**The Armed Forces Institute of Pathology**
**Department of Veterinary Pathology**
**WEDNESDAY SLIDE CONFERENCE**
**2003-2004**

**CONFERENCE 17**
3 March 2004

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## CASE I - 0300052 (AFIP 2891626)

**Signalment:** 644-day-old male Fischer 344 rat, *Rattus norvegicus*.

**History:** This rat was from the low-dose group of a 2-year carcinogenicity study in Fischer 344 rats. The rat exhibited clinical signs of opacity of the right eye, an ulcerated mass in the inguinal area, nasal discharge and posterior paralysis. The rat was sacrificed on day 602 of the study.

**Gross Pathology:** Macroscopic findings were: an ulcerated preputial gland mass, 20x20x15 mm; a mottled white right testicle; an opaque right eye; multiple pale nodules up to 3x3x3 mm in the lungs; and a 30x30x20 mm mottled red mass in the lumbar vertebra.

**Laboratory Results:** None reported.

**Contributor's Morphologic Diagnosis:** Chordoma with metastasis to the lung.

**Contributor's Comment:**
Description

The site of origin for the tumor was the lumbar vertebra (Fig. 1). The tumor (arrows) infiltrated the bone of the vertebra (SP = spinous process) and surrounding muscle. The tumor cells were arranged in masses and cords separated by fine connective tissue septae. Metastatic tumors were numerous in the lung filling blood vessels and extending into the parenchyma (Fig. 2). The metastatic cells had the same morphology as the neoplasm at the primary site. The tumor cells were polyhedral with clear or vacuolated cytoplasm, a distinct cytoplasmic border, and round to oval nuclei with central nucleoli (Fig. 3).

Discussion

Chordomas are believed to arise from residual notochordal tissue in the axial skeleton[1,2]. They have a predilection for the proximal and distal extremes of the axial skeleton and are most common in the lumbosacral spinal cord of Fischer rats[3]. Chordomas have been reported in humans, rats, mice, dogs, cats, ferrets, and mink.

An incidence of 0.05% has been reported[4] in the NTP's database of 115,000 Fischer 344 rats from 300 toxicity/carcinogenicity studies. Metastasis to the lung occurred in 56% of the cases and in 43% of the cases diagnosis was made from the metastatic lung site without the primary site being found. There was a higher incidence in treated versus control but no association with treatment was evident. Most of the chordomas occurred as a single tumor within a study. The incidence in males was three times that observed in females. Rats with chordoma died from 74 to 138 weeks of age.

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**AFIP Diagnoses:**

1. Vertebral body: Chordoma, Fischer 344 rat, rodent.
2. Lung: Chordoma, metastatic.

**Conference Comment:** Closely packed polygonal cells with distinct cell borders and multiple, large, clear intracytoplasmic vacuoles (physaliferous cells) are a characteristic feature of this tumor. Chordomas are typically composed of three zonal components: a central zone of trabecular bone, often with bone marrow elements; a zone of cartilage; and lobules of physaliferous cells at the periphery. A mucinous matrix often surrounds the physaliferous cells. The mitotic rate is generally low. By immunohistochemistry, chordomas are positive for keratin and vimentin and variably positive for S-100 and neuron-specific enolase (NSE). These immunohistochemical markers differentiate chordomas from liposarcomas and myxoid chondrosarcomas, two differentials for this tumor.[5,6]

Although these tumors are uncommon in general, chordomas are the most frequently reported musculoskeletal neoplasm of ferrets. Chordomas are generally slow growing, locally invasive, often recur following excision, and occasionally metastasize. Chordomas can occur anywhere along the axial skeleton but predilection sites differ among species. In ferrets, they are typically located distal to the last caudal vertebra and most often expand the tip of the tail to form a club-shaped mass. Excision is generally curative in this location in ferrets; however, there are rare reports of chordomas arising within the cervical and thoracic vertebrae. In these locations, excision is difficult. Cutaneous metastasis and

neurological signs from spinal cord compression can occur. In other species chordomas are more commonly located in the sacrococcygeal region.[5,6,7,8,9]

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**References:**

1. Spjut HJ, Dorfman HD, Fechner RE, Ackerman LV: Atlas of Tumor Pathology, 2nd series, fasc. 5, Tumors of Bone and Cartilage, p. 411. Armed Forces Institute of Pathology, Washington, DC, 1971
2. Rubenstein LJ: Atlas of Tumor Pathology, 2nd series, fasc. 6, Tumors of the Central Nervous System, pp. 315-318. Armed Forces Institute of Pathology, Washington, DC, 1972
3. Leinninger JR, Riley MGI: Bones, joints, and synovia. *In*: Pathology of the Fischer Rat, eds. Boorman GA, Eustis SL, Elwell MR, Montgomery CA, Jr., Mackenzie WF, pp. 209-226. Academic Press, San Diego, California, 1990
4. Stefanski SA, Elwell MR, Mitsumori K, Yoshitomi K, Dittrich K, Giles HD: Chordomas in Fischer 344 rats. Vet Pathol **25**(1):42-47, 1988
5. Koestner A, Bilzer T, Fatzer R, Schulman FY, Summers BA, Van Winkle TJ: Histological Classification of Tumors of the Nervous System of Domestic Animals, 2nd series, vol. V, p. 36. Armed Forces Institute of Pathology, Washington, DC, 1999
6. Li X, Fox JG: Neoplastic diseases. *In*: Biology and Diseases of the Ferret, ed. Fox JG, 2nd ed., pp. 432-435. Lippincott Williams & Wilkins, Philadelphia, Pennsylvania, 1998
7. Williams BH, Eighmy JJ, Berbert MH, Dunn DG: Cervical chordoma in two ferrets (*Mustela putorius furo*). Vet Pathol **30**:204-206, 1993
8. Koestner A, Higgins RJ: Tumors of the nervous system. *In*: Tumors in Domestic Animals, ed. Meuten DJ, 4th ed., pp. 728-729. Iowa State Press, Ames Iowa, 2002
9. Pye GW, Bennett RA, Roberts GD, Terrell SP: Thoracic vertebral chordoma in a domestic ferret (*Mustela putorius furo*). J Zoo Wildl Med **31**(1):107-111, 2000

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## CASE II - A030390049/A030390049-2 (AFIP 2893493)

**Signalment:** 1-2 month old female, Holstein, Bovine.

**History:** Calf is from a commercial 2,000-head calf farm that has had approximately 20 calves in the past week appear weak one day and found dead the next. They are fed unpasteurized withheld whole milk usually from cows being

treated for mastitis. This calf was reported "skinny", semi-comatose and the joints appeared slightly swollen.

**Gross Pathology:** None reported.

**Laboratory Results:** Bacterial isolation: *Listeria monocytogenes*.

**Contributor's Morphologic Diagnoses:** Acute multifocal necrotizing, purulent hepatitis and multifocal purulent interstitial nephritis.

**Contributor's Comment:** Scattered randomly through out the liver are numerous large and sometimes coalescing foci of necrosis with intense infiltrate of neutrophils and mononuclear cells. With special stains many small gram-positive bacilli are evident in the foci of necrosis and inflammation. In the kidney there are a few scattered cortical and medullary interstitial infiltrates of neutrophils. The histologic lesions are compatible with visceral listeriosis. Bacterial culture supports the diagnosis.

The pathogen, *Listeria monocytogenes* is a gram-positive facultative intracellular bacillus found in the environment and soil. Ingestion and traumatic penetration of the mucosa or skin are considered routes of infection[1]. It affects many species and is a public health concern for humans[2]. In ruminants the sporadic disease occurs in three, seldom overlapping syndromes: septicemia with visceral miliary abscesses, encephalitis and infection of the pregnant uterus with abortion [3].

In this case, the disease appeared to affect several herd mates and had a fairly sudden onset. The brain was not available for examination.

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**AFIP Diagnoses:**
1. Liver: Hepatitis, necrotizing, acute, random, marked, with bacilli, Holstein, bovine.
2. Kidney: Nephritis, necrotizing, acute, multifocal, marked, with bacilli.

**Conference Comment:** The contributor mentions three syndromes associated with *Listeria monocytogenes* infection: encephalitis, abortion, and septicemia; in addition, conjunctivitis and mastitis have also been described. Human infections caused by *Listeria monocytogenes* are usually the result of food-borne outbreaks and manifest as encephalitis, abortion, or septicemia.[7]

The encephalitic form is also known as "circling disease", based on the clinical signs associated with brainstem lesions. Ruminants become infected when eating

silage that is poorly preserved, which favors listerial survival. Rather than hematogenous spread, evidence suggests that the pathogenesis of the encephalitic form involves local invasion through a defect in the oral mucous membranes, followed by migration along the trigeminal nerve to the brainstem. The typical histopathological findings are meningoencephalitis centered on the pons and medulla, with microabscesses and lymphocytic leptomeningitis. Trigeminal neuritis and ganglionitis are also described. Ruminants are most commonly affected, but listerial meningoencephalitis has also been reported in pigs, horses, and dogs.[1,4,5,6]

The abortion syndrome usually occurs late-term and does not cause systemic illness in the aborting ruminant. This syndrome is thought to occur via hematogenous spread where the organism localizes in the uterus, causing metritis and abortions.[1,5]

The septicemic disease causes miliary abscesses in multiple organs, principally the liver. It occurs most frequently in neonates and may be a continuation of an intrauterine infection. Septicemic disease has also been reported in pigs, rabbits, guinea pigs, chinchillas, and birds.[1,4,5]

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**References:**

1. Jubb K, Huxtable C: The nervous system. *In:* Pathology of Domestic Animals, eds. Jubb KVF, Kennedy PC, Palmer N, 4th ed., vol. 1, pp. 393-397. Academic Press, San Diego, California, 1993
2. Woo-Sam N: Listeriosis in a Holstein cow. Can Vet J **40**:506-508, 1999
3. Kidd A, Terlecki S: Visceral and cerebral listeriosis in a lamb. Vet Rec **78**(13):453-454, 1966
4. Summers BA, Cummings JF, de Lahunta A: Veterinary Neuropathology, pp. 133-135. Mosby, St. Louis, Missouri, 1995
5. McGavin MD, Carlton WW, Zachary JF: Thomson's Special Veterinary Pathology, 3rd ed., pp. 441-442. Mosby, St. Louis, Missouri, 2001
6. Jones TC, Hunt RD, King N: Veterinary Pathology, 6th ed., pp. 461-463. Williams and Wilkins, Baltimore, MD, 1997
7. Radostits OM, Gay CC, Blood DC, Hinchcliff KW: Veterinary Medicine, 9th ed., pp. 736-741. W.B. Saunders, London, England, 2000

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**CASE III - 03-5830 01 (AFIP 2888628)**

**Signalment:** Seven-year-old spayed female ferret (*Mustela putorius furo*).

**History:** This animal was owned by a small zoo for its entire life, and had no previous significant health problems. It presented to the referring veterinarian after a one-week history of diarrhea, with vomiting for one day. On physical examination, the animal was thin and dehydrated, with a palpable cranial abdominal mass, which was deemed non-operable upon exploratory laparotomy. The animal was subsequently euthanized.

**Gross Pathology:** At the root of the mesentery there was an approximately 5 cm diameter, firm, nodular, pale mass, with fibrous adhesions to several sections of intestine, and thickened, fibrotic mesentery. There were numerous, firm, 1 to 2 mm diameter, white masses throughout omentum and mesentery. A smaller, 1 cm diameter, pale pink, firm mass was present in the wall of a segment of colon.

Formalin-fixed sections of affected intestine and mesenteric lymph node were submitted for histopathologic examination.

**Laboratory Results:** None reported.

**Contributor's Morphologic Diagnosis:** Intestine: Mucin-producing intestinal adenocarcinoma with lymph node metastasis.

**Contributor's Comment:** There is diffuse infiltration and thickening of mesentery, subserosa and muscularis of multiple sections of intestine by a pleomorphic population of epithelial cells forming undulating ribbons and nests embedded between bands of proliferating fibrous connective tissue. In some areas, ribbons of cells form distinct tubules of varying diameter, some containing luminal pale eosinophilic material or granular, necrotic cellular debris. Most cells are polygonal, clustered in small groups or aligned along basement membranes, with scant basophilic cytoplasm, large round to ovoid nuclei, lacy basophilic chromatin and distinct nucleoli. Other cells are distended with pale basophilic mucin, with flattened, marginated nuclei, consistent with features of goblet cells. Sections of subserosa and muscularis are markedly expanded, with nests of cells between muscle bundles in muscularis and multifocal lymphatic invasion. Variably-sized lakes of wispy, pale basophilic mucin markedly expand invaded lymphatics and stroma, with suspended ribbons and tubules. There are scattered tubules in lamina propria of some sections. Moderate follicular aggregates of lymphocytes expand the mesentery. In the mesenteric lymph node there are ribbons and clusters of tubules formed by cells that invade subcapsular, cortical and medullary sinuses.

Primary intestinal neoplasia is generally uncommon in domestic species[1]. In ferrets, there are two brief references to intestinal tumors, but no published descriptions[2,3]. Mucus-producing or mucinous adenocarcinomas are seen with

variable frequency in many species, including dogs, cats, pigs and non-human primates[1]. In humans, this type comprises approximately 15% of colorectal tumors, commonly arising from rectum[4]. The primary tumor does not appear to be represented in the submitted tissues. However, the differentiation of this mass to mucin-producing cells suggests a possible colonic origin. Diagnosis of mucinous adenocarcinoma requires that greater than 50% of the mass be composed of mucin in cysts or extracellular pools, and might be properly applied to some areas of this neoplasm. Lymphatic metastasis is well demonstrated in this case, with spread of the tumor to regional lymph nodes, which is typical. The marked scirrhous mesenteric response to this tumor is also common to intestinal carcinomas.

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**AFIP Diagnoses:**

1. Small intestine and mesentery: Mucinous adenocarcinoma, ferret, mustelid.
2. Small intestine: Enteritis, lymphocytic, diffuse, severe, with villous blunting and fusion, and lymphangiectasia.
3. Lymph node: Mucinous adenocarcinoma, metastatic.

**Conference Comment:** In addition to the intestinal adenocarcinoma, conference attendees discussed the enteritis, which is characterized by marked expansion of the lamina propria and transmigration of the epithelium by lymphocytes. The severity of the lymphocytic response is an unusual finding in association with intestinal neoplasia in ferrets (Williams BH, personal communication). It is possible that, given the additional findings of lymphangiectasia and villous blunting and fusion, there may be concurrent inflammatory bowel disease. The inflammation, neoplasia, or both could cause the lymphangiectasia.

As noted by the contributor, there are very few reports of intestinal adenocarcinoma in ferrets.[3,5,7] Gastric adenocarcinoma, however, has been documented in ferrets and is reported to be associated with *Helicobacter mustelae* infection. Much like *Helicobacter pylori* infection in humans, *H. mustelae* causes increased gastric epithelial proliferation, presumably due to chronic inflammation. This suggests that gastric adenocarcinoma in ferrets may be a potential model for studying *Helicobacter* sp.-associated gastric carcinogenesis in humans.[6,7]

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**References:**

1. Head KW, Else RW, Dubielzig RR: Tumors of the alimentary tract. *In*: Tumors in Domestic Animals, ed. Meuten DJ, 4th ed., pp. 461-468. Iowa State Press, Ames, Iowa, 2002
2. Goad MEP, Fox JG: Neoplasia in ferrets. *In*: Biology and Diseases of the Ferret, ed. Fox JG, pp. 274, 281-282. Lea and Febiger, Philadelphia, Pennsylvania, 1988
3. Hoefer HL: Gastrointestinal diseases. *In*: Ferrets, Rabbits and Rodents: Clinical Medicine and Surgery, eds. Hillyer EV, Quesenberry KE, pp. 26, 33. W. B. Saunders Co., Philadelphia, Pennsylvania, 1997
4. Rosai J: Gastrointestinal tract. *In*: Ackerman's Surgical Pathology, p. 771. Mosby, St. Louis, Missouri, 1996
5. Li X, Fox JG, Padrid PA: Neoplastic diseases in ferrets: 574 cases (1968-1997). JAVMA **212**(9):1402-1406, 1998
6. Fox JG, Dangler CA, Sager W, Borkowski R, Gliatto JM: *Helicobacter mustelae*-associated gastric adenocarcinoma in ferrets (*Mustela putorius furo*). Vet Pathol **34**(3):225-229, 1997
7. Fox, JG: Biology and Disease of the Ferret, 2nd ed., pp. 333-334, 422-427. Lippincott Williams & Wilkins, Philadelphia, Pennsylvania, 1998

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**CASE IV - 2784/03 (AFIP 2899509)**

**Signalment:** Six-week-old calf, male, limousin, *Bos taurus*, bovine.

**History:** On an organic beef cattle farm two calves died in a short period at the age of 5-6 weeks without having any previous symptoms. This calf was found dead with foam in the mouth and nostrils. Earlier some of the newborn calves had been weak, some had died.

**Gross Pathology:** Normal body condition. Heart muscle mottled and pale. Multiple scars in the myocardium. Lung oedema. Marked, symmetrical enlargement of both lobes of the thyroid gland.

**Laboratory Results:** None reported.

**Contributor's Morphologic Diagnoses:**
Thyroid gland: diffuse hyperplasia, lack of colloid. Hyperplastic goiter.
(Myocardium, not submitted: myocarditis, multifocal, chronic, fibrotizing with multiple fibrotic scars.)

**Contributor's Comment:** Goiter is a non-neoplastic and noninflammatory enlargement of the thyroid gland. It is caused by iodine deficient diet, goitrogenic compounds that interfere with thyroxinogenesis or genetic enzyme defects in the

biosynthesis of thyroid hormones. These factors result in inadequate thyroxine synthesis and decreased blood levels of thyroxine and triiodothyronine. This is detected by hypothalamus and pituitary gland. They increase the secretion of thyrotropin, which results in hypertrophy and hyperplasia of the follicular cells of thyroid gland. Paradoxically also dietary iodine excess can cause goiter.[1]

In cattle the most prominent clinical signs of goiter are abortion, stillbirth and weakness in newborn calves. Newborn animals show thyroid gland enlargement. The thyroid gland can be so large that it compresses the large blood vessels in the region of the neck, causing haemostasis in the neck and the cranium and pressure on the larynx and trachea resulting in dyspnoea and high heart and breathing rates. The neck can be oedematous and swollen. Calves seem to be more resistant than lambs, pigs and goats, and they may recover if they survive the calving and the first two days but often they need special veterinary care. In adults thyroid gland enlargement is rather rare. Loss of libido in bulls and failure to express estrus in cows can be observed.[1,2,3]

Gross pathology of the goitrous thyroid gland usually shows symmetrical enlargement of both lobes of the gland. In cattle, the isthmus is also wider. In hyperplastic goiter, the thyroid gland is darker due to hyperaemia and the lobular structure is more expressed.[3]

Histologically the follicles of the thyroid gland are irregular in size and shape because of varying amounts of colloid in lumen and some are collapsed due to lack of colloid. The follicles are lined by single or multiple layers of hyperplastic follicular cells which may form papillary projections into the lumen of some follicles. The epithelial cells are columnar, the cytoplasm is eosinophilic and the nuclei are small and hyperchromatic. The nuclei are often situated in the basilar part of the cell. The changes can be observed throughout the thyroid gland.[1]

The death of this animal was caused by cardiac failure caused by chronic fibrotizing myocarditis. However, the herd problem was iodine deficiency causing goiter.

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**AFIP Diagnosis:** Thyroid gland: Hyperplastic goiter, limousin, bovine.

**Conference Comment:** The contributor gives a concise review of the pathogenesis, clinical signs, and gross and histologic findings with diffuse hyperplastic goiter. Colloid goiter represents the involutionary phase of diffuse hyperplastic goiter. With resolution, T3 and T4 serum levels return to normal and stimulation of TSH is diminished. Follicles, however, continue to progressively distend with colloid

because TSH-induced endocytosis of colloid is reduced. Grossly colloid goiter, like diffuse hyperplastic goiter, causes diffuse enlargement of the thyroid gland, but the thyroid gland is more translucent and lighter in color than hyperplastic goiter. This difference in gross appearance is due to reduced vascularity and to distension of macrofollicles with colloid. The follicular cells lining the distended follicles become flattened, inactive, and atrophic, with a smooth interface between the colloid and the luminal surface of epithelial cells.[1,4]

Goiter may be caused by iodine deficiency or, paradoxically, iodide excess. Some causes of iodine deficiency include goitrogenic plants (white clover, rape, kale), goitrogenic compounds (sulfonamides, thiouracil), or an iodine deficient diet. Iodide excess causes goiter because high blood iodide interferes with thyroxinogenesis and leads to low blood thyroxine levels with a compensatory increase in pituitary TSH secretion. In addition, excess iodine interferes with the proteolysis of colloid in thyroid follicular cells and blocks the release of T3 and T4.[1,4]

Congenital dyshormonogenetic goiter is an inherited disorder of thyroid hormone synthesis and secretion in sheep (Corriedale, Dorset Horn, Merino, and Romney breeds), Afrikander cattle, and Saanen dwarf goats. The thyroid lobes are symmetrically enlarged at birth and these animals have clinical signs of hypothyroidism, including subnormal growth rate, rough sparse hair coat, myxedema, weakness, and sluggish behavior. Histologically, there is diffuse hyperplasia of follicular cells and follicles are lined by tall columnar epithelium; however, follicles are collapsed due to marked endocytosis and lack of colloid.[1,4]

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**References:**

1. Jubb KVF, Kennedy PC, Palmer N: Pathology of Domestic Animals, 4th ed., vol. 3, pp. 315-319. Academic Press, San Diego, California, 1993
2. Radostits OM, Blood DC, Gay CC: Veterinary Medicine, 8th ed., pp. 1395-1397. W.B. Saunders, London, England, 1994
3. Durdevic D, Stojic V, Jovanovic M: Enzootic congenital goiter in calves. I. Etiology, clinical and pathohistological findings. Acta Veterinaria (Beograd), **42**(2-3):85-92, 1992
4. Capen CC: Endocrine system. *In*: Thomson's Special Veterinary Pathology, eds. McGavin MD, Carlton WW, Zachary JF, 3rd ed., pp. 298-300. Mosby, St. Louis, Missouri, 2001

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*Sponsored by the American Veterinary Medical Association, the American College of Veterinary Pathologists and the C. L. Davis Foundation.