

Case Report

Abdominal Wall Endometriosis in a Rhesus Macaque (*Macaca mulatta*)

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Endometriosis is the presence of endometrium outside of the uterus. Although endometriosis occurs in both pelvic and extrapelvic locations, extrapelvic locations are less common. The development of abdominal wall or incisional endometriosis in women is associated with gynecologic surgeries and is often misdiagnosed. Because they naturally develop endometriosis similar to women, Old World NHP, including rhesus macaques, provide excellent opportunities for studying endometriosis. Here, we describe a case of abdominal wall endometriosis in a rhesus macaque that had undergone cesarean section. Microscopically, the tissue consisted of pseudocolumnar epithelium-lined glands within a decidualized stroma, which dissected through the abdominal wall musculature and into the adjacent subcutaneous tissue. The stroma was strongly positive for vimentin and CD10 but was rarely, weakly positive for estrogen receptors and negative for progesterone. Close examination of extrapelvic endometriosis in rhesus macaques and other NHP may promote increased understanding of endometriosis in women.

Endometriosis is a chronic condition in which hormone-responsive endometrium develops outside of the uterus. Endometriosis affects as many as 10% of reproductive-age women and results in pelvic or abdominal pain and infertility.⁹ The most common site for endometriosis is within the pelvic cavity, although extrapelvic locations including the abdomen and thorax can be involved. Cutaneous or incisional endometriosis, the development of endometriosis tissue within the subcutaneous adipose tissue or muscle, is often associated with gynecologic surgery, Caesarean section, or hysterectomy and occurs in about 2% of cases. These lesions range from a few millimeters to several centimeters in diameter, and the tissue is often nodular and firm with a myxoid, mucoid, or fibrinous appearance.⁸ Endometriosis in surgical scars may be misdiagnosed as hematomas, lipomas, granulation tissue, hernias, abscesses, fibromatosis, and sarcomas or other malignancies. Surgical-scar endometriosis may also mimic malignancy histologically, when exhibiting nuclear atypia.¹

Old World NHP, including rhesus macaques, naturally develop endometriosis with a similar presentation to that in women and are established models for studying disease pathophysiology and therapeutic interventions.⁵ In addition, NHP develop endometriosis in extrapelvic locations, allowing for the study of molecular differences in this tissue in different locations and in eutopic endometrium.² Here we describe a case of abdominal-wall endometriosis in a rhesus macaque.

Case Report

A 12.6-y old intact female rhesus macaque (*Macaca mulatta*) diagnosed with endometriosis at the Wake Forest School of Medi-

cine presented for treatment of a foot laceration, at which time an abdominal scar, which had begun to dehiscence, was noticed. The macaque underwent exploratory laparotomy and because of the extent and severity of the endometriosis, euthanasia was elected.

Approximately 6 y before necropsy, the macaque had undergone a cesarean section at a prior institution to terminate an overdue pregnancy. The animal was postoperatively treated with sulfamethoxazole–trimethoprim (20 mg/kg PO), buprenorphine (0.01 mg/kg IM), and ketoprofen (5 mg/kg IM). Over the next several days, she received sulfamethoxazole–trimethoprim (20 mg/kg PO BID) and carprofen (4 mg/kg PO BID). The incision healed slowly yet completely with development of excessive granulation tissue. Approximately 3 y later, the macaque was diagnosed with endometriosis before her transfer to Wake Forest. Depot medroxyprogesterone acetate was administered every 60 to 90 d to treat symptoms from the time of diagnosis until death. Periodic diarrhea diagnosed as stress colitis was often observed associated with menses. Otherwise the medical history was unremarkable. Wake Forest is an AAALAC-accredited institution and operates under the guidelines in the *Guide for Care and Use of Laboratory Animals*.⁶ All animals at Wake Forest are housed and treated in concordance with IACUC-approved protocols.

A complete necropsy was performed by a board-certified veterinary pathologist. On gross examination, fibrous adhesions bound the viscera together and to the abdominal wall. Dark-brown, fluid-filled cysts were present within the incision site and extended from the muscular wall into the subcutaneous adipose tissue. Similar cysts were present in the abdominal cavity on the uterine surface and surrounding both ovaries and fallopian tubes.

Microscopic evaluation of the lesions stained with hematoxylin and eosin revealed endometrial glands lined by pseudocolumnar epithelium within a decidualized stroma within the abdominal incision (Figure 1 A) and on the surfaces of the uterus, small intestine, ovary, and urinary bladder. The endometriosis tissue in

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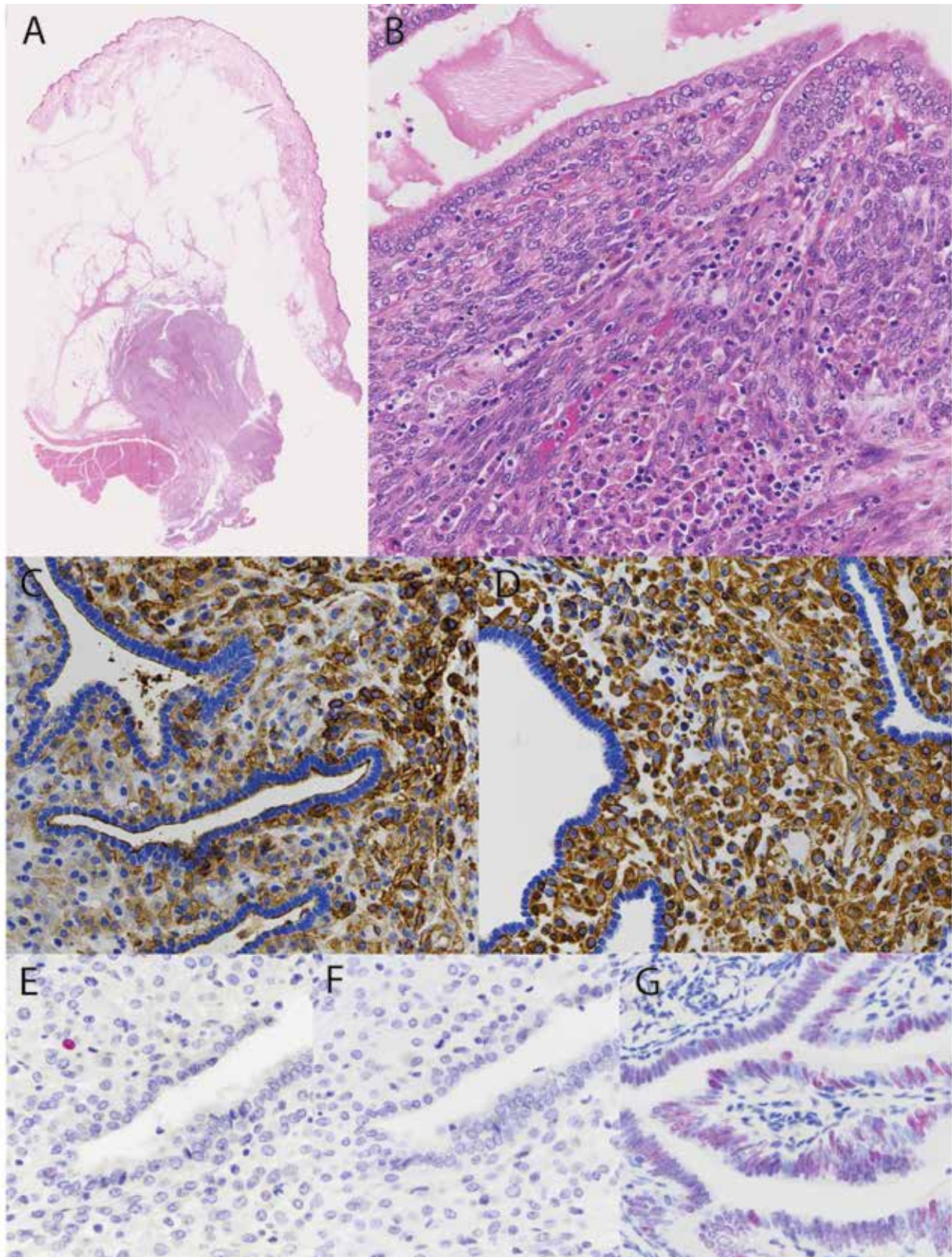


Figure 1. Abdominal wall incisional endometriosis, rhesus macaque. (A) Subgross image of a poorly demarcated mass of endometriosis tissue (asterisk) within the subcutaneous adipose tissue and skeletal muscle underneath a section of haired skin. Hematoxylin and eosin stain; magnification, 4 \times . (B) The tissue is composed of pseudostratified columnar epithelium-lined glands within a densely cellular decidualized stroma. The stromal cells are polygonal with large vesicular nuclei and single nucleoli. Hemosiderin-laden macrophages are scattered throughout. Hematoxylin and eosin stain; magnification, 200 \times . (C) Immunohistochemical stain for CD10 demonstrates moderately strong cytoplasmic staining of the stromal cells. Magnification,

the abdominal wall extended from the subcutaneous muscle and into the adipose tissue. Decidualized stromal cells were polygonal, often with large, vesicular nuclei and as many as 2 nucleoli. Aggregates of hemosiderin-laden macrophages and fewer small granular lymphocytes were scattered throughout (Figure 1 B). Neutrophilic inflammation and fibroplasia were present at the junction of the endometriosis tissue and the subcutaneous adipose tissue.

The tissue from the abdominal incision was stained for vimentin (1:3000; clone V9, BioGenex, Fremont, CA), CD10 (1:100; common acute lymphoblastic leukemia antigen [CALLA], clone 56C6, Leica Microsystems, Wetzlar, Germany), cytokeratin (1:400; clone AE1/AE3, Dako, Glostrup, Denmark), estrogen receptor α (1:300; clone 6F11, mouse monoclonal, Leica Microsystems), and progesterone receptor (1:40; clone 1A6, mouse monoclonal, Novocastra, Vision Biosystems, Newcastle upon Tyne, United Kingdom) by using validated protocols on an automated stainer (Leica Biosystems). Vector Red (Vector Laboratories, Burlingame, CA) or 3,3'-diaminobenzidine (Leica Microsystems) were used as chromogens, and tissues were counterstained with Mayer hematoxylin. All slides were validated with positive controls. The cytoplasm of the decidualized stroma stained moderately to strongly positive for CD10 (Figure 1 C) and strongly positive for vimentin (Figure 1 D). The stromal tissue was less than 10% weakly positive for estrogen receptor α (Figure 1 E), negative for progesterone receptor (Figure 1 F), and negative for cytokeratin. The glandular epithelium was 100% strongly positive for cytoplasmic cytokeratin. In addition, uterine and ovarian tissue were stained to determine whether the negative progesterone and poor estrogen receptor α staining were similar to that of the endometriosis tissue, and both tissues were negative for both antigens, although about 50% of the fallopian tube epithelium demonstrated weak nuclear immunoreactivity for estrogen receptor α (Figure 1 G).

Discussion

Here, we report the case of a rhesus macaque with abdominal wall endometriosis that dissected through the abdominal wall muscle and subcutaneous adipose tissue. Endometriosis occurs at a rate of approximately 31% in captive NHP populations.¹² However, its presence in a cesarean section scar of an NHP has not been reported previously. In the current case, the aberrant endometrial tissue developed within a visibly healed cesarean section scar more than 6 y after the procedure. There are 2 possible explanations for the tissue's origin. First, it may have extended from the abdomen into the incision, following the path of granulation tissue, and then slowly proliferated, resulting in dehiscence. Alternatively the incision might have been inadvertently seeded with endometrial stem cells at the time of cesarean section, with slow development through the body wall. Given the extent of endometriosis tissue within the abdomen, we suspect that the incisional tissue developed as an extension from the abdomen.¹ Treatment with depot medroxyprogesterone acetate may not have resulted in tissue acyclicity if the tissue was initially

progesterone-resistant. As many as 50% of women have endometriosis tissue that inherently lacks or has diminished expression of progesterone receptor B, thus contributing to progestin resistance.¹¹ Prolonged treatment (longer than 6 mo) with progestins can lead to progesterone resistance in women.⁴

The incisional endometriosis tissue in our rhesus macaque had typical characteristics of pelvic and abdominal endometriosis, having both glands and stroma, and the stroma was decidualized due to long-term treatment with depot medroxyprogesterone acetate. The decidualized stroma was CD10- and vimentin-positive, similar to reported cases of decidualized endometriosis within the body cavity.¹⁰ Unlike previous reports in both NHP and humans, the macaque's endometrial stroma was negative for estrogen and progesterone receptors.⁸ Treatment with depot medroxyprogesterone acetate downregulates relative estrogen and progesterone receptor expression, and we have previously shown the expression of both receptors in endometriosis lesions of NHP treated with the drug, although reports examining the effects of medroxyprogesterone acetate on endometrial expression in rodents describe a relative decrease in immunoreactivity.^{3,7} The lack of estrogen receptor α and progesterone receptor expression is most likely related to the prolonged duration of treatment (approximately 3 y).

Cases of cutaneous and abdominal-wall endometriosis after gynecologic surgery further validate the use of macaques in endometriosis research. Through careful evaluation of cases of incision-site endometriosis, we can better understand factors that support the development of endometrium outside of the uterus and thus improve diagnoses.

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200 \times . (D) Immunohistochemical stain for vimentin shows strong cytoplasmic staining of the stromal cells. Magnification, 200 \times . (E) Rare stromal cells are positive for estrogen receptor α . Magnification, 200 \times . (F) Both the stroma and epithelial cells are negative for progesterone immunoreactivity. Magnification, 200 \times . (G) Approximately 75% of the epithelium lining a fallopian tube embedded within the endometriosis tissue stains weakly positive for estrogen receptor α . Magnification, 200 \times .

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