CASE I: Z16753 (AFIP 3138054).

**Signalment:** 5-year-old, female, American Staffordshire terrier dog (*Canis familiaris*).

**History:** The dog presented with imbalance, a stiff gait, urinary incontinence, anorexia, inappetence and lethargy. Electromyography showed lesions at the promixal muscles of the forelimbs and the masticatory muscles. MRI revealed no abnormalities. On radiographic examination, masses were detected in the lung, multiple ribs and the dorsal processes of T2 and T5. Osteophytes were seen radiographically on the forelimb and scapulae.

**Gross Pathology:** Numerous flat, subperiostal, bony proliferations were detected on the diaphysis and metaphysis of humeri, scapulae, femora and tibiae. These dense proliferations varied in size from 3 mm to 2 cm in length. Multiple irregular, osseus proliferations were present on several ribs, processus dorsalis of T2 and T5 and corpus spinalis of L2. The anteroventral lung lobes showed bilaterally poorly demarcated, infiltrative growing, firm, white-tan masses.

**Histopathologic Description:** Rib. Two main lesions are present. The first consist of circumferential proliferation of trabecular woven bone perpendicular to the cortex (periosteal new bone formation). The cortical bone is decreased in thickness and shows a high porosity (osteopenia). Within the medullary cavity, a neoplastic mass is present (second lesion). It consists of neoplastic cells showing papillary growth in the existing bone marrow. There is an increase in fibrous tissue. Neoplastic cells are cuboidal to polygonal, 20 \( \mu \)m in diameter with a moderate amount of eosinophilic, poorly demarcated cytoplasm. The nucleus is round with a single prominent nucleolus and finely stippled chromatin. There is marked anisokaryosis and anisocytosis. The mitotic index is 1 per HPF. Multifocally, there are numerous islands of tumor cells with central necrosis and infiltration of neutrophils.

**Contributor’s Morphologic Diagnosis:** Reactive periosteal new bone formation. Bone metastasis of papillary adenocarcinoma. Lesions consistent with pulmonary hypertrophic osteopathy.

**Contributor’s Comment:** Hypertrophic osteopathy is also known as hypertrophic pulmonary disease and is characterized by new bone formation along the distal parts of the limbs. It occurs in humans and several animal species. Unlike in humans, where the condition is also called “hypertrophic osteoarthropathy,” articular surfaces are not affected in animals. It is a paraneoplastic condition generally associated with a lesion located in the thoracic cavity. In dogs it has been described in association with renal pelvis carcinoma(1,3), congenital megaesophagus(6), parasitic infection(4) and endocarditis.(2) Hypertrophic osteopathy is considered to be a reversible condition if the underlying lesion is corrected. The pathogenesis of the condition is still unclear.(2)

**AFIP Diagnosis:** Bone, rib: Carcinoma, metastatic.

**Conference Comment:** In concurrence with the contributor, conference participants identified a metastatic carcinoma, and many, including the conference moderator, favored the contributor’s more specific diagnosis of metastatic adenocarcinoma based on the formation of vague tubules within the neoplasm. In the absence of a clinical history, other participants suspected a metastatic transitional cell carcinoma based on the presence of “signet ring cells” among the neoplastic population; given the history of urinary incontinence and presence of metastasis to the thoracic vertebrae, this remains a reasonable possibility. While very common in humans, metastatic bone disease
is considered rare in domestic species, with carcinomas of the mammary gland, thyroid gland, prostate gland, ovary, and lung being the most common sites of origin. Ultimately, we favored the less specific diagnosis of carcinoma based on the histologic features in the preponderance of slides available for evaluation, including the absence of distinct tubules in most sections. Additionally, some slides contain multinucleate neoplastic cells.

Conference attendees carefully considered the contributor’s diagnosis of hypertrophic osteopathy (HO); however, most participants interpreted the florid periosteal new bone as a reactive lesion secondary to invasion by metastatic carcinoma cells, rather than the paraneoplastic condition of hypertrophic osteopathy, for the following histologic and clinical reasons:

1. In the submitted case, the vast majority of the pre-existing cortical bone is lost and replaced by woven bone, and there are moderate numbers of osteoclasts within Howship’s lacunae, indicating active bone resorption. By contrast, in HO, pre-existing lamellar cortical bone generally remains intact, with the formation of periosteal trabeculae of new woven bone oriented perpendicular to the cortex.
2. In many of the submitted slides, there is both endosteal and periosteal new bone growth, which is best appreciated at low magnification; endosteal new bone growth is not typical of HO.
3. The rib is not a predilection site for the development of HO lesions. Periosteal new bone formation attributed to the condition of HO is typically confined to the limbs, and preferentially affects the metacarpals, metatarsals, radius, ulna, and tibia, with sparing of the articular surfaces, upper limbs, and phalanges.

While we cannot exclude the possibility of HO at other anatomic sites in this dog, the contributor’s gross description of bony proliferation exclusively affecting the bones of the upper limbs would be highly unusual, because HO classically spares the upper limbs, or affects them late in the disease process following initial and more severe lesions on the distal limbs. We thank the contributor for submitting this very interesting and edifying case.

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References:

CASE II: 07-161 (AFIP 3103929).

Signalment: Adult male Long-Evans rats (Rattus norvegicus).

History: As part of a cerebral aneurysm study, rats were made hypertensive by ligation of left renal artery, fed a high salt diet, and implanted with pellets of deoxycorticosterone acetate (DOCA). To further cerebral aneurysm formation, the right carotid artery was surgically occluded, and rats were fed beta-aminopropionitrile (BAPN). Animals had been on study for at least two months at the time of death.

Gross Pathology: On radiographs and gross examination bilateral irregular firm white nodular masses, approximately 4 x 5 x 7 mm, were noted on the medial proximal femoral diaphyses and at the site of insertion of the pectineus and adductor longus muscles. The masses were intimately associated with these muscles. Both rats died of exsanguination due to ruptured abdominal arterial aneurysms and hemoabdomen.
Histopathologic Description: Submitted is a longitudinal section of the proximal femur including femoral head and adjacent soft tissues. Arising from the proximal medial cortex of the diaphysis and separating, surrounding and dissecting myocytes of adjacent skeletal muscle is a nodular, unencapsulated, moderately cellular mass consisting of short streaming bundles of plump spindloid cells in a coarse fibrous matrix. There is a well-differentiated proliferation of immature and mature bone adjacent to the cortex, which is multifocally absent (remodeling). These proliferations often incorporate hematopoietic elements within marrow spaces. In some sections, there are foci of hyaline cartilage, some of which transition to bone. At the soft tissue edges of the mass, there are numerous haphazardly arranged, variably sized, but generally small, spicules of osteoid. Spindle cells are plump with a proliferative appearance, but are cytologically relatively bland. There is minimal anisocytosis or anisokaryosis, and mitotic figures are rare (one per ten 400x HPF). There is secondary atrophy of entrapped myocytes.

Contributor’s Morphologic Diagnosis: Femurs, proximal, bilateral, periosteal fibroplasia, florid, atypical, with cartilaginous and osseous differentiation and marrow formation (exostoses), chronic, moderate to severe, consistent with osteolathyrism.

Contributor’s Comment: Beta-aminopropionitrile (BAPN) is a principle toxic agent of the sweet pea, *Lathyrus odoratus*, and is an irreversible inhibitor of lysyl oxidase.(5) Lysyl oxidase is required for the oxidative deamination of hydroxylysine residues in collagens and lysine residues in collagens and elastin. These deaminated aldehyde derivatives form spontaneous intermolecular covalent bonds, cross-linking molecules and providing strength. Copper is a necessary cofactor for lysyl oxidase, and thus copper deficient diets result in functional inhibition of lysyl oxidase. BAPN intoxication and copper deficiency are phenotypically similar, although BAPN does not produce anemia.

Yeager and Hamre provide excellent descriptions of the evolution of the lesions of osteolathyrism.(7) Briefly, the exostoses develop at the site of the insertion of the tendons of the pectineus and adductor longus muscles on the periosteum of the femur through two distinct phases. In the preliminary proliferative stage, the inner layer of the periosteum becomes a highly cellular and less organized mass of tissue resembling a fibroma or fibrosarcoma. The second osteogenic stage occurs as soon as 7 to 8 days after initiation of a sweet pea diet, and consists of intramembranous ossification at the periphery of the mass. No distant metastases were noted in any osteolathyrism studies, despite the infiltrative growth pattern, high cell density, and immature cytologic characteristics of the fibroblasts. Lesions may also develop at the deltoid ridge of the humerus, the gluteal trochanter of the femur, and the lamboidal ridge of the skull.

Although Yeager and Hamre observed no gross or histologic evidence of trauma at the site of the exostoses (7), additional studies noted that muscle tension was required for lesion development, as transected or denervated muscles failed to produce lesions, while lesions did develop at the sites of insertion of muscles that provided functional compensation for transected muscles.(1) Ponseti suggests that lifting of the periosteum is required for exostosis formation.(4)

AFIP Diagnosis: Long bone, femur, proximal epiphysis, metaphysis and diaphysis: Atypical periosteal fibroplasia, focally extensive, moderate to marked, with reactive new bone and osseous metaplasia.

Conference Comment: The contributor provides an excellent review of the effects of BAPN in adult rats. Although this is a rare condition, the case provided an excellent exercise in descriptive pathology, and conference attendees found this to be a very challenging slide. For conference attendees, the predominant differential diagnosis was osteosarcoma based on the proliferation of spindled cells and presence of osteoid. Although a reasonable consideration, especially without knowledge of the case history, the bland nature of the spindle cells, paucity of mitotic figures, and the presence of well-differentiated bone containing normal bone marrow in the nodular masses are not consistent with osteosarcoma. The bilaterally symmetric distribution, of which conference attendees were not aware prior to the conference, also is more consistent with a non-neoplastic process.

In addition to the detailed description of the lesion provided by the contributor, the moderator and attendees noted foci of new bone formation in the area of the trochanteric fossa and the lateral aspect of the proximal femur. In agreement with the contributor’s description, the Armed Forces Institute of Pathology’s Department of Musculoskeletal and Soft Tissue Pathology summarized the lesion as a broad-based periosteal proliferation of new bone with a poorly-formed fibrocartilagenous cap and an overlying area composed of a large cellular proliferation of fibroblastic and myofibroblastic type cells that in one area blend with tendon and muscle cells; the possibility of an exuberant myofibroblastic reaction to an avulsive injury at a tendon insertion site was considered.
Ectopic ossification is the neoformation of non-neoplastic trabecular bone at extraosseous sites, and is distinct from ectopic or heterotopic mineralization, which lacks bone formation. Most occurrences of ectopic ossification are common, clinically insignificant findings, e.g. dural ossification (ossifying pachymeningitis) in aged dogs and ectopic bone formation in the lungs of dogs and cattle; or occur in the supporting stroma of certain neoplasms, such as mammary carcinoma in dogs. Two specific diseases associated with ossification of soft tissues are fibrodysplasia ossificans progressiva and myositis ossificans; the former is characterized by progressive, symmetrical ossification of the subcuticular and epimysial connective tissue of the neck, dorsi, and limbs. In contrast, myositis ossificans is characterized by localized and asymmetric lesions containing a peripheral zone of orderly maturation from fibrous tissue to mineralized osteoid, which is replaced by lamellar bone.(6)

The contributor provides a useful description of the effects of BAPN on lysyl oxidase and its similarity to the pathologic effects of copper deficiency. During the conference, the effects of BAPN and similar toxins produced by members of the genus *Lathyrus* on domestic animals and humans were discussed. The *Lathyrus* genus is composed of variety of species (e.g. *Lathyrus sylvestris*, *L. sativus*); toxins produced by this genus include BAPN (*L. odoratus*), diaminobutyric acid (*L. sylvestris*), and beta-oxalyl-diamino-propionic acid (*L. sativus*). In limited amounts, *Lathyrus* species of legumes are a nutritious source of protein for domestic animals and humans; however, consumption of large quantities of these legumes over prolonged periods (weeks to months) results in the disease condition referred to as “lathyrism.” Because of the plant’s ability to survive in poor soils, flood and drought, outbreaks of lathyrism often occur in impoverished areas of the world during prolonged drought conditions.(3)

In contrast to rats, which develop skeletal deformities referred to as osteolathyrism, ingestion of *Lathyrus* spp. in humans and most domestic animals results in neurologic disorders termed neurolathyrism. Neurolathyrism is characterized by degeneration and loss of neurons in the spinal cord, resulting in gradual paralysis of the posterior limbs in cattle, horses, pigs, humans, and other species. Peripheral nerves, such as the vagus and recurrent laryngeal, are also affected. In cattle, toxicosis also leads to blindness, torticollis, and skin anesthesia. In horses, paralysis of the recurrent laryngeal nerve results in “roaring”. Horses and pigs appear to be more susceptible than cattle. Death usually results from respiratory paralysis. Teratogenic effects in sheep and other species and aortic aneurism in rats and turkeys are other pathologic effects of *Lathyrus* intoxication.(3)

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**References:**

5. Tinker D, Rucker RB: Role of selected nutrients in synthesis, accumulation, and chemical modification of connective tissue proteins. Physiol Rev 65:607-657, 1985
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**CASE III:** 14879-08 (AFIP 3113795),

**Signalment:** 9-year-old, male neutered Golden Retriever dog (*Canis familiaris*).

**History:** The right rear leg fractured and was pinned. One year later the leg was amputated.
**Histopathologic Description:** The mass has a complex histology with tumor trabecular bone, necrotic tumor and tumor bone, foci of chondro-osseous matrix, chondroid matrix, undifferentiated sarcoma, fibrosarcoma and reactive trabecular bone. Undifferentiated tumor cells, sometimes in bundles, form either densely cellular or moderately cellular sheets; pleomorphic nuclei have coarse chromatin and some are giant. Mitotic figures are common in some fields. Separating the nuclei in various regions is either an osseous, chondro-osseous or chondroid matrix as well as dense collagen. There is extensive necrosis of tumor trabecular bone and the undifferentiated cells between these trabeculae. Reactive trabecular cortical bone is at the periphery and is bordered by atrophied and fibrotic skeletal muscle.

**Contributor’s Morphologic Diagnosis:** Bone, rear leg, telangiectatic osteogenic sarcoma.

**Contributor’s Comment:** Medullary osteogenic sarcomas have been reported to occur at fracture sites with intramedullary pin fixation.

**AFIP Diagnosis:** Bone: Osteosarcoma.

**Conference Comment:** For many conference participants, the differential diagnosis included chondrosarcoma and reactive new bone (e.g. callous associated with fracture repair). Those favoring chondrosarcoma based the diagnosis on the striking degree of chondroid differentiation present throughout many sections; however, careful evaluation reveals the presence of malignant osteoblasts surrounding and investing osteoid in a disorderly orientation, most consistent with osteosarcoma (OSA). Those favoring a reactive process based the diagnosis on the proliferation of irregular trabeculae of new woven bone, a feature found not only in some cases of OSA, but also in a number of inflammatory bone lesions and in less aggressive neoplasms. Histologic differentiation can be difficult, but in reactive bone the trabeculae are interconnected and lined by a single layer of well-differentiated osteoblasts, with the intervening spaces occupied by non-neoplastic connective tissue; in the present case, spicules of neoplastic bone are lined and surrounded by haphazardly arranged pleomorphic osteoblasts.(3) Ancillary changes present in many of the slides include focally extensive skeletal muscle atrophy and fibrosis.

While the conference moderator and vast majority of conference participants concurred with the contributor’s diagnosis of OSA, none of the slides evaluated by the attendees contained blood-filled spaces lined by neoplastic osteoblasts, the histologic features diagnostic for the telangiectatic subtype. The gross appearance of telangiectatic osteosarcoma is distinctive, and reflects multiple blood-filled spaces reminiscent of hemangiosarcoma; the contributor did not provide a gross description of the bone tumor in this case.

Osteosarcoma represents the single most common primary neoplasm of the appendicular skeleton in dogs and cats, where it accounts for 80% and 70% of primary bone neoplasms, respectively. In dogs, OSA is characterized by rapid progression and early metastasis to the lungs, resulting in an early and high mortality rate. The appendicular skeleton is affected far more commonly than the axial skeleton, and the forelimbs are affected more commonly than the hind limbs. The neoplasm exhibits a strong predilection for the metaphyses of the distal radius, proximal humerus, distal femur, and proximal tibia.(2,3)

Osteosarcoma can be categorized based on its site of origin, with the majority of tumors being central, i.e. arising within bones, and fewer being categorized as one of two types of peripheral OSA, i.e. arising within the periosteum. Peripheral osteosarcoma includes the periosteal subtype, which clinically behaves similar to central OSA; and parosteal OSA, which is slower-growing and more well-differentiated, with a more favorable overall prognosis. The conference moderator cautioned participants that, because of the marked intratumoral histologic variability, OSAs can be difficult to accurately classify; nevertheless, subclassification into one of six categories based on the predominant histologic pattern is well-described in veterinary pathology, and summarized below:(2,3,4)

- **Poorly differentiated:** undifferentiated neoplastic cells range from primitive mesenchymal to large and pleomorphic; identification as OSA depends on identifying small quantities of tumor osteoid; highly aggressive, osteolytic tumor frequently associated with pathological fractures
- **Osteoblastic:** anaplastic osteoblasts with angular cell borders, variable amounts of basophilic cytoplasm, and hyperchromatic, often eccentric nuclei predominate; further subclassified as nonproductive or productive based on presence or absence of tumor bone production
- **Chondroblastic:** neoplastic cells produce both prominent chondroid and osteoid matrices
- **Fibroblastic:** interlacing fascicles of spindle shaped cells, resembling those of fibrosarcoma, that produce osteoid or tumor bone
- **Telangiectatic**: subtype associated with the least favorable prognosis; consists of solid areas and large blood-filled spaces lined by malignant osteoblasts that occasionally form spicules of osteoid
- **Giant cell**: tumor giant cells predominate in large areas of the neoplasm, which otherwise resembles nonproductive osteoblastic OSA

Based on the classification scheme above, and assuming the examined sections are representative of the entire neoplasm, the histologic features of the present case are most consistent with the chondroblastic subtype.

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**References:**

**CASE IV:** NCAH 2009-1 (AFIP 3134609).

**Signalment:** 1-year-old, male white-tailed deer (*Odocoileus virginianus*).

**History:** Tissues are from 1 of 20 white-tailed deer being restrained in a drop-floor chute located outside. Deer were being restrained to obtain skin biopsies of tuberculin skin test sites, as part of an on-going project. Handling and restraint began in early morning when ambient temperatures were cooler, but by the end of the exercise ambient conditions were hot and humid. This deer was the last of the 20 deer to be processed through the chute. Upon entering the chute, the deer showed markedly increased respiration (panting), frothy saliva around the mouth, and was hyperthermic to the touch, although a body temperature was not recorded. The deer was doused profusely with cool water and given several cool water enemas. Respirations slowed toward normal, but the animal remained subjectively hyperthermic. The deer was moved to an interior, cooler location. Several hours later the deer was in sternal recumbency, alert, but did not rise when approached. Eighteen hours after restraint, although alert, the animal was unable to rise and was euthanized.

**Gross Pathology:** The deer was in adequate nutritional status. The forestomachs contained moderate amounts of dry ingesta. Multifocal areas of both pallor and hemorrhage were present in muscles of the hindlimbs, forelimbs, epaxial and sublumbar muscles as well as the diaphragm. Lesions were bilateral but not symmetrical. Affected muscles appeared drier than normal. The heart was grossly unaffected. Bilaterally the kidneys were characterized by focally extensive black discoloration extending superficially through the cortex and involving as much as 75% of the cortical surface. The bladder contained a moderate amount of red-brown colored urine.

**Histopathologic Description:** The cross-section of skeletal muscle is characterized by focally extensive myofiber degeneration and necrosis. Slides vary with 20-60% of myofibers affected. Myofibers have lost visible cross-striations and vary greatly in size, many being large and swollen with flocculent, pale eosinophilic cytoplasm while others are smaller with hyalinized eosinophilic cytoplasm. Affected myofibers have pyknotic or karyorrhectic nuclei. Within some myofibers there is basophilic, punctate to granular staining interpreted as mineralization. Endomysial and perimysial spaces are mildly expanded due to edema and a cellular infiltrate composed of low numbers of both neutrophils and macrophages.

**Contributor’s Morphologic Diagnosis:** Skeletal muscle: degeneration and necrosis, focally extensive, with mineralization, white-tailed deer (*Odocoileus virginianus*).
Contributor’s Comment: Capture myopathy (exertional myopathy, exertional rhabdomyolysis) is characterized by damage to skeletal muscle, and sometimes cardiac muscle, and is commonly observed after capture, immobilization (chemical or manual), and transport. It is an important cause of morbidity and mortality in captured and handled wild animals, including birds, and should always be considered in planning and designing wildlife capture and handling events. All ages and sexes are susceptible and warm environmental temperatures, such as those in the present case, predispose animals to the condition.

Animals with capture myopathy may die suddenly or develop clinical signs hours, days or weeks later. Capture myopathy has been diagnosed up to a month after capture. Clinical syndromes of capture myopathy have been described based on time until onset of clinical signs as hyperacute, acute, subacute and chronic (reviewed in 4). More recently, other authors have based the classification of clinical syndromes on pathophysiology; capture shock syndrome, ataxic and myoglobinuric syndrome, ruptured muscle syndrome and a rare, poorly characterized delayed-peracute syndrome. (2) The ataxic and myoglobinuric syndrome is the most common, and is consistent with the present case.

Under normal conditions wild animals are not subjected to prolonged, maximal muscular exertion. However, during pursuit and capture such conditions may exist. Therefore, the earliest clinical signs of capture myopathy are similar to those of maximal exertion, increased respiratory and cardiac rates. Body temperature is usually elevated. Other early clinical signs may include depression, weakness, ataxia, muscle stiffness, and muscle tremors. Death may occur immediately post-capture due to marked metabolic acidosis, shock and circulatory collapse.

Animals surviving hours or even days may continue to show signs of depression, hyperthermia, tachypnea, tachycardia, weakness, and ataxia. Difficulty standing may progress to recumbency. Dark colored urine due to myoglobinuria may be seen. For weeks survivors may continue to show lameness, ataxia, muscle stiffness, and weight loss. Occasionally rupture of damaged muscle groups may occur. The gastrocnemius muscle is especially prone to rupture under such conditions.

The pathophysiology of capture myopathy is related to both shock and metabolic acidosis. The stress of pursuit and capture results in strong and prolonged sympathetic stimulation of microvasculature and eventual exhaustion of sympathetic vascular tone. Lack of vascular tone leads to visceral pooling of blood, decreased venous return, decreased cardiac output, hypotension, and hypoxia. In spite of hypoxia, tissue metabolism continues, relying on anaerobic glycolysis and resulting in increased levels of intracellular pyruvic and lactic acid. Lactic acid diffuses into the blood at levels that overwhelm the capacity of the liver, heart and other tissues to convert lactic acid to useable energy and lactic acidosis develops.

Prolonged hypoxia and acidosis result in generalized tissue deterioration. Active transport of sodium and potassium is reduced due to low intracellular pH. Intracellular sodium and chloride levels rise as do extracellular potassium levels. Mitochondrial activity decreases, lysosomes rupture, releasing damaging enzymes. Tissue necrosis ensues, especially in skeletal muscle, heart, liver and lung. Renal lesions of capture myopathy are characterized by moderate to severe tubular epithelial cell degeneration and necrosis with protein (myoglobin) and cellular casts. Renal lesions are primarily the result of renal ischemia.

Hyperthermia exacerbates tissue necrosis. Heat is generated from muscle myofilament action, glycolysis, recovery heat production as metabolic processes attempt to restore muscle to a resting equilibrium, and the environment. Heat from the environment can be transferred to muscle cells during exertion. (1)

Capture myopathy is similar to march myoglobinuria or exertional rhabdomyolysis in untrained athletes or military recruits following heavy exercise at high ambient temperatures. (2)

AFIP Diagnosis: Skeletal muscle: Myocyte degeneration and necrosis, focally extensive, moderate, with mineralization and edema.

Conference Comment: The contributor provides an outstanding review of the entity. Although skeletal muscle is a remarkably plastic tissue capable of a variety of responses to injury (e.g. necrosis, degeneration, regeneration, atrophy, hypertrophy, splitting, and fiber-type conversion), segmental necrosis and regeneration is a common result of a number of causes that merit inclusion in the differential diagnosis, and definitive determination of the underlying etiology is often difficult based solely on gross and microscopic lesions. Conference participants considered nutritional myopathy due to selenium and vitamin E deficiency or imbalance, toxic myopathy (e.g.
ionophore toxicosis), and other types of exertional myopathies (e.g. polysaccharide storage myopathy) which could produce identical microscopic lesions, but strongly suspected capture myopathy based on the signalment. Characterizing the distribution and duration of the lesions, and in particular, classifying necrotic skeletal muscle lesions as monophasic or polyphasic, is sometimes helpful in narrowing the differential diagnosis. For instance, monophasic necrosis, as in the present case, is more consistent with an exertional or acute toxic myopathy, while polyphasic necrosis is more consistent with muscular dystrophy, selenium deficiency, or ongoing intoxication.\(^{(3)}\)

Participants reviewed the basic stages of skeletal muscle necrosis, repair, and regeneration. Because myofibers are multinucleate, these changes can occur segmentally and are initially characterized by hyalinization of the sarcoplasm with loss of cross striations, followed by sarcoplasmic fragmentation often with mineralization. Effective skeletal muscle regeneration depends on the presence of an adequate blood supply, an intact basal lamina, and viable satellite cells. In the presence of adequate blood supply, macrophages derived from blood monocytes, with or without other leukocytes, are quickly recruited to the site of necrosis, traverse the basal lamina, and clear cytoplasmic debris. Simultaneously, satellite cells, juxtaposed between the sarcolemma and basal lamina, are activated and begin division into myoblasts in support of the regenerative effort. The remaining intact basal lamina forms a scaffold, i.e. “sarclemmal tube,” which excludes fibroblasts and guides proliferating myoblasts, which then fuse end-to-end to form myotubes that eventually produce thick and thin filaments and mature into myofibers. By contrast, if large numbers of satellite cells are killed, even with persistence of the basal lamina, healing occurs by fibrosis rather than regeneration. In cases typified by loss or disruption of the basal lamina, even with persistence of viable satellite cells, regeneration is ineffective and healing is characterized by the formation of muscle giant cells (large, bizarre multinucleated giant cells) accompanied by fibrosis.\(^{(3)}\)

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**References:**