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Tumor das células da granulosa-teca em Macaco-Prego (*Sapajus sp.)*

Granulosa-theca cell tumor in Capuchin monkey (*Sapajus* sp.)

JULLIA DE PINHO BORBA

CUIABÁ-MT
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Trabalho de Conclusão de Curso apresentada ao Programa de Residência Uniprofissional em Medicina Veterinária, área de concentração: Medicina de Animais Selvagens, para a obtenção do título de especialista em Medicina de Animais Selvagens.

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JULLIA DE PINHO BORBA

ARQUIVO BRASILEIRO DE MEDICINA VETERINÁRIA E ZOOTECNIA

Tumor das células da granulosa-teca em Macaco-Prego (*Sapajus sp.)*

(Granulosa-theca cell tumor in Capuchin monkey (*Sapajus* sp.)

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ABSTRACT

Background: Sapajus sp. (capuchin monkey), belongs to the Cebidae family and the order Primate, being considered a species of little concern in the list of endangered species. Understanding the causes of morbidity and mortality in non-human primates is essential for the conservation of species. The occurrence of ovarian tumors in non-human primates is considered low, although recent studies have shown that in captive animals, there is a higher incidence of neoplasms. The objective of this work is to report the diagnosis and surgical treatment of an ovarian tumor in a specimen of capuchin monkey from the wild that was received in the Wildlife Center at the Veterinary Hospital. After ultrasound exams, an increase in the uterus and ovaries was identified. Subsequently, the animal was submitted to hysterosalpingo-oophorectomy, the material was sent for histopathological analysis and tumor of

granulosa-theca cells in the left ovary was identified, in addition to accentuated multifocal cystic endometritis, metritis and mild multifocal perimetritis and severe fibrosis in the uterus.

Keywords: hysterosalpingo-oophorectomy, primates, neoplasia, ovarian

INTRODUCTION

Studies carried out on non-human primates are of significant importance not only for the development of veterinary medicine, mainly for conservation of species (Gillespie, et al 2008), but also for human medicine due to the phylogenetic similarity with humans, which allows pathophysiology studies with greater accuracy than studies using other experimental models, such as guinea pigs, dogs and rabbits. In relation to the New World primate models, *Sapajus* sp. it is one of the most studied species due to its adaptability and reproductive success in captivity, long life expectancy, high rate of encephalization, tendency to exploitation and manipulation of tools and complex social behaviors (Fragaszy, et al 2004).

Cebus/Sapajus (capuchin monkey), belongs to the Cebidae family, Platyrrhini infra-order (New World primates) and Primate order, they are classified as neotropical primates (Guimarães, et al 2016). They are omnivorous, and the diet consists mainly of fruits and a small amount of insects, and can also feed on seeds, flowers, buds and small vertebrates (Fragaszy, et al 2004). Classified as medium-sized primates, they weigh between 1.3 kg and 4.8 kg, growing up to 48 cm in length without the tail, and sexual dimorphism is associated with the larger size of adult males.

The basic structure of the female capuchin reproductive system is similar to other mammals, consisting of gonads, accessory organs and genitalia. Similar to humans and also to other neotropical primate, the reproductive cycle of females capuchin is menstrual, lasting from 15 to 21 days, with females showing very slight bleeding (Lemmens, 2018). Females reach sexual maturity between three to four years of age, while males reach around the seventh to eighth year of life (La Salles, et al 2017).

Ovarian tumors are classified according to the embryological origin of the tissue and the histological similarity with the components of the endocrine apparatus of the ovary: epithelial, germinative or stromal of the sexual cords (Agnew and Maclachlan, 2017). They can be differentiated into granulosa-theca cell tumors and interstitial cell tumors (Nagarajan, et al 2005). Neoplasms are usually unilateral, have low malignancy and may recur after 5 to 10 years (Cline, 2004). Tumors derived from sex cords can be hormonally active and secrete steroidal, female and male hormones (Agnew and Maclachlan, 2017). The production of these hormones influences the reproductive behavior of the

affected animal, such as persistent anestrus, intermittent estrus or masculinization (Agnew and Maclachlan, 2017).

Tumors originating from sexual cords are the most common in domestic animals and primates, whereas in humans, the most common ovarian neoplasms originate from epithelial cells. In humans, granulosa-theca cell tumors are rare neoplasms originating from strings cells of sexual cords, and represent about 2-3% of ovarian malignancies (Bezerra and Lorenzato, 2004). Granulosa cell tumors are described in two subtypes: juvenile (TCGJ) and adult (TCGA). Approximately 95% of cases occur in women in the peri or post-menopause, above 50 years of age. The tumor staging of granulosa-theca cells is the main prognostic indicator (Moraes, 2021). In New World primates, recent studies have shown that in captive animals there is a higher incidence of neoplasms (Lowestine, 1985), although the occurrence of this tumor in platyrrhines is considered low (Chaffee and Magden, 2018).

For the diagnosis of neoplasms, both clinical history and routine exams, such as radiographic exams and ultrasound exams, are essential tools. In addition, immunohistochemistry is also important for the identification of ovarian tumors (Baker, 2004), since it helps in the differential diagnosis of neoplasms (Kriplani and Patel 2013). It is important that a panel of markers is used to be positive and negative in several tumors. Kriplani and Patel (2013) also found that antibody to cytokeratin-7 (CK7) is an important marker for differentiation from primary ovarian tumor and metastatic colorectal adenocarcinoma.

CASE REPORT

A specimen of capuchin monkey (*Sapajus* sp.), female, adult, weighing 1.76 kilograms from the wild, was rescued by the Fire Department on a pavement in a residential neighborhood in Várzea Grande, MT, after the animal was delivered to the Military Police for Environmental Protection (BPMPA), who transfered it for physical examination by the Center of Wildlife of the Veterinary Hospital (HOVET). Initially, electrocution and trauma by stoning were suspected, but with no consistent history because it is an animal from the wild.

The patient was physically restrained for physical and clinical evaluations, it was active and responsive to stimuli and presented vocalization. Small dermatological lesions with scabs, an advanced healing process and significant alopecia were found in the dorsal region of the chest. The patient was dehydrated, the presence of multiple bone calluses and consolidated fractures in thoracic and pelvic limb phalanges was observed, but it did not present other significant alterations in clinical examination. Blood samples were collected for blood count and serum biochemistry through tests of total protein (PT) and creatinophosphokinase (CK), creatinine and ALT, in addition to stool samples for coproparasitological examination. The blood and feces samples were sent to the Clinical Pathology and Parasitology Laboratory (respectively) sectors of the Veterinary Hospital. The clinical conduct of

evaluation and choice of complementary exams were carried out in accordance with the clinical signs presented.

For laboratory evaluation, reference values found in the literature for the species were used. The erythrogram showed normal values when compared to the parameters for the species, but they were close to the lower limit. The platelet count and total plasma proteins also showed values within the reference range for the species. The leukogram showed marked leukocytosis, due to the elevation of the levels, in absolute values, of segmented neutrophils, eosinophils and lymphocytes. Regarding the results of serum biochemistry, creatinine and ALT were within the range of reference values for the species, both total protein and creatinophosphokinase were above the reference values.

During the hospitalization period, the animal was subjected to four clinical evaluations, in which chemical restraints were necessary. The anesthetic protocols used associated Ketamine 8mg / kg and Midazolam 0.2 mg / kg, intramuscularly (IM), as pre-anesthetic medication. Venopuncture of the left cephalic vein was performed to place venous access for administration of fluid therapy with Ringer's lactate solution. Subsequently, inductions were performed with Propofol 4mg / kg, as an intravenous bolus in access. The animal was not intubated in any of the evaluations, however, it was submitted to oxygen supplementation via facial mask. In all clinical evaluations, which were carried out with chemical restraints, the patient was submitted to a 12-hour food and water fasting.

Cough and sialorrhea were observed during the first clinical evaluation, but without compromising the animal's general condition during anesthesia. In this clinical evaluation, radiographic and ultrasound examinations were performed, in addition to the scraping of superficial and deep skin, for fungal culture, bacterial culture, trichogram and ectoparasite research.

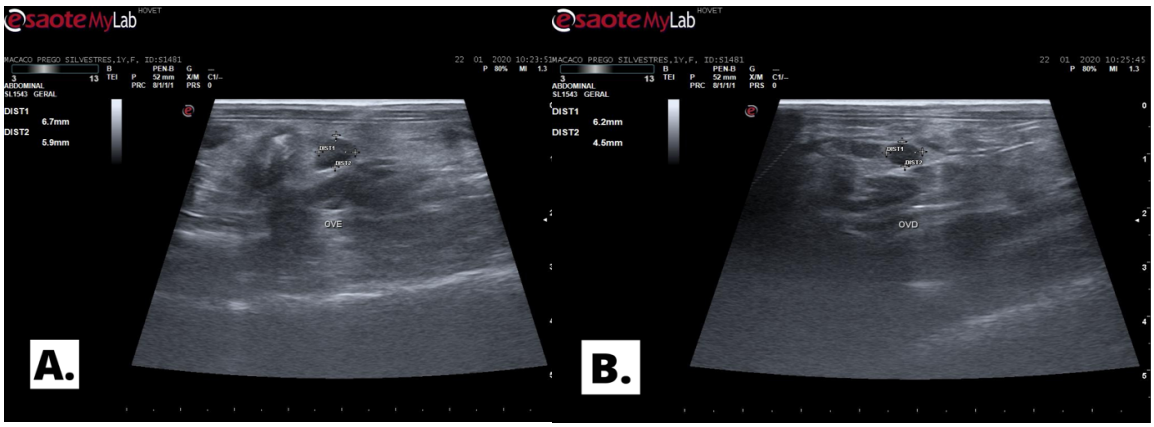

Figure 1. Longitudinal ultrasound images of the left and right ovaries of Capuchin monkeys. Ovaries enlarged in size A. Left ovary presents an enlarged volume with the presence of a circular anechoic area, measuring 0.67 cm x 0.59 cm. B. Right ovary has an increased volume, measuring 0.62 cm X 0.45 cm. Source: Personal Archive

The radiographic examination showed radiopacity in a ground-glass pattern associated with a discrete bronchocentric pattern, diffusely distributed through the pulmonary parenchyma, in latero-lateral and ventro-dorsal projections; in addition to the presence of bone calluses and fractures in phalanges of all limbs. There was also an increase in the hepatic silhouette, suggestive of hepatomegaly

or compatible with the animal's age range. The ultrasound examination showed an increase in size with reduced echogenicity in the liver, spleen with reduced echogenicity, enlarged mesenteric lymph node. Among uterine alterations, there is an increase in uterine horns and uterine body (Figure 1), associated with echogenic content, thick wall and presence of vascularized hypoechoic luminal structure.

The results of the imaging exams were compatible with pneumonia, therapeutic treatment with Amoxicillin with Potassium Clavulanate at a dose of 13.3mg / kg twice a day, for 14 days orally (PO), Ranitidine at a dose of 0.5mg / kg twice a day for 14 days PO as a medication to protect the gastric mucosa, Meloxicam at a dose of 0.2mg / kg once a day for three days via subcutaneous (SC), acetylcysteine at a dose of 10mg / kg, PO, and nebulization with saline solution for 15 minutes, twice a day. As vitamin and mineral supplementation, vitamin C was started at a dose of 6mg / kg, Apevitin BC® at a dose of 1.5mg / kg and EnergyPet®, administered orally and Glicofarm® at a dose of 0.5mg / kg by PO. Additionally, albendazole was administered at a dose of 25mg / kg, due to the positive result of coproparasitological examination, with evidence of Strongyloidea (Ancylostomatidae) eggs. After the 14-day interval, the antibiotic was replaced by enrofloxacin at a dose of 5mg / kg, twice a day for 14 days, PO, due to the greater sensitivity to gram-negative bacteria and also greater efficacy for the treatment of the respiratory system.

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After 3 weeks of hospitalization, the patient was submitted to a new chemical restraint to perform computed tomography, in order to identify and map the mass in the uterus. It was not possible to administer iodine-based contrast intravenously due to a moderate degree of dehydration, as it could result in nephrotoxicity. The same anesthetic protocol for the combination of Ketamine and Midazolam was used, with the addition of Morphine at a dose of 2mg / kg, IM, and induction with Propofol at a dose of 5mg / kg administered intravenously into the left cephalic vein and maintenance with isoflurane by face mask. New blood samples were collected for blood count and serum biochemistry for reassessments of the animal's general condition, especially regarding pneumonia. Urea, creatinine, albumin, alanine aminotransferase and alkaline phosphatase were requested. The results of the hemogram indicated normochromic macrocytic anemia, with formation of rouleaux in erythrocytes, marked leukocytosis and thrombocytosis and hyperproteinemia, indicating a worsening in relation to the previous hemogram due to changes in erythrogram and leukogram.

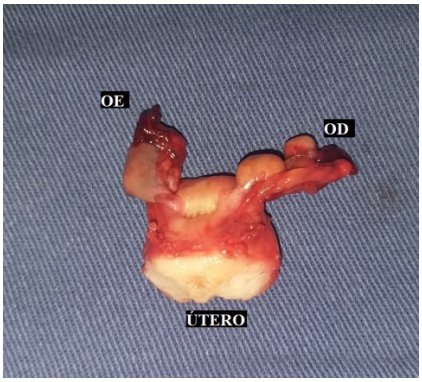

Figure 2. Reproductive tract of a female capuchin monkey removed during surgery for ovariosalpingohisterectomy. Presence of white mass, firm in uterus. There is also asymmetry of ovaries, with the left one being larger in size and showing a brownish color in relation to the right ovary. Source: Personal Archive

In the face of a possible uterine neoplasia, evidenced by the uterine enlargement observed in ultrasound and tomography exams, exploratory laparotomy and ovariosalpingohisterectomy were performed, performed on the same day of the tomography, in order to remove organs from the reproductive system and forward samples ovaries and uterus for histopathology. The technique chosen for the surgery was the same commonly used in dogs and cats: complete ovariosalpingohisterectomy, respecting the anatomical particularities of the species, and there were no complications during the surgical procedure. An incision of approximately 5 cm was made longitudinally from the umbilical scar along the ventral midline followed by muscle divulsion, and then the organs of the reproductive system were exposed. The body of the uterus was found dorsally to the urinary bladder. The technique of placing three clamps on the uterine stump, followed by section and suture surrounding and transfixing the uterine body, was used 3-0 nylon thread. Likewise, three clamps were used on both ovarian pedicles, which were incised and ligated with 3-0 nylon thread. The synthesis of the abdominal wall was done in two planes: 1) muscle and subcutaneous and 2) skin, with simple and continuous suture pattern, without exposure of the thread. Fluid therapy with Ringer's Lactate solution was administered at a dose of 10ml / kg intravenously hour during the procedure. After the procedure, the animal had excellent recovery from anesthesia and post-surgery, with no complications as the sutures did not show any reaction at the site. The sutures were not removed because they were internally, the skin was made with absorbable material and there was no reaction at the site. For treatment and monitoring of the postoperative period, new medications were added: Sulfadiazine with Trimethoprim at a dose of 25mg / kg, twice a day PO, morphine 2mg / kg, IM, every four hours on the first postoperative day, and later switched to Tramadol hydrochloride, at a dose of 4mg / kg, twice a day PO, Meloxicam 0.2mg / kg once a day, PO, Dipyrone 25mg / kg twice a day, PO, Scopolamine 0.1mg / kg four times a day , PO, Ranitidine 0.5mg / kg twice a day PO; in addition to oral vitamin and mineral supplements, nebulization with saline twice a day, cleaning the suture region with saline and 2% chlorhexidine twice a day, followed by application of 1% topical Rifaminica at the suture site. The antibiotic was replaced by sulfadiazine with trimethoprim due to its greater efficiency in the reproductive system, soft tissues and skin.

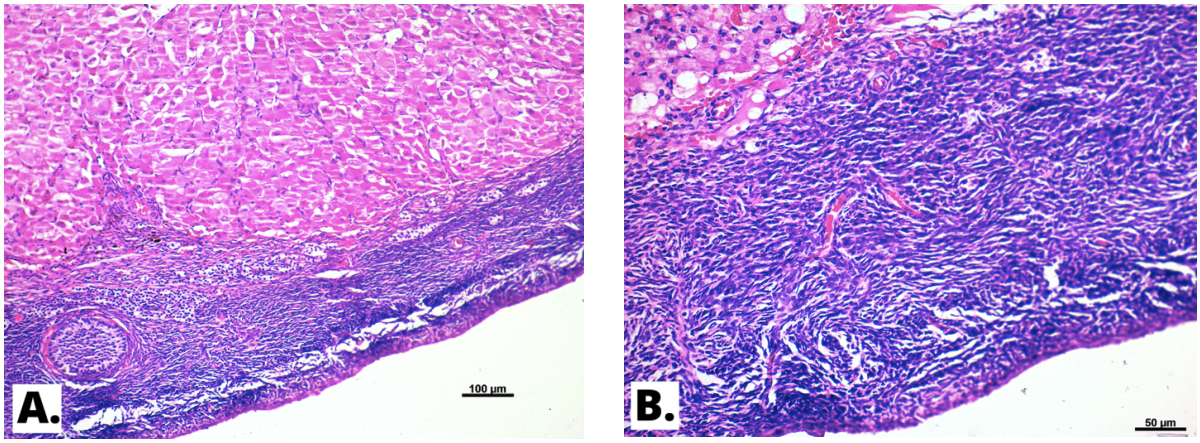

Figure 3. Histopathological exam images of the left capuchin monkey ovary. A. Ovarian cortex with spindle-shaped gonodal neoplastic cells. HE, obj.10x. B. Ovarian cortex with spindle cells and elongated basophilic nucleus, with dense chromatin and inconspicuous nucleolus. HE, obj.20x. Source: Personal Archive.

The material removed, uterus and ovaries, was sent to the Veterinary Pathology Laboratory of the Veterinary Hospital for histopathological examination. Macroscopically, the uterus was white and firm in consistency, while the ovaries were brownish to orange and smooth (Figure 2). Microscopically, there was an accentuated and diffuse proliferation of fibroblasts in the uterus, permeating and replacing the myocytes of the myometrium. The uterine glands had two or more layers of epithelial cells and a small amount of weakly eosinophilic amorphous content inside. There was also a marked multifocal lymphocytic inflammatory infiltrate in the endometrium and mild in myometrium and perimeter. In the ovaries, there was an accentuated, diffuse and limited proliferation of spindle-shaped gonadal neoplastic cells and to a lesser extent rounded cells in the region of the ovarian cortex, preventing the development of ovarian follicles (Figure 3). The spindle cells showed an elongated basophilic nucleus, with dense chromatin and inconspicuous nucleolus. The cytoplasm slightly eosinophilic, scarce and poorly delimited. The rounded cells had a large, round, basophilic nucleus with loose chromatin, eosinophilic and poorly marked cytoplasm. Based on the findings, a uterus with severe multifocal cystic endometritis was diagnosed; metritis and mild multifocal perimetritis and severe fibrosis, and in ovaries the presence of a granulosa-theca cell tumor.

After four weeks of the surgical procedure, a new clinical evaluation was performed. The animal was chemically contained with the association of Ketamine and Midazolam as pre-anesthetic medication and induction performed with Propofol, as previously used; and underwent further radiographic and ultrasound examinations. Blood samples were collected for blood count and serum biochemistry by means of ALT and gamma glutamyl transferase (GGT) tests, for liver assessment. There were no significant changes in the tests requested in relation to the reference values of the species. The sutures showed a satisfactory healing process during this interval. Considering the patient's clinical and post-surgical improvement without complications, the animal was discharged and could be sent to a faithful depository for mild reintroduction to a group of capuchin monkeys kept in captivity.

DISCUSSION

As with domestic animals, the occurrence of ovarian tumors in non-human primates is considered low (Chaffee and Magden, 2018). In women, the most common location for reproductive neoplasms is the uterus, followed by the ovaries and the cervix (Kitsoulis, 2020). In the case of the capuchin monkey in this report, uterine neoplasia was initially suspected, due to the findings of radiographic and ultrasound examinations; although the animal did not present clinical symptoms.

Guimarães (2012) morphologically described the female reproductive system of Sapajus sp, it was observed that the ovaries are compact and symmetrical. Histologically, the ovary has two regions, medullary and cortical, containing several follicles at different stages of maturation, classified as primordial, primary and secondary follicles. According to the result of the histopathological examination of the material collected in this case, the ovaries showed a marked proliferation of spindle-shaped gonadal neoplastic cells and rounded cells in the region of the ovarian cortex, preventing the development of ovarian follicles. The study by Guimarães (2012) also described the uterus of Sapajus sp. as simple and located in the pelvic region, morphologically, a globular aspect was observed at the junction of the fallopian tubes and a short portion of the cervix, which extends through the vaginal canal. In adult females, the average length is 2.36 cm and 0.93 cm wide. Histologically, the uterus has endometrium, myometrium and perimeter. While in this case, the ultrasound examination highlighted an increase in the uterine horns and body of the uterus, with the presence of echogenic content; and histopathological examination

According to Bezerra and Lorenzato (2004), who carried out a study with twenty-four women diagnosed with granulosa cell tumors of the ovaries, the carrier patients presented non-specific symptoms, with abdominal pain and distension. While the capuchin monkey in the case did not present abdominal distention or pain on abdominal palpation. Farman (2005) describes that hormonal secretion by the tumor, that is, the occurrence of hyperestrogenism, can result in other clinical manifestations such as menometrorrhages and intermenstrual bleeding. Although hormonal measurements of steroid hormone metabolites were not performed, for the purpose of studying seasonality (Cerda-Molina, et al 2006), bleeding was not observed in the capuchin patient, it was also observed that the animal's dorsal alopecia improved after the surgical procedure, this fact suggests a relationship with hyperestrogenism.

Another predisposing factor for the occurrence of tumor in primates is age, although the patient in this case was a young adult (Kitsoulis, 2020). The effect of hormones on carcinogenesis is associated with increased cell proliferation (Cline, 2004). In the case of this capuchin monkey, it is a rescued free-living animal and it is assumed that it has not been kept in captivity previously, so it is suggested that the development of this tumor is related to other hormonal changes, of congenital or genetic origin.

Ovarian tumors in non-human primates are not uncommon (Nagarajan, 2005). Among the cases of ovarian tumors already reported in neotropical primates are carcinomas and ovarian teratoma (Haworth, 2003), a granulosa-theca cell tumor in a scented monkey (Chalifoux, 1993). Often, granulosa tumors secrete estrogen resulting in endometrial cystic hyperplasia and occasionally endometrial adenocarcinoma (Patterson, 2003); According to Miller (2012), the majority of ovarian tumors grow unilaterally, which was observed in the case of the specimen treated at the Veterinary Hospital, only the left ovary presented a granulosa-theca cell tumor.

The prognosis correlates with the stage of the disease, grade of the tumor, mitotic index and spread of neoplastic cells to other tissues (Kota, S. 2012). Although the granulosa-theca cell tumor has a low potential for malignancy, long-term monitoring for monitoring is important, since there may be a recurrence of the tumor (Kota, S. 2012). The occurrence of metastasis in sex cord tumors varies between species, being more common in cats (Agnew and Maclachlan, 2017). In this case, samples were not collected from other organs for histopathological analysis to determine whether there was dissemination to other organs.

In addition, the prognosis is also related to the general state of the animal. He showed clinical improvement in terms of pneumonia and also in terms of alopecia.

CONCLUSION

The use of the total ovariosalpingohisterectomy technique for removal of uterus and ovaries proved to be effective for the treatment of granulosa-theca cell tumor in an adult specimen of capuchin monkey (Sapajus sp.).

Although it is known that the occurrence of neoplasms in cebids is higher in animals kept in captivity, tumors of granulosa-theca cells are rarely reported in capuchin monkeys. Therefore, further studies aiming at the occurrence and diagnosis based on imaging and laboratory tests are necessary.

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