

## Case Report

# Uterus-like Masses in a Rhesus Macaque (*Macaca mulatta*)

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Endometriosis is a relatively common condition in women and some populations of adult female rhesus macaques. However, endometriosis with extensive smooth muscle proliferation, as occurs in endomyometrioma and uterus-like mass (ULM), is rare in women. This report describes a case of endometriosis with extensive smooth muscle metaplasia resembling multiple ULM in a 20-y-old female rhesus macaque. During a protocol-related procedure, a large, smooth, globoid, freely moveable mass was palpated in the midabdomen. Ultrasonography revealed a cystic structure from which dark brown fluid was aspirated. During exploratory laparotomy, an 8-cm spherical mass in the greater omentum and 3 additional masses (diameter, 2 to 5 cm) attached to the omentum were excised. Microscopic examination of the masses revealed numerous foci of ectopic endometrial glands and stroma frequently surrounded by bundles of smooth muscle and fibrous connective tissue. The gross and histologic lesions in this macaque bore many similarities to ULM in women. To our knowledge, this case represents the first report of endometriosis resembling a uterus-like mass in a NHP.

**Abbreviations:** LPD, leiomyomatosis peritonealis disseminata; ULM, uterus-like mass

Endometriosis is defined as the presence of endometrial tissue outside of the uterine cavity. This condition only occurs in species that undergo menstrual cycles: Old World monkeys, great apes, and humans. In humans, endometriosis is estimated to affect approximately 10% of reproductive-age women<sup>43</sup> and most commonly presents as pelvic pain or infertility. Endometriosis is a common condition in adult female rhesus macaques (*Macaca mulatta*) and has been associated with a history of hysterotomy or other reproductive tract manipulation,<sup>12,16</sup> genetic predisposition,<sup>44</sup> certain toxins,<sup>38</sup> and ionizing radiation.<sup>11</sup> The incidence may be as high as 31.4% in some populations.<sup>44</sup> The disease is typically characterized by cysts and fibrous adhesions throughout the pelvic cavity.<sup>9,11</sup> Endometriotic foci are comprised of tissue resembling eutopic endometrium and are often accompanied by variable amounts of inflammation and fibrous connective tissue. Common clinical signs mirror those described in women and include uterine enlargement, irregular menses, and signs associated with dysmenorrhea. Complications such as endometriotic cyst rupture with subsequent hemoperitoneum and obstruction of the bowel or bladder related to adhesions may occur.<sup>15,25</sup>

Endomyometriosis, uterus-like masses (ULM), and extrauterine adenomyosis comprise a group of masses composed of benign ectopic endometrium surrounded by bundles of smooth muscle. They are considered to be exceedingly rare in humans.<sup>30</sup> The lesions share a common presentation of a mass with a central cavity lined with endometrial tissue surrounded by a thick wall

of smooth muscle recapitulating the uterine organoid structure. Lesions have been reported in female genital tract and gastrointestinal tract as well as remote locations in the abdomen and the terminal portion of the spinal cord.<sup>4,20</sup> Women most commonly present with dysmenorrhea and abdominal pain.<sup>24</sup> To our knowledge, the condition has not been reported in NHP. Here we present a case of endometriosis with extensive smooth muscle metaplasia resembling uterus-like masses in an aged rhesus macaque.

## Case Report

A 20-y-old, captive-reared, female, Indian-origin rhesus macaque was obtained from a primate facility in Texas 15 y previously. She was currently enrolled in an IACUC-approved AIDS vaccine protocol at the AAALAC-accredited Oregon National Primate Research Center. All animals are maintained and used in accordance with the *Guide for the Care and Use of Laboratory Animals*.<sup>19</sup> Routine husbandry parameters include 12:12-h light:dark cycles; controlled temperature, humidity, and ventilation; commercial primate chow (Purina 5000, Purina Mills, St Louis, MO); daily dietary supplementation with fresh fruits and vegetables, and unrestricted water.

The patient had a history of 4 hysterotomies; slightly prolonged, irregular menses; and mild uterine enlargement. Routine health care was provided biannually through physical examination, CBC and serum chemistry analysis, and ultrasonography. The macaque had recently been undergoing mucosal challenge with SIV. During a routine physical examination under ketamine anesthesia (10 mg/kg IM; Ketathesia, Butler Schein Animal Health, Dublin, OH), moderate uterine enlargement and ventral

Received: 08 Nov 2016. Revision requested: 09 Dec 2016. Accepted: 12 Dec 2016.

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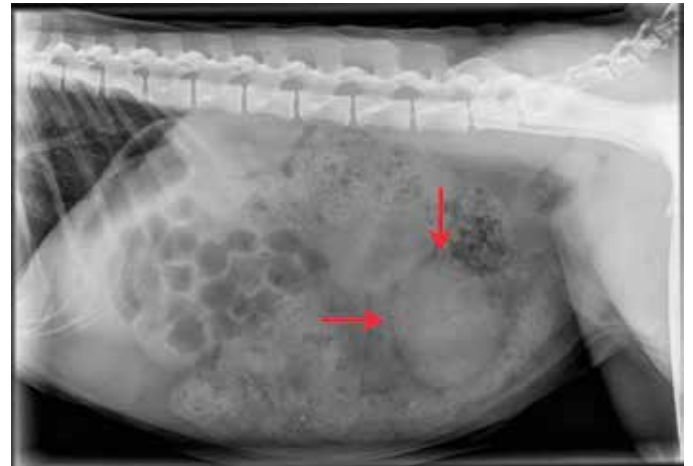
adhesions prompted further diagnostic evaluation. Other significant findings at the time included a grade II/VI left basilar systolic heart murmur and excess body condition, with a body condition score of 4/5<sup>8</sup>. Serum chemistry and CBC analysis and thoracic radiographs were unremarkable. A circular, soft-tissue-density mass effect was noted in the caudal lateral abdomen on right lateral and ventrodorsal radiographs (Figure 1). The mass could not be confirmed by palpation, presumably due to abdominal adiposity. On ultrasound evaluation, the uterus was enlarged, but no abnormal cystic structures corresponding to the radiographic findings were identified.

At a follow-up examination, smooth, globoid, freely moveable, intraabdominal mass (diameter, approximately 6 cm) was palpated along the ventral midline. Ultrasound examination at this time revealed a homogenous, hypoechoic cyst with disorganized hyperechoic areas (Figure 2). Percutaneous aspiration of the cyst yielded dark-brown fluid that on cytology consisted mostly of amorphous cellular debris with occasional neutrophils and macrophages. Follow-up CBC and serum chemistry findings were unremarkable, and a fecal occult blood series, to screen for gastrointestinal adenocarcinoma, was negative. Given her clinical history and findings, the macaque was diagnosed with presumptive endometriosis with cyst formation ('chocolate cyst' or endometrioma). The case was discussed with the investigative staff, and an exploratory laparotomy was scheduled.

**Surgery.** The macaque was sedated with ketamine hydrochloride (15 mg/kg IM) combined with glycopyrrolate (0.01 mg/kg IM; West-Ward, Eatontown, NJ). A local block consisting of 0.5% bupivacaine (0.8 mL ID; Hospira, Lake Forest, IL) combined with 1% lidocaine with epinephrine (0.2 mL ID; APP Fresenius Kabi USA, Lake Zurich, IL) was administered at the proposed laparotomy site. The animal was intubated, and general anesthesia was maintained with 1% to 3% isoflurane (Piramal Healthcare, Andhra, India) combined with 100% oxygen. Hydromorphone hydrochloride (0.05 mg/kg IV; Hospira) was administered for analgesia, and electrolyte solution (10 mL/kg/h IV; Lactated Ringer Solution, Baxter Healthcare, Deerfield, IL) was provided throughout the procedure.

With the animal in dorsal recumbency, a ventral midline laparotomy was created, revealing a spherical mass (diameter, approximately 8 cm) firmly attached to the greater omentum. On exteriorization of the mass, 3 additional masses (diameter, 2 to 5 cm) attached to adjacent regions of the omentum were identified. Each mass was excised by using electrocautery and placed into formalin for histopathologic evaluation. The remaining abdominal contents were examined and appeared normal, with the exception of the uterus, which was approximately 4 times the normal size. The ovaries were excised to prevent future signs associated with endometriosis and submitted for histopathology to confirm complete excision.

Standard postoperative analgesia was provided (hydromorphone hydrochloride at 0.2 mg/kg IM every 4 to 6 h during the day; buprenorphine at 0.03 mg/kg IM once daily in the evening; Hospira) for 72 h after surgery. Daily postoperative monitoring and assessment of pain and distress were provided by surgical veterinary staff. The macaque recovered well from the procedure. A mild anemia and intermittent bloody vaginal discharge was observed during the first week of postsurgical recovery and resolved without intervention. A ferrous fumarate supplement (6 mg PO daily for 14 d; PolyVitamin Chew with Iron, Rugby,



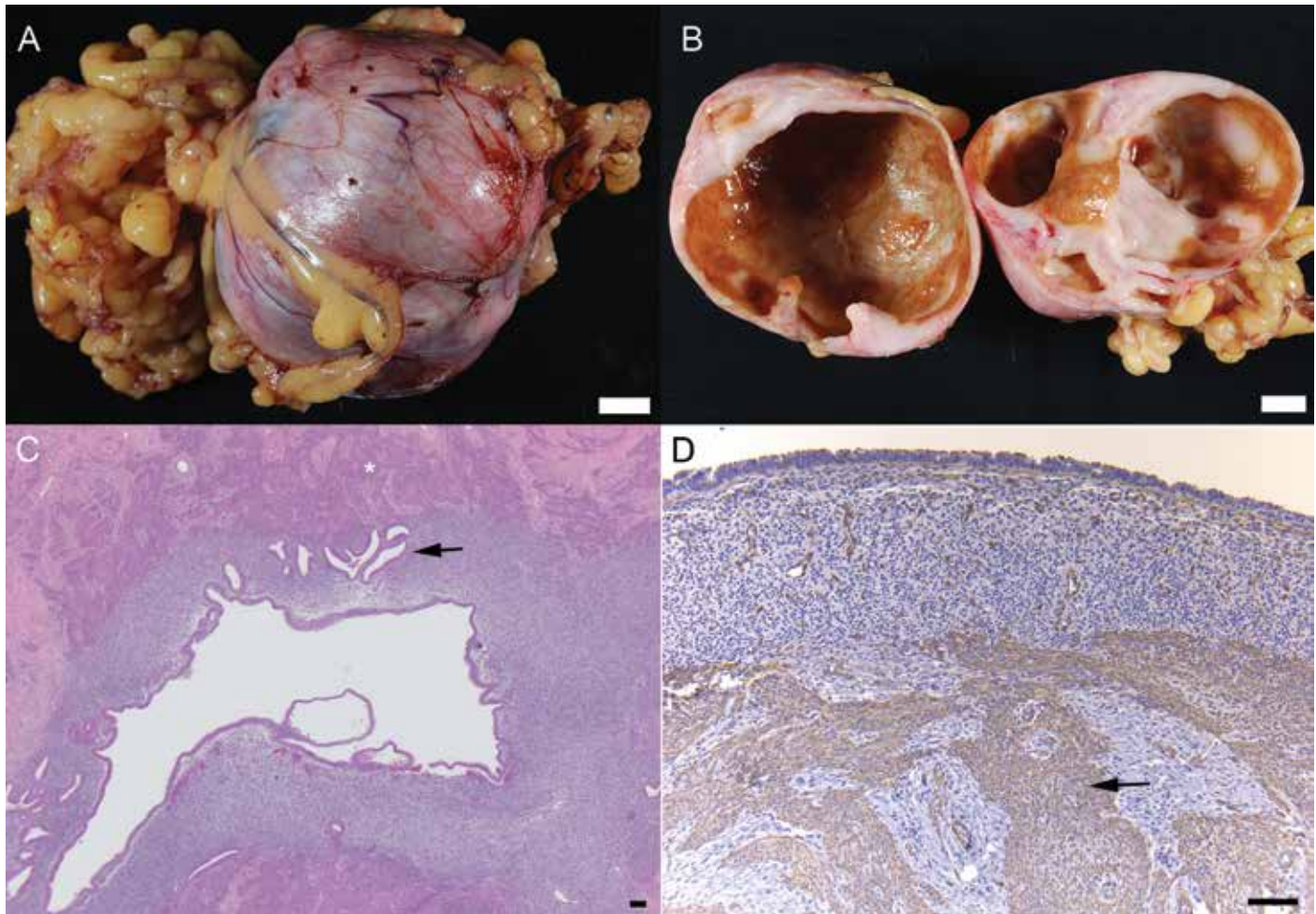
**Figure 1.** Right lateral abdominal radiography demonstrates a soft-tissue-density mass (approximately 8 × 6 cm) in the caudal abdomen.



**Figure 2.** Abdominal ultrasonography of uterus-like mass reveals a homogenous, hypoechoic cyst with disorganized hyperechoic areas. Percutaneous aspiration yielded dark-brown fluid.

Livonia, MI) was administered in light of the anemia, which was resolved at follow-up CBC analysis approximately 7 wk later.

**Pathology.** The 4 resected masses had smooth, off-white walls and contained dark reddish-brown fluid (Figure 3 A and B). The largest was 8 × 6 × 6 cm<sup>3</sup>; the smaller masses were 2 to 3.5 cm in diameter. On microscopic examination, the cystic spaces were lined by endometrial tissue consisting of variably proliferative columnar epithelium with apical blebs supported by highly cellular spindle-cell stroma. These endometriotic foci were surrounded by abundant fascicles of smooth muscle, variably interspersed with a densely collagenous stroma and in places appeared to recapitulate normal uterine architecture (Figure 3 C). Complete ovarian excision was confirmed. Immunohistochemistry was performed to confirm the histologic nature of the tissues, by using an avidin-biotin complex method (Vector ABC HRP Kit Standard, Burlingame, CA) with DAB chromogen visualization. Smooth-muscle actin (1:1000; monoclonal mouse antihuman, clone 1A4, code M0851, Dako, Glostrup, Denmark) positively stained the



**Figure 3.** Abdominal uterus-like masses in a rhesus macaque. (A) The largest of several cystic masses present in the omentum. Bar, 1 cm. (B) Sectioned surfaces of 2 of the masses reveal a cystic cavity containing reddish-brown fluid and velvety reddish-brown lining. Bar, 1 cm. (C) Histologic section reveals central lumen lined by endometrial tissue with endometrial glands (arrow) surrounded by dense bundles of smooth muscle (asterisk) and fibrous connective tissue. Hematoxylin and eosin stain; bar, 100  $\mu$ m. (D) Immunohistochemistry for smooth muscle-actin highlights bundles of smooth muscle (arrow) forming the wall of the uterus-like mass. DAB with hematoxylin stain; bar, 100  $\mu$ m.

smooth-muscle bundles within the cyst walls (Figure 3 D). Omental endometriosis with smooth muscle metaplasia was diagnosed in view of the clinical and pathologic findings.

**Follow-up.** The macaque continued to do well for approximately 12 wk after the surgery. Subsequently, she developed signs associated with protocol-related SIV disease and was euthanized at a defined project endpoint. At necropsy, the uterus was enlarged. The lumen contained a broad-based, firm, whitish-pink polypoid mass ( $2.9 \times 2.0 \times 2.0$  cm<sup>3</sup>). A smaller ( $0.5 \times 0.3$  cm<sup>2</sup>) mass was present at the internal cervical os, and a 0.3-cm droplet-shaped mass in the cervical lumen was attached by a thin (2-cm) stalk to the uterine lumen. There was moderate fibrous adhesion of the uterus to colonic serosa. There was no evidence of endometriosis or a uterus-like mass at necropsy. Uterine masses were confirmed as endometrial stromal polyps. Other necropsy findings were attributed to SIV-related disease.

## Discussion

Masses composed of well-organized endometrium and smooth muscle have been variably referred to in the literature as endo-

myometriomas, ULM, and extrauterine adenomyosis with uterus-like features. All refer to masses with a central cavity lined by benign endometrial glands and stroma surrounded by thick walls of myometrial smooth muscle. ULM was first described in the ovary, and a similar lesion, termed endomyometriosis, was described in an obturator lymph node, both in 1981.<sup>10,32</sup> These lesions are rare in women; approximately 30 cases have been described since the first case report.<sup>29</sup> The majority have occurred within the abdomen involving the female genital tract including the ovary, uterus, and broad ligament.<sup>3,4,24,27,30,34,40,41</sup> Additional abdominal sites include the small intestine, appendix, and colon and respective mesentery as well as the retroperitoneum and liver.<sup>17,18,22,28,36,39</sup> Extraabdominal locations include the terminal spinal cord (conus medullaris and filum terminale)<sup>20,33,35</sup> and the occurrence of endomyometriosis in men in the scrotum, paratestis, and bladder serosa associated with hormonal therapy for prostate cancer.<sup>14</sup> Malignant transformation, including clear cell carcinoma and endometrioid carcinoma, has been reported rarely.<sup>29,31</sup>

ULM has also been reported in a case of leiomyomatosis peritonealis disseminata (LPD) with endometriosis.<sup>5</sup> LPD is another

rare benign disease in women and is characterized by multiple peritoneal masses composed of benign smooth muscle. LPD has a reported association with endometriosis.<sup>1,5</sup> There is some overlap in the histologic description of these cases with endomyometrioma.<sup>5,42</sup> Multiple ULM have been reported both in association with LPD and extrauterine adenomyomas.<sup>4,5</sup> In addition, endometriotic foci may undergo significant smooth muscle metaplasia,<sup>13,23</sup> and their histologic features may overlap with those of ULM. To our knowledge, no data are available regarding ULM or endomyometrioma in NHP.

Several pathogenetic mechanisms have been proposed regarding the development of ULM in women. These include 1) Muellerian duct defects, 2) subcoelomic mesenchymal transformation (metaplasia), and 3) developmentally misplaced Muellerian tissue (muellerianosis or heterotopia). The occurrence of congenital genitourinary anomalies in human patients with endomyometriosis lends support to the theory of ULM as a Muellerian duct fusion defect or partial duplication of the Muellerian system, in which the uterus-like structures develop under the influence of steroid sex hormones.<sup>6,21,26</sup> The association of ULM with endometriosis and its occurrence in the ovary in numerous cases has led many authors to support the metaplastic theory.<sup>10,13,23,28,32,34</sup> The rate of endometriosis among cases of ULM is much higher than in the general population, and the anatomic distribution of ULM is similar to that of endometriosis.<sup>34</sup> The third theory regarding the origin of ULM is heterotopia—the presence of histologically normal tissue in an abnormal location—and is postulated in cases of ULM in the lumbosacral region.<sup>2,35</sup>

Differentials for abdominal masses in macaques include endometriosis; foreign body; abscess; and neoplasia such as leiomyoma, adenoma, adenomyoma, or other carcinomas and sarcomas, as well as less common entities such as endomyometriosis (ULM) and LPD. Clinical signs are often similar for these lesions, making microscopic examination important for diagnosis. Leiomyomas are the most common uterine neoplasia described in rhesus macaques.<sup>7,37</sup>

No differences in treatment recommendations or outcomes have been reported for ULM compared with endometriosis. Most reports describe surgical removal of the masses through laparotomy or laparoscopy, with subsequent resolution of clinical signs. Removing the hormonal influence through oophorectomy or hysterectomy is likely important, as in endometriosis. Oophorectomy to remove endogenous estrogen is a standard therapy for macaques with endometriosis.<sup>11</sup> Medical therapy has been described for ULM in women, generally for masses that are determined to be unresectable. Therapy with agonists of gonadotropin-releasing hormone prevents ovulation and assisted in stabilizing disease and resolving symptoms in 2 cases.<sup>4</sup> Medroxyprogesterone can be used to treat abnormal bleeding from the uterus, and its use ameliorated symptoms in one case, although it did not stabilize the growth of the mass, which subsequently doubled in size several years later.<sup>21</sup> Treatment with medroxyprogesterone in the case with LPD-related disease resolved symptoms and appeared to stabilize disease progression over a short follow-up period.<sup>5</sup> A recent publication describes and recommends minimally invasive surgical techniques for the excision of uterus-like masses in women.<sup>40</sup> In our case, surgical removal of the masses with concurrent oophorectomy resolved symptoms until the macaque was euthanized at a protocol-related endpoint 12 wk later.

In summary, this case represents the first report of endometriosis with features of ULM in a NHP. Endomyometriomas and ULM are similar to endometriosis in their presentation and can be distinguished through histopathology. As such, ULM should be considered as a differential diagnosis when endometriosis is suspected in a NHP. Further research is needed to identify the origin of these lesions and whether they require unique management strategies.

## Acknowledgments

We acknowledge the expertise and contribution of J Mark Cline, DACVP. This work was supported in part by NIH support for the Oregon National Primate Research Center (grant no. P51OD011092).

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