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Neoplasia in Ferrets

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OUTLINE

Neoplasia has long been studied as a common cause of disease in ferrets in the United States,[52,95] but it is now the most common disease in ferrets presenting to hospitals in Asia and Europe,[22,41,57] showing the ubiquitous nature of neoplasia in domestic ferrets on a worldwide scale. The probability is good that most ferrets will develop a neoplasm of the endocrine system during the "golden age" for tumors (4–6 years) and high that some type of neoplasm will become evident over the course of a lifetime.

One tenet should be considered by all veterinarians treating ferrets with neoplasms: a ferret is not a cat or a dog. The clinical behavior, prognosis, and paraneoplastic syndromes in ferrets are often far different from what is seen with similar neoplasms in dogs or cats. For example, insulinoma in ferrets is a neoplasm that rarely metastasizes, as opposed to the same neoplasm in dogs and cats, which metastasizes widely and rapidly and results in short survival times. Adrenocortical carcinoma, a neoplasm prone to metastasize widely in dogs in most cases, warrants a good prognosis with early removal or treatment in ferrets. Mast cell tumors, often malignant (and fatal) in dogs, are invariably benign and associated with a good prognosis in ferrets. Thus extrapolating diagnostic and therapeutic options from comparable syndromes in more traditional pet species can be problematic.

ETIOLOGY

Little information is definitive on the causes of many common neoplasms in ferrets. Many theories abound but only rarely with supportive evidence, and some neoplasms may be multifactorial in origin. Three main schools of thought are the following:

1. Husbandry issues. The "domestication" of the ferret as a pet species involves varying degrees of environmental and surgical manipulation of the animal itself. Several factors relating to this have been postulated as causative for common neoplasms in this species—early neutering, as well as indoor housing and artificial lighting (adrenocortical neoplasia)[8,76,77] or feeding high-carbohydrate diets and treats (islet cell tumors).[76]
2. Genetic (familial) predisposition. Although genetic or chromosomal aberrations are yet to be studied in domestic ferrets, the high incidence of neoplasia in American bloodlines of ferrets compared with their European counterparts, as well as the documentation of multiple endocrine neoplastic syndromes[31] (resulting from genetic point mutations in people), lends credence to this belief.
3. Infectious agents. Infectious causes have been proposed for neoplasms in ferrets, including retroviruses (lymphoma)[5,26] and *Helicobacter mustelae* (gastric adenocarcinoma[30,31,49] and gastric B-cell [mucosal-associated lymphoid tissue] lymphomas[25]).

DIAGNOSIS

Initial diagnostic testing for suspected neoplasia in ferrets includes the judicial use of blood tests and diagnostic imaging. A complete blood count (CBC) and serum/plasma biochemical analysis is mandatory to evaluate the patient's overall health status and may lead directly to a definitive diagnosis (e.g., hypoglycemia associated with islet cell tumors or hyperproteinemia resulting from myeloma).

Radiography and ultrasonography are used not only to diagnose tumors but also to help stage neoplastic disease, plan therapy, and monitor response to therapy. More advanced diagnostic imaging modalities, such as computed tomography, magnetic resonance imaging, and contrast studies, are useful in a wide variety of neoplastic diseases and are becoming more widely available.

In most cases of neoplasia, definitive diagnosis requires sampling of the neoplasm and microscopic analysis. Although examination of cytologic preparations helps to develop a diagnostic plan and in some cases yields a definitive diagnosis, biopsy usually results in a definitive diagnosis and often yields additional information about tumor phenotype (important in lymphoma), staging, and prognosis.

TREATMENT

Before initiating treatment, practitioners should always discuss therapeutic goals, potential outcomes, prognosis for cure, and adverse effects of treatment options versus the effects of palliative care in cases of life-threatening disease.

Potential therapies in oncology include the following:

- *Surgery.* Surgery is the treatment of choice for curing solitary tumors with limited metastatic potential. Surgery is used to obtain biopsy samples, debulk tumors as an adjunct to radiation or chemotherapy, or simply for palliation of symptoms. Cryosurgery or hyperthermia can be used with small solitary solid tumors.
- *Chemotherapy.* Several chemotherapeutic protocols for ferrets have been reported. In addition to primary treatment, chemotherapy may be used before surgery or radiation therapy to decrease tumor size or after surgery to eliminate small foci of metastasis, to prevent recurrence after incomplete surgical excision, or as palliative treatment when a definitive cure is not an option. Reported chemotherapeutic agents used in ferrets are listed in Tables 8.1, 8.2, and 8.3. When calculating chemotherapeutic doses, a ferret-specific formula for body surface area can be used (Table 8.4); however, there are only minor differences between this formula and the feline-derived formula.
- *Radiation.* Use of radiation therapy in ferrets has been reported with variable success. It is used for control of local solid tumors, either alone or in combination with surgery, or as a palliative treatment when surgery is not an option.
- *Supportive care.* As with any oncologic patient, supportive care and management of paraneoplastic symptoms is paramount. Appropriate nutrition and hydration, proper analgesia, maintenance of hydration, antiemetic therapy, and control of secondary infections is paramount in ferrets undergoing treatment.

TABLE 8.1 Modified COP Protocol (IV, PO, SC drugs) for 52 Weeks' Duration, Gulf Coast Veterinary Specialists[3]

Week	Drug	Dosage
0, Day 3	L-asparaginase	400 U/kg SC (pretreat with diphenhydramine @ 1 mg/kg IM)
1	Cyclophosphamide	10 mg/kg PO or SC
	Prednisone (throughout therapy)	1 mg/kg PO every 24 h until week 13, then 1 mg/kg PO every 48 h
	Vincristine	0.12 mg/kg IV
2	Vincristine	0.12 mg/kg IV
3	Vincristine	0.12 mg/kg IV
4	Cyclophosphamide	10 mg/kg PO or SC
	Vincristine	0.12 mg/kg IV
7 - Repeat every 3 wk (i.e., week 10, 13, 16, etc.) until week 52, then restage	Cyclophosphamide	10 mg/kg PO or SC
	Vincristine	0.12 mg/kg IV
Rescue	Doxorubicin	1-2 mg/kg IV over 20 min

Weekly CBCs are also performed to ensure the neutrophil count is remaining ≥ 1000 cells/μL. If the neutrophil count is <1000 cells/μL, delay treatment by 1 week and repeat another neutrophil count.
CBC, Complete blood count; *COP,* cyclophosphamide, vincristine (Oncovin), and prednisone; *IV,* intravenously; *PO,* orally; *SC,* subcutaneously.

TABLE 8.2 Tufts University "No-IV" Chemotherapy Protocol

Week	Drug	Dosage
1	L-asparaginase	10,000 IU/m^2 SC
	Cyclophosphamide	250 mg/ m^2 PO, give with 50 mL/kg of LRS
	Prednisone (throughout therapy)	2 mg/kg PO every 24 h × 7 days, then 2 mg/kg PO every 48 h
2	L-asparaginase	10,000 IU/m^2 SC
	CBC	
3	L-asparaginase	10,000 IU/m^2 SC
	Cytarabine	300 mg/m^2 SC every 24 h × 2 days (dilute 100 mg with 1 mL sterile water for injection)
4	CBC	
5	Cyclophosphamide	250 mg/m^2, give with 50 mL/kg of LRS
7	Methotrexate	0.8 mg/kg IM
8	CBC	
9	Cyclophosphamide	250 mg/m^2 PO, give with 50 mL/kg of LRS
11	Cytarabine	300 mg/m^2 SC every 24 h × 2 days (dilute 100 mg with 1 mL sterile water for injection)

Continued

TABLE 8.2 Tufts University "No-IV" Chemotherapy Protocol—cont'd

Week	Drug	Dosage
	Chlorambucil	2 mg tablet PO once or 1 mg (1/2 tablet) PO every 24 h × 2 days
12	CBC	
13	Cyclophosphamide	250 mg/m^2 PO, give with 50 mL/kg of LRS
15	Procarbazine	50 mg/m^2 PO q24h × 14 days
16	CBC	
17	CBC	
18	Cyclophosphamide	250 mg/m^2 PO, give with 50 mL/kg of LRS
20	Cytarabine	300 mg/m^2 SC every 24 h × 2 days (dilute 100 mg with 1 mL sterile water for injection)
	Chlorambucil	2 mg tablet PO once or 1 mg (1/2 tablet) PO every 24 h × 2 days
23	Cyclophosphamide	250 mg/m^2 PO, give with 50 mL/kg of LRS
26	Procarbazine	50 mg/m^2 PO every 24 h × 14 days
27	CBC, biochemistry	
*If not in remission, continue weeks 20–27 for three cycles		

CBC, Complete blood count; *IM,* intramuscularly; *IV,* intravenously; *LRS,* lactated Ringer's solution; *PO,* orally; *SC,* subcutaneously. Courtesy Dr. Joerg Mayer, University of Georgia.[56,95] Non invasive chemotherapy protocol (PO, SC drugs) for 26-week duration. If the CBC results show myelosuppression, reduce the dose by 25% the next treatment.

TUMORS OF THE ENDOCRINE SYSTEM

Most neoplasms in domestic ferrets arise in the endocrine system, with tumors of the pancreatic islets and the adrenal cortex being the two most common neoplasms in these species. Detailed descriptions of these disease syndromes and treatment options are discussed in Chapter 7.

Islet Cell Tumors (Insulinoma)

Although multiple studies have pointed to insulinomas (also known as *islet cell tumors*, arising from the β cells of the pancreatic islets) as the most common neoplasm of ferrets, these tumors may be slightly overrepresented because of their relatively obvious symptomatology, response to surgical excision, and tendency to recur over time.[2,4,9,10,23,52,57,89,95] This neoplasm is most commonly seen in middle-aged ferrets, with the incidence slightly higher in males than in females; however, this may reflect a bias of ferrets that present to hospitals with clinical signs rather than a true sex predilection.[9,23,89]

Insulinoma in the ferret exhibits a far different behavior than in the dog or cat.[9,89] In the dog and cat, these are highly malignant neoplasms with marked metastatic potential, leading to a short survival time. In ferrets, these same neoplasms have low metastatic potential and respond well to surgical excision, resulting in a symptom-free or medication-free interval,[89] and nonsurgical patients may be medically managed for long periods of time. Recurrence is relatively common with surgical management of insulinoma in ferrets; however, true metastasis, the translocation of malignant cells to a distant organ or lymph node, is uncommon.

Adrenocortical Neoplasms

The second most common neoplasm in domestic ferrets is also of endocrine origin and originates in the adrenal cortex.[2,4,9,10,23,52,57,73,89,95] In the intact ferret, seasonal stimulus of the hypothalamus results in the release of a variety of hormones, including luteinizing hormone, which stimulates sex steroid production from the ovaries or testes. In neutered animals, the absence of gonads results in a lack of negative feedback for the hypothalamus, and, under the constant stimulation of luteinizing hormone, pluripotential cells of the zona reticularis differentiate into cells capable of producing estrogen and other intermediate sex steroid metabolites, including androstenedione and hydroxyprogesterone.[75] Multiple studies have reported the average age of ferrets with adrenal disease at approximately 4.5 years,[9,88,95] but the disease has also been reported in ferrets under 12 months of age,[52] with no sex predilection.

The relatively obvious clinical signs exhibited by most ferrets with adrenal disease contribute significantly to the frequency of their presentation for treatment. Affected ferrets exhibit a constellation of cutaneous, behavioral, and reproductive signs that make them easily identifiable. Characteristic bilateral truncal alopecia develops in about half of affected animals, and patchy hair loss in others. Vulvar swelling may be seen in up to 90% of affected neutered jills.[73,82] The effects of estrogen on the prostatic glandular epithelium in male ferrets may result in dysuria due to prostatic cysts or abscesses; if not treated promptly, azotemia, obstruction, and ultimately uremia are probable sequelae. Finally, the presence of increased levels of testosterone in the male or estrogen in the female may result in a return to intact sexual behavior such as mounting, urine marking, and aggression.

Proliferative lesions of the adrenal cortex are distributed equally between the left and right adrenal glands, and approximately 20% are bilateral.[95] From a clinical (and prognostic) standpoint, proliferative lesions in the adrenal cortex fall into a spectrum ranging from hyperplastic lesions to benign or malignant neoplasms (Fig. 8.1). A good prognosis appears warranted in the case of most extirpated lesions, regardless of location, histologic grade, or completeness of excision.[82,95] It is important to inform owners that lesions in the contralateral adrenal gland occasionally develop, resulting in recurrent disease at a later date, and metastatic disease may be seen in a low percentage of highly anaplastic carcinomas.[66]

Other neoplasms may arise in the ferret adrenal gland. Leiomyosarcomas of the adrenal capsule are common.[36]

TABLE 8.3 Published Dosages of Drugs Used to Treat Tumors in Ferrets

Drug	Dosage	Mechanism of Action	Use	Adverse Effects
Bleomycin	10 U/m^2 SC[38]	DNA cleavage	Metastatic squamous cell carcinoma in a ferret[38]	• Pulmonary fibrosis in humans
Chlorambucil	• 1 mg/kg PO every 7 d[44] • 20 mg/m^2 PO[68]	Nitrogen mustard derivative, alkylating agent	Lymphoma	• Myelosuppression, (neutropenia and thrombocytopenia)
Cyclophosphamide	• 200 mg/m^2 PO, SC × 4 consecutive days weekly[31] • 10 mg/kg PO[2,9,92] • 80 mg/m^2 PO every 24 h × 3 days every 2 wk[68]	Nitrogen mustard derivative, alkylating agent	Lymphoma	• Myelosuppression, (neutropenia) seen in one ferret at 150 and 200 mg/m^2 SC necessitating discontinuation of medication[44] • GI (nausea, vomiting, diarrhea) • Hemorrhagic cystitis (therefore usually given with SC fluids)
Cytarabine (cytosine arabinoside)	300 mg/m^2 SC every 24 h × 2 days[56]	Competitive inhibitor of DNA polymerase α, incorporated into DNA	Leukemia, lymphoma (especially with CNS involvement)	• Myelosuppression • Mild GI disturbances
Doxorubicin	• 20 mg/m^2 IV[44] • 2 mg/kg[44] • 2.8 mg/kg IV every 3 wk × 3 doses[68] • 30 mg/m^2 IV[68] • 1 mg/kg IV every 3 wk × 4 treatments[2]	Multimodal mechanism of cellular toxicity	Lymphoma, osteosarcoma, and most mesenchymal and epithelial neoplasms	• Hypersensitivity (infusion rate–dependent) • Myelosuppression • GI toxicity • Cardiotoxicity (cumulative dose-related) • Renal tubular damage (cats—repeated dosing) • Tissue necrosis with extravasation
Isotretinoin	2 mg/kg every 24 h PO[72]	Exact mechanism unknown but suspect induction of apoptosis	Cutaneous epitheliotropic lymphoma in a ferret,[72] rarely to prevent squamous cell carcinoma in humans	• Teratogen when taken PO in humans • Myelosuppression in humans • Dry skin, chelitis in humans
L-Asparaginase	• 400 IU/kg SC, IM[44,95] • 5000 IU[68] • 10,000 IU/m^2 SC[56]	Inhibition of protein synthesis in tumor cells lacking L-asparagine synthetase	Lymphoma (in dogs and cats used for cases of relapsed lymphoma to prevent resistance)	• Hypersensitivity reactions (higher risk after repeated exposures); therefore pretreat with diphenhydramine (1 mg/kg IM) or dexamethasone (0.5 mg/kg SC, IM, IV)
Methotrexate	0.5 mg/kg IV[9,68]	Folate analog—depletes the usable folate that is required for purine and thymidylate biosynthesis	Lymphoma (currently it is rarely used in cats and dogs)	• GI toxicity • Myelosuppression at high doses
Prednisone/Prednisolone	• 2 mg/kg every 24 h[40,92] • 1 mg/kg every 48 h[26] • 20 mg/m^2 every 24 h × 2 mo then every 48 h[44] • 2 mg/kg PO every 24 h × 7 days then every 48 h[56] • 1 mg/kg PO every 24 h × 13 weeks then every 48 h[3] • 40 mg/m^2 PO every 24 h[29]	Induction of apoptosis of hematopoietic cancer cells through the glucocorticoid receptor	Lymphoma, brain tumors, can be used to manage hemorrhagic cystitis and hypersensitivities	• Eventually tumor cells of hematopoietic origin resist steroid-induced killing • Polydipsia and hyperglycemia seen at 40 mg/m^2 PO every 24 h that resolved when dose decreased to 30 mg/m^2 PO every 24 h[44]
Procarbazine	50 mg/m^2 PO every 24 h × 14 day[56]	Inhibition of DNA and RNA synthesis	Lymphoma	• Neurotoxicity if given IV in humans
Vincristine	• 0.75 mg/m^2 IV every 7 d[44] • 2 mg/m^2 IV[44] • 0.12 mg/kg IV[2,9] • 0.2 mg/kg IV[95] • 0.5 mg/kg IV every 7 d[26]	Vinca alkaloids, inhibits microtubule assembly	Lymphoma	• Myelosuppression • Peripheral neurotoxicity • Ileus • Tissue necrosis with extravasation (not as severe as doxorubicin)

CNS, Central nervous system; *GI,* gastrointestinal; *IM,* intramuscularly; *IV,* intravenously; *PO,* orally; *SC,* subcutaneously.

TABLE 8.4 Weight-to-BSA Conversion Chart for Ferrets

Weight (kg)	BSA (m^2)
0.2	0.034
0.3	0.045
0.4	0.054
0.5	0.063
0.6	0.071
0.7	0.078
0.8	0.086
0.9	0.093
1.0	0.099
1.1	0.106
1.2	0.112
1.3	0.118
1.4	0.124
1.5	0.130
1.6	0.136
1.7	0.141
1.8	0.147
1.9	0.152
2.0	0.158
2.1	0.163
2.2	0.168
2.3	0.173
2.4	0.178
2.5	0.183
2.6	0.188
2.7	0.193
2.8	0.197
2.9	0.202
3.0	0.207

Calculations based on ferret-specific formula BSA (m^2) = 9.94 × (body weight in grams)$^{2/3}$ × 10^{-4}.
BSA, Body surface area.
Modified from Jones KL et al. Evaluation of a ferret-specific formula for determining body surface area to improve chemotherapeutic dosing. *Am J Veter Res.* 76.2 (2015):142–148.

These firm neoplasms resemble tumors of the adrenal cortex and cannot be differentiated at surgery. The presence of these tumors may also mask the presence of proliferative adrenocortical lesions on histologic examination unless multiple sections at 1 mm or more are examined. Estrogen receptors have been demonstrated on the smooth muscle cells in several of these tumors, suggesting a possible cause for their development.[61]

Thyroid Neoplasms

Thyroid neoplasms are rare in ferrets. A nonfunctional thyroid follicular adenocarcinoma was reported in one ferret with infiltration into the surrounding tissue,[96] and in another ferret a tumor was identified that had metastasized to the cervical lymph nodes and liver.[11] One case of a C-cell carcinoma (seen along with concurrent adrenocortical adenoma and insulinoma) has been reported.[31] Clinical signs were not observed in any ferret with a thyroid tumor.

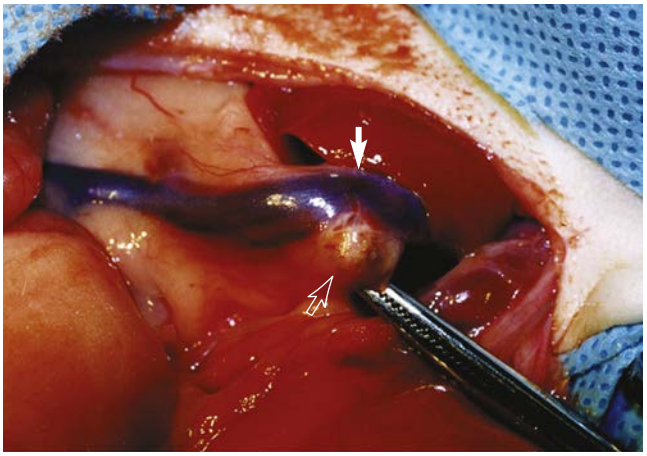

Fig. 8.1 Carcinoma of the right adrenal gland in a ferret *(open arrow),* demonstrating the proximity between these neoplasms and the caudal vena cava *(closed arrow).* Note that degree of malignancy cannot be determined by size or degree of invasiveness as visualized at surgery.

TUMORS OF THE HEMOLYMPHATIC SYSTEM

Lymphoma (malignant lymphoma, lymphosarcoma) is the most common hemolymphatic malignancy in domestic ferrets and the third most common neoplasm overall,[4,9,10,23,52,57,89,95] accounting for 10% to 15% of ferret neoplasms in the United States[52] and Europe.[4,22]

Although causative genetic mutations are well documented in people and in some domestic animal species with lymphoma, these aberrations have not been elucidated in the ferret, and environmental and infectious triggers have yet to be identified. Horizontal transmission of lymphoma in ferrets by using cell or cell-free inoculum in clustered outbreaks has prompted speculation that some variants of lymphoma in ferrets may be the result of a retroviral infection.[26–28]

Classification of Lymphoma

Appropriate classification of lymphoma is paramount to achieve the best therapeutic outcome and requires surgical biopsy in all cases. Clinicians should obtain as much descriptive information as possible for all cases, following the guidelines below, to ensure the most appropriate diagnosis and treatment for each individual. This may also improve prognostic ability in the future.

All diagnostic workups should include both *grading* (histologic description in as much detail as possible), *staging* (classification of disease based on spread of the neoplasm), and *phenotyping* (identifying T- vs B-cell origin).[39] The most commonly accepted grading system in companion animal medicine is the National Cancer Institute Working Formulation, which differentiates cells based on morphology.[59,63] The most commonly accepted staging system in veterinary medicine is the World Health Organization staging system, which is also generally accepted by the American College of Veterinary Pathologists (ACVP).[59] The importance of phenotypic information is illustrated by one study of ferrets with lymphoma treated with chemotherapy, in which those with B-cell lymphoma lived almost twice as long as those with T-cell lymphoma, (8.8 vs 4.3 months, respectively).[1]

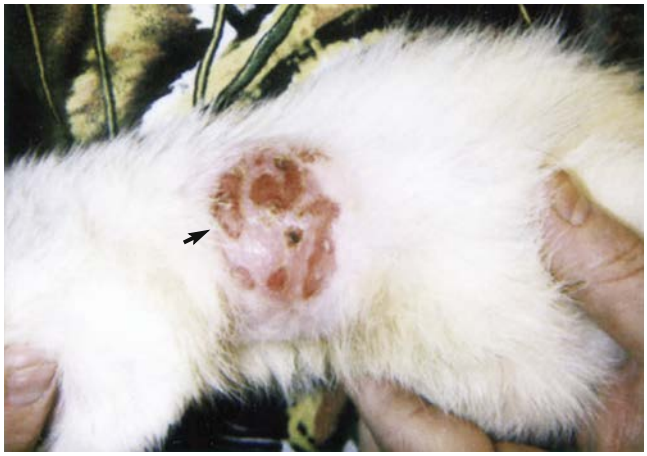

Fig. 8.2 Cutaneous lymphoma in a ferret. Surgical excision of this ulcerated neoplasm *(arrow)* was accomplished and, despite several recurrences, the ferret was still alive 3 years later.

Two other types of lymphoma seen in ferrets are cutaneous lymphoma and gastric lymphoma. Cutaneous epitheliotropic lymphoma is of T-cell origin and possesses a mature lymphocytic phenotype and a profound affinity to infiltrate epithelial structures, such as the epidermis and hair follicles (Fig. 8.2). It alone among the ferret lymphomas does not warrant a poor prognosis at onset, because prolonged survival times (possibly up to 3–4 years) are often seen, especially in cases in which skin lesions are rapidly excised. Unlike epitheliotropic lymphoma (mycosis fungoides) in dogs and people, epitheliotropic lymphoma in ferrets does not necessarily progress to systemic involvement (Sézary's syndrome). It is commonly seen in the feet and extremities of ferrets, resulting in grossly swollen, hyperemic, alopecic feet. Untreated, these lesions grow in size, and multiple lesions will develop. Complete surgical excision of cutaneous lesions can result in prolonged disease-free intervals; chemotherapeutic attempts, both topical and systemic, have generally proved unsatisfactory.[50,72]

Gastric lymphomas, or mucosal-associated lymphoid tissue lymphomas, have also been reported in four ferrets.[25] Considered akin to lymphomas associated with *Helicobacter pylori* infection in people, these neoplasms arise in the stomach of ferrets infected with *Helicobacter mustelae*. Although neoplastic cells varied in phenotype (two lymphocytic and two lymphoblastic forms), all four cases were composed of monoclonal B lymphocytes.[25]

Signalment and Clinical Signs

There is no universal signalment or clinical presentation for lymphoma in ferrets. It may develop at any age and has been reported in ferrets as young as 2 months, and no sex predilection is apparent. Although early reports linked more aggressive, lymphoblastic lymphomas with younger animals,[24,27] more recent studies have demonstrated this not to be the case.[1,63]

The clinical presentation of ferrets with lymphoma is nonspecific and likely reflects the organ systems affected. Ferrets may present with varying degrees of lethargy, inappetence, weakness, diarrhea, dyspnea, or respiratory signs, or they may be completely symptom free. Although splenomegaly and lymphadenopathy may be seen in ferrets with lymphoma, they are not pathognomonic for these conditions and are seen in several other common diseases. Splenomegaly is a common finding in ferrets with various inflammatory conditions, especially of the gastrointestinal tract; enlargement of the mesenteric lymph nodes can also be seen in these conditions. Fat deposits, seen in older ferrets and often seasonally during the winter, may be deposited around peripheral nodes, mimicking lymphadenomegaly.

Laboratory Evaluation

Anemia is the most consistent laboratory abnormality in ferrets with lymphoma and is consistently nonregenerative.[1,81] Lymphocytosis and thrombocytopenia are rare, and neutropenia is only occasionally identified.[1] These findings suggest that results of CBCs and peripheral blood smears may yield valuable information in some cases but are rarely diagnostic for lymphoma. Persistently high lymphocyte counts cannot be used as evidence of lymphoma; as in other species, chronic smoldering infection is a far more common cause of lymphocytosis in ferrets. The ubiquitous nature of *Helicobacter* and coronavirus infection in the U.S. ferret population has tremendous potential for inciting this nonspecific change.

Serum/plasma biochemical results are also inconsistent in patients with lymphoma, with abnormalities more relevant to the location of the disease or organ involvement than to any specific cause.[81] Hyperproteinemia and hyperglobulinemia are rare in ferrets with T-cell lymphoma,[81] and hypoalbuminemia has been documented in animals with intestinal forms. Hypercalcemia was present in 2 of 28 ferrets (both with T-cell lymphoma).[1]

Diagnostic Imaging

Radiography is necessary in ferrets suspected of having lymphoma, although results are not considered diagnostic. Radiographs should be examined for the presence of mediastinal masses, thoracic lymphadenopathy, and pleural effusion, as well as enlargement of the liver, spleen, or kidneys. The absence of radiographic abnormalities, however, does not rule out the possibility of lymphoma.

Ultrasonography is perhaps the most valuable clinical tool available to most practitioners in evaluating ferrets for lymphoma. In addition to evaluating the abdominal and mesenteric lymph nodes, ultrasound also enables the clinician to assess the liver, spleen, kidneys, mediastinum, and sometimes even the gastrointestinal (GI) tract for infiltrative disease. Figs. 8.3 and 8.4 show the gross and ultrasound images of ferrets with lymphoma infiltrating the liver and spleen. Fig. 8.5 demonstrates radiographic findings in a ferret with lymphoma affecting the abdominal lymph nodes. Note that abdominal nodes are often enlarged in older ferrets as a result of chronic bowel inflammation; the finding of severely enlarged abdominal nodes should never be considered evidence of lymphoma without biopsy. Normal radiographic and ultrasound findings for the abdominal lymph nodes and the spleen are published.[65,81a]

In one study, abdominal lymphadenopathy (12 of 14), peritoneal effusion (11 of 14), and splenomegaly (8 of 14) were reported as the most common findings in ferrets with lymphoma.[81] Pleural effusion and osteolytic lesions were less commonly identified in ferrets in this series.[81]

Cytologic and Histologic Description

Histologic or cytologic examination is the only reliable tool with which to diagnose lymphoma. The definitive diagnosis of lymphoma is best accomplished by a pathologist experienced in evaluating ferret lymph nodes, as often the histologic picture of lymphoma overlaps considerably with that of other non-neoplastic causes of lymphadenomegaly. Avoid biopsy (either needle or excisional) of abdominal lymph nodes whenever possible, because chronic GI inflammation, a common problem in older ferrets, may yield reactive changes almost indistinguishable from lymphoma. Peripheral nodes, such as popliteal and scapular nodes, are less likely to be affected by local inflammation; excisional biopsy of these nodes is easily accomplished, and complications of this procedure are extremely rare (Fig. 8.6).

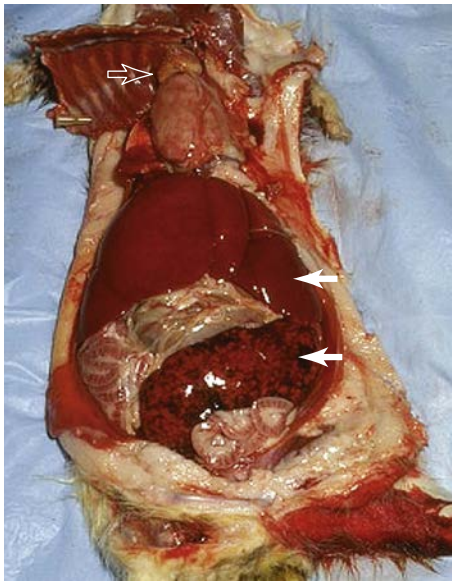

Fig. 8.3 Multicentric lymphoma in a 1-year-old ferret. Note the thymic mass *(open arrow)* and marked hepatosplenomegaly *(closed arrows)* as a result of massive infiltration by this neoplasm.

In many cases, fine-needle aspirates are performed as part of an initial examination, especially when clinical signs strongly suggest lymphoma. Aspirates of enlarged nodes may result in a diagnosis in the hands of a trained pathologist or experienced practitioner, but erroneous diagnoses may result from sample preparation, reactive changes, and neoplasms composed of well-differentiated lymphocytes. The possibility of erroneous diagnosis is increased when aspirates of abdominal nodes are performed. Reference results for cytologic populations of mesenteric lymph node aspirates in ferrets are available.[65]

In cases of suspected leukemia, a bone marrow aspiration via the proximal femur using an 18- to 20-gauge collection needle may yield good results. An alternate technique for obtaining a sample is a core bone biopsy, which may provide a better diagnostic yield. In most cases of leukemia, the bone marrow is hypercellular and often monomorphic. Microscopic examination reveals a significant decrease or total absence of normal marrow elements such as fat.

Pathologists are commonly asked to evaluate splenic aspirates from animals with enlarged spleens. More than 95% of these cases are the result of extramedullary hematopoiesis (EMH), a stereotypical response to chronic (GI) inflammatory disease. Evidence of erythrocyte precursors, megakaryocytes, and abundant peripheral blood on splenic aspirates suggests a diagnosis of EMH. Alternatively, cases of splenic lymphosarcoma are identified by the presence of a monomorphic population of neoplastic lymphocytes with large nuclei, prominent nucleoli, and minimal cytoplasm as well as an absence of erythrocyte precursors and minimal peripheral blood elements. Mitotic figures should be present within the monomorphic cell population.

Treatment

The goal in treating any patient with cancer is to achieve improvement in their clinical signs and quality of life. Comparative data on the various published protocols and chemotherapeutic agents used in ferrets do not exist as they do for human and canine patients; therefore any protocol followed should be based on the

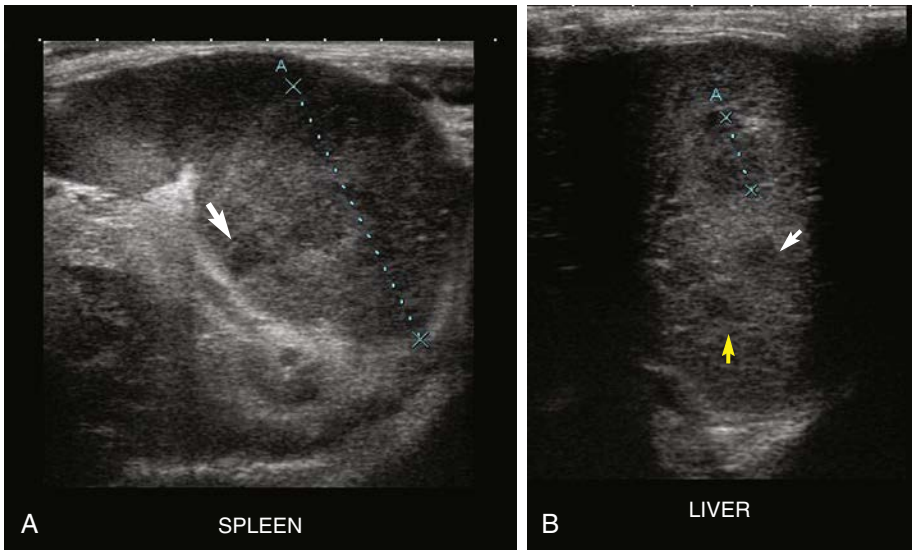

Fig. 8.4 Ultrasound images from a ferret with lymphoma demonstrating infiltrative disease in the spleen (A) and liver (B). Note the mottled appearance and hypoechoic regions *(arrows)* in both tissues. (Courtesy of Dr. Jantra Suran.)

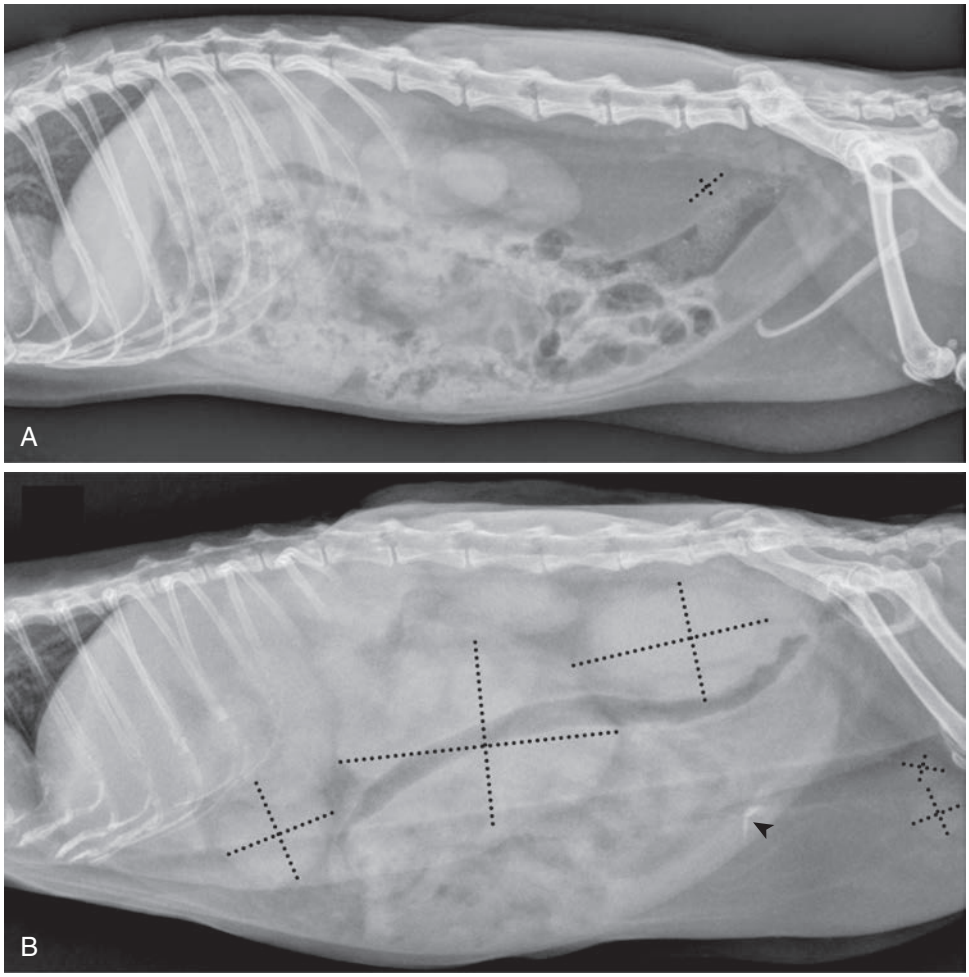

Fig. 8.5 (A) Lateral abdominal radiograph of a clinical healthy ferret demonstrating the size of a normal caudal mesenteric lymph node *(dotted lines)*; Lateral abdominal radiograph of a ferret with lymphoma (B). Enlarged lymph nodes *(dotted lines)* displace viscera. Enlarged inguinal node are visible *(dotted lines* at right.) Wet hair artifact (arrowhead) is superimposed on the caudoventral abdominal body wall. (Courtesy of Dr. Jantra Suran.)

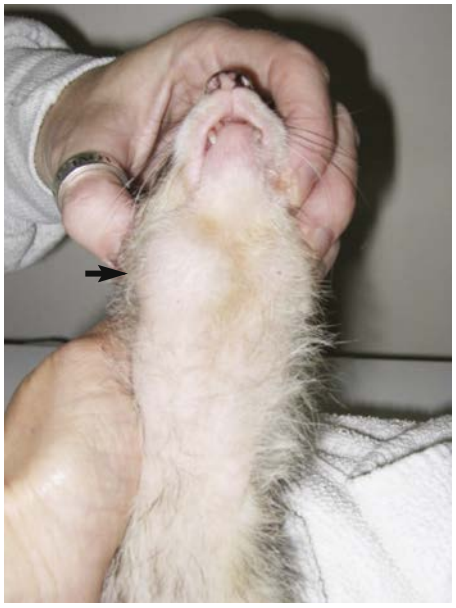

Fig. 8.6 Presentation of submandibular lymph node enlargement *(arrow)* in a ferret with lymphoma.

ease of administration, client and veterinary preference, level of comfort for the patient, and the owner's goals (i.e., achievement of complete remission vs palliation).

In most cases, lymphoma is a systemic disease requiring chemotherapy. In rare cases where a single organ is affected (usually extranodal lymphoma), surgery or radiation therapy can lead to a successful cure, but the patient must be closely monitored to look for signs of recurrent disease or spread. Combination therapy may be useful in ferrets as in other domestic species.

Chemotherapy

Chemotherapy may be used for induction, maintenance, reinduction, or as a rescue for patients with lymphoma. Most lymphoma protocols published for ferrets use some modification of the CHOP (cyclophosphamide, hydroxydaunorubicin [doxorubicin], vincristine [Oncovin], and prednisone) protocol that was adapted from human oncology; cyclophosphamide, doxorubicin (hydroxydaunorubicin), vincristine (Oncovin), and prednisone. In two published ferret protocols using modified COP (cyclophosphamide, vincristine/oncovin, prednisone) or CHOP, both incorporated L-asparaginase, and one also incorporated methotrexate. Several

case reports using a modified COP protocol have resulted in long-term clinical improvement.[9,20,22,24,44,74] Based on the evidence in canine[43,69] and feline patients, the CHOP protocol (or its variants) should be reserved for those ferrets with intermediate- to high-grade lymphoma. For ferrets with small cell or indolent lymphoma, a protocol using chlorambucil and prednisone similar to that used in cats may be more appropriate. The recommended dosage for cats with small cell, mucosal alimentary lymphoma is chlorambucil (20 mg/m^2 by mouth [PO] every 2 weeks or 2 mg PO every other day) and prednisone or prednisolone (initially 1–2 mg/kg PO daily, reduced to 0.5–1.0 mg/kg every other day over several weeks).[85] In addition to multimodal chemotherapy, single-agent therapy with doxorubicin has been described in ferrets with lymphoma with variable success.[56] The indolent nature of small cell lymphoma in some ferrets is supported by the fact that some ferrets can survive up to 2 years with no treatment at all.[56]

In cases where multiple intravenous drugs will be administered, placing a subcutaneous venous access port (VAP) may be helpful to prevent repeated sedation for intravenous (IV) drug administration. Specific VAPs are made for ferrets; VAPs designed for rats are also available and may be more useful, especially in small ferrets. If a VAP is not placed, the ferret must be sedated because chemotherapeutic agents should never be administered into a vessel that has had multiple attempts at IV placement.

Because intravenous access may be difficult in ferrets, a novel chemotherapy protocol has been established that uses only oral or subcutaneous chemotherapeutic agents. This 27-week protocol uses prednisone (PO), L-asparaginase (subcutaneously [SC]), cyclophosphamide (PO), cytarabine (SC), methotrexate (intramuscularly [IM]), chlorambucil (PO), and procarbazine (PO). The only drawback to this protocol is the compounding requirement for oral chemotherapeutic drugs; these liquid agents should only be administered at a veterinary hospital and not by the owner.

Palliative Chemotherapy

Palliative chemotherapy is used to diminish clinical signs in cases of unresectable, disseminated, or recurrent disease. When using chemotherapy with the goal of improved comfort and organ function, the agents are not usually administered based on a specific schedule but instead on the status of the patient and the discretion of the owner and client. Prednisone or prednisolone (PO), chlorambucil (PO), and L-asparaginase (SC), or a combination of the three, are used for this purpose because of their ease of administration and mild adverse effects.[56] Prednisone may be used alone to reduce tumor bulk and improve the ferret's appetite and attitude.

Doses may be used from published protocols with the dosing interval altered to best suit the patient. For treatment of lymphoma, prednisone has been used at dosages of 0.5 mg/kg PO every 12 hours,[78] 1 mg/kg PO every 24 hours,[3] 40 mg/m^2 PO every 24 hours,[29] and 2 mg/kg PO every 24 hours for 1 week and then 2 mg/kg PO every 48 hours or 1 mg/kg PO every 24 hours.[56] L-asparaginase has been used at doses of 10,000 IU/m^2 SC and 400 IU/kg IM.[56] Chlorambucil has been used in ferrets at 1 tablet (2 mg) PO every 24 hours or ½ tablet (1 mg) PO every 24 hours for 2 days in a row.[56] One of the authors (N.W.) has used prednisone (1 mg/kg PO every 24 hours) and L-asparaginase (400 mg/kg SC) for palliative treatment of lymphoma. Additionally, the author (N.W.) uses oral prednisone and an initial dose of L-asparaginase to decrease tumor size in patients and then a second dose of L-asparaginase when the tumor regrows.

Adverse Effects of Chemotherapy

As with other species, adverse effects of chemotherapy in ferrets are gastrointestinal damage, myelosuppression,[29] and loss of pelage.[3] After certain immunosuppressive chemotherapeutic agents such as cyclophosphamide are administered, evaluate a complete blood count within 7 to 10 days for evidence of leukopenia, specifically neutropenia (which often manifests as diarrhea in affected animals). Administration of antimicrobials and gastroprotectants may be required for severely neutropenic animals. In cases such as these, even diminished doses of the same agent may result in precipitous drops in leukocyte numbers, requiring a change to a different chemotherapeutic agent. Another common adverse effect of prednisone/prednisolone is hyperglycemia, requiring glucose monitoring (and possible dose reduction) while this agent is being used.

The proteinaceous nature of L-asparaginase may result in anaphylaxis; hence, it is not recommended for use more than three or four times in the same patient. Pretreatment with diphenhydramine (1 mg/kg IM) may be beneficial. Note that the period of asparagine depletion in ferrets is unknown.

Nausea is a common adverse effect of many chemotherapeutic agents. Pretreatment with antiemetics such as metoclopramide, ondansetron, or maropitant citrate is recommended in most cases; GI protectants may also be beneficial.

Radiation Treatment

Lymphoma is highly responsive to radiation therapy. With the advent of more advanced equipment such as linear accelerators, radiotherapy offers a safe modality for either primary or adjunctive treatment. It is most beneficial in a single neoplasm in the abdominal cavity but can also be used on a single peripheral lymph node. Although multiple treatments to a site are preferred, even a single dose of radiation will shrink most tumors and greatly improve outcomes. Radiation can also be used as a rescue treatment for solid masses not responding to chemotherapy. Half- and total-body irradiation protocols are used in other species, but only limited data is available for its use in ferret.[56] Radiation therapy may also be used as a palliative therapy for patients that have localized disease such as rectal lymphoma, mediastinal lymphoma (when dyspnea or precaval syndrome is present), or focal bone involvement.[85]

Ancillary Treatments

The most important ancillary treatment in any cancer patient is the provision of proper nutrition.[62] Cancer cachexia is a well-documented paraneoplastic syndrome in all species, consisting of progressive weight loss despite adequate nutritional intake.

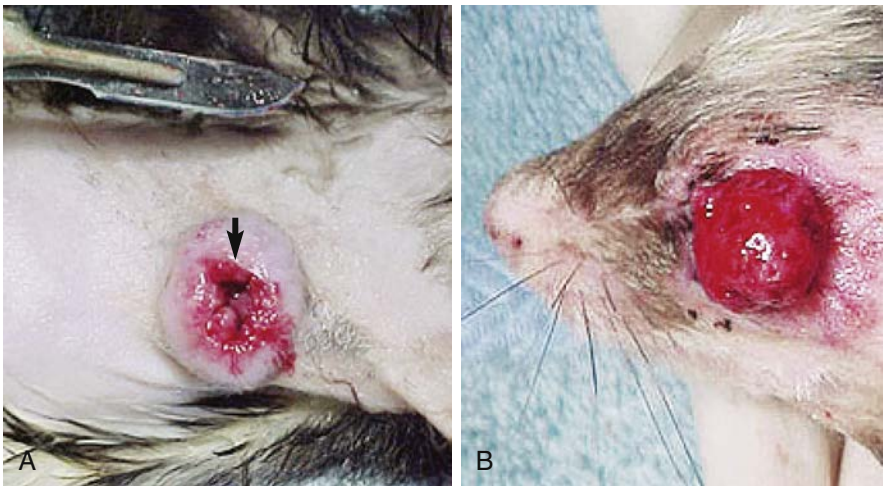

Fig. 8.7 Multiple sebaceous adenomas in a ferret on the thorax (A) and face (B). The neoplasm on the face did not involve the orbit. Occasionally, the centers of these neoplasms may be cavitated *(arrow)*. Although these lesions were impressive in appearance, surgical removal was curative.

Maintaining nutritional status improves immune response, GI function, and surgical healing and may also improve a cancer patient's chances of remission. Most high-quality ferret diets are ideal because of their high protein and fat content. Supplementation can also be provided with formulas available for ferrets (Carnivore Care, Oxbow Animal Health, Murdock, NE; Emeraid IC Carnivore, EmerAid LLC, Cornell, IL) or, in their absence, commercial gruel diets used for cats. Most ferrets can be encouraged to eat or are easily force-fed.

Although clients often ask about holistic or herbal therapies, free radical scavengers, or immune stimulants, avoiding these products is recommended for patients receiving chemotherapy. The goal of chemotherapy is to suppress the immune system and often to induce cell death and free radicals; immune stimulants may interfere with this process. If necessary, consult with both a veterinary oncologist and a veterinarian trained in holistic/herbal medicine before initiating any alternative therapies. In addition, ferrets that have received chemotherapy should not be vaccinated for the remainder of their lives, because vaccines stimulate the immune system, which may terminate remission.

Other types of hematopoietic neoplasms are rarely seen, with the spleen as the most common site of origin. Myelolipoma, a benign neoplasm of immature leukocytes admixed with well-differentiated adipocytes, may occasionally present as a space-occupying mass in the spleen, but it is of no clinical significance.[51] Histiocytic sarcoma, a malignant hematopoietic tumor of histiocytes, is a rare aggressive malignancy most often arising in the spleen. In a recent report of four ferrets with this tumor, splenomegaly or splenic nodules, as well as mesenteric lymphadenopathy were common findings. Surgical and chemotherapeutic intervention resulted a survival time of 9 days to 5 months.[84] Thymoma, a neoplasm involving the epithelial elements of the thymus, may present as a mass lesion of the anterior thorax and can be easily confused for thymic lymphoma; presenting signs include vomiting, lethargy, and dyspnea.[83] Malignant plasma cell tumors are rarely documented in ferrets. In a study of six cases, the most common clinical sign was hind limb paresis (5/6), the most common hematologic abnormality was hyperglobulinemia (5/6), and osteolysis was seen on radiographs of 3 of 4 ferrets. Most ferrets (5/6) had tumors in more than four locations. Chemotherapy was attempted in one ferret that showed no response to treatment. Prognosis was poor, with most (4/6) ferrets being euthanized less than a week after diagnosis, although one survived for 107 days after diagnosis.[14] Osteolytic lesions have been reported in several other cases.[29,53,54]

TUMORS OF THE SKIN AND SUBCUTIS

The skin and subcutis is the third most common location for neoplasia in ferrets, accounting for approximately 20% of cases in most reports.[52,64,95] Most neoplasms of the skin are benign and can be successfully treated with surgical excision alone or together with radiation therapy.[46] A single ferret can have multiple cutaneous tumors that are the same or a differing type.[46,87] Mast cell tumors and tumors of basal cell origin are the two most commonly diagnosed skin tumors.

Unlike mast cell tumors in the dog and cat, ferret mast cell tumors are universally benign, do not metastasize, and warrant a good prognosis.[46,87] Recent studies have shown a preponderance in males with an average age of 4.5 to 5 years,[46] and 30% of ferrets had more than one mast cell tumor.[87] Grossly, these neoplasms are discrete, flat, round, plaque-like, and crusted[87] and are often pruritic. Mast cell tumors can be readily diagnosed by cytologic examination, but slides must be viewed with non-Wright's stains (including Diff-Quik) to properly demonstrate granules.[87]

Tumors of basal cell origin, including sebaceous adenoma and sebaceous epithelioma, are warty, exophytic neoplasms (Fig. 8.7) that may attain a large size and ominous appearance (largely as a result of self-trauma) but are almost invariably benign. These tumors are common on the head and neck and occur in ferrets at an average age of 5.2 years with no apparent sex predilection.[46] Tumors occasionally cause irritation, and the resulting self-trauma may result in local inflammation and infection. In very rare cases, these tumors may give rise to squamous cell carcinoma.[95] Surgical excision is curative and should be accomplished early.

Neoplasms of apocrine scent glands are the third most common neoplasm seen in the skin and subcutis in ferrets. Unlike the above-described neoplasms, tumors of apocrine glands are largely restricted to the deeper layers of the skin and subcutis and have a distinct predilection for malignant behavior. Apocrine neoplasms are most common in areas where scent glands are concentrated (head, neck, prepuce, and vulva). Approximately 75% of preputial neoplasms of apocrine origin (100% of the less common perianal and perivulvar tumors) are malignant, exhibiting aggressive infiltration of local tissues, metastasis to local nodes, and occasionally pulmonary metastasis. Complete surgical excision of apocrine malignancies is difficult because of their rapid and aggressive growth, as well as the distinct possibility of presurgical metastasis. To minimize the potential for metastasis, excise any suspected apocrine neoplasms with wide surgical margins. Use advancement flaps or Y-plasty, if necessary, to close or reconstruct the prepuce. In cases of apocrine carcinoma of the prepuce, appropriate surgical treatment may entail amputation of the prepuce and urethrostomy. Radiation therapy may be a valuable postoperative treatment to aid in eliminating any local residual malignant cells, and chemotherapy can be used as an adjunct to decrease the risk of metastasis.

Low-grade subcutaneous sarcomas are occasionally seen in the subcutaneous tissues. Many of these neoplasms arise from smooth muscle (erector pili) associated with hair follicles along the dorsal midline (piloleiomyosarcomas).[71] These raised, often ulcerated nodules occur most commonly on the head and neck in male ferrets with an average age of 3.1 years.[46] Although cutaneous fibrosarcomas may also be seen in the skin of ferrets[95] and have been reported in association with vaccination in this species,[60] these neoplasms do not manifest the aggressive behavior associated with vaccine-related sarcomas in cats.[60] Regardless of their derivation, subcutaneous sarcomas are generally low-grade malignancies with a slow growth rate and low metastatic potential; they all respond well to wide surgical excision.

Mammary gland neoplasms are rare in ferrets. One report of six cases described only benign mammary neoplasms[95]; a second report of nine cases described seven benign tumors and two malignancies (both in males).[46] Three cases of simple mammary hyperplasia have also been reported,[58] two of which were seen in conjunction with adrenal carcinoma.

A range of other neoplasms of the skin and subcutis have been reported in ferrets. Benign neoplasms seen in the skin include lipomas, squamous papillomas, and tumors of sebaceous or eccrine sweat glands.[80] Reported malignancies include adenocarcinomas of the ears[32] and lacrimal glands,[13] liposarcomas,[18,34] epitheliotropic lymphoma (as previously discussed), and squamous cell carcinoma (which may occasionally arise from the lining of the anal sac).[95]

Subcutaneous neoplasms of the ventral abdomen with marked morphologic and immunohistochemical similarities to adrenocortical tumors have been reported.[80] In each case, the ferret did not display systemic signs associated with endocrinopathy, and a primary adrenocortical tumor could not be identified.

General guidelines for treating cutaneous neoplasms in ferrets are similar to those in traditional pet species. Early surgical intervention is the rule with cutaneous neoplasms; most neoplasms are benign, and most malignancies are of low grade and can be successfully treated with early surgical excision with wide margins. Submit all neoplasms for histopathologic evaluation to provide an accurate diagnosis, as well as recommendations for additional treatment, if any. Surgically excise all preputial or perivulvar/perianal neoplasms as early as possible, after careful palpation and survey radiographs to detect potential metastasis. Follow-up radiation therapy may be useful in malignancies in which sufficient surgical margins cannot be obtained.

Vascular neoplasms (hemangioma, hemangiosarcoma) of the skin and subcutis are occasionally seen in ferrets. (See vascular neoplasms below.)

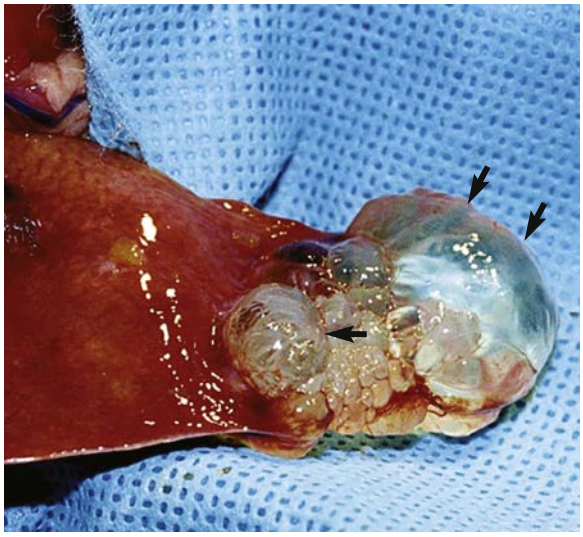

Fig. 8.8 Biliary cystadenoma in a ferret. Because of their aggressive nature, these histologically benign tumors *(arrows)* are best treated with lobectomy or, at a minimum, wide surgical excision.

TUMORS OF THE GASTROINTESTINAL TRACT

Neoplasms of the gastrointestinal tract are frequently seen in ferrets. The liver is a particularly common site for metastasis, particularly malignant lymphoma and adrenocortical carcinoma.[95] It is also a relatively common site for the development of primary neoplasms. Biliary cystadenoma/cholangioma is by far the most frequent; however, cholangiocarcinoma, hepatocellular carcinoma, and hepatoma are also observed.[95] In most cases, ferrets with hepatic neoplasia are presented for nonspecific signs or are asymptomatic. Increases in alanine transaminase or alkaline phosphatase activity are occasionally present, but clinicopathologic abnormalities are usually mild and nonspecific. A cranial abdominal mass may be identified by palpation or on radiographs but is most readily apparent on abdominal ultrasound scanning.

Diagnosis of biliary neoplasia is especially important in this species because of the predilection for neoplasms that appear benign to exhibit malignant behavior (replacing one or more lobes of the liver and ultimately resulting in hepatic failure) (Fig. 8.8). Biliary cystadenocarcinomas are differentiated from biliary cysts or cystadenomas (a common incidental finding in this species) by one or more of the following: the presence of clinical signs, abnormalities

in liver-specific biochemical results, or expansive growth over time documented by serial abdominal ultrasound scanning. Hepatic carcinoma and cholangiocarcinoma will, over time, result in high hepatic enzyme levels, eventual hepatic failure, and other clinical signs such as profound anemia, hemoperitoneum, and ascites.

When possible, biopsy all hepatic neoplasms, especially those involving multiple liver lobes. Peripheral indices of clotting are recommended before any invasive procedure, including fine-needle aspirate; if this is not possible, pretreatment with vitamin K may be prudent to minimize the risk of bleeding.

If a neoplasm is confined to one lobe of the liver, lobectomy is recommended. Lobectomy of two lobes is possible but may lead to further compromise of the patient. Because of the aggressive nature of biliary tumors in ferrets, remove any cystic lesion of the liver with wide surgical margins or lobectomy. Neoplasms involving multiple lobes warrant a poor long-term prognosis; however, survival times of several months or more may be seen with hepatocellular carcinoma in ferrets. Ferrets with malignancies of the biliary system usually die within a short time frame.

Neoplasms of the exocrine pancreas are occasionally seen in ferrets and are most often malignant, exhibiting infiltrative growth, explantation, compression of ducts within the pancreas and liver,[42,70,90] and metastasis to additional organs.[90] Complete surgical excision of these tumors is unlikely before they begin to extend into other areas of the abdominal cavity.

Malignant lymphoma is the most common neoplasm affecting the GI tract. This is understandable considering that (1) the GI tract contains more than half of all lymphoid tissue in the body of ferrets, and (2) the high prevalence of chronic inflammatory disease in the stomach and intestine. In lymphomas arising in the gastrointestinal tract, the intestine is the most common site of origin, followed by the stomach, liver, colon, and oral cavity. Lymphoma of the intestine carries a poor prognosis because of the disruption of the intestinal barrier and absorption of toxins from the GI tract; therefore it can be refractory to treatment.[9] The incidence of intestinal lymphoma may be even higher than reported, because many ferrets with variable GI signs do not undergo biopsy and remain undiagnosed. In some cases, steroids likely are used to alleviate clinical signs without biopsy, which may lead to incorrect assumptions regarding potential survival times and response to therapy.

Adenocarcinomas develop primarily in the stomach and intestines and are locally aggressive, often infiltrating multiple layers of the wall with metastasis to local lymph nodes. Intestinal adenocarcinoma tends to incite a prominent scirrhous response, often resulting in obstruction (as opposed to intestinal lymphomas, which do not result in a scirrhous response). This same scirrhous response, however, tends to entrap the malignant epithelial cells, allowing visualization of the tumor margins and facilitating complete excision. Prognosis is heavily influenced by the presence or absence of presurgical metastasis. These masses can be identified by palpation and diagnostic imaging such as ultrasound, computed tomography, or a GI contrast study. Perform a resection and anastomosis whenever solitary intestinal masses are present without gross evidence of metastatic disease. Other uncommon tumors of the GI tract, including colonic polyps[12] and gastrointestinal stromal tumors,[35] have been reported.

Tumors of the oral cavity are occasionally seen, are commonly malignant, and are usually associated with a poor prognosis. Squamous cell carcinoma, the most common, is an aggressive neoplasm of the alveolar lining epithelium that invades underlying bone, resulting in tooth loss, disfigurement, and inappetence. In treating ferrets with this neoplasm, reports of chemotherapy[37] and combined surgical and radiation therapy[38] showed poor to equivocal results. Intralesional chemotherapy may also be attempted, following current recommendations for companion animals. Early, aggressive treatment provides the best opportunity for resolution of squamous cell carcinoma. Other malignancies, including fibrosarcoma[9] and melanoma,[19] have been reported in the oral cavity and respond poorly to all forms of treatment.[9]

TUMORS OF THE REPRODUCTIVE TRACT

Whereas earlier reports indicated a high prevalence of these neoplasms,[6,17] the common practice of early neutering makes them a rarity today. Clinical signs of reproductive neoplasia in ferrets vary and are often nonspecific; many are found as incidental finding during neutering procedures. In most cases, surgical excision of affected gonads is curative.

Testicular neoplasms are most common in retained testes. Affected males may show signs of hyperestrogenism, including intact sexual behavior, aggression, a prominent musky odor, and a poor, greasy hair coat. Multiple neoplasms may be seen in retained testes; in one testis, four distinct neoplasms (interstitial cell, seminoma, Sertoli cell, and a carcinoma of the rete testis) were seen.[95] Smooth muscle tumors of the testis have also been reported.[45]

Ovarian tumors often result in no overt signs; in a few cases, affected animals exhibit reproductive failure or abnormal reproductive status.[55] Ovarian tumors (granulosa cell tumors, teratomas, thecoma,[55] Leydig cell tumors, and sex cord-stromal tumors)[95] have been reported, often as incidental findings during routine spays. Teratomas may attain a size that is obvious on routine palpation or may be identified via survey radiographs as a result of the presence of bone within the tumor mass. One reported Leydig cell tumor metastasized to a regional lymph node.[95]

Most neoplasms of the ferret uterus are of smooth muscle origin. Whereas approximately 75% are malignant based on histologic appearance,[95] metastatic disease has not been reported, and surgical excision is curative. Nonmuscular tumors of the uterus are extremely rare in ferrets. One uterine adenocarcinoma and one deciduoma have been seen by the author (B.W.). On histologic examination, regressing implantation sites in female ferrets may be mistaken for uterine carcinoma as a result of the profound atypia of maternal presymplasmal cells.

TUMORS OF THE MUSCULOSKELETAL SYSTEM

Neoplasms of the skeletal system are occasionally seen in ferrets and generally result in a clinical appearance that is

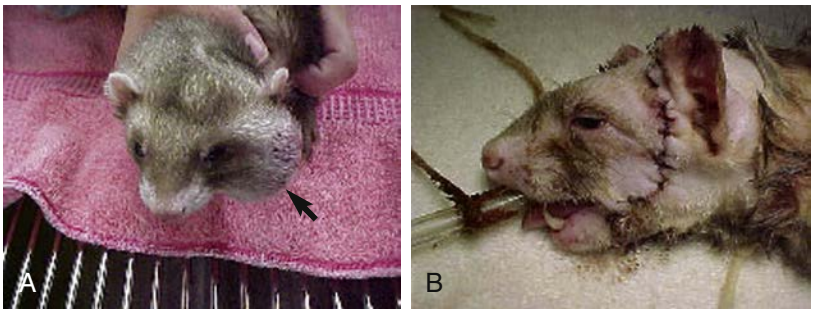

Fig. 8.9 Preoperative (A) and postoperative (B) images of a malignant peripheral nerve sheath tumor *(arrow)* in a ferret. Removal was achieved with cryosurgery; however, facial nerve paralysis was encountered after surgery. (Courtesy Dr. Darrell Kraft, Pet's Choice Animal Hospital, Woodinville, WA.)

obvious to both owner and practitioner. Chordomas are the most common neoplasm of the musculoskeletal system in ferrets.[95] They most commonly appear as irregularly round, whitish gray, firm, club-like swellings of the tail tip. This low-grade malignancy (arising from primitive notochord) also may develop in a vertebrae in any region of the spinal column.[21] These neoplasms are locally aggressive, destroy the vertebral body in which they arise, but only rarely metastasize.[33,93] Radiographs reveal a focally extensive vertebral lesion that is both lytic and proliferative. Tail tip chordomas may be easily cured by amputation, but they carry a poor prognosis when they affect other parts of the spinal column because of their infiltrative nature.

True bone tumors (osteomas, osteosarcomas, and chondrosarcomas) are seen occasionally. Osteomas most commonly arise on flat bones, including the skull and ribs, and progress slowly. Surgical removal may be accomplished with the help of radiographic imaging to more easily delineate margins; however, many osteomas regrow when excision is incomplete. Osteosarcomas are rarely reported in ferrets[91] and may arise on either flat or long bones. If possible, amputate the affected limb, because these malignancies are locally destructive, and incompletely excised neoplasms can recur. Noncore biopsy of malignant bone tumors may result in an erroneous diagnosis because of the pronounced periosteal reactions surrounding these neoplasms.

Tumors of skeletal muscle are extremely rare in ferrets.[95] Rhabdomyosarcomas (malignant tumors of skeletal muscle) have been reported.[52,95] These neoplasms are treatable by radical excision or amputation if present on the limbs.

TUMORS OF THE NERVOUS SYSTEM

Neoplasms of the nervous system are rare, accounting for fewer than 0.5% of reported tumors in ferrets.[95] These tumors equally affect the central nervous system (brain and spinal cord) and peripheral nervous system (peripheral nerves and ganglia). Tumors of the central nervous system (CNS) generally lead to the development of neurologic signs, including ataxia and seizures, whereas those of the peripheral nervous system result in body-surface masses that owners usually notice before any neurologic signs develop.

When the cause of neurologic signs in ferrets is being considered, intracranial tumors are very unlikely, ranking as only the third most common cause of neurologic signs. Hypoglycemia due to insulinoma is by far the most common cause of neurologic signs in ferrets, followed by bacterial infections of the CNS.

Clinical signs associated with intracranial tumors vary and are often nonspecific. Lateralizing signs, such as turning toward the side of the lesion, head tilt, ataxia, cranial nerve deficits, normocellular cerebrospinal fluid, and uncontrolled seizure activity in the presence of normal blood glucose levels suggest an intracranial neoplasm, although nonspecific. Hindlimb weakness and ataxia, although suggestive of a spinal cord tumor, are extremely common presenting signs for a wide variety of diseases in ferrets. Currently, successful treatment of CNS tumors has not been reported.

The most common neoplasm of the CNS (including the eyes) in ferrets is malignant lymphoma. Primary tumors of the brain and spinal cord are rare and usually result in severe neurologic deficits over time. Astrocytomas are the most common primary brain tumors, followed by granular cell tumors,[79] meningiomas,[52,95] primitive neuroendocrine tumors, and a choroid plexus papilloma.[86] Primary spinal cord tumors are more rare, with a single intradural teratoma reported.[48] Of all primary brain tumors, meningiomas show the most promise for surgical excision because they are discrete neoplasms arising from the meninges and tend not to infiltrate the neuropil. Antemortem diagnosis of meningioma is a significant challenge; computed tomography scanning or magnetic resonance imaging is used to detect the presence of the tumor; meningioma should be suspected when any tumor is located along the meninges.

Neoplasms of the peripheral nervous system carry a significantly improved prognosis over those in the CNS, as they tend to be restricted to the skin and subcutis. Prognosis is based on the degree of malignancy and infiltration of local tissue. In one review, both benign and malignant peripheral nerve sheath neoplasms were identified.[95] Malignant peripheral nerve sheath tumors generally exhibit rapid growth and tend to infiltrate adjacent tissue to a higher degree than their benign counterparts, rendering complete excision more difficult (Fig. 8.9). In many cases, repeat surgery is required to effect a cure. Although these neoplasms may be seen at any site in the body, the head (and, interestingly, the eyelids) appear to be a common site. Tumors of nerve sheath origin may be misdiagnosed as fibrosarcoma or leiomyosarcoma when immunohistochemical procedures are not used. Excise these tumors with wide surgical margins as soon as possible after diagnosis,

because growth in areas with high skin tension may result in large defects that are difficult to close. Moreover, incomplete excision of these tumors often results in a recurring neoplasm that shows both increased cytologic and behavioral malignancy, to include more rapid growth and infiltration. Radiation therapy may help minimize or prevent recurrence at the surgical site or may be used to reduce tumor size before surgery.

Ganglioneuromas are rare neoplasms of the peripheral nerve ganglia.[52,95] These well-differentiated neoplasms with neurons and glia in a matrix of neural tissue are reported close 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. These tumors have no apparent clinical signs and on gross inspection are often misjudged to be adrenal tumors.

TUMORS OF THE URINARY SYSTEM

Although rare (comprising less than 1% of tumors in one study),[9] primary neoplasms of the kidneys and bladder have been reported in ferrets. As with other species, signs of neoplasia in the urinary system include hematuria and stranguria or dysuria. Diagnostic workups should include abdominal radiographs, ultrasound, and urinalysis (with urine culture if warranted) to rule out more common causes such as adrenal-associated prostatic cysts, crystalluria, or urolithiasis.

As with other systems, the most commonly reported tumor in the urinary system is lymphoma.[95] The most common primary neoplasm of the urinary tract is transitional cell carcinoma and has been reported in the kidneys[7,95] and bladder.[9] In the bladder, transitional cell carcinoma is generally associated with a poor prognosis. Because the presenting signs are vague, diagnosis is generally achieved only after extensive local invasion has occurred.[9] Once identified, these tumors likely would be a surgical challenge, especially in the area of the trigone. For unresectable tumors, chemotherapeutic agents that inhibit 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, but appropriate dosages in ferrets have not been defined.

Renal carcinomas and adenomas have been reported in ferrets.[47,52] These unilateral neoplasms of the kidney are most often encountered at necropsy, because most tend to be slow-growing with low metastatic potential. In one case, metastasis was noted in multiple organs.[47] On ultrasound examination, renal neoplasms generally present as cystic areas within the kidney, similar to benign renal cysts. If biopsy is not feasible, serial ultrasound examinations are recommended to monitor for continued growth and a change in echogenicity.

TUMORS OF THE RESPIRATORY SYSTEM

Neoplasms involving the lung are generally of metastatic origin, although one undescribed primary neoplasm of the lungs has been reported.[52] The lungs are a common site for the metastasis of lymphoma; clinical signs may include marked pulmonary edema or effusion, which may be significant enough to mask the radiologic signs associated with a disseminated tumor. Pulmonary metastasis of other neoplasms would likely go unnoticed in most cases. Chemotherapy may be of benefit in metastatic lymphoma.

VASCULAR NEOPLASMS

Hemangiomas and hemangiosarcomas are occasionally seen in ferrets. Most arise in the skin or subcutis,[95] although endothelial neoplasms are also seen in the liver,[15] spleen, pancreas, lymph nodes, and free-floating in the abdomen. The incidence is equal in male and female ferrets, and the average age is 4 years.[46] Although more than half of cutaneous vascular neoplasms exhibit histologic evidence of malignancy, they are low-grade malignancies with slow growth, and metastasis is not seen.[95] Excision of cutaneous neoplasms is curative. Coat color and pigmentation do not appear to be risk factors in the development of this neoplasm (as in other domestic species).

However, the prognosis for animals with visceral hemangiosarcoma is significantly worse. These tumors tend to grow more aggressively within abdominal organs and may rupture at any time, seeding the abdomen with metastatic tumors[16] or resulting in fatal hemorrhage. For ferrets with visceral hemangiosarcomas, prognosis is guarded, and early surgical intervention is indicated when the neoplasm is restricted to a single site.[16] One report of combined surgical/metronomic chemotherapeutic treatment of a hepatic hemangiosarcoma is available.[67]

MISCELLANEOUS NEOPLASMS

Mesotheliomas are uncommon malignancies of ferrets that bode extremely poorly for any affected animal.[94] These tumors arise in the abdominal cavity and spread extensively before the appearance of clinical signs. The most common clinical sign is profound ascites ("malignant" ascites).[94] Abdominocentesis is recommended in such cases; identifying rafts of atypical mesothelial cells may accomplish diagnosis. Because normal mesothelial cells may be seen in any abdominal tap, exercise care to avoid misdiagnosis.

Anaplastic neoplasms are those in which the level of cellular differentiation is below that needed to identify a cell of origin by its microscopic resemblance to normal tissue. Sophisticated techniques such as immunohistochemistry or electron microscopy may yield clues to a tumor cell's origin even if it does not resemble the parent tissue. In a retrospective study from a large referral laboratory using advanced diagnostic techniques, the tissue of origin could not be identified in only 2% of cases; however, in 80% of cases, a broad category of epithelial versus mesenchymal origin was obtained.[95] Even this limited classification has therapeutic importance, as epithelial and round cell tumors tend to be significantly more responsive to chemotherapy than sarcomas are. Sarcomas of the skin were the largest single classification of poorly differentiated tumors but likely the most responsive to treatment (i.e., surgery). Because skin sarcomas tend to have low metastatic potential, 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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