Ferret Oncology

Diseases, Diagnostics, and Therapeutics

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KEYWORDS

• Neoplasia • Neoplasm • *Mustela putorius furo* • Hyperadrenocorticism • Insulinoma • Lymphoma

KEY POINTS

- Tumors are commonly seen in ferrets after the age of 3 years, and the endocrine, hemolymphatic, and integumentary systems are most commonly affected.
- The 3 most common tumors in ferrets are adrenal tumors, insulinoma, and lymphoma, making up more than 40% of all tumors seen in ferrets.
- It is extremely common for ferrets to have multiple types of tumors simultaneously; ferrets with up to 4 types of concurrent tumors have been seen.
- Although with surgery a neoplasm can be removed, both adrenal tumors and insulinoma can be managed medically with an even better, or similar, mean survival period compared with surgically managed cases.
- Providing ferrets with a depot gonadotrophin-releasing hormone-containing implant and feeding them a diet with a high protein and fat content and a low carbohydrate content have been suggested as measures to prevent the occurrence of adrenal tumors and insulinoma, respectively; however, proof that these measures work has not been published to date.

INTRODUCTION

In recent decades it has become clear that the previous conception that neoplasia in ferrets are rare is false.[1] A large range of case reports have been published on a wide variety of tumors, and more information has become available on the most common neoplasia of ferrets. In addition, ferrets have recently been introduced as lung cancer research models in which lung cancer could be induced after exposure to either tobacco smoke or a specific tobacco carcinogen.[2]

Most tumors in ferrets are seen after the age of 3 years.[3–5] The endocrine, hemolymphatic, and integumentary systems are most commonly affected, with adrenocortical

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tumors and insulinoma making up more than 40% of all tumors seen.[4,5] The third most commonly seen neoplasm in ferrets is the lymphoma.[3–5] In up to 20% of ferrets with a tumor, multiple tumors of different origin (up to 4) can be found simultaneously.[3,4,6]

Aside from the 3 common types of neoplasia in ferrets, any other type of tumor may be diagnosed. **Table 1** provides an overview of the different types of spontaneously occurring neoplasia reported in ferrets. For an overview of the general diagnostic and therapeutic options in oncological patients (see van Zeeland's article, "Rabbit Oncology: Diseases, Diagnostics and Therapeutics," in this issue). Examples of the most sophisticated diagnostic techniques available to diagnose oncological disease in ferrets include computed tomography (CT), MRI, and scintigraphy. Although these techniques are not as easily available and are more expensive compared with radiology and ultrasonography, these advanced imaging techniques may enable visualization of masses that otherwise would remain undetected (**Fig. 1**),[16,34] and allow the volume of tissues to be calculated, thereby enabling monitoring of their growth. In addition, CT may help visualize the extent of the tumor and its potential invasiveness in other tissues (**Fig. 2**). Scintigraphy may also help detect neoplasia, whereby the distribution of radiopharmaceutical agents in specific tissues, such as the thyroid gland, can be visualized by using a gamma camera.[43] Specific ferret-related diagnostic and therapeutic options are discussed here in relation to the endocrine, hemolymphatic, and integumentary tumors in this species.

ENDOCRINE TUMORS

Adrenocortical Tumors

Hyperadrenocorticism, also referred to as adrenocortical disease or adrenal gland disease, is the most common endocrine tumor seen in ferrets. Although hyperadrenocorticism is considered similar to hypercortisolism (Cushing disease) in dogs, cats, and humans, in ferrets plasma androstenedione, 17α-hydroxyprogesterone, and estradiol concentrations are increased. In line with the latter three increased hormone concentrations, no atrophy is seen in the nonneoplastic, contralateral adrenal gland.[44] Histologic changes of the adrenal glands range from (nodular) hyperplasia to adenocarcinoma and everything in between. However, an indication of the prognosis based on the histologic diagnosis cannot be given.

Cause

Although early neutering (at the age of 6 weeks) has long been postulated as the cause for the high prevalence of adrenal tumors in ferrets, it is not likely that the time of neutering is the most important factor in the development of these tumors. It is likely that the increased concentrations of gonadotropins, which occur after neutering because of the loss of negative feedback, persistently stimulate the adrenal cortex, which eventually results in adrenocortical growth. Support for this hypothesis can be found in the fact that luteinizing hormone receptors have been detected in the adrenal glands of ferrets with hyperadrenocorticism. These receptors are considered to be functional, because plasma concentrations of adrenal androgens increase after intravenous injection of a gonadotrophin-releasing hormone (GnRH) agonist.[45] In addition, the depot GnRH agonist, deslorelin, is currently used successfully in managing the clinical signs of ferrets with hyperadrenocorticism.

When ferrets are kept indoors, it is likely that the length of (day)light they receive is longer than that received by ferrets that are housed outdoors. Because gonadotropins are secreted during the time when ferrets are kept in light for longer than 12 hours per day, indoor ferrets are longer under the influence of these hormones and may thus

Table 1
Reported (spontaneous) neoplasms in ferrets

Organ System	Tissue of Origin	Reported Tumor Types	Incidence	Clinical Signs	Diagnosis and Work-up	Treatment and Prognosis
Reproductive tract (female)[3–5,7,8]	Ovary; uterus	• Ovarian spindle cell tumors, leiomyoma, leiomyosarcoma, sex cord stromal tumor (including thecoma, granulosa cell tumor [arrhenoblastoma]), adenocarcinoma • Ovarian remnant: thecoma, granulosa cell tumor • Uterine (fibro)leiomyoma, leiomyosarcoma, teratoma, deciduoma, adenocarcinoma	In general, not well reported in the veterinary literature because of neutering	• Most neoplasms of the reproductive tract are clinically silent • Reproductive failure • Ovarian (remnant) tumors may result in symmetric alopecia and a swollen vulva	• Abdominal palpation • Hormone analysis • Radiography • Ultrasonography • Cytology (FNA) • Histopathology • Exploratory laparotomy	Metastatic disease has not been reported and surgical resection of the tumor is usually curative

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Table 1
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Organ System	Tissue of Origin	Reported Tumor Types	Incidence	Clinical Signs	Diagnosis and Work-up	Treatment and Prognosis
Reproductive tract (male)[3,4,9–13]	Testicles; prostate; preputial gland	• Testicular seminoma; Sertoli cell tumor; interstitial cell tumor; leiomyosarcoma; mixed germ cell–sex cord–stromal tumor; peripheral nerve sheath tumor. Neoplasms of (up to 4) different tumor types can occur simultaneously • Prostate (adeno) carcinomas • Preputial gland adenocarcinoma	• Testicular tumors not well reported because of frequency of neutering; incidence is considered higher in cryptorchid animals. A ferret that was chemically neutered with a deslorelin-containing implant developed a testicular tumor • Prostate tumors are extremely rare • Preputial gland tumors are frequently seen in (neutered) ferrets	—	• Clinical signs • Ultrasonography • Histopathology	Bilateral orchidectomy. Testicular tumors seldom metastasize Preputial gland tumors are locally invasive and require aggressive surgery in which margins of at least 1 cm are recommended. Radiation therapy has been used in conjunction with surgical resection with varying degrees of success

Mammary glands[3–5,7]	—	Simple and complex mammary adenomas Adenocarcinomas	Rare in ferrets	Mammary gland enlargement	• FNA (cytology) or biopsy (histopathology) • Thoracic radiographs to check for lung metastases	Mastectomy and ovariohysterectomy. Prognosis depends on the presence of metastasis
Hematopoietic and lymphatic systems[3–5,7,14–16]	May be localized in every organ system, but most prominent in lymph nodes, blood, thymus, spleen, liver, bone marrow, GI tract, and skin	Lymphoma; leukemia (lymphoblastic, lymphocytic, myeloid, megakaryocytic myelomonocytic, erythremic); myeloma; myelolipoma; thymoma	Lymphoma is the third most common neoplasia in ferrets and is seen in ferrets <1 y old to adult; may be of B-cell or T-cell origin; T cell is most common	• Highly variable in lymphoma, dependent on the site affected (eg, enlarged lymph nodes, renomegaly/splenomegaly/hepatomegaly, general malaise, cutaneous or ocular lesions, diarrhea) • Coughing and regurgitation may be seen in case of a mediastinal mass	• Clinical signs • Ultrasonography, thoracic radiographs, or CT imaging • FNA (cytology) or biopsy (histology) • CBC or blood smear may reveal marked lymphocytosis and neoplastic cells (lymphoblasts) • Lymphopenia is seen in older ferrets with lymphoma • Hypercalcemia • Necropsy • Gammopathy in case of myeloma	With only 1 anatomic lesion surgical removal may be curative. Median survival without treatment and/or chemotherapy is 6 month

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Organ System	Tissue of Origin	Reported Tumor Types	Incidence	Clinical Signs	Diagnosis and Work-up	Treatment and Prognosis
Integument[3–5,7,13,17–23]	Skin; ears; eyelids	Basal cell tumor (sebaceous epithelioma, sebaceous adenoma); mast cell tumor; apocrine sweat gland tumor (see preputial gland adenocarcinoma); ceruminous gland adenocarcinoma; trichoblastoma; hemangioma; hemangiosarcoma; hamartoma; lipoma; liposarcoma; (mucoid) fibroma; (vaccination-site) fibrosarcoma; myxosarcoma; squamous cell carcinoma; adrenocortical-like cutaneous tumor; histiocytoma; melanocytoma; epitheliotropic lymphoma	Most common tumors after the endocrine and hemolymphatic tumors Basal cell tumors account for approximately 60% of skin tumors. Viruses (eg, papilloma virus) and vaccination may play a role in the cause of some neoplasia (squamous cell carcinoma, fibroma)	• Solitary, well-circumscribed, cutaneous or subcutaneous masses with or without the presence of crusts. Multiple sebaceous epithelioma and piloleiomyomas can be present simultaneously • Tumors may be located anywhere on the body surface, although predilection sites may be recognized for some tumors (eg, prepuce, ear for apocrine gland tumors; along the head, neck, or dorsal midline for piloleiomyosarcoma)	• Clinical presentation • FNA (cytology) or excisional/incisional biopsy (histology)	• Treatment of choice is general surgical excision of the mass. Adjunct chemotherapy or radiation may be considered depending on the tumor type involved. Prognosis varies depending on the type of neoplasia and location • For basal cell, mast cell tumors, hemangioma, hemangiosarcoma, surgical excision is considered curative • Apocrine sweat gland tumors vary in malignancy. Prepuce and perivulvular tumors have a high malignancy. Wide margins are needed during surgical resection. Radiation therapy may have a supplemental effect

GI tract[3–5,7,24–29]	Oral cavity; stomach; small and large intestines; liver and bile duct; exocrine pancreas	Lymphoma, squamous cell carcinoma; gastric adenocarcinomas; GI stromal tumor; colonic adenomatous polyp The liver is a common site for metastasis Hepatocellular adenoma and carcinoma; peliod hepatocellular carcinoma Biliary cystadenoma; cholangiocellular carcinoma Pancreatic exocrine adenocarcinoma; salivary gland carcinoma; peritoneal mesotheliomas; malignant mesenchymoma	Lymphoma is the most common tumor of the GI tract Squamous cell carcinoma is the most common tumor in oral cavity Biliary cystadenoma is the most common tumor of the biliary tract. A novel *Helicobacter* species has been associated with biliary malignancies	• Squamous cell carcinoma in the oral cavity results in pain and difficulty eating • Animals with GI tumors may present with lethargy, anorexia, and distended abdomen (eg, hepatomegaly)	• Clinical presentation (squamous cell carcinoma in the oral cavity). Abdominal palpation • Ultrasonography, radiography (barium GI series) or CT imaging • FNA or biopsy • Explorative laparotomy • Necropsy	Squamous cell carcinoma: invasive surgical excision. Extensive bone involvement may limit effect of surgery Most gastric and intestinal tumors are likely to be diagnosed only in an advanced stage, thereby carrying a grave prognosis
Urinary tract[3–5,7,30]	Kidney; bladder	Transitional cell carcinoma; renal carcinoma, adenoma Nephroblastoma	Tumors of the urinary tract are rare in ferrets	• Hematuria, dysuria, and incontinence • Unilateral renal enlargement	• Ultrasonography, (contrast) radiography • Necropsy	Unilateral nephrectomy may be curative in case of renal neoplasia Bladder carcinoma has a poor prognosis

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Organ System	Tissue of Origin	Reported Tumor Types	Incidence	Clinical Signs	Diagnosis and Work-up	Treatment and Prognosis
Respiratory tract[3–5,7,31]	Trachea; lungs	An adenosquamous carcinoma of the trachea. Mast cell tumor; mesothelioma No primary lung tumors described, although ferrets are used as a lung cancer model by exposing them to a tobacco carcinogen and thereby inducing lung neoplasia	Uncommon	Progressive dyspnea and tachypnea	Tracheoscopy and CT	No treatment described
Cardiovascular system[3–5]	Vascular endothelium	Hemangioma; hemangiosarcoma; lymphangioma	—	—	—	—
Musculoskeletal system[3–5,7,32–39]	Bones; muscle; joints	Chordoma; chordosarcoma; osteoma; osteosarcoma; chondrosarcoma; intramedullary lumbosacral teratoma; fibrosarcoma; synovial cell sarcoma; leiomyoma; leiomyosarcoma; piloleiomyosarcoma; rhabdomyosarcomas	Chordomas are fairly common tumors arising from notochord remnants The other types of tumors are rare	• Chordoma: irregularly round, whitish gray, firm, clublike swelling at the end of the tail. However, they may arise in any of the vertebra • Chordomas in the cervical and thoracic spine, result in paresis or paralysis caused by spinal cord compression and/or pathologic vertebral fracture • Progressive, unilateral lameness in cases of appendicular tumors	• Radiographs may reveal osteolysis or a swollen joint in case of the synovial cell sarcoma • CT may be useful to determine the extent of the tumor (also for surgical planning) • FNA and cytology • Histopathology	Amputation of the tail tip is curative in chordoma. When other vertebrae are effected, no treatment is available In case of appendicular tumors, amputation of the affected limb is recommended because no metastases are reported

Nervous system[3–5,7,40]	Brain; spinal cord; peripheral nerves; eyes	Meningioma; granular cell tumor; choroid plexus papilloma; ocular lymphoma; melanocytoma; peripheral nerve sheath tumor (also known as schwannoma), neurofibroma, neurilemmoma and neurofibrosarcoma); ganglioneuroma; spinal cord lymphosarcoma	Uncommon	• Clinical signs depend on the location of the tumor and may include ataxia, seizures, (hemi)paresis/paralysis, and other neurologic deficits • Peripheral nerve sheath tumors predominantly occur in the face and eyelids	• Use of advanced diagnostic techniques such as CT or MRI is generally required • Histopathology	In case of peripheral nerve sheath tumors, surgical resection is often not considered because with each unsuccessful attempt the remaining neoplastic cells show increasingly malignant behavior, including more rapid growth and infiltration of adjacent tissue Similar to other animals, radiation therapy may be considered as palliative treatment but overall prognosis is considered poor

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Table 1
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Organ System	Tissue of Origin	Reported Tumor Types	Incidence	Clinical Signs	Diagnosis and Work-up	Treatment and Prognosis
Endocrine system[3–5,7,41,42]	Adrenal glands; thyroid gland; endocrine pancreas	ACA; pheochromocytoma; insulinoma; thyroid carcinoma; C-cell carcinoma; adrenal neuroblastoma; adenocarcinoma of lachrymal gland origin	Adrenocortical tumors and insulinoma are the most common tumors in ferrets and represent >50% of all neoplasia seen in this species	• ACA: symmetric alopecia; recurrence of sexual behavior after neutering; dysuria may occur in male ferrets. Enlarged mammary glands may be seen in females • Insulinoma: lethargy, stargazing, weakness in the hind limbs, coma, ptyalism, pawing at the mouth, and a glazed look in the eyes	• ACA: ultrasonography, CT (hormone analysis) • Insulinoma: plasma glucose, insulin • Necropsy	• ACA: adrenalectomy was the former treatment of choice. Deslorelin-containing implants are now considered the treatment of choice with an average disease-free period of 16.5 mo • Insulinoma: partial pancreatectomy and medical treatment (diazoxide or prednisolone) result in a mean disease-free period of approximately 1 y. Resection of only the tumor (nodulectomy) is considered to result in a shorter disease-free period

Abbreviations: ACA, adrenocortical adenoma/carcinoma; CBC, complete blood cell count; CT, computed tomography; FNA, fine-needle aspiration; GI, gastrointestinal.

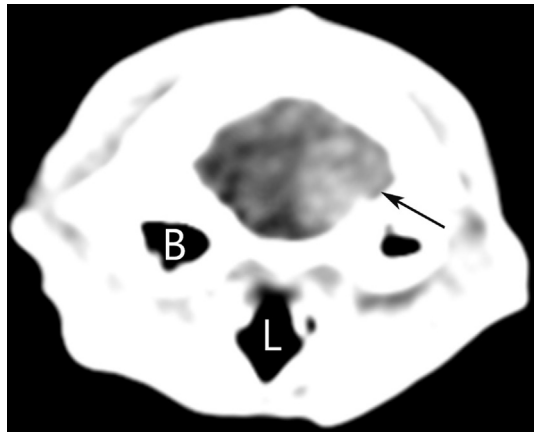

Fig. 1. CT image of ferret skull after administration of intravenous contrast. On the right side of brain the large, space-occupying, contrast-enhancing lesion is seen (*arrow*), which proved to be a choroid plexus papilloma. B, tympanic bulla; L, larynx. (*From* van Zeeland YRA, Schoemaker NJ, Passon-Vastenburg M, et al. Vestibular syndrome due to a choroid plexus papilloma in a ferret. J Am Anim Hosp Assoc 2009;45:97–101)

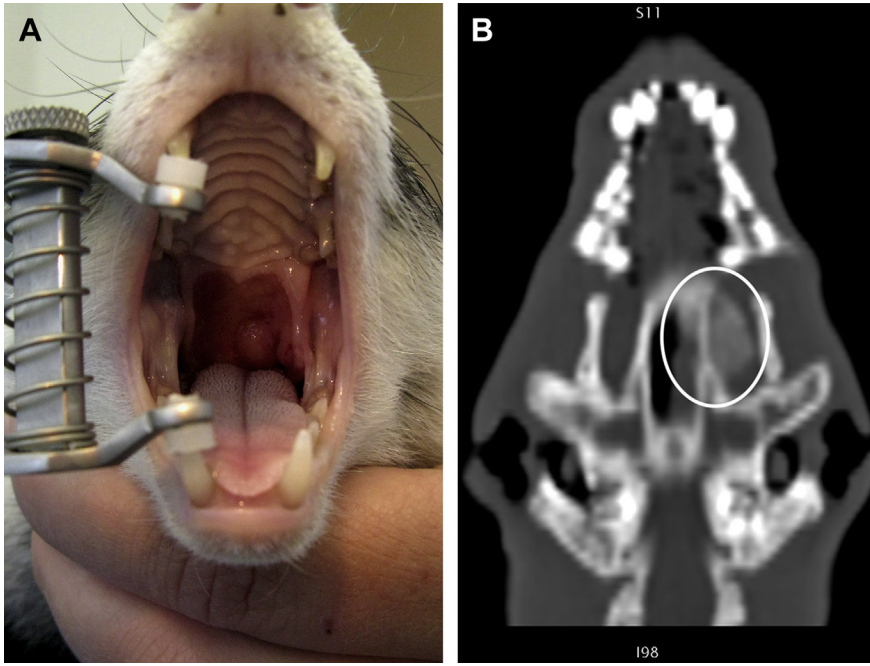

Fig. 2. A 6-year-old male ferret was presented with a history of progressive weight loss since 6 months. Oral inspection revealed a mass on the left side of the soft pallet (*A*). CT imaging (*B*) enabled visualization of the extent of involvement of this oral tumor and revealed that it had resulted in osteolysis of the skull, and thereby an unfavorable prognosis. Histology revealed this tumor to be an adenocarcinoma, likely of salivary gland origin, with regional metastasis and metastasis in the lungs.

have a higher chance of developing hyperadrenocorticism compared with ferrets housed outdoors.[46,47]

A genetic background may also play a role in the cause of this disease. Studies have been performed in search for candidate genes that may play a role in the development of tumor formation in ferrets. Although alterations of specific genes (ie, sfrp1 and Foxl2) have been found in adrenocortical tumors,[48,49] it is still not clear what the pathway is for the development of these tumors.

Clinical signs

The most prominent signs of hyperadrenocorticism in ferrets are symmetric alopecia (**Fig. 3**), a swollen vulva in neutered female ferrets, return of sexual behavior after neutering in male ferrets, and pruritus. The skin is usually not affected, although some excoriations may be seen. In male ferrets, urinary obstruction caused by periprostatic or periurethral cysts and prostatic enlargement may be seen. Occasionally mammary gland enlargement in jills is also seen. There is no sex predilection in the occurrence of this disease. Although signs of hyperadrenocorticism may be seen in ferrets as young as 2 years, more than 80% are more than 5 years of age. Polyuria and polydipsia are reported in ferrets with hyperadrenocorticism. However, these signs may be caused by concurrent kidney disease in these (mostly elderly) ferrets.[50]

Differential diagnosis

The most important differential diagnoses include a nonovariectomized female or the presence of active remnant ovaries. The investigators have also seen a ferret with severe alopecia and pruritus caused by a food allergy.[50] Plasma and urine hormone analysis, in combination with an abdominal ultrasonography, could not find any changes associated with an enlarged, or hyperfunctioning, adrenal gland. Changing the diet in this ferret resolved the alopecia and pruritus. Infectious skin diseases should also be considered in cases of alopecia and pruritus. In these cases, the skin is affected. Seasonal alopecia, a condition that is characterized by a seasonal occurrence of

Fig. 3. Severe alopecia in a 5-year-old male, neutered ferret with bilateral adrenal tumors that were seen on ultrasonography. Multiple small crusts can be seen, which were the result of the constant scratching performed by this ferret.

alopecia, with hair loss predominantly occurring on the tail, is also commonly mentioned as a differential diagnosis. Although the cause for this condition is not known, the author suspects that it may be an early sign of hyperadrenocorticism.[50]

Diagnosis

Aside from the clinical signs, abdominal palpation is useful in obtaining the diagnosis of hyperadrenocorticism in ferrets. Palpation of an enlarged adrenal gland helps locate the affected adrenal gland, although the right adrenal gland is more difficult to palpate because of the overlying caudate liver lobe. The most widely reported diagnostic technique is measuring serum/plasma hormone concentrations. The reported hormones that are diagnostic are androstenedione, estradiol, and 17α-hydroxyprogesterone. However, increased levels of 1 or more of these hormones are also seen in intact female ferrets during estrus,[51] and therefore they do not helpful in the differentiation between a ferret with hyperadrenocorticism and one with an active ovarian remnant.

Although in ferrets with adrenocortical disease the urinary corticoid/creatinine ratio (UCCR) is higher than the reference value of 2.1×10^{-6},[52] this ratio is also not useful in the differentiation between a ferret with hyperadrenocorticism and one with an active ovary because the UCCR is also increased in intact ferrets during the breeding season.

An abdominal ultrasonographic examination is the most useful tool to determine whether 1 or both adrenal glands are affected, or whether an ovarian remnant is present. In the past it was considered difficult to correctly identify the adrenal glands ultrasonographically. However, using specific landmarks, the adrenal glands can easily be identified. The left adrenal gland is located ventrolateral to the aorta, at the level of the origin of the cranial mesenteric artery. The right adrenal gland is located more cranial than the left, and is attached to the dorsolateral surface of the caudal vena cava, at the level of the origin of the cranial mesenteric artery, and lies adjacent to the caudomedial aspect of the caudate process of the caudate liver lobe. The adrenal glands of ferrets with hyperadrenocorticism have a significantly increased width (>3.9 mm), a rounded appearance, a heterogeneous structure, an increased echogenicity, and sometimes contain signs of mineralization.[53]

CT has recently been suggested as useful when evaluating the adrenal glands in ferrets. When using this technique, intravenous contrast medium is needed to delineate the adrenal gland better from the caudal vena cava and enable better visualization of the size of this gland.[50]

Treatment

The most commonly used modalities for treating ferrets with hyperadrenocorticism are surgery and/or the use of a long-acting GnRH analogue. The choice of treatment is influenced by many factors. Criteria such as the age of the ferret, presence of concurrent disease (eg, renal failure, lymphoma, and/or cardiomyopathy), risk of surgery (which is higher when the right or both adrenal glands are involved), and/or financial limitations may lead owners to decline surgery. Comparing the average disease-free period following both treatment modalities, treatment with a deslorelin-containing implant has an average disease-free period of 16.5 months (range, 3–30 months), whereas this period is 13.6 months (range, 0–38 months) for surgical intervention.[54]

Surgical treatment

The left adrenal gland can be fairly easily removed, in which only the phrenicoabdominal vein needs to be ligated. Resection of the right adrenal gland is more difficult because of its dorsolateral attachment to the caudal vena cava and close proximity to the liver. Complete resection or partial resection combined with cryosurgery had a less favorable outcome compared with partial resection of the right adrenal gland.[55]

Debulking of the right adrenal gland also did not result in a less favorable survival time compared with complete resection of the left adrenal gland.[55] When both adrenal glands are affected, it has been proposed to remove the entire left adrenal gland and part of the right adrenal gland. This treatment modality led to an addisonian crisis in 5% of these patients.[56] Following surgical removal, disease may recur in approximately 15% of the ferrets because of development of disease in the remaining adrenal gland tissue.[56] In addition, up to 6% of ferrets may die perioperatively.[54,56]

Medical treatment

The depot GnRH agonist deslorelin (Suprelorin-F, Virbac) is the only drug licensed for use in the treatment of hyperadrenocorticism in ferrets. The drug suppresses the release of gonadotropins by continuously releasing deslorelin into the circulation, thereby overriding the pulsatile release of GnRH that is needed for the release of gonadotropins.[47] Because the drug initially results in a (short-lived) release of gonadotropins and potentially associated worsening of clinical signs, the effect is delayed by approximately 2 weeks after placement of the implant. In the experience of the author, the tumor does not decrease in size after placement of the implant. Autonomous production of steroids by the adrenal gland may occur over time, resulting in a loss of efficacy of the implant and recurrence of clinical signs.

Drugs that have been found to be ineffective, or are discourage, in the treatment of hyperadrenocorticism in ferrets include ketoconazole, mitotane (o,p'-DDD) and melatonin. When using melatonin, alleviation of clinical signs is seen, but hormone concentrations did not decrease and the tumors continued to grow.[57] Trilostane, a 3β-hydroxysteroid dehydrogenase (3β-HSD) blocker, has been used anecdotally in ferrets. Although the drug, in theory, is effective in the treatment of hyperadrenocorticism in ferrets (because 3β-HSD is necessary for the synthesis of androstenedione and 17-hydroxyprogesterone), deterioration of clinical signs was seen in a ferrets with hyperadrenocorticism after receiving 5 mg of trilostane by mouth once daily. It is hypothesized that the decrease in 3β-HSD level lead to activation of 17,20-lyase and thus activation (instead of deactivation) of the androgen pathway. This drug is therefore not recommended before understanding the mode of action in ferrets.[50]

Adrenomedullary Tumors

Adrenomedullary tumors (eg, pheochromocytoma and neuroblastoma) are seldom reported, particularly compared with the high incidence of adrenocortical tumors in ferrets.[42] Pheochromocytomas produce excessive amounts of catecholamines and are exclusively seen in the adrenal medulla, whereas a neuroblastoma is a neuroendocrine tumor that can occur in any tissue containing neural crest cells. Only 1 case of a neuroblastoma in the adrenal gland of a ferret has been described,[42] whereas several (presumed) pheochromocytomas have been described. Histologic confirmation of a pheochromocytoma has only been performed in 1 case,[6] whereas the secretion of catecholamines has been confirmed in none.

Insulinoma

Insulinomas are, usually, small (0.5–2 mm) tumors of the pancreatic beta cells (**Fig. 4**) that result in hypoglycemia caused by the excessive production of insulin. Tumor types may be described as hyperplasia, adenoma, or carcinoma. Most are well circumscribed, but infiltration in surrounding tissues may occur. In contrast with dogs, insulinomas in ferrets rarely metastasize.

The distribution of insulinomas is equal among the sexes. With a reported prevalence of 20% to 25% of the diagnosed neoplasms in ferrets, insulinomas are among

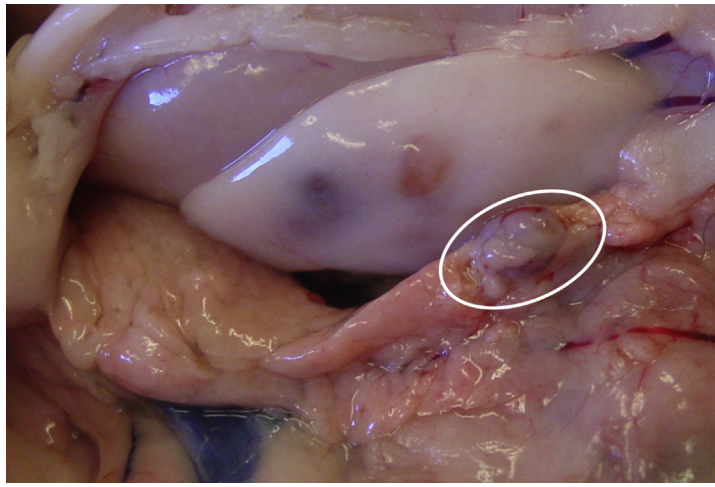

Fig. 4. In the pancreas of this 4-year-old, male castrated ferret, which presented with recurrent signs of stargazing and weakness in the hind legs, an approximately 1-cm mass was present (*circle*), which turned out to be an insulinoma. In general, insulinomas are only 2 to 3 mm in diameter.

the most commonly diagnosed tumors in middle-aged to older ferrets, with a median age of 5 years (range, 2–8 years).[58]

Cause/pathophysiology

The cause of insulinomas in ferrets is currently unknown. It has been suggested that, based on the natural carnivorous diet of mustelids, diets high in carbohydrates may contribute to the development of these tumors. A diet high in protein (42%–55%[a]), high in fat (18%–30%[1]), low in carbohydrates (8%–15%[1]), and low in fiber (1%–3%[1]) has therefore been advised to reduce the incidence.[59] However, no scientific evidence is available to back up any claims on the cause of insulinoma, nor has it been proved that the incidence is reduced when ferrets are fed low-carbohydrate kibble.

Clinical signs

Clinical signs vary from lethargy, stargazing, and weakness in the hind limbs to complete collapse, generalized seizures, and coma. Ptyalism and pawing at the mouth, signs of nausea, may also be seen. In addition, owners may notice a glazed look in the eyes of their ferrets. An important feature in ferrets with an insulinoma is that the clinical signs most likely resolve after the ferret has eaten some food.

Differential diagnosis

The differential diagnosis of hind limb weakness consists of neurologic diseases (eg, trauma, intervertebral disk disease, Aleutian disease), cardiac disease, generalized weakness, and metabolic disorders.[60]

Within the differential diagnosis of hypoglycemia, excessive glucose-consuming conditions, such as rapid multiplying neoplastic cells, severe hepatic disease, severe malnutrition or starvation, sepsis, or iatrogenic insulin overdose should be considered.[58] These conditions can usually be ruled out based on the results of the history, physical examination, and/or diagnostic work-up.

[a] On a dry matter basis.

Diagnosis

Blood glucose concentrations lower than 3.3 mmol/L (<60 mg/dL; reference range, 5.0–7.0 mmol/L [90–125 mg/dL]), after withholding food for 4 hours, are highly suggestive of an insulinoma when ferrets display the signs mentioned earlier. In ferrets with blood glucose concentrations between 3.3 and 5.0 mmol/L (60–90 mg/dL), another 2 hours of starving is advised.

The measurement of plasma insulin concentrations is debatable because concentrations within the reference range may be seen. Because insulin plasma concentrations should be low during a hypoglycemic event, insulin concentrations within the reference range should be considered abnormal during a hypoglycemic crisis.[58]

Insulinomas are occasionally visualized by ultrasonography, but are also frequently missed. Diagnostic imaging in the form of radiography or ultrasonography examination is therefore not routinely advised to localize the tumors.

Treatment

The treatment of insulinomas may consist of surgical removal of the neoplasm and/or providing one of the available drugs. Many factors, such as age of the ferret, desire of the owner to have an instant solution, and/or financial restrictions, may play a role in the decision-making process.

Surgical treatment

To fully eliminate the source of excess insulin production, surgical removal is seemingly the best therapeutic option. A partial pancreatectomy has been recommended rather than pancreatic nodulectomy in order to remove as much undetectable islet cell tumor as possible and increase the mean disease-free state after surgery to about 1 year.[61] Recurrence of clinical signs is mainly caused by the occurrence of new insulinomas and not by metastases of the removed tumor. If too much of the pancreas is removed, complications such as diabetes mellitus may occur. It should be stressed that every effort should be taken to avoid this condition from occurring, because the medical management of insulinoma is far easier than that of diabetes mellitus.[50]

Medical treatment

Prednisone and diazoxide are the most commonly used drugs for treating insulinomas. Octreotide, a synthetic long-acting analogue of somatostatin, has also been reported as a treatment option in ferrets, but no clear beneficial effects were seen compared with the other 2 modes of treatment.[58]

Corticosteroids (eg, prednisone, prednisolone, dexamethasone), which induce gluconeogenesis, are frequently used as the drugs of first choice. Ferrets seem to be fairly refractory to developing side effects caused by glucocorticoid administration, and generally respond well to the treatment protocol. However, iatrogenic Cushing disease has been reported in ferrets that have received glucocorticoids for prolonged periods of time.[62] In addition, the gluconeogenic mode of action of glucocorticoids results in an increase of glucose levels, which may be contraindicated in ferrets with insulinomas because of the risk of stimulating the secretion of insulin.

Diazoxide, a drug licensed for the treatment of human patients with insulinoma, inhibits insulin release. Because this drug addresses the cause of the hypoglycemia it is recommended rather than the use of glucocorticoids.[50] Treatment is started at an oral dose of twice-daily 5 mg/kg diazoxide. A gradual increase of the dose may be needed depending on the disappearance or continued presence of clinical signs. Although there is no upper dose of diazoxide, prednisone may be added to the treatment protocol in a concentration of 0.2 to 1 mg/kg by mouth once daily, when the needed diazoxide increases to more than 15 to 20 mg/kg. Medical management based on the

aforementioned protocol is usually sufficient to control hypoglycemia for a period of up to 18 months, with some ferrets in the author's clinic even surviving up to 2 years on medical treatment.[50,58]

Recently, the use of constant-rate infusion of glucagon has been described as an emergency treatment of a severely hypoglycemic ferret. A dosage of 15 to 40 ng/kg/min (as extrapolated from data in dogs and cats) proved effective in increasing blood glucose concentrations and alleviating the clinical signs in an elderly ferret that did not respond sufficiently to other types of therapy.[63]

Owners are advised to monitor their ferrets closely for signs of hypoglycemia and feed the ferret immediately if mild signs of hypoglycemia are noted. In the event of a seizure or comatose condition, the owner is advised to give a carbohydrate-rich or protein-rich liquid food to the ferret. This diet may help to temporarily relieve the clinical signs so that the ferret can safely be transported to the veterinary clinic.

Prognosis

In ferrets, the prognosis is better compared with dogs, in which metastases are very common. Although metastases are rare in ferrets, multiple tumors and recurrent signs are common. Recurrent signs are probably caused by the development of new tumors rather than metastases of the earlier tumor.

HEMOLYMPHATIC TUMORS

Lymphoma

Lymphoma is the third most common tumor found in ferrets, and is frequently found in association with adrenocortical tumors and/or insulinomas.[14,29] It is also the most common hemolymphatic tumor. Lymphomas can be diagnosed as early as 9 months of age, and may be localized in all hemolymphatic organs, such as lymph nodes, spleen (**Fig. 5**), liver, and bone marrow. Lymphoma of the skin, also known as mycosis

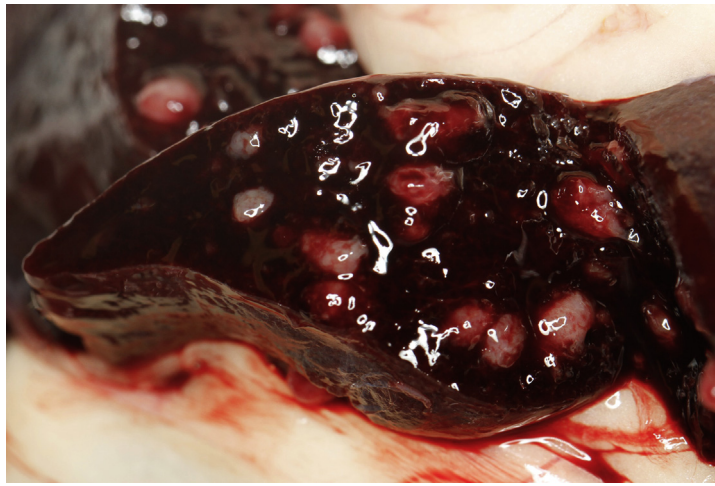

Fig. 5. Cross section of the spleen of a 5-year-old, female neutered ferret that had lost body weight in the past weeks. Splenomegaly was detected on abdominal palpation. On ultrasonography examination the spleen had an irregular aspect. Lymphoma was suspected as cause for the irregular aspect. Although the options of surgical treatment were discussed, the owner elected euthanasia. Histologic examination of the tumor confirmed the suspicion of lymphoma.

fungoides, is also seen in ferrets. An equal distribution among the sexes is seen. A transmission study has shown that at least certain types of lymphoma are transmittable.[64]

Clinical signs

Clinical presentation of ferrets with lymphomas is often nonspecific and may include loss of appetite, weight loss, and peripheral lymph node enlargement. When pleural effusion and mediastinal masses are present, dyspnea, and coughing may be seen.

Diagnosis

Because lymphoma is a tumor from the hemolymphatic system, it is important not only to look at tissue alterations but also at all the hemolymphatic cells. Therefore, a complete blood cell count (CBC) and bone marrow aspiration helps to determine whether the lymphoma is leukemic. Diagnostic imaging characteristics of lymphoma in ferrets are similar to those previously reported in dogs, cats, and humans.[65] Radiographs can be useful in detecting masses in the anterior mediastinum and bony structures.[65,66] CT has an added value when lesions are present in the bony structures.[65] With ultrasonography examination, a more precise diagnosis can be made in both the thoracic as well as the abdominal cavity, in which enlarged lymph nodes, alterations in the spleen and liver, and pleural and abdominal effusions can be visualized. Enlarged lymph nodes are frequently seen during the abdominal ultrasonography examination. Chronic inflammation (eg, *Helicobacter mustelae*) is usually the result of these hyperplastic/reactive lymph nodes. Ultrasonography-guided fine-needle aspiration (**Fig. 6**) biopsies or full-thickness biopsies are useful in differentiating between a reactive lymph node and lymphoma. These biopsies are therefore essential for confirming the diagnosis. Based on the cytologic or histologic findings, lymphoma (in ferrets) can been classified according to the Revised European-American Lymphoma Classification for Domestic Animals by the World Health Organization and/or the National Cancer Institute Working Formulation.[67–69] Based on these classifications, a classification has been described of low, intermediate, and high grade in which, in low-grade cases, predominately diffuse small lymphocytic lymphoma was seen; in the intermediate cases, mixed-cell lymphoma was seen; and in the high-grade cases, diffuse immunoblastic lymphoma was seen.[68] For further differentiation, immunohistochemistry is extremely valuable.

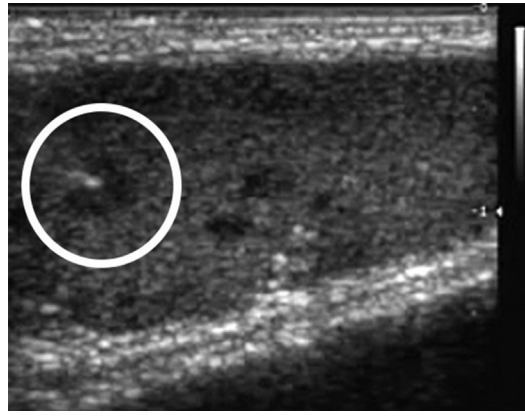

Fig. 6. Fine-needle aspiration biopsy of a nodule in an enlarged spleen of a ferret. The tip of the needle can be seen as the bright white spot in the circle. Cytology revealed this to be lymphoma.

The most commonly used markers are CD3 (cluster of differentiation 3), which is the marker for T-cells, and CD79α is B-cell marker. Both markers have been validated for use in ferrets.[67] In different studies, T-cell lymphoma consistently was shown to be the predominant type of lymphoma seen in ferrets.[14,67,69]

It has been recommended to perform a complete clinical staging of lymphoma to determine the degree of illness affecting the patient, which may help in discussing the prognosis with the owner. Recently, an updated clinical staging system has been proposed[68] in which the higher the stage, the poorer the prognosis:

Stage 1: single anatomic lesion
Stage 2: single lesion with regional lymph node involvement limited to 1 side of the diaphragm
Stage 3: lesions on both sides of the diaphragm, including intra-abdominal or gastrointestinal locations
Stage 4: multiple sites on both sides of the diaphragm are affected with or without the visceral organs
Stage 5: manifestation in the blood and involvement of bone marrow and/or other organ systems

Treatment

Depending on the stage of lymphoma and the wishes of the owner, different protocols can be used for the treatment of lymphoma in ferrets. Surgery (splenectomy, lymph nodectomy) can be performed if only a single anatomic structure is affected (stage 1). In more advanced cases, chemotherapy may be used, for which different protocols have been described for use in ferrets.[1,68,70]

Chemotherapeutic agents that have been used in ferrets are prednisolone, L-asparaginase, chlorambucil, cyclophosphamide, cytarabine, doxorubicin, methotrexate, procarbazine, and vincristine.[68] Chemotherapy can also be used in combination with radiation therapy.

Dosages of chemotherapeutic agents are usually based on body surface area rather than weight, and a recent study determined a reliable method for calculating body surface areas in ferrets based on CT imaging.[71] The investigators concluded that their formula ($9.94 \times [\text{body weight}]^{2/3}$) did not differ significantly from the feline-derived formula and would therefore not contribute to a change in the currently used dosages.

The overall mean survival of ferrets with lymphoma has been reported to be 6 months (range, 2 weeks to 19 months).[14] The same investigators report that the mean survival for ferrets with T-cell lymphoma is 5 months (range, 0.5–14.0) and for ferrets with B-cell lymphoma is 8.4 months (range, 2–19 months). Ferrets that received chemotherapy had similar survival rates (4.3 months [range, 0.5–14.0 months] and 8.8 months [range, 2.0–19.0 months] for T-cell lymphoma and B-cell lymphoma, respectively).[14] It is therefore debatable whether chemotherapy provides any added value in the treatment of lymphoma in ferrets. In addition, note that treatment with cyclophosphamide and vincristine is frequently associated with therapy-limiting neutropenia.[14] Glucocorticoids are also frequently used in ferrets with lymphoma. The added value of this treatment is just as debatable as the use of chemotherapy, because the mean survival period also did not increase with the use of this medication.

INTEGUMENTARY TUMORS

Sebaceous epitheliomas (**Fig. 7**) and mast cell tumors (**Fig. 8**) are the most common integumentary tumors seen in ferrets, representing approximately a third of the integumentary tumors each.[20] The other third of the integumentary tumors consist of a wide

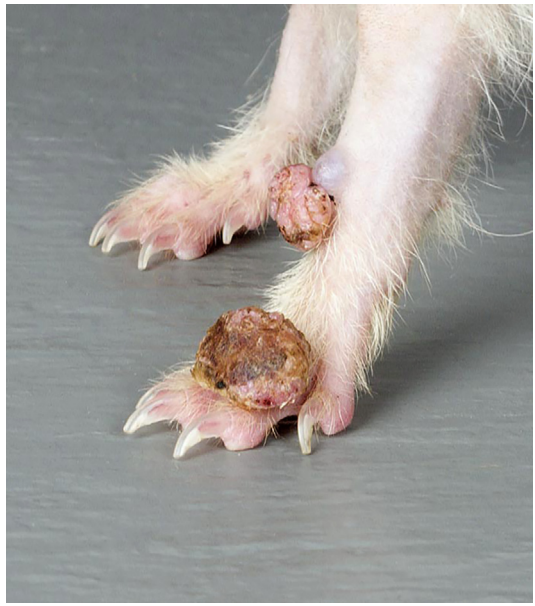

Fig. 7. Close-up of one of multiple skin masses in a 7.5-year-old female, neutered ferret. Histologic evaluation confirmed this mass to be a sebaceous epithelioma.

variety of types of tumors, such as preputial cell tumors (Fig. 9) and cutaneous lymphoma (Fig. 10).

Sebaceous epitheliomas are of basal cell origin and only involve the skin and not the subcutis. Although these tumors both grossly and histologically appear aggressive, with increased mitoses, cellular atypia, and apparent infiltration at inflamed margins, they are all benign and can easily be removed. However, multiple tumors and recurrence of new tumors are frequently seen.

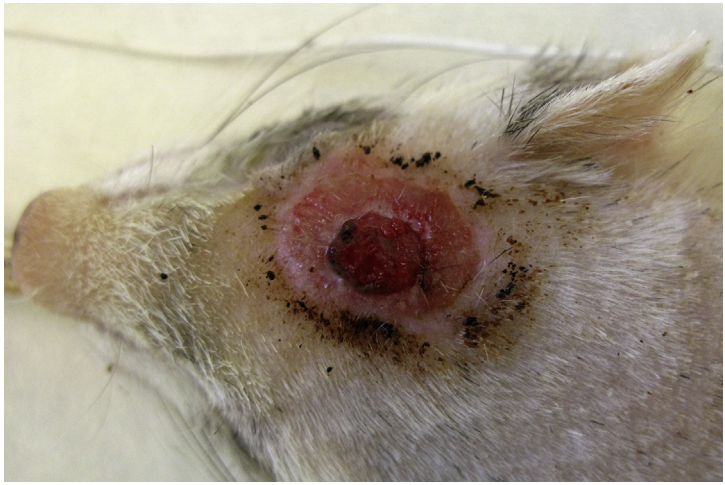

Fig. 8. Mast cell tumor on the head of a 5-year-old, male neutered ferret. The tumor was easily and successfully surgically removed, without any recurrence of the tumor.

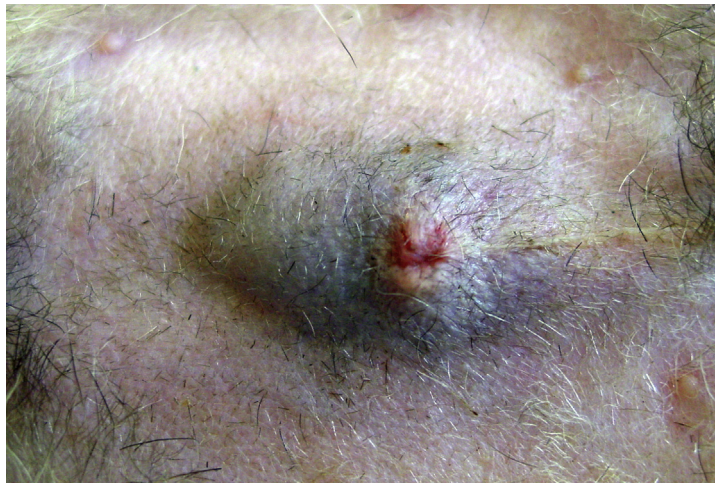

Fig. 9. Apocrine tumor of the preputial gland in a 5-year-old intact male ferret.

Mast cell tumors in ferrets are, like sebaceous epitheliomas, benign tumors. This characteristic is in sharp contrast with mastocytoma in dogs and cats. The overlying skin in these tumors is frequently eroded as a result of self-trauma because of pruritus. The tumors can easily be surgically excised and do not require pretreatment with antihistamines. However, mast cell tumors may reappear at a different site, which should not be seen as an indication of a poor prognosis because these tumors may also be removed without local metastasis.

In contrast with the excellent prognosis of sebaceous epitheliomas and mast cell tumors in ferrets, preputial tumors in ferrets are malignant and invade the surrounding tissues with local metastasis as a frequent result.[13] These tumors are of apocrine gland origin and are seen in middle-aged to geriatric ferrets. A minimal margin of

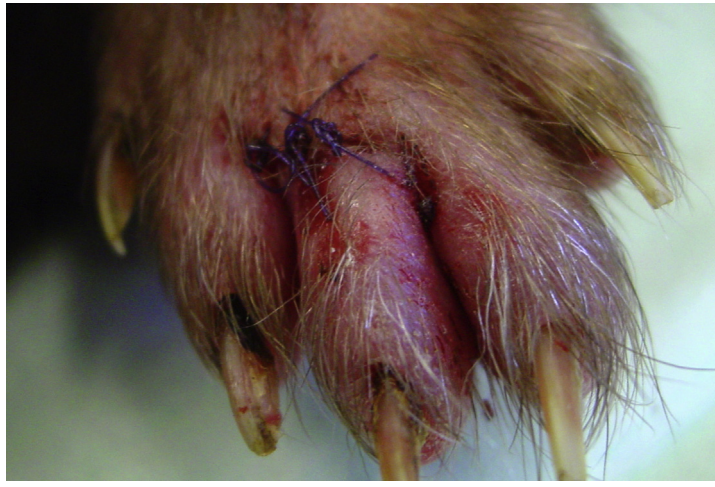

Fig. 10. Swollen and red foot of a 5-year-old, male neutered ferret. Skin biopsies revealed this to be cutaneous lymphoma (not further specified).

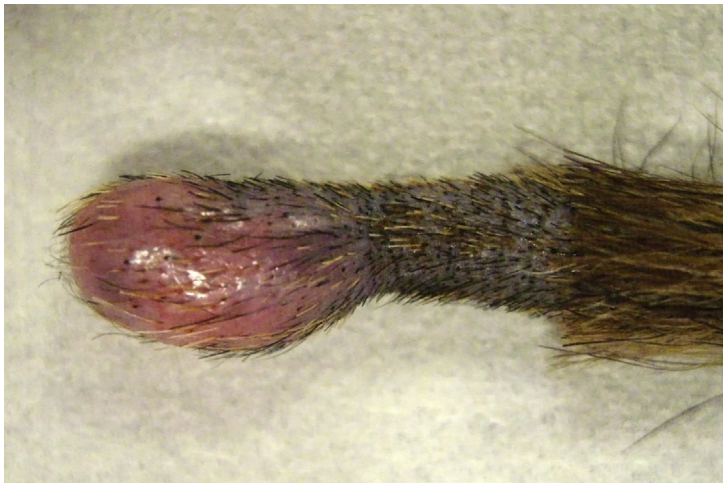

Fig. 11. The typical presentation of a chordoma in a ferret. These tumors can easily be removed when they are present at the tip of the tail.

1 cm is recommended during surgical resection to allow for the best possible postoperative prognosis. However, such a large margin may require (partial) resection of the penis.[13] Radiation therapy has also been used in these tumors, but this was not always successful.[13]

TUMORS IN OTHER SYSTEMS

Chordoma

A tumor that is fairly common in ferrets is chordoma, which is an intraosseous neoplasm originating from mesoderm-derived notochord. Chordomas develop twice as frequently in female ferrets as in male ferrets.[72] The most characteristic aspect of this tumor is the accumulation of mucus in the extracellular myxoid stroma. Almost all of these tumors are considered low grade, slowly growing tumors and are found at the tip of the tail (91%) (**Fig. 11**). Because of their location and their slow rate of development, they are fairly easy to remove, with 1 or 2 extra coccygea being removed as margin. In other species (eg, rats, dogs, cats, humans) chordomas frequently metastasize.[32] Although this is not commonly reported in ferrets, 1 case of suggested cutaneous metastasis has been described,[73] and in a recent case lung metastasis was seen.[33] If the tumor is located further up the spinal column, no therapy is possible.[33] During progression of the disease, pathologic fractures occur, making euthanasia inevitable.

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