CASE I - 991622.4 (AFIP 2739904)

Signalment: Canine, Brie sheepdog, male, 14 week-old.

History: This dog was presented for polyuria-polydipsia, emaciation, prostration, vomiting, and terminal seizures.

Gross Pathology:
Remarkable lesions were:
- A diffuse thickening of the cranial bones and of the mandible (Figures 1 and 2).
- An elasticity of the same bones as well as the ribs.
- Both kidneys appeared retracted, deformed and fibrous (Fig. 3).
- Parathyroids were enlarged (Fig. 4).

Laboratory Results:
Clinical investigations revealed:
- BUN > 4g/l; creatinine > 200mg/l
- Aregenerative anemia (Hb = 7.2g/100ml, reticulocytes = 0/l).

Contributor’s Morphologic Diagnosis: Congenital renal dysplasia (primitive lesion) bilateral, fibrous osteodystrophy, Brie sheepdog, canine.
Some mandibular sections contain a tooth with its alveolus.

Contributor’s Comment: Renal lesions consist of immature (fetal-like structures) glomeruli throughout the cortex and dilatation of Bowman’s spaces. There is a separation of renal tubules by immature connective stroma minimally infiltrated by inflammatory cells (lymphocytes and plasmocytes). Many tubules are atrophic or
dysplastic. Some sections reveal focal calcifications in tubules as well as some luminal granular eosinophilic casts. No cartilage nodules are noted.

Bone tissue of the mandible shows osteopenia (trabecular paucity) with osteolysis and medullary fibrosis (immature connective tissue). The number of osteoclasts is greatly increased; the associated trabecular surface is particularly eroded (numerous Howship’s lacunae). In this disorganized tissue, we can observe osteoid material surrounded by some activated osteoblasts (particularly in some sections around the tooth alveolus).

The diagnosis of renal dysplasia was made based on the macroscopic appearance of kidneys and histological appearance of mesenchymal tissue with primitive tubules. Although the dog is 14 weeks old, this lesion is interpreted as a primitive dysplastic lesion because immature glomeruli are not merely present in the subcapsular zone. Secondary hyperparathyroidism is confirmed by the hyperplasia of parathyroids and fibrous osteodystrophy.

AFIP Diagnoses:
1. Kidney: Dysplasia with diffuse severe fibrosis, fetal glomeruli, and tubular adenomatous hyperplasia, Brie sheepdog, canine.

Conference Comment: Renal secondary hyperparathyroidism, or renal fibrous osteodystrophy, is a complex syndrome caused by elevated parathyroid hormone levels in response to hypocalcemia. It is initiated by decreased glomerular filtration rate and the resultant inability to excrete phosphate, and inadequate production of 1,25-dihydroxycholecalciferol (calcitriol). Hyperphosphatemia, due to the mass law effect, results in concomitant hypocalcemia which stimulates the parathyroid glands to secrete parathyroid hormone (PTH). Parathyroid hormone acts principally on the bone and kidney. Parathyroid hormone stimulates bone resorption and mobilization of calcium stores, resulting in the characteristic marked softening of bones and replacement with fibrous connective tissue. The diseased kidney is unable to facilitate production of calcitriol, which normally suppresses PTH secretion, thus impairing this negative feedback system allowing the parathyroid glands to continue to produce PTH. In addition, hyperphosphatemia inhibits calcitriol production. With time, continued stimulation of PTH secretion causes parathyroid chief cell hyperplasia (renal secondary hyperparathyroidism).7-9

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References:

CASE II - 03-7103 (AFIP 2908326)

Signalment: 17- week old, female B6.129S6-Cybb<sup>tm1Din</sup> mouse (<i>Mus musculus</i>).

History: This mouse was from a production colony maintained in conventional housing at The Jackson Laboratory. The mouse was submitted to the diagnostic laboratory because it was found to be thin with a submandibular mass.

Gross Pathology: There was a solitary, white, 1.4 x 1.0 cm, subcutaneous, multinodular mass containing pale yellow amorphous material. The lungs had multiple, randomly distributed, raised, white nodules of various sizes up to 2 mm in diameter.

Laboratory Results: Bacterial culture positive for <i>Staphylococcus</i> sp. coagulase negative.

Contributor’s Morphologic Diagnoses:
1. Tongue, mandible and adjacent soft tissue: Myositis, osteomyelitis and periodontitis (some sections), severe, multifocal, pyogranulomatous with intra-lesional Splendore-Hoeppli material centered on bacterial colonies.
2. Lymph node: Lymphadenitis, severe, multifocal, pyogranulomatous with intra-lesional Splendore-Hoeppli material and plasmacytosis.

**Contributor’s Comment:** The B6.129S6-Cybb<sup>tm1Din</sup> mouse was generated by the targeted disruption of the gp91<sup>phox</sup> gene<sup>1</sup>. This gene is located on the X chromosome and encodes the β subunit of the phagocyte oxidase cytochrome b 558. Oxidase cytochrome b is a membrane component of NADPH oxidase, which generates superoxide, a critical component in the process known as the respiratory burst. The absence of respiratory-burst-derived oxidants in phagocytes results in defective microbicidal activity. Neutrophils and macrophages from Cybb<sup>tm1Din</sup> hemizygous male and heterozygous females mice lack respiratory burst oxidase activity<sup>1</sup>. The lesions in the Cybb<sup>tm1Din</sup> mouse have previously been described<sup>2</sup>.

The lungs of this mouse also had acidophilic macrophage pneumonia, characterized by the presence of large numbers of alveolar macrophages many containing eosinophilic, Ym1 crystals<sup>3</sup>. Acidophilic macrophage pneumonia has previously been reported in Cybb<sup>tm1Din</sup> mice and is a prominent lesion in motheaten mice (Hcph<sup>me</sup>/Hcph<sup>me</sup>). Hcph encodes the SHP-1 protein-tyrosine phosphatase, which is expressed primarily in hematopoietic cells. SHP-1 is a critical negative regulator in multiple signaling pathways in the hematopoietic and immune systems. Interestingly, in undifferentiated myeloid cells SHP-1 activity has been shown to decrease transcription of Cybb<sup>4</sup>.

Pyogranuloma formation with intra-lesional Splendore-Hoeppli material is a background lesion found in some mice housed in our conventional facilities. While the lesion is often more extensive in immunodeficient mice such as the Cybb<sup>tm1Din</sup> mouse, it is also found in immunocompetent mice. The pathogenesis of pyogranuloma formation in these mice is unknown. However, we believe that the nidus for such lesions may be a hair foreign body secondary to grooming activity. Penetration and disruption of the oral mucosa facilitates the spread of bacteria into adjacent structures. Generally these lesions involve the cervicofacial tissues with spread to cervical lymph nodes and on occasion as this case demonstrates lymphogenous spread to the lungs. Coagulase-positive *Staphylococcus aureus* is the bacteria most commonly associated with botryomycosis, however in our mice coagulase-negative *S. hominus* and *S. xylosus* are most frequently recovered.
AFIP Diagnoses:
1. Mandible, tongue, skeletal muscle, and tooth: Osteomyelitis, glossitis, myositis, and periodontitis, pyogranulomatous, focally extensive, severe, with Splendore-Hoeplli material, and colonies of cocci, B6.129S6-Cybb<sup>tm1Din</sup> mouse, rodent.
2. Lung: Bronchopneumonia, neutrophilic, multifocal, marked, with Splendore-Hoeplli material, and colonies of cocci.
3. Lung: Numerous intra-alveolar macrophages with eosinophilic intracellular crystals.

Conference Comment: Some slides also contain lymph node with a similar pyogranulomatous inflammatory infiltrate.

Botryomycosis is a term used to describe the chronic granulomatous infection caused by coagulase-positive staphylococci, most commonly <i>Staphylococcus aureus</i>. These lesions usually follow some type of skin trauma and begin as microabscesses around a small colony of organisms and may progress to large granulomas. The colonies are often imbedded within Splendore-Hoeplli material, which represents antigen-antibody complexes, and forms a characteristic, radiating corona of brightly eosinophilic, homogenous club-shaped bodies. Macroscopically, the bacterial colonies and Splendore-Hoeplli material are described as “grains”, or tiny white granules present within purulent exudate.  

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References:
CASE III - 1795/02 (AFIP 2888772)

Signalment: 4-month old male fennec, *Vulpes zerda* (Zimmermann, 1780).

History: In a litter of five captive-born fennecs of a zoological park in Southern Germany, increased incidence of respiratory problems and weight loss were observed. Animals were treated with penicillin, streptomycin, dexamethasone and furosemide, without any clinical improvement. The clinician noted microclimatic problems (smell) in the kennel. Within one week, two animals were euthanized due to deterioration of their body condition and resistance to therapy. Both were submitted for necropsy. One year ago the same symptoms had occurred in a litter of fennecs of the same zoological park, but the patients had recovered after antibiotic treatment.

Gross Pathology: One animal was emaciated (800g) and exhibited purple, firm and atelectatic cranial lung lobes. Bronchi were filled with mucus and edema fluid. Caudal lung lobes were emphysematous. Other organs were unaltered. The second animal exhibited numerous 10-20 mm filiform nematodes in the trachea and bronchi.

Laboratory Results: Large amounts of parasite eggs compatible with *Capillaria* sp. were found in the feces. Microbiological examination of the first animal did not lead to isolation of pathogenic bacteria.

Contributor’s Morphologic Diagnoses:

1. Lung: Pneumonia, pyogranulomatous and eosinophilic, focally extensive, severe, with adult nematodes and numerous bipolar plugged, embryonated eggs within alveoli consistent with *Capillaria aerophila*; alveolar hemorrhage, multifocal, moderate, fennec, *Vulpes zerda*, canidae.
2. Bronchi and bronchioli: Bronchitis and bronchiolitis, lymphoplasmacytic and histiocytic, multifocal, severe, chronic, with bronchiectasia, peribronchial fibrosis and intraluminal adult nematodes and nematode eggs, fennec, *Vulpes zerda*, canidae.

Contributor’s Comment: A fennec is a small member of the genus Vulpes which populates the desert of Sahara and the peninsula of Arabia and Sinai. These small smart foxes are often kept in zoological parks.

*Capillaria aerophila* (Creplin, 1839), an aphasmid worm, is a lung parasite of foxes, badgers, martens, hedgehogs, cats, dogs and, occasionally, humans\(^1\).\(^6\).
Germany, about 72% of necropsied free-ranging red foxes (*Vulpes vulpes*) and 0.9% of stray cats are affected[^4,^6]. In the UK and Spain, a prevalence between 0.24 and 67.2% was reported[^2,^5]. *Capillaria aerophila* infestation is a common health problem in fox farms[^6]. *Capillaria aerophila* were also found in arctic foxes, Tsushima leopard cats, racoons, bobcats, coyotes, black bears and opossums. Male *Capillaria aerophila* worms are about 16-25 mm and females are 25-32 mm in length. Adult parasites live in the trachea and bronchi, sometimes in the nasal cavity or the paranasal sinuses of the host[^6]. Histologically, a characteristic feature of aphanid worms is distinct hypodermal lateral cords (bacillary bands) and a row of esophageal gland cells called stichocytes that form a stichosome. In contrast to phasmids, females have only one genital tract[^3]. Eggs are released into the environment via the respiratory and alimentary tract of the host and develop well in humid soil. The life cycle is not known but is considered as direct or, more likely, indirect. Earthworms have been considered as intermediate hosts. After ingestion of infected earthworms, larvae migrate via lymphatics and blood vessels to the lung within 7 days. The prepatent period is about 4 weeks and the patent period is 10 to 11 months long[^6].

In general, mild infestations remain clinically inapparent or induce a mild bronchitis. With severe infestations, however, bronchitis, tracheitis and rarely rhinitis and sinusitis are observed. Secondary bacterial infections are common. Infected animals show coughing, sneezing, reduced general state of health, cachexia and anemia[^6].

An aetiological diagnosis is feasible by demonstration of embryonated, bipolar and plugged eggs in feces and tracheal mucus. The outer egg wall is structured, which renders the differentiation between *Capillaria* sp. and *Trichuris* sp. possible. Another parasite in the paranasal sinus of foxes and sometimes of dogs is *Capillaria boehmi* (Supperer, 1953)[^3,^6].

Respiratory problems often occur in litters kept in kennels with inadequate microclimate. In the present case, all members were affected. It can be hypothesized that a massive accumulation of infectious larvae in the environment leads to the severe nematode load, whereas adults are often subclinically infected and serve as reservoir.

Other parasites in the respiratory tract of carnivores are *Crenosoma vulpis* (dogs, foxes), *Crenosoma globel* (raccoons), *Crenosoma mephiditis* (skunks); *Crenosoma striatum* (hedgehogs), *Filaroides osleri* and *Aleurostrongylus abstrusus* (cats).
AFIP Diagnosis: Lung: Bronchopneumonia, chronic-active and eosinophilic, multifocal, severe, with hemorrhage, bronchiolar epithelial hyperplasia, and intraepithelial and intraluminal aphasmid adults and eggs, fennec fox (*Vulpes zerda*), canine.

Conference Comment: This case was reviewed in consultation with Dr. Chris Gardiner, AFIP consultant in veterinary parasitology. The contributor gives a concise review of the morphologic and clinical characteristics of *Capillaria aerophila*. An important feature of *Capillaria* sp. is its intraepithelial location in the host. Other intraepithelial nematodes include *Trichosomoides crassicauda*, *Gongylonema* sp., and *Anatrichosoma* sp.

Adult female *Trichosomoides crassicauda*, also known as the bladder threadworm, parasitize the urothelium of rats. Adult males are much smaller and live within the lumen of the urinary tract, or within the uterus of the female. *Gongylonema* sp. affect ruminants, pigs, horses, nonhuman primates, and occasionally rodents. They are characteristically seen as thin, red, serpentine nematodes imbedded in the esophageal mucosa. *Anatrichosoma* sp. are found in the nasal epithelium of nonhuman primates where infection is usually subclinical. Grossly, lesions may be characterized by white, serpentine tracks on the palms of the hands or soles of the feet caused by adult parasite migration through the epithelial/subepithelial layers of the skin, which has been described as creeping eruption.

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References:
CASE IV - 0065 296 (AFIP 2900352)

Signalment: About 800-day old female Sprague-Dawley rat.

History: The rat was a control from a carcinogenicity study with a restricted access to rodent diet (17 g/day) and daily gavage with 0.4% methylcellulose. A small mammary gland mass was found on Day 722. The rat was sacrificed on Day 731 in good condition, at the terminal necropsy.

Gross Pathology: Principal findings included 15 x 15 mm, smooth, firm, pedunculated mass attached to the right side of the enlarged (20 x 5 mm) uterine body, a 25 x 25 mm mammary gland mass, small thymus, right pulmonary adhesions, enlarged dark-red adrenal glands, and bilateral cage sores.

Laboratory Results: Hematologic laboratory results were within normal limits.

Contributor’s Morphologic Diagnoses:
1. Malignant uterine granular cell tumor (GCT).
2. Hypertrophy of the uterine body and cervix (portio vaginalis uteri).

Other principal findings (slides not included) were mammary gland adenocarcinoma, unilateral pheochromocytoma, hepatocellular basophilic focus, focal hepatic angiectasia, minimal foreign body bronchopneumonia and focal pleural fibrous adhesions consistent with the sequela of a gavage accident, focal C-cell hyperplasia of the thyroid gland, severe thymic and mild ovarian atrophy consistent with aging, hypercellular bone marrow and mild pododermatitis. Pituitary gland was not available for examination.
Contributor’s Comment: An expansile, circumscribed, spherical, not encapsulated mass, except for a single layer of squamous epithelium covering the surface, was attached over a small area to the uterine body. The mass consisted of a uniform population of large cells with abundant granular cytoplasm, indistinct cellular borders, small, round, dark, centrally located nuclei with indistinct nucleoli, and eosinophilic collagenous matrix. Dissociation of cells, foci of hemorrhage, occasional apoptotic bodies and mitotic figures, proliferating blood vessels and a few mast cells were evident. The boundary between the tumor and uterine wall was irregular as the tumor infiltrated the outer layer of the myometrium. The large size of the tumor, cellular dissociation, occasional apoptotic bodies, mitotic figures and areas of hemorrhage suggested a malignant variant\(^6\). No regional or distant metastases were found.

Age-related endometrial stromal fibrosis and hypertrophy of the uterine body and cervix were the cause of the enlargement of the uterine body\(^4\).

Histological methods for characterization of granular cell tumors (GCTs), including electron microscopy (for detection of basal lamina and desmosomes characteristic of Schwann cell); application of the immunohistochemical markers S-100, neuron-specific enolase, and glial fibrillary acid protein (antigens related to cells of neural crest), muramidase (histiocyte-associated antigens), desmin (muscle-associated antigens), and vimentin (connective tissue associated antigens); and periodic acid-Schiff (PAS) with diastase digestion, were not utilized. Granular cell tumors are usually positive for NSE, S-100 and vimentin, variably positive for desmin and muramidase, and negative for GFAP. Cytoplasmic granules are PAS positive and diastase resistant\(^3,11\).

Granular cell tumors and granular cell foci occur spontaneously in various species, tissues, and organs, and were described for the first time in 1854 by Weber\(^1\) and in 1926 by Abricossoff\(^2\). The first uterine GCT in a rat was characterized in 1991 by Nyska et al.\(^8\). In rats, GCTs are usually found in the meninges, uterus and vagina\(^9\). In humans, as in rats, they are rare, more common in middle aged females\(^7\), and appear as solitary or multiple, small nodules in the dermis, subcutis, tongue, breast, in the respiratory tract, esophagus, ovary, cervix and vulva. The characteristics of GCT (dermal “myoblastoma”) from a female patient\(^11\) and of 13 vulvar tumors\(^1\) paralleled those of the typical GCT of the rat.

The positive correlation between the occurrence of granular cell alterations and estrogen levels has been proposed\(^5\). For example, in a study using Donryu rats, known for age-related increases in estrogen-to-progesterone ratio, granular cell foci were found in 11/855 rats in the endometrial stroma (lamina propria) of the uterine horns\(^9\).
The etiology of the GCT is not known, but several authors suggest a neuroectodermal origin, common to both the GCT and Schwannoma. Thus the GCT may arise from neoplastic Schwann cells, and from the pituicytes (modified astrocytes) of the pars nervosa\textsuperscript{2,10}. At first human granular cell tumor was thought to be a granular cell myoblastoma\textsuperscript{2}; however, the histochemical and ultrastructural evidence indicated a relationship with the peripheral nerve sheath tumors and some are associated with small nerves\textsuperscript{7}. It has been suggested that the PAS-positive, diastase digestion-resistant cytoplasmic granules are the secondary lysosomes\textsuperscript{3} containing some insoluble polysaccharide\textsuperscript{2}.

\textbf{AFIP Diagnoses:}
1. Uterus: Granular cell tumor, Sprague-Dawley rat, rodent.
2. Portio vaginalis uteri\textsuperscript{4}: Hypertrophy, marked.

\textbf{Conference Comment:} As mentioned by the contributor, a characteristic feature of granular cell tumors is the presence of PAS positive, diastase resistant cytoplasmic granules. Ultrastructurally, granular cell tumors contain densely packed lysosomes and phagosomes (myelin figures). Differential diagnoses for other tumors with granular cytoplasm include oncocytoma and rhabdomyoma. Features that differentiate these from granular cell tumors were discussed. The cytoplasmic granules in oncocytomas are due to the presence of numerous mitochondria, an ultrastructural feature that is diagnostic for that tumor. Rhabdomyomas are immunohistochemically desmin and myoglobin positive and are ultrastructurally characterized by intracytoplasmic myofibrils and Z lines.\textsuperscript{12,13}

As mentioned by the contributor, the primary sites for granular cell tumors in rats are the meninges and uterus. In dogs, granular cell tumors primarily affect the tongue. In horses, granular cell tumors are the most commonly reported primary lung neoplasm. They are generally adjacent to, and often invade, bronchi and bronchioles.\textsuperscript{14}

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\textbf{References:}

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