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Pathology in Practice

Sanjeev Gumber, DVM, PhD, Melissa I. Stovall, DVM, Devon C. Owens, DVM, Jennifer N. Davis, DVM, and Maria M. Crane, DVM

Divisions of Pathology (Gumber) and Animal Resources (Stovall, Owens, Davis, Crane), Yerkes National Primate Research Center, Emory University, Atlanta, GA 30324

Sanjeev Gumber: sgumber@emory.edu

History

A 33-year-old 84.5-kg (185.9-lb) ovariectomized female chimpanzee (*Pan troglodytes*) residing in a social group was evaluated by the Yerkes National Primate Research Center Veterinary Services because of lethargy of 2 days' duration. The animal had had acute pneumonia and septicemia approximately 7 to 8 months earlier.

Clinical and Gross Findings

The chimpanzee was sedated for a complete physical examination and diagnostic workup. During examination, the chimpanzee became apneic and was moved immediately to the hospital for emergency treatment. Several attempts to intubate the chimpanzee were each unsuccessful. A laryngeal mask airway was placed between intubation attempts to provide manual ventilation, and, because no heartbeat or pulses were detected, thoracic compressions were initiated immediately on arrival. Several attempts to revive the animal, including administration of epinephrine, doxapram hydrochloride, and atropine, were also unsuccessful. Following death, the chimpanzee was submitted for necropsy.

Postmortem examination revealed clear peritoneal (2 L) and pleural effusions (800 mL). The heart was markedly enlarged, and the pericardial sac contained approximately 70 mL of blood-tinged fluid. The left ventricular lumen was completely obliterated by the hypertrophic left ventricular wall. The lungs were diffusely congested and contained multifocal to coalescing pale tan foci (0.2 to 0.5 cm in diameter). There was moderate hepatomegaly and severe congestion. The uterus was markedly enlarged (15 × 8 × 3.5 cm; Figure 1). On cut surface, the uterine lumen was obliterated and the myometrium was expanded by a pale white mass with a focal area of necrosis. The neoplasm extended into and distorted the uterine cervix and vagina. No other major gross findings were noticed.

Dr. Davis' present address is Office of Animal Welfare, Office of Regulatory Affairs, University of Pennsylvania, Philadelphia, PA 19104.

^aEnVision+ System-HRP Labeled Polymer (DAB), Dako North America Inc, Carpinteria, Calif.

Histopathologic Findings

At necropsy, various tissue samples were collected and fixed in neutral-buffered 10% formalin, routinely processed, paraffin-embedded, sectioned at 5- μ m intervals, and stained with H&E stain. Microscopically, the uterine mass was an unencapsulated, moderately cellular neoplasm composed of spindle cells arranged in interlacing streams and bundles that expanded the myometrium and were supported by fine fibrovascular stroma (Figure 2). Neoplastic cells were densely packed with indistinct cell borders and frequently contained moderate amounts of eosinophilic fibrillar cytoplasm. Nuclei were oblong to cigar-shaped with finely stippled chromatin. No mitotic figures were present in 30 hpfs (400 $\times$). When treated with biotinylated mouse anti-human α -smooth muscle actin monoclonal antibody (clone 1A4) by the streptavidin-biotin-peroxidase method,^a neoplastic cells in the uterine mass were diffusely labeled (Figure 3). The other notable lesions included hypertrophic cardiomyopathy, severe chronic passive congestion of the liver, severe multifocal to coalescing necrohemorrhagic pneumonia, moderate tubulointerstitial nephritis, moderate duodenal Brunner gland hyperplasia, and moderate eosinophilic to lymphoplasmacytic enteritis. Severe pneumonia and hypertrophic cardiomyopathy caused the sudden death of this animal.

Morphologic Diagnosis and Case Summary

Morphologic diagnosis: uterine leiomyoma, hypertrophic cardiomyopathy, severe chronic passive hepatic congestion, severe multifocal to coalescing necrohemorrhagic pneumonia, moderate tubulointerstitial nephritis, moderate duodenal Brunner gland hyperplasia, and moderate eosinophilic to lymphoplasmacytic enteritis.

Case summary: uterine leiomyoma in a chimpanzee.

Comments

Nonhuman primates are commonly used as models of human diseases because their genomic, physiologic, and immunologic profiles are so very similar to those of humans. Chimpanzees are genetically most similar to humans, with 98% sequence homology.¹ Old World primates are unique among nonhuman species in that they have a similar endometrial physiology to that of humans, with regular menstrual cycles in great apes² and macaques.³ Neoplasia in nonhuman primates is becoming increasingly common owing to the emphasis on aging research, which entails maintenance of animals until old age.^{4, 5} A survey of the incidence of neoplasia in the chimpanzees at the Southwest National Primate Research Center and Yerkes National Primate Research Center revealed that, in females, the urogenital system was most commonly affected, followed by the integumentary, endocrine, alimentary, respiratory, musculoskeletal, and cardiovascular systems. The most common tumor in female chimpanzees was leiomyoma of the uterus, cervix, or vagina.⁵ Another recent study⁶ at Alamogordo Primate Facility and Keeling Center for Comparative Medicine and Research revealed that uterine leiomyoma was diagnosed in 55 of 195 (28.2%) chimpanzees. The mean $\pm$ SD age at time of uterine leiomyoma diagnosis was 30.4 ± 8.0 years, and advanced age (> 30 years) was associated with increased incidence.⁶ Uterine

leiomyoma is also common in other nonhuman primates.^{7–9} The main differential diagnosis on the basis of gross necropsy findings in the case described in this report was a neoplastic process, such as leiomyoma or leiomyosarcoma. Uterine endometrial polyps and uterine adenomyosis were also included as differential diagnoses. However, the histopathologic features of the uterine mass were consistent with benign leiomyoma.

Uterine leiomyomas are benign fibroid tumors that originate from the smooth muscle cells of the uterus.¹⁰ They may grow completely within the uterine wall (intramural or interstitial form), protrude into the uterine cavity (submucosal form) or peritoneal cavity (subserosal and pedunculated form), or grow from the uterine cervix (cervical form).¹⁰ In the chimpanzee of the present report, the tumor was classified as intramural; it most likely originated from the uterus and extended into the uterine cervix. Uterine leiomyomas are usually subclinical and develop in 70% to 80% of women between 30 and 50 years of age. In clinical cases, heavy menstrual bleeding is the most common clinical sign; pelvic pain, uterine prolapse, and fertility complications are occasionally reported.¹⁰ In chimpanzees, obstructive uropathy secondary to uterine leiomyoma has been reported.¹¹ Risk factors include increased age, obesity, nulliparity, and an interval since last parturition > 5 years.^{10, 12} On ultrasonographic examination, uterine leiomyomas appear spherical in shape, with well-defined borders and solid hyperechoic texture.¹³ Although differential diagnoses may include endometrial polyps and endometriosis, these conditions can be ruled out on the basis of ultrasonographic examination findings; endometrial polyps have poorly defined margins, and endometriosis is often visualized as a fluid-filled cystic structure.¹⁴ Medical management of uterine leiomyomas includes administration of progesterone-based contraceptives and gonadotropin-releasing hormone agonists. In chimpanzees, progesterone-based contraceptives can have a protective effect and may diminish or delay the development of leiomyoma.¹⁰ The chimpanzee of the present report was 33 years old, was ovariectomized, and had no history of pregnancy in the last 5 years, which may have contributed to the development of uterine leiomyoma. In addition, several reports^{15–17} suggest that hypertension enhances risk for fibroid development^{15, 17} or growth in the uterine smooth muscle similar to atherosclerotic changes in the arterial smooth muscle.¹⁶ It has been proposed that high blood pressure may cause smooth muscle cell injury or cytokine release, thereby increasing the risk of uterine fibroid onset.^{15–17} Therefore, hypertrophic cardiomyopathy likely had a role in precipitating uterine fibroid development in the chimpanzee of the present report.

Acknowledgments

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Figure 1. Photographs of a uterine mass (surface [A] and cross-section [B] views) in a 33-year-old female ovariectomized chimpanzee that died suddenly following evaluation for lethargy and pneumonia. Notice the thickening of the uterus (arrow) and cervix (arrowhead) and displacement of the vagina (asterisk) in panel A and obliterated uterine lumen (arrowhead) in panel B.

Figure 2.

Photomicrograph of a section of tissue obtained from the uterine mass in Figure 1. The myometrium is diffusely expanded by an unencapsulated, moderately cellular neoplasm composed of tightly packed spindle cells with elongated cigar-shaped nuclei and arranged in bundles and streams. H&E stain; bar = 20 μ m.

Figure 3.

Photomicrograph of another section of tissue obtained from the uterine mass in Figure 1. Diffuse immunohistochemical staining of the population of neoplastic cells indicates that they are positive for α -smooth muscle actin. Vascular smooth muscle cells (internal positive control [arrowhead]) were also labeled. Immunoperoxidase with 3,3'-diaminobenzidine with Mayer hematoxylin counterstain; bar = 20 μ m.