleen, pancreas, lymph node, and free-floating in the abdomen. Although 16 of 25 neoplasms showed histologic evidence of malignancy, only one showed evidence of metastasis. Most cutaneous vascular neoplasms are malignant, but they are low-grade malignancies with slow growth and no metastatic potential (Fig. 9-10). Complete excision of these tumors is curative. Rarely, multiple hemangiosarcomas may be seen; however, the prognosis for these cases is no different than that for animals with single neoplasms.

The prognosis, however, for animals with hemangiosarcoma within the abdomen is guarded. These tumors tend to grow more aggressively within abdominal organs and may rupture at any time, seeding the abdomen with metastatic tumors or resulting in fatal hemorrhage. Early surgical intervention should be the rule when the neoplasm is restricted to a single site. An incidence of 22% of hepatic hemangiosarcoma was reported in one colony[7]; the cause of this high incidence is uncertain, and this phenomenon has not been repeated since.

Neoplasms of smooth muscle are extremely common in ferrets. Smooth muscle is a structural component of blood

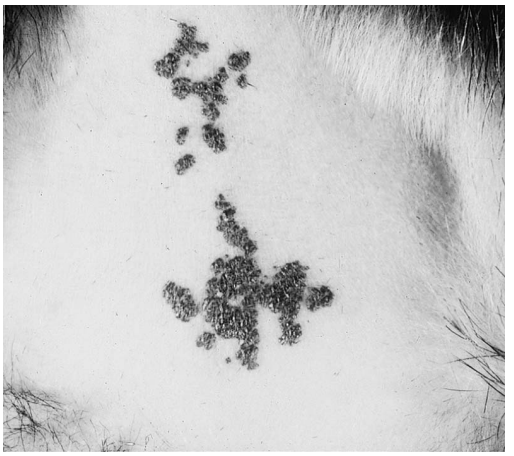

Figure 9-10 Benign cutaneous hemangioma in a ferret.

vessels; erector pili muscles of hair follicles along the dorsal midline and tail; and the predominant muscle in the gastrointestinal, reproductive, and lower urinary tracts. Additionally, smooth muscle is seen in the capsule of the ferret adrenal gland.[18] In this review, 48 (3%) of 1525 of the tumors were of smooth muscle origin: 5 leiomyomas and 43 leiomyosarcomas. The prognosis of a malignant smooth muscle tumor and a benign one, regardless of the site, is similar. Although they may attain a large size, they have little metastatic potential and excision is considered curative at any location.

Leiomyosarcomas of the adrenal capsule are occasionally encountered in ferrets[18] and may result in confusion on the part of the practitioner and the pathologist. These neoplasms may lead practitioners to perform adrenalectomy on normally functioning adrenal glands. The presence of the tumor may also mask the presence of proliferative adrenocortical lesions from the pathologist unless multiple sections at 1 mm or more are examined.

Smooth muscle tumors of the skin are also common findings and likely arise from smooth muscle associated with hair follicles.[28] Surgical excision of these tumors is considered curative and, in general, a good prognosis is warranted.

Leiomyosarcoma is also often seen in association with organs of the reproductive system. The ovary is a common site for development of this neoplasm, and the number of tumors seen would likely be much greater if not for the high frequency of neutering of North American ferrets. As opposed to other domestic species, smooth muscle tumors of the gastrointestinal tract are not common.

Mesotheliomas are uncommon malignancies of ferrets that carry an extremely poor prognosis.[40] These tumors arise in the abdominal cavity and spread extensively before the appearance of clinical signs. The most common clinical sign in affected animals is profound ascites ("malignant" ascites).[40] Abdominocentesis and identification of clusters of atypical mesothelial cells may aid in diagnosis. Because mesothelial cells may be seen in any abdominal tap, take care to prevent misdiagnosis.

Anaplastic neoplasms are those in which the level of cellular differentiation is below that needed to identify a cell of origin. Neoplasms tend to recapitulate their tissue of origin morphologically (e.g., insulinomas look like islets of Langerhans, pancreatic exocrine tumors look like exocrine acini). Sophisticated techniques may yield clues to a tumor cell's origin even if it does not resemble the parent tissue. Immunohistochemical procedures to identify tissue-specific intermediate filaments or ultrastructural analysis of cellular organelles by electron microscopy may identify characteristic organelles for a particular cell type. Today the use of sophisticated techniques at large referral laboratories may help in identifying the origin of a particular neoplasm, thereby enabling the practitioner to develop a strategy for the treatment and prognosis of these tumors. However, many smaller laboratories are not equipped to routinely perform these tests, and a broad diagnosis of poorly differentiated carcinoma, sarcoma, or round cell tumor is often the result.

In this review, the diagnosis of "poorly differentiated" tumors was made only after special staining, immunohistochemical procedures, and electron microscopy were attempted. Even with specialized techniques, a number of malignancies are poorly differentiated enough that they will not disclose information regarding a tissue of origin and are put in broad classifications of epithelial origin (carcinoma) or mesenchymal origin (sarcoma). In some cases, a broad morphologic classification is given (malignant round cell tumor), and in rare instances of extreme anaplasia, even this information cannot be identified and a diagnosis of malignant neoplasm is assigned.

A tissue of origin could not be identified in 32 (2%) of 1525 cases reviewed; however, in 27 of these cases, a broad category of epithelial versus mesenchymal origin was obtained. Even this limited classification has therapeutic importance, because epithelial and round cell tumors tend to be significantly more responsive to chemotherapy than the sarcomas. Sarcomas of the skin were the largest single classification of poorly differentiated tumors but the most responsive to treatment (i.e., surgery.) Because sarcomas of the skin tend to have low metastatic potential, a definitive identification of cell of origin (smooth muscle, skeletal muscle, fibrocyte, etc.) is of little clinical importance. However, the remainder of the poorly differentiated neoplasms generally carry a poor prognosis, especially those present in abdominal organs.

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