

## Case Report

# Spontaneous Urinary Bladder Leiomyoma in a Rhesus Macaque (*Macaca mulatta*)

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Here we report the case of a urinary bladder leiomyoma in a rhesus macaque. The animal was clinically normal and had a lipoma localized to the stifle. Endovesicular leiomyomas are the most common form of urinary bladder leiomyoma in humans. In contrast, this macaque's tumor exhibited extravascular localization in the bladder. Urinary bladder leiomyomas account for less than 0.5% of all bladder tumors in humans, with only 250 cases reported in total.

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## Case Report

All primates in the Massachusetts Institute of Technology animal facility are housed in accordance with the *Guide for Care and Use of Laboratory Animals* (8th edition) in an AAALAC-accredited facility and are used in accordance with IACUC-approved protocols.<sup>20</sup> Animals are maintained in a 12:12-h light:dark cycle and receive a commercially formulated primate diet (Lab Diet 5038, PMI Nutrition International, St Louis, MO), which is fed twice daily. Primates are supplemented with a foraging mixture of fruit, vegetables, nuts, and cereal. Water is freely available except when water regulation is required under approved protocols. Macaques are pair-housed, except when precluded by established behavioral incompatibility or for medical reasons, as determined by a veterinarian. Environmental enrichment includes food puzzles, toys, mirrors, videos, and positive interaction with care staff. Incoming primates undergo a quarantine period and must be confirmed serologically negative for *Simian retrovirus*, *Simian T-lymphotropic virus 1*, *Cercopithecine herpesvirus 1* (B virus), and SIV. Hct, total protein, and a fecal exam for endoparasites using a passive sodium nitrate float are performed at quarterly physical exams.

A 19-y-old female rhesus macaque (*Macaca mulatta*) underwent perfusion and necropsy after an intracranial viral injection procedure. The animal's history included a 7-y history (1996 to 2003) of involvement in neurocognitive research, which involved water regulation as required under approved protocols. In addition, the macaque had a 2-y history of a static soft-tissue subcutaneous mass proximal to the left stifle joint.

On necropsy, gross examination revealed a focally thickened bladder wall (approximately 1 cm) that lacked well-circumscribed borders, with smooth and regular mucosa and a soft circumscribed dermal mass (lipoma) proximal to the left stifle joint. Histopathologic examination of the urinary bladder revealed a discrete, well-circumscribed neoplastic mass expanding the adventitia. Mason Trichrome stain was applied to differentiate elastic fibers, collagen fibers, and muscle. The

tumor was composed of well-differentiated neoplastic spindle cells arranged in fascicles supported by fine fibrovascular connective tissue. Neoplastic cells had indistinct cell borders, abundant eosinophilic fibrillar cytoplasm, round to oval nucleus with stippled chromatin and variably distinct nucleoli, and occasional mitotic figures (Figure 1).

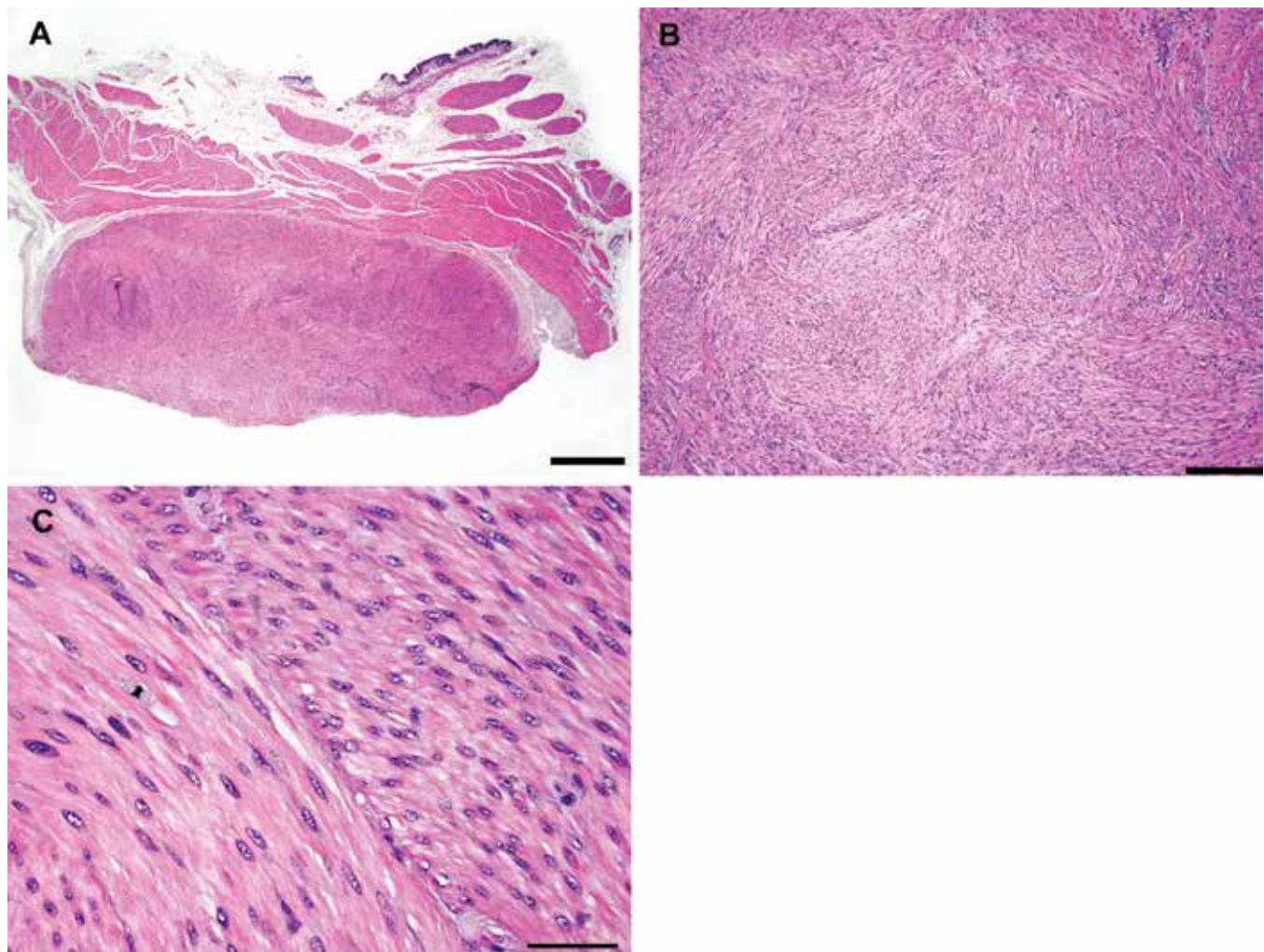
Immunohistochemistry was performed to further characterize the neoplastic cell population. The following primary antibodies were applied to differentiate tissue sections: vimentin (M0725, clone V9, Dako, Carpinteria, CA; dilution, 1:100), desmin (MA1-06401, clone D9, Thermo Scientific, Waltham, MA; 1:100), pancytokeratin (CM011B, clone AE1/AE3, Biocare Medical, Pacheco, CA; 1:75), smooth muscle actin (MA5-11547, clone 1A4, Thermo Scientific; 1:400), and S100 (CM128A, clone 15E2E2, Biocare Medical; 1:100). Primary antibody incubation was followed by incubation with mouse antimouse secondary antibody (MM620, Biocare Medical) followed by DAB as a chromagen (Betazoid kit, BDB2004, Biocare Medical). The neoplastic cells stained positive for vimentin, smooth muscle actin, and desmin and negative for pancytokeratin and S100, thus confirming that the tumor was a leiomyoma (Figures 2 and 3).

## Discussion

In macaques, leiomyomas are the most common uterine tumor (termed 'fibroids') and have also been reported in the small intestine of macaques and at the gastroesophageal junction in a chimpanzee.<sup>1,4,9,16</sup> Urinary leiomyoma, like uterine fibroids, contain smooth muscle cells with variable amounts of dense collagenous matrix.<sup>9</sup> Urinary bladder leiomyomas have been reported in humans, dogs, cats, and goats.<sup>10,18,31,33,40</sup> Approximately 250 human cases of bladder leiomyomas have been reported in total.<sup>21,35</sup> This rare tumor occurs 3 times more often in females as in males; this difference is likely due to increased detection through more frequent pelvic examinations in female patients.<sup>10</sup> In addition, estrogen has been theorized to play a contributing role.<sup>19,29,42</sup> These smooth muscle tumors can exhibit intramural, endovesical, and extravascular localization in the urinary bladder.<sup>15,25</sup> Endovesical tumors are most common and expand into the bladder lumen, making them more likely to cause obstructive uropathy.<sup>21,23,28,32</sup> The most common reported symptoms of

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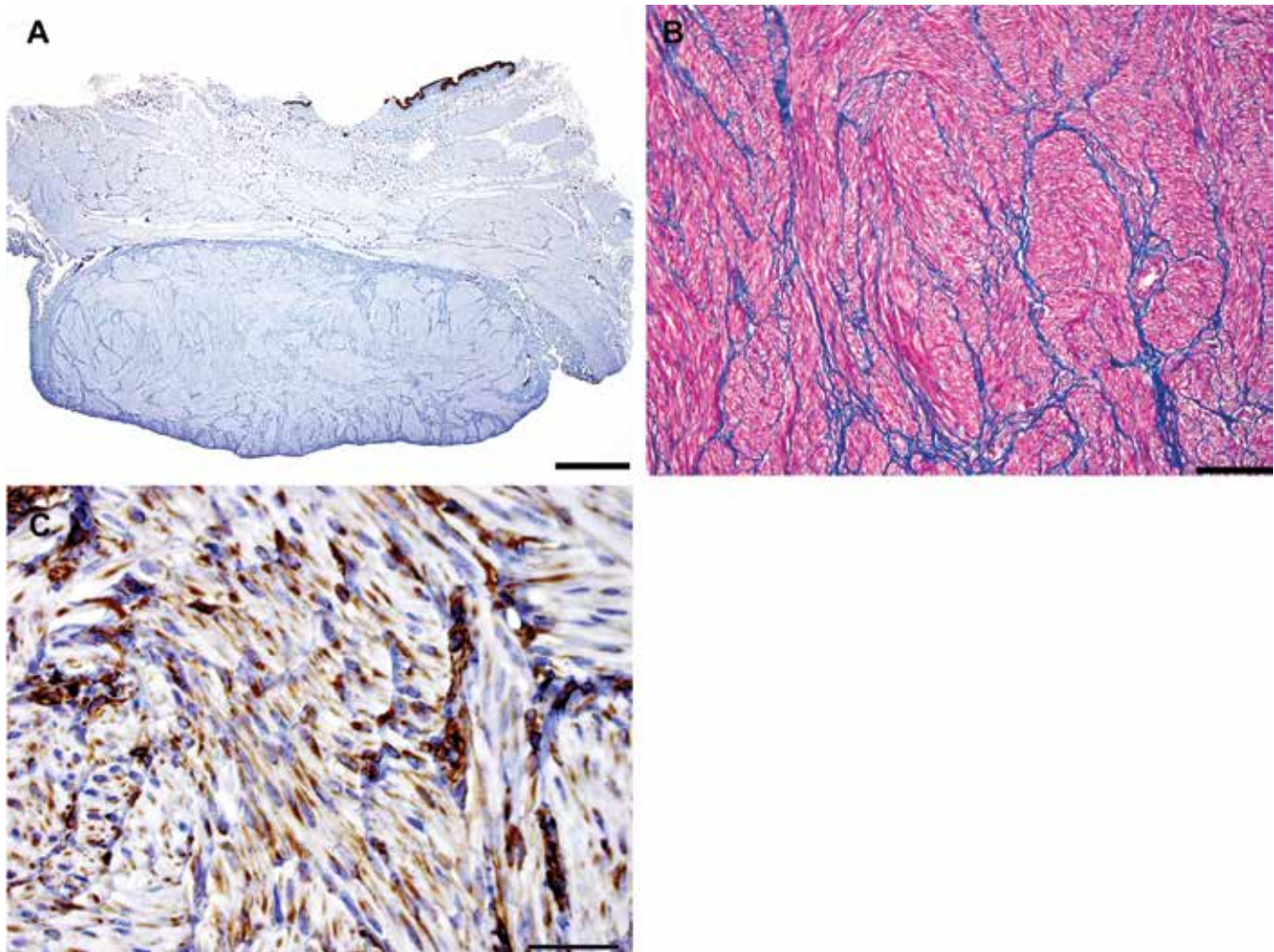
**Figure 1.** (A) Discrete, well-circumscribed neoplastic mass expands the adventitia of the urinary bladder. Hematoxylin and eosin stains; scale, 1 mm. (B) Neoplasm was composed of spindle cells arranged in interlacing fascicles supported by fine fibrovascular connective tissue. Hematoxylin and eosin stains; scale, 200  $\mu$ m. (C) Neoplastic cells have indistinct cell borders, abundant eosinophilic fibrillar cytoplasm, round to oval nucleus with stippled chromatin and variably distinct nucleoli, and occasional mitotic figures. Hematoxylin and eosin stains; scale, 50  $\mu$ m.

leiomyomas include pollakiuria, dysuria, and hematuria.<sup>15,21</sup> Intramural and extravescicular localizations are reported less frequently than endovesicular lesions and are more likely to be asymptomatic.<sup>25,37</sup> Excision of a leiomyoma tumor is curative, and the rate of reoccurrence is low.<sup>15,21,29,32,42</sup> In the case we present here, the macaque lacked clinical signs, likely due to the small size of the extravescicular tumor.

Differential diagnoses for a urinary bladder mass in an aged rhesus macaque include ectopic endometrial tissue (endometriosis) and transitional cell carcinoma. In addition, mineralization of embryonic remnants in the adventia and intramural ectopic ovarian tissue of the urinary bladder has been reported.<sup>6,34</sup> The incidence of endometriosis in aged macaques can be as high as 30% in some populations,<sup>2,3</sup> with ectopic endometrial tissue commonly affecting the urinary bladder.<sup>36</sup> The incidence of urinary bladder endometriosis in women is 12%, and the trigone area of urinary bladder is considered to be the most common site.<sup>26</sup> Symptoms of urinary bladder endometriosis include dysuria, pollakiuria, caudal abdominal pain, and cyclic hematuria, but the condition can also be asymptomatic.<sup>26</sup> Endometriosis can be treated with surgical resection or hormonal therapy.<sup>26,27</sup> In contrast, transitional cell carcinoma is the most common tumor of the urinary bladder in humans, dogs, and cats but has rarely been reported in macaques to occur spontaneously.<sup>5,7,13,17,38,41</sup>

Transitional cell carcinomas have been induced with carcinogens, including aflatoxin and 2-naphthylamine, in rhesus macaques and are associated with schistosomiasis in a talapoin monkey, a capuchin monkey, and gibbons.<sup>8,30,39</sup> In dogs, transitional cell carcinomas compromise 2% of all tumors, and common clinical signs include hematuria, stranguria, and pollakiuria.<sup>13,24</sup> As an aggressive tumor, transitional cell carcinoma has been reported to reoccur after radical cystectomy in humans and often leads to metastasis.<sup>22</sup> Complete resection of transitional cell carcinomas from the bladders of dogs is difficult, given that the mass typically localizes to the trigone.<sup>13</sup> Both endometriosis and transitional cell carcinoma can be differentiated from other disease processes through histologic examination, which is necessary for definitive diagnosis.<sup>13,14</sup>

Leiomyosarcoma, an aggressive tumor of smooth-muscle origin, accounts for less than 1% of human bladder malignancies. Leiomyosarcomas often present with painless hematuria and pollakiuria.<sup>11</sup> Overall, urinary tumors can be detected by radiology, ultrasonography, CT, and MRI.<sup>15,21,29,37,42</sup> Diagnosis of leiomyoma or leiomyosarcoma is confirmed through histology and immunohistochemistry, because differentiating between mesenchymal tumors by using routine histologic methods can be difficult.<sup>32,40,42</sup> In addition, symptoms of bladder cancer often mimic the clinical signs of urinary tract infections (pollakiuria



**Figure 2.** (A) Negative pancytokeratin immunoreactivity indicated that the mass was not of epithelial origin. DAB and hematoxylin stains; scale, 1 mm. (B) Mason trichrome staining revealed neoplastic cells (red) separated by minimal amounts of fibrous connective tissue (blue). Scale, 100  $\mu$ m. (C) Neoplastic cells showed positive immunoreactivity for vimentin, indicating that they were mesenchymal in origin. DAB and hematoxylin stains; scale, 50  $\mu$ m.

and dysuria) and therefore should be considered as a differential diagnosis in patients with urinary clinical infections.<sup>12</sup>

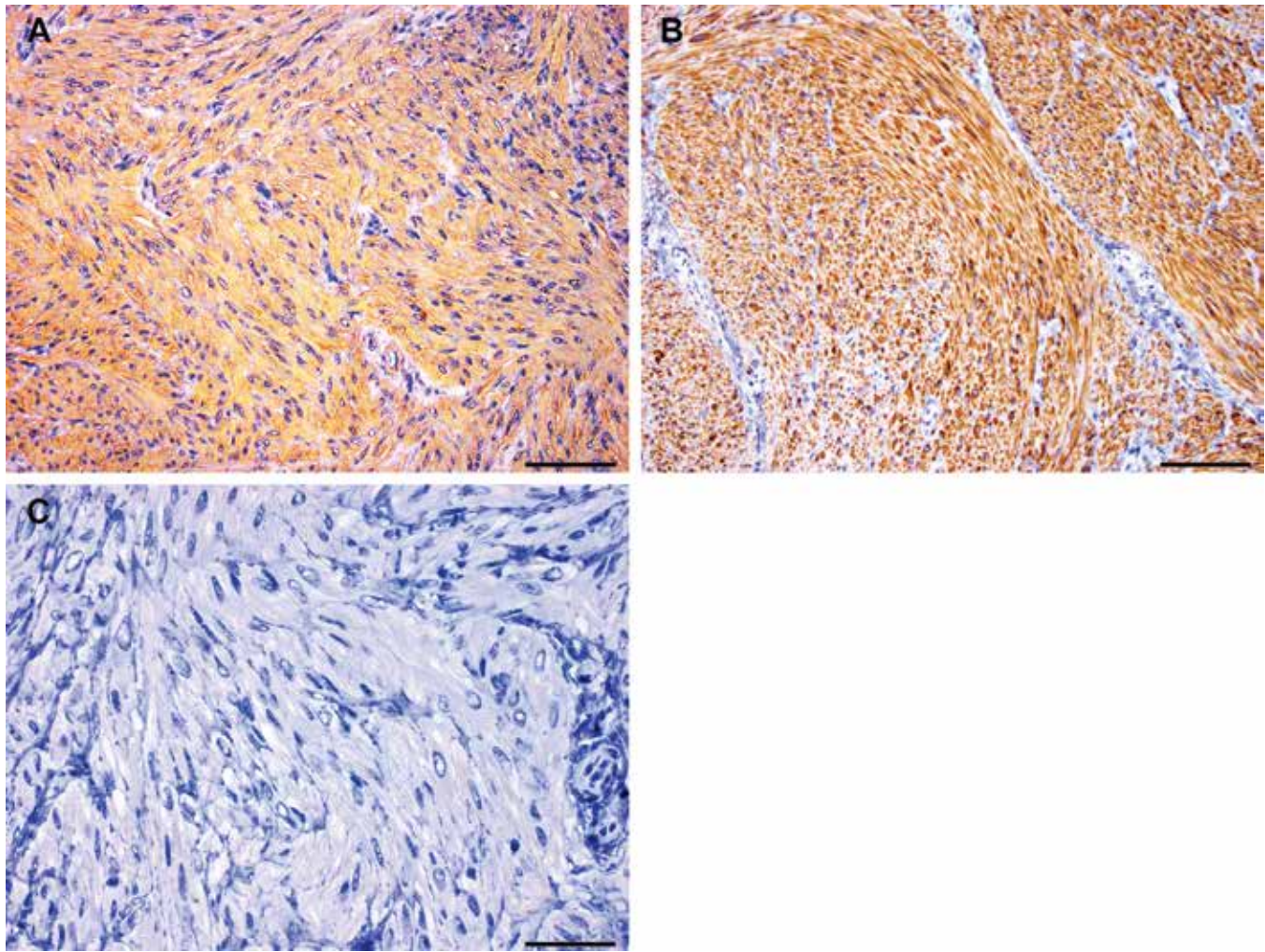
In conclusion, this case represents the first report of urinary bladder leiomyoma in a rhesus macaque. The macaque lacked any clinical signs of urinary tract disease, and the lesion was found incidentally at necropsy. Overall, leiomyoma of the urinary bladder is a rare occurrence in many species, including humans, but should be considered as a differential diagnosis for urinary tumors.

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**Figure 3.** (A) Neoplastic cells stained positive for desmin antibody, indicating that the neoplasm was of muscle origin. DAB and hematoxylin stains; scale, 50  $\mu$ m. (B) Positive immunoreactivity to smooth muscle actin antibody confirmed that the neoplastic cells were of smooth-muscle origin. DAB and hematoxylin stains; scale, 50  $\mu$ m. (C) Negative immunoreactivity to S100 indicated that the neoplastic cells did not originate from the neural crest. DAB and hematoxylin stains; scale, 50  $\mu$ m.

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