Case I - 2 (AFIP 246 0166)

Signalment. Rhesus macaque: M. mulatta - 2 days, female

History. A 247 gm 2-day-old female rhesus macaque was found dead and presented for necropsy. This neonate had been delivered vaginally, was considered premature and had failed to nurse vigorously. Radiographs taken shortly after birth had revealed proliferation of bone along the diaphysis of the femurs, tibia, radius and ulna. Changes were considered diagnostic of the condition infantile cortical hyperostosis.

Gross Pathology. The neonate was considered to be moderately dehydrated and approximately 1 month premature. The thighs and antibrachia were thickened and firm on palpation. There was decreased range of motion in the elbows and stifles. On dissection, the femur, tibia, radius and ulna were grossly deformed bilaterally. This deformation was caused by proliferation of a rough firm tan to pink tissue which resulted in enlargement of these bones. This tissue had infiltrated and replaced the surrounding musculature. On cross section the medullary cavity was light red and the original cortical bone was present but incomplete and difficult to discern. The joints and epiphyses were grossly normal.

The lungs were heavy, wet and mottled dull red and purple. There were no other gross lesions.

Laboratory Results. Lung, bacterial culture - E. coli.

Contributor's Diagnosis and Comments. 1. Femur, diaphysis: Marked circumferential subperiosteal and periosteal fibroblastic, chondroblastic and osteoblastic proliferation with hyperostosis, periostitis and reduction of cortical bone.

2. Skeletal muscle of thigh: Moderate diffuse atrophy and fibrosis.

Congenital, juvenile and sporadic forms of idiopathic hyperostosis have been described in humans, dogs, pigs and rhesus macaques. The infantile (congenital) form seen at our center shows some similarities to Caffey's disease in human infants. The etiology of this infrequent condition in macaques is unknown and although a genetic component is suspected, this is unconfirmed.

This animal was born approximately one month premature. There was dystocia at parturition. A review of breeding records indicates that this infant was not directly related to the previously described cases. The immediate cause of death was most likely prematurity and bacterial suppurative pneumonia. Occasionally these infants may survive the neonatal period with complete spontaneous regression of the lesions with adolescence.

The submitted section of femur demonstrates the marked subperiosteal
proliferation comprised of islands of cartilage and bone dispersed within a loose mesenchymal network. This proliferation is found to surround rudimentary cortical bone and is most severe in the mid diaphysis. Growth plates and articular cartilage are normal. Multifocally within the proliferating tissue and surrounding soft tissue are aggregates of neutrophils, lymphocytes and plasma cells. There is marked atrophy of the surrounding skeletal muscle which is infiltrated to a variable extent by the abnormal periosteal tissue. Hematopoietic elements are present within the poorly defined medullary regions but reduced or absent from the mid diaphysis.

The present case differs in several minor features from those previously described. These differences are: 1) presence of inflammatory cells, 2) lack of well defined periosteum, and 3) the large amount of cartilage and mesenchymal tissue present between intervening bony spicules. The significance of these differences is unknown but may relate to the degree of immaturity and time of death.

AFIP Diagnosis. Femur, diaphysis (per contributor): Cortical dysplasia, with periosteal hyperplasia and cartilage and bone formation, rhesus monkey (Macaca mulatta), nonhuman primate.

Conference Note. All conference participants diagnosed infantile cortical hyperostosis, based on the examined sections and the intrauterine and postnatal radiographs supplied by the contributor. The group's interpretation of the section is that the innermost aggregation of discontinuous trabecular bone represents the femoral cortex. It is suspected that the cortex is poorly developed because the markedly thickened, hyperostotic periosteum likely protected it from stimulation normally induced by mechanical forces in utero. It is unclear whether the cortex failed to develop into compact bone or was remodeled to appear cancellous. Regarding the cellular infiltrate in the periosteum, the consensus is that the majority of the cells are hematopoietic elements, with a greater proportion of inflammatory cells present in the outermost areas. The central medullary cavity in the presented section contains minimal marrow elements, whereas hematopoietic elements in previously reported cases were present in high numbers in the original marrow cavity and rare in the hyperostotic bone.(1)

The AFIP Department of Orthopedic Pathology reviewed this case. They interpret the periosteal proliferation present in the histologic section and radiographs as fracture calluses and suspect that the condition affecting this monkey may be a variant of osteogenesis imperfecta. The concentric lamina in the extracortical tissue are interpreted as repair zones. As in this case, human newborns with repairing fractures exhibit medullary marrow depletion. They further propose that repair prevents visualization of fractures in the radiographs.

The differential diagnosis for marked intrauterine and perinatal periosteal proliferation include the two entities as mentioned above; in older animals, hypertrophic osteopathy, which is usually secondary to an intrathoracic lesion or neoplasia, would appear similar. Osteogenesis imperfecta is well-documented in humans, Holstein and Charolais calves, Barbados blackbelly lambs and in a kitten. Reported abnormalities include skeletal fragility, dental fragility (not in sheep), blue sclera and joint laxity. Multiple intrauterine skeletal fractures are common. Inheritance is reportedly autosomal dominant in cattle and humans, and autosomal recessive in sheep. The genetic defect results in production of either quantitatively insufficient type I collagen or weak, qualitatively defective type I collagen. Quantitative and qualitative collagen assays are used to subclassify osteogenesis imperfecta in humans.

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References.
Case II - 93-1054 (AFIP 2458428)

Signalment. Three-month-old male Yorkshire Terrier

History. Four days prior to euthanasia, the dog presented with acute signs of ataxia which responded for 3 days to steroids. On the day of euthanasia, there was acute paresis with loss of proprioception and pelvic limb motor function.

Gross Pathology. Several hard, nonmovable nodules, each 1-2 cm in diameter, were present at the costochondral junctions of the ribs. An 8 mm hard nodule attached to the vertebral arch compressed the spinal cord at T9.

Contributor's Diagnosis and Comments.
1. Thoracic vertebra: Osteochondroma of the vertebral arch.
2. Spinal cord: Compression atrophy, hemorrhage and acute fibrinoid vasculitis.

Etiologic diagnosis: Multiple cartilaginous exostoses.

Since the specimen was small, variation exists among the microslides. The acute onset of clinical signs was likely due to the fibrinoid vasculitis and hemorrhage, which are likely secondary to ischemia from compression. Some sections have conspicuous cartilage in the vertebral body; this likely is a frontal section through a physis rather than osteochondroma. This condition is supposed to be autosomal dominant in humans, dogs and horses. Information on siblings of this dog was not available. The pathogenesis of the lesion is not understood. The endochondral growth phase is under the same influence as normal physes. Malignant transformation in older dogs is reported.


Conference Note. Osteochondromas are benign, exostotic, cartilage-capped bony tumors arising on the external surface of a bone. If multiple tumors are present, the condition is termed multiple cartilaginous exostoses or osteochondromatosis. These tumors usually arise in bones formed by endochondral ossification, and are very often adjacent to growth plates. The scapulae, ribs, vertebrae, pelvis and long bones are most commonly affected. Multiple cartilaginous exostoses are usually diagnosed in young animals during the period of rapid skeletal growth. Tumors may impinge on nerves, tendons and blood vessels to produce pain and musculoskeletal dysfunction. Solitary osteochondromas may go unnoticed until discovered as an incidental lesion in older animals. Like the species mentioned, the disease in humans is inherited as an autosomal dominant trait. In cats, the disease differs in several respects, as tumors arise in adult animals, affect skull bones formed by intramembranous ossification, and rarely occur on long bones. Some affected cats are serologically positive for feline leukemia virus and viral particles can be demonstrated in the cells of the cartilage caps.
suggesting an inductive role.

Presumably, osteochondromas result from displacement of growth plate cartilage, which then proliferates to produce cartilage-capped endochondral bone. Attachment to the underlying bone may be pedunculated or sessile. The cortex and periosteum of the underlying bone blends with that of the tumor, and the marrow cavities of the tumor and parent bone communicate. Growth usually stops when the patient's growth plates close at skeletal maturity. In adults, these tumors can consist almost entirely of bone.

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References.

International Veterinary Pathology Slide Bank.
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Case III - N94-272 (AFIP 2472329), photo

Signalment. 4-year-old male rhesus monkey (Macaca mulatta)

History. Jun 91 - Diarrhea; culture positive for Campylobacter jejuni; Tx: Erythromycin BID X 7.

Aug 91 - Trauma to left leg/foot with swelling. Three days later open wound with sloughing of overlying skin on tibial surface.

Sep 91 - Robert Jones bandage placed. Reduced joint mobility noted for the left leg.

Dec 93 - Animal lying down, favoring right leg. Radiographically both knees are affected. Febrile (103.8). Inguinal lymph nodes enlarged. Right knee was warm, heart murmur detected. PCV 33%, WBC 38,000, SEGs 71%. Dx: Septic arthritis; Rx: Chloramphenicol Bid X 5 days.

Jan 94 - Anemia, leukocytosis with left shift, electrophoresis. Dx: Possible rheumatoid arthritis, blood submitted for ANA [antinuclear antigen] and RA [rheumatoid arthritis factor].

Feb 94 - ANA + RA are within normal limits. Hypoproteinemina/hypoalbuminemia are noted. Tx: Prednisolone 5 mg SID X 40 days.

May 94 - Euthanasia requested due to loss of range of knee motion bilaterally (osteoarthritis), unresolved diarrhea and weight loss.

Gross Pathology. There was a generalized weight loss. The colon was full of air with several mucosal streaks of hemorrhage. Cecum and colon contain green fluid ingesta with normal odor. The small intestine and stomach empty (though plenty of food in cage). The other organs were within normal size limits. Cultures of synovia (knee), distal colon (area of hemorrhage), and cecum were taken. Bilaterally, the lateral surface of the femoral articular surfaces demonstrates deep erosions of femoral trochlea with patellar proliferation.

Laboratory Results. Microbiologic Cultures: June 91 - Campylobacter jejuni; Necropsy: Knee: No growth. (May 94) Cecum/colon: No enteric pathogens.

Contributor's Diagnosis and Comments. 1. Femur (distal): Osteoarthritis,
suppurative, erosive, bilateral, chronic, severe.  2. Liver: Amyloidosis, sinusoidal, diffuse, moderate.  3. Liver: Atrophy, hepatocellular, diffuse, moderate.

Severe progressive osteoarthritis of the knees of rhesus macaques has a complex multifactorial etiology, complicated by delayed onset of clinical lameness after initial proposed insult. Three cases of osteoarthritis associated with colitis and amyloidosis have been seen in the last year in unrelated 3-4 year old rhesus monkeys at a breeding facility at Brooks Air Force Base. Cultures of intestinal contents at 1 year of age have sporadically yielded Campylobacter jejuni and Shigella flexneri. Animals developed progressive debilitating bilateral degenerative disease of the femorotibial and patellar joints and were euthanized. Leukocytosis (18-25,000) with 75-80% PMN's as well as synovial leukocytosis were seen. No bacteria have been isolated from the synovial fluid, although Ureaplasma and Mycoplasma sp. cultures were attempted. Disease course was not altered with the administration of antibiotics or anti-inflammatories. RA factors are negative.

Systemic amyloidosis in macaques is associated with chronic inflammatory disease, including arthritis and colitis. Campylobacter sp. and Shigella sp., well known enteric pathogens, have been associated with reactive osteoarthritis in macaques. Another published cause of arthritis in rhesus monkeys has been the development of calcium pyrophosphate crystals in the knee and elbow joints (pseudogout). Scanning electron microscopy on preparations taken from two of our cases of osteoarthritis did not demonstrate crystals. A diagnosis of rheumatoid arthritis cannot be eliminated based on lack of RA factor alone.

Human ankylosing spondylitis, a specific form of osteoarthritis, has been associated with the presence of human leucocyte antigen B27. This disease syndrome has been associated with inflammatory bowel disease and amyloidosis. In addition, amyloidosis is reported to occur in 14-26% of human cases with rheumatoid arthritis.

AFIP Diagnosis. 1. Femur, trochlea: Arthritis, erosive, chronic-active, focally extensive, severe, with pannus formation and subchondral bone loss, rhesus monkey (Macaca mulatta), nonhuman primate. 2. Liver: Amyloidosis, diffuse, moderate, with hepatocellular atrophy. 3. Liver: Hepatitis, portal, lymphoplasmacytic, diffuse, mild.

Conference Note. There is an extensive pannus-covered, centrally located ulcer of the articular cartilage, and variable peripheral erosion. Moderate numbers of viable neutrophils and lesser plasma cells and lymphocytes are present in the pannus and subjacent bone. There is growth arrest characterized by a thin, open growth plate producing scant primary spongiosa. Small numbers of the previously mentioned inflammatory cells are present in the synovium.

Most conference participants favored an immune-mediated arthritis, suspecting either rheumatoid arthritis or a type II collagen hypersensitivity. Dr. Weisbrode favors reactive, immune-mediated arthritis. He believes that the pannus resorbing the articular cartilage arose from subjacent bone rather than synovium, and progressed centripetally. Although the cause of this lesion is not known, morphologic features of this case are not compatible with several arthritides: 1) osteoarthritis/degenerative joint disease (DJD): neutrophils are uncommon in DJD; pannus, if present, forms peripherally in DJD; subchondral osteosclerosis and osteophyte formation are typical of DJD; 2) Bacterial arthritis: nondegenerate neutrophils and mild synovitis are inconsistent with bacterial infection, and Gram stains did not reveal bacteria; 3) rheumatoid arthritis: typical features of this disease that are absent in the presented lesion include synovial hyperplasia and lymphofollicular plasmacytic synovitis (extensive pannus formation, articular cartilage erosion with eventual joint destruction and ankylosis are features of rheumatoid arthritis).

A number of rheumatoid factor-negative spondyloarthropathies are described in humans. Among these is reactive arthritis associated with or induced by bacterial bowel infections including Yersinia, Salmonella, Shigella, Campylobacter and Klebsiella, or
chlamydial urogenital infections. Most persons with reactive arthritis have knee and ankle involvement and possess human leucocyte antigen B27 (HLA-B27). Joint involvement may occur weeks to months after the associated enteric or urogenital infection. The pathogenesis of reactive arthritis is not fully understood. Research has suggested that joints transiently infected with these bacteria may be cleared of bacteria but retain bacterial cell wall antigens. Subsequent extraarticular infections by these agents can activate immune responses to the remaining antigens and incite recurrent or chronic arthritis. Other studies have demonstrated T cell recognition of pathogen heat-shock proteins and have shown that there is close sequence homology between human and bacterial heat-shock proteins. These findings suggest immunologic cross-reactivity may be involved in the pathogenesis of reactive arthritis. Rheumatoid arthritis may also be a reactive arthritis. The Epstein-Barr virus, other viruses, mycobacteria, Borrelia and Mycoplasma have been proposed as initiating agents.

Rheumatoid arthritis and the rheumatoid factor-negative spondyloarthropathies may be associated with systemic amyloidosis. For comments on amyloidosis and its presentation in nonhuman primates, see Wednesday Slide Conference results for conference 15, case IV.

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References.

International Veterinary Pathology Slide Bank
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Case IV - 92N-369 (AFIP 2461127)

Signalment. African hedgehog (Atelerix albiventris), male, 2-years-old

History. This hedgehog was euthanized after a several day course of anorexia, incoordination, weakness and intermittent diarrhea. The animal had a firm swelling over the right maxilla. Radiography revealed multiple bony exostoses of the skull, ribs, spine and extremities.

Gross Pathology. A firm, white, 1x1x2 cm, bony mass protruded from the right maxilla. There were also multinodular homogenous firm white soft tissue masses arising from multiple skeletal sites. The largest measured approximately 2x2x2 cm and
surrounded the dorsal aspect of the lumbar vertebral column. Smaller, firmer masses
surrounded the right radius and fibula and several small hard spherical 1 mm nodules
were present on the pleural surface of multiple ribs.

Other extraskeletal lesions included severe subacute nephrosis, multifocal renal
infarction, hepatic lipidosis and mild aspiration pneumonia.

Contributor's Diagnosis and Comments. Parosteal sarcoma, lumbar
vertebrae. Osteochondroma, maxilla. Osteomas, multiple, ribs.

Lumbar mass -- The majority of the tissue was composed of aggregates of
spindle-shaped cells, subdivided into nodules by thin bands of fibrovascular connective
tissue. The outermost rim of cells consisted of compact small elongated spindle-shaped
cells, analogous to periosteum. Toward the center of the nodules the cells were less
dense and more round, and there was a variable, often large, amount of hyalinized
amphophilic extracellular (cartilaginous) matrix, often with single round cells trapped in
lacunae. In many places, this chondroid material was eosinophilic and necrotic and
sometimes mineralized. In rare areas, the tissue within the centers of the nodules was
osteogenic with the formation of osteoid spicules surrounding entrapped osteoblasts. In
some areas, this tissue was anaplastic with cellular and nuclear atypia and
hyperchromasia including multinucleate and occasional giant cells.

Maxilla -- The maxillary mass consisted of a cellular and bony mass bordered on
the outermost edge by a thin rim of periosteum which gave rise to a deeper zone of
proliferative spindle cells. Within this deeper zone of proliferation was the formation of
cartilage with subsequent ossification forming numerous anastomosing bone spicules
which extended down to and blended with the pre-existing outer maxillary cortex.
Extensive portions within the center of the mass were necrotic and infarcted.

Ribs -- (not submitted) The hard white nodules on multiple ribs were osteomas
composed of solid well differentiated bone with entrapped osteoblasts, surrounded by a
thin rim of periosteum.

Ultrastructural findings: The lumbar neoplasm was composed of undifferentiated
mesenchymal cells with highly ruffled cell membranes embedded in an extracellular
stroma containing variable amounts of collagen and vast numbers of extracellular viral
particles. Viral particles were enveloped, approximately 110 nm in diameter with a
centrally located, electron dense nucleoid averaging 55 nm in diameter, often
surrounded by a thin fuzzy line, suggestive of a core protein shell and were always
found extracellularly. Occasionally (approximately 1 per 100), particles with slightly
larger cores with a central area of lucency ("ring form") were present scattered among
mature particles. Viral particles were often adjacent to the plasma membrane and
crescent-shaped outward protrusions of the plasmalemma, suggestive of viral budding,
were observed, although rarely.

Comment: Parosteal sarcoma is a neoplasm arising from the connective tissue
on the bone surface. The term parosteal sarcoma is preferred over osteosarcoma as
tissue produced by the periosteal lining may take on various forms, as in this case. In
some areas, the most prominent variant was a chondroid differentiation while other
areas were fibroblastic or more rarely osteogenic. However, the behavior and
appearance of the osteoid forming portions of this lesion were not that of a typical
osteosarcoma.

The morphologic features and location of the observed virions are highly
suggestive of retroviruses. Retroviruses are 80-140 nm enveloped RNA viruses which
replicate within the cytoplasm and bud from the plasma membrane, thereby acquiring
an envelope derived from the host cell. Immature (recently budded) particles contain a
somewhat larger core with a central lucency, the so-called "ring form." Mature retroviral
particles are present extracellularly (or within cisternae) but are not present within the
nucleus. One common classification scheme further subdivides retroviruses into Type
A, B, C, D, E (lentivirus) and F (spumavirus) particles, which can be distinguished morphologically. The particles observed in the present cases most closely resemble Type C oncoviroses with a centrally located electron dense core. C particles form by the condensation of viral nucleic acid and core proteins beneath the plasmalemma with subsequent evagination forming a characteristic crescent-shaped bud. Slight evagination suggestive of budding was observed in these cases. C particles lack precursor intracytoplasmic (Type A) particles, which helps to distinguish them from Type B and D retroviruses. We propose that this virus may represent a C Type oncivirus unique to hedgehogs. Differentiation from endogenous retroviral expression within a neoplasm could not be ruled out based on morphologic evidence alone. Attempts to more definitively identify the virus from formalin fixed tissues using PCR are currently under way.

Two additional related (sibling) hedgehogs have been identified with similar multicentric osteomas/osteosarcomas and identical viral particles have been identified in one case examined ultrastructurally.

The multicentric pattern in this case was reminiscent of retroviral induced osteochondromatosis in the feline. In the cat, there is multicentric viral induction of the periosteum leading to multicentric bony exostosis. Budding C-particles have been observed within the proliferative cartilage cap and the syndrome is believed to be related to FeLV infection.


Conference Note. These apparently virus-induced tumors were difficult to classify. The lumbar mass includes anaplastic areas as well as areas of well-formed cartilage and bone. Although chondro-osseous metaplasia associated with the anaplastic sarcoma was considered, foci in which neoplastic cells appeared to have produced osteoid and cartilage were present. Thus, it could be argued that a diagnosis of osteosarcoma is justified, but given the unusual features of the tumor, its association with retroviral infection, and the lack of information on this recently recognized disease, the descriptive diagnosis of anaplastic sarcoma with chondro-osseous differentiation was preferred. The contributor's diagnosis of parosteal sarcoma also seems appropriate. Although some areas that suggested infiltrative growth are present in the maxillary mass, osteochondroma seemed to reflect the over all features reasonably well. In the sections examined, there is a minute proliferative lesion of the bone of a nasal turbinate consisting of dense woven bone. Although cellular preservation is poor, this lesion is likely an osteoma and was probably similar to those reported on the ribs.

Virus associated osteosarcomas, parosteal sarcomas and chondrosarcomas are reported in mice infected with the FBJ retrovirus. Although these tumors are invasive, metastasis is not reported. These murine malignant neoplasms arise de novo, not by malignant transformation of retroviral associated osteochondromas as occurs in the cat.

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References.


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