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A CASE OF METASTATIC UTERINE ADENOCARCINOMA IN A SOUTHERN WHITE RHINOCEROS (*CERATOTHERIUM SIMUM SIMUM*)

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Abstract: A 39-yr-old, acyclic, uniparous, female white rhinoceros with a history of recurrent vaginal bleeding was euthanized following a period of respiratory distress and ill-thrift. The rhinoceros' uterus had previously been evaluated by ultrasound and diffuse endometrial hyperplasia and two benign uterine leiomyomas had been diagnosed. At necropsy examination, a large, infiltrative, metastatic uterine adenocarcinoma was found multifocally throughout the uterus, scattered within the peritoneal cavity, on the diaphragm, the splenic capsule, the pleural surface of the lung and mesenteric lymph nodes. A large volume (100 L) of ascites fluid was present in the abdominal and pleural cavities.

Key words: Adenocarcinoma, *Ceratotherium simum simum*, rhinoceros, uterus.

CASE REPORT

Published reports of neoplasia in rhinoceroses are rare. Previous cases of reported neoplasia have been localized to the reproductive system and were benign. The recent use of ultrasonography to evaluate the reproductive health of aging female rhinoceroses led to the reporting of endometrial hyperplasia, uterine leiomyoma, and uterine adenoma.[3,4,9,10] There has been a single case report of benign seminoma in an aged male white rhinoceros.[8] To date, this is the first documented case of uterine adenocarcinoma with a diffuse malignant spread throughout the abdominal and thoracic cavities in a white rhinoceros.

A 39-yr-old, uniparous, female southern white rhinoceros (*Ceratotherium simum simum*) had been residing in the Dublin Zoo for 12 yr, during which time she had shown irregular estrous behaviour. In 2001, at the age of 32, the rhinoceros presented with a bloody vulvar discharge which continued intermittently despite repeated oral antibiotic treatment.

In September 2002, the rhinoceros' reproductive organs were examined by transrectal ultrasonography, under general anesthesia, as part of a large study on the reproductive pathology of captive rhinoceroses.[4] The ultrasound examination revealed hyperechoic masses in the right uterine horn, to the left of the uterine body, and as a large mass distending the left uterine horn (Fig. 1). A large (10 cm) hypoechoic mass was located at the cranial end of the left uterine horn, and a similar smaller (1 cm) round mass was found in the cervix. Multiple small cysts were present throughout the uterine body and horns. The hypoechoic masses were interpreted as leiomyomas, based on ultrasonographic appearance, and the hyperechoic mass of the left horn was interpreted as an adenoma. Diffuse cystic endometrial hyperplasia was also present. Eleven months later, a follow-up transrectal ultrasound examination showed little change except for a small increase in the size of the left uterine horn hypoechoic mass.

In April 2008, the rhinoceros developed labored breathing. Increased lung sounds were auscultated, and a course of oral antibiotics was administered. Despite therapy, the animal continued to deteriorate and developed ocular and nasal discharge, productive coughing, abdominal swelling, inappetence, and was lethargic. The animal was euthanized in May 2008.

A postmortem examination revealed that the thoracic cavity contained a small amount of serosangineous fluid. The cranioventral lung lobes were collapsed, with numerous thick, fibrous adhesions between the thickened pericardial sac and pleural surface. Multiple small (1–5 mm), pink, irregularly shaped, friable nodules were present on the pleural surface of the caudal lung lobes and on both thoracic and abdominal aspects of the diaphragm.

The abdomen was filled with a large volume (75–100 L) of serosangineous, watery fluid.

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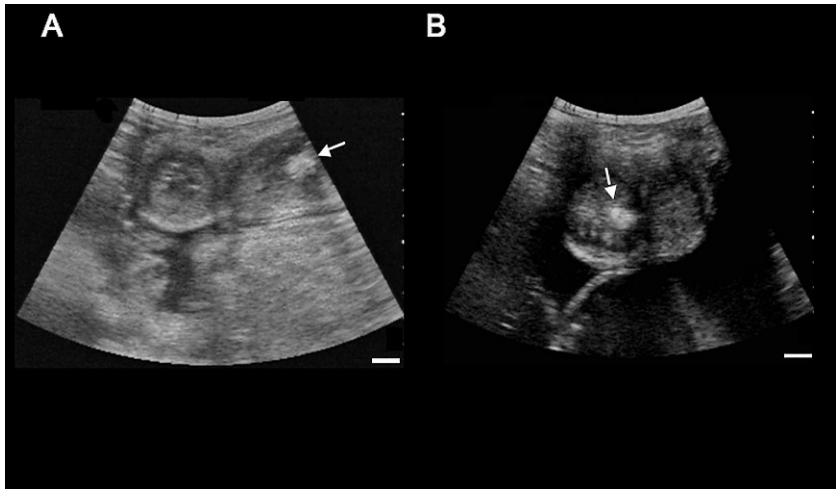

Figure 1. Ultrasound images of the uterine horns of a rhinoceros. **A.** Left uterine horn in cross section and left uterine horn in longitudinal plain beyond the uterine bifurcation. Note the hyperechoic mass in the lumen of the right uterine horn. **B.** Left uterine horn, another hyperechoic structure in the lumen of the horn. Luminal hyperechoic structures in the uterus are distinctively different from the hypoechoic leiomyomas of the uterus.

Fibrin tags were present on the capsules of both the liver and spleen. Nodules similar to those on the pleural surface were present throughout the omentum and on the serosal aspects of the abdominal organs. There was some shallow ulceration in the nonglandular stomach.

Both ovaries were small and without evidence of recent cyclic activity. Vulva, vagina, and cervical os were macroscopically normal. The uterus contained multifocal to coalescing, large, up to 15 cm in diameter, firm nodules, distending the external macroscopic outline of the uterine horns and extending to the uterine body. The uterine mucosa was wet and swollen in appearance and thrown into numerous short (2–5 mm), longitudinal folds. The large, externally visible nodules corresponded to thick, white, dense, firm circumferential masses occluding the lumen. In addition, there were multiple variably sized (1–2 cm), raised, white, firm, umbilicated nodular masses. The uterine mucosa also had multiple small (3 mm), clear, fluid-filled cysts (Fig. 2).

Microscopically, the large uterine masses were composed of large pseudoencapsulated, multilobulated nests of cells arranged as acini. The cells were cuboidal in shape with luminal cilia. Cell nuclei were large, oval, and basally located with clumped chromatin and prominent, sometimes paired nucleoli. Mitotic index ranged from 2–4 per high-power field. Lobules were often surrounded by a dense, fibroblast-rich connective tissue (desmoplasia). Acinar ducts contained a granular to fibrillar, pale eosinophilic matrix. Occasionally, there was a loss of polarity of the duct epithelial cells (Fig. 3).

Cells of the mesenteric masses were arranged as nests and were a mixture of highly mitotic cuboidal cells and angular pleomorphic cells, separated by abundant intracellular fibrillar eosinophilic matrices. Occasionally, neutrophilic inflammation was found associated with the masses. Similar cell populations were found on the splenic capsule, lung pleura, diaphragm, and within the mesenteric lymph nodes. The uterine masses were interpreted as uterine adenocarcinoma and the mesenteric masses, due to their similar morphological con-

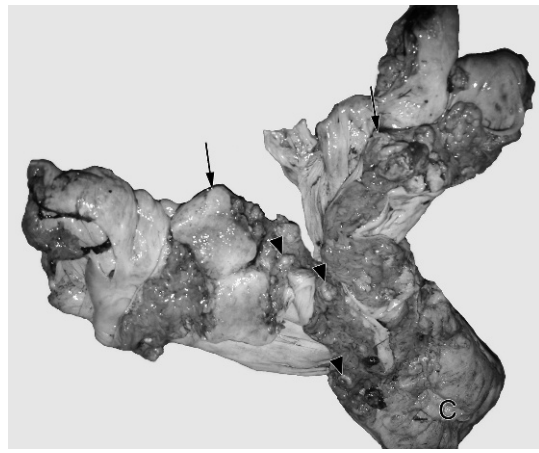

Figure 2. Rhinoceros uterus with multifocal, large, transmural (arrows) and multifocal umbilicated adenocarcinoma masses (arrow heads). C = cervix.

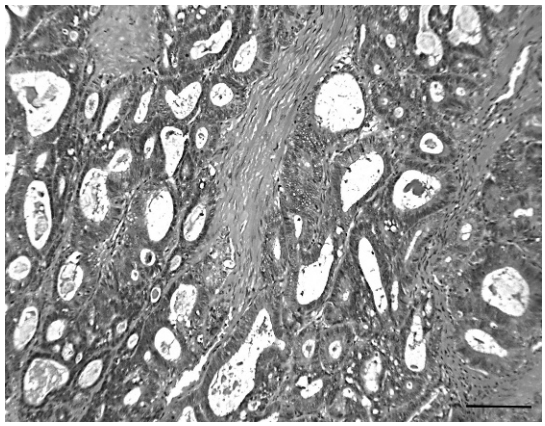

Figure 3. Rhinoceros uterine adenocarcinoma. Section showing diffuse acinar proliferation and desmoplasia. Bar = 100 μm. H&E, ×10.

formation, cell shape, and matrix production, were interpreted as an anaplastic metastatic form of the uterine adenocarcinoma.

Vaginal bleeding in nonprimate veterinary species is a rare, but nonspecific, event. It can be secondary to vaginal trauma, hymen tearing, varicose veins, urinary tract infections, or uterine tumours. A chronic mucohemorrhagic vulval discharge was reported previously in a white rhinoceros.[10] Even though, in that case, a thickened uterine horn and abnormal uterine fluid were detected by ultrasound, a definitive diagnosis was not possible.

Up to 10% of human cases of ascites are associated with neoplasia.[7,12] Most commonly, it is associated with ovarian tumors, but can also been seen in tumors of the pancreas, stomach, or uterus. In human patients, it is only seen in advanced malignancies and is associated with a poor prognosis. Ascites develops secondary to tumor obstruction of diaphragmatic lymphatics, in conjunction with increased production of peritoneal fluid. Malignant ascites is often associated with transcoelomic metastasis.

In both humans and domestic animals, transcoelomic abdominal metastasis is most commonly associated with ovarian tumors; however, it can also occur in other malignancies.[12] Most commonly, epithelial tumors spread by expansile growth and via lymphatics or hematogenous metastasis. As the tumor expands, it extends to the peritoneal surface of the organ. Subsequently, individual tumor cells may detach, and the natural flow of peritoneal fluid will transport them, thus allowing seeding on other organs of the peritoneum (carcinomatosis). This transcoelomic route also provides ready access to lymphatics and lymph nodes.[12]

The use of ultrasonography in recent years as an aid to captive breeding programs has greatly enhanced scientific knowledge of age-related changes in the white rhinoceros uterus.[2,3,4,5,9,11] The most common uterine pathology documented in the white rhinoceros is endometrial hyperplasia, and it has been described with multiple vesicles similar to that described here.[1,4] It is associated with increased age, nulliparity, and acyclicity. The most common uterine tumor described in the rhinoceros is leiomyoma, and this is also associated with age and acyclicity.[4] An endometrial adenoma has also been described. Other pathologies associated with the female white rhinoceros reproductive system include endometrial fibrosis, hydromucometria, and ovarian cysts.[4]

Other animal species, especially dogs, may develop endometrial hyperplasia, although uterine adenocarcinoma is not common in animals. Similarly, while endometrial hyperplasia has been documented in captive white rhinoceroses, uterine adenocarcinoma has not been reported.[1,4]

In women, uterine cancers are the fourth most-common cancer, with the majority arising from the endometrial glands and which are classified as endometrial adenocarcinomas.[6] Risk factors in women for this type of cancer include age, obesity, diabetes, hypertension, nulliparity, excessive estrogen, and endometrial hyperplasia.[6] Excessive estrogen in women also predisposes them to endometrial hyperplasia. The main, presenting clinical sign for women with endometrial hyperplasia or endometrial carcinoma is abnormal, often postmenopausal, vaginal bleeding.[6]

Since the reproductive history of captive female white rhinoceroses and their associated reproductive pathology is so different from free-living white rhinoceroses, there is a growing concern about the premature reproductive aging of captive female white rhinoceroses.[1,2,3,4] It is thought that this may be the result of excessive estrogen stimulation.[3,4] In the wild, a female white rhinoceros will attain sexual maturity around 6 yr of age, with an average gestation length of 16 mo; females produce a single offspring every 2–3 yr. Hence, a wild female white rhinoceros will spend most of her adult life pregnant, with a dominance of the progesterone hormone, and can remain fertile well into her 20s. Captive female white rhinoceroses reach maturity at a similar age. However, the vast majority of them do not mate successfully and remain nulliparous or uniparous

for life; their dominant reproductive hormone is the endometrial-stimulating estrogen. Endometrial hyperplasia is a common, age-related change in these captive female white rhinoceroses, leading to the suggestion that prolonged estrogen exposure is a risk factor for endometrial hyperplasia in this species.[4]

Malignancy is rare in the white rhinoceros, and it is believed that this is the first documented case of metastatic malignancy in this species. Ultrasonographic evaluation of the uterus in this species has greatly increased the knowledge of rhinoceros' reproductive pathology. In addition, a metastatic uterine malignancy has not been previously reported. In this species, the association of chronic estrogen stimulation with endometrial hyperplasia and asymmetric reproductive aging has already been reported. It remains to be documented if chronic estrogenism, as in humans, could be associated with an increased risk of uterine adenocarcinoma.

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