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Case Study

Endometrial Decidualization and Deciduosis in Aged Rhesus Macaques (*Macaca mulatta*)

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Superficial decidualization of the endometrial stroma is an essential feature of the implantation stage of pregnancy in rhesus macaques and other primates. Decidualization involves proliferation of the endometrial stromal cells, with differentiation into morphologically distinct decidual cells. Previous reports involving nonpregnant rhesus monkeys have described localized and widespread endometrial decidualization in response to administration of progesterone and synthetic progestogens. Ectopic decidua or 'deciduosis' describes the condition in which groups of decidual cells are located outside of the endometrium, most often in the ovaries, uterus and cervix but also in various other organs. In humans, most cases of deciduosis are associated with normal pregnancy, and ectopic decidua can be found in the ovary in nearly all term pregnancies. Here we describe pronounced endometrial decidualization in 2 rhesus macaques. Both macaques had been treated long-term with medroxyprogesterone acetate for presumed endometriosis, which was confirmed in one of the macaques at postmortem examination. In one animal, florid extrauterine and peritoneal serosal decidualization was admixed multifocally with carcinomatosis from a primary colonic adenocarcinoma. Cells constituting endometrial and serosal decidualization reactions were immunopositive for the stromal markers CD10, collagen IV, smooth muscle actin, and vimentin and immunonegative for cytokeratin. In contrast, carcinomatous foci were cytokeratin-positive. To our knowledge, this report describes the first cases of serosal peritoneal decidualization in rhesus macaques. The concurrent presentation of serosal peritoneal decidualization with carcinomatosis is unique.

Abbreviations: GnRH, gonadotropin-releasing hormone; PAS, periodic acid–Schiff; SMA, smooth-muscle actin.

Superficial decidualization of the endometrial stroma is an essential feature of the implantation stage of pregnancy in rhesus macaques and other primates.[13,27,29,37] This process typically begins, and is most prominent, adjacent to the spiral arteries, eventually expanding to affect the endometrium uniformly.[35] The endometrial stroma surrounds and supports the endometrial glands and is composed mainly of endometrial stromal cells and blood vessels.[35] Decidualization involves proliferation of the endometrial stromal cells, with differentiation into morphologically distinct decidual cells.[7,27,38] Endometrial stromal cells transform into large, polyhedral, cytoplasm-rich cells with large amounts of stored glycogen and are often binucleated or polyploid in character.[6,13,27,30,35] Ultrastructurally, decidualized cells have numerous ribosomes, prominent rough endoplasmic reticulum and Golgi complexes, and cytoplasmic accumulation of glycogen and lipid droplets.[13,35] Consistent with their stromal origin, decidualized cells express mesenchymal immunohistochemical markers, such as vimentin, desmin, and muscle-specific actin.[6,7,14,16,20,22]

Initiation of decidualization by attachment of the blastocyst to the uterine epithelium depends on previous sensitization by progesterone secretion, after a brief priming by estrogen.[12,13,27] Estrogen and progesterone regulate a series of complex interactions at the interface between the developing embryo and the cells in the stromal compartment, leading to the formation of a differentiated maternal tissue (decidua) that supports embryo growth and maintains early pregnancy.[27] Postovulatory levels of circulating progesterone increase and help maintain the differentiation of decidual cells.[7,13,33,37,38]

Ectopic decidua or 'deciduosis' describes the condition in which groups of decidual cells reside outside of the endometrium, most often in the ovaries, uterus, and cervix; the fallopian tubes, peritoneum, omentum, diaphragm, liver, skin, spleen, appendix, abdominal–pelvic lymph nodes, renal pelvis, and lungs of women have also been reported as affected.[6,14,18,20,22,28,29,38] In humans, most cases of deciduosis are associated with normal pregnancy, and ectopic decidua have been reported in the ovary in 90.5% to 100% of term pregnancies.[6-8,14,20,22,28-30,38] Occasional cases in nonpregnant or postmenopausal women have been attributed to progesterone-secreting active corpora lutea, progesterone secretion by the adrenal cortex, trophoblastic disease, exogenous progestational agents, and pelvic irradiation.[6-8,14,18,20,22,28,38] Deciduosis is usually an incidental finding that regresses postpartum within 4 to 6 wk; rarely, florid reactions have been reported to cause peritonitis, adhesions, hydronephrosis and hematuria, acute bowel obstruction or perforation (or both), abdominal pain mimicking appendicitis, massive and

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occasionally fatal hemoperitoneum, vaginal bleeding, and pneumothorax.[6,7,14,18,20,22,28,29,31]

Previous reports involving nonpregnant rhesus macaques have described localized and widespread endometrial decidualization in response to the administration of progesterone, synthetic progestogens, or progesterone-releasing bioactive intrauterine devices and intravaginal rings and have referred to these changes as 'pseudodecidualization' to indicate the absence of pregnancy in these animals.[12,33,35,37] In macaques given low (but superphysiologic) levels of progestogens, decidual changes have been noted in localized regions (around spiral arteries and underneath superficial epithelium), whereas high doses of progesterone or synthetic progestagens can cause a more pronounced and extensive reaction.[35]

In cynomolgus macaques, extrauterine decidual cell plaques are rare histologic findings in the subcoelomic mesenchyme of the ovarian cortex.[8,30] Despite the frequency of the condition in women, deciduosis is postulated to be a rarely documented lesion in primates because it is most often observed in conjunction with pregnancy, and pregnant cynomolgus macaques are seldom used in toxicity studies.[8] Here we describe the pronounced endometrial decidualization of 2 rhesus macaques, one of which also had florid extrauterine and peritoneal decidualization that was admixed multifocally with carcinomatosis. Both macaques had been treated long-term with medroxyprogesterone acetate for presumed endometriosis, which was confirmed in one of the macaques at postmortem examination. To our knowledge, this report describes the first cases of peritoneal decidualization in rhesus macaques as well as the concurrent occurrence of carcinomatosis, endometriosis and peritoneal decidualization in a macaque. The extensive intermixing of the cell populations presented a diagnostic challenge at pathologic examination, and accurate diagnosis was achieved only through the use of multiple immunohistochemical markers.

Case Report

Case 1. A 28-y-old female intact rhesus macaque on a behavioral testing protocol was presented for necropsy with a history of palpable abdominal masses first noted in August 2010. She had a 1-d history of anorexia and lying down in her cage, and abdominal ultrasonography revealed an irregular intestinal wall with free abdominal fluid. Given her clinical signs, advanced age, and physical exam and ultrasound findings, she was euthanized. This animal had been used as a breeder and had a history of 6 caesarean sections and one aborted fetus. She was treated with monthly leuprolide (1.88 mg IM from May 2003 until December 2004 and 0.9 mg IM from January 2005 until May 2008) and then was switched to monthly medroxyprogesterone acetate (40 mg IM) until May 2012 for presumed endometriosis. The macaque tested seronegative annually for *Macacine herpesvirus 1*, measles virus, SIV, simian T-cell leukemia virus types I and II, and *Mycobacterium tuberculosis*.

Opening the abdomen revealed extensive multifocal to coalescing slightly raised, cream-colored, nodular to linear flat lesions of the serosa (Figure 1 A). These were most severe in the lower peritoneal cavity and enclosed the uterus, ovaries, bladder, and distal rectum. Nodular lesions felt clinically were revealed to be multiple, large (maximum, 7 cm) fecoliths embedded in narrow-necked evaginations of the left descending colon (diverticulosis); a single firm nodule (1.5 cm × 0.5 cm × 0.5 cm) was associated

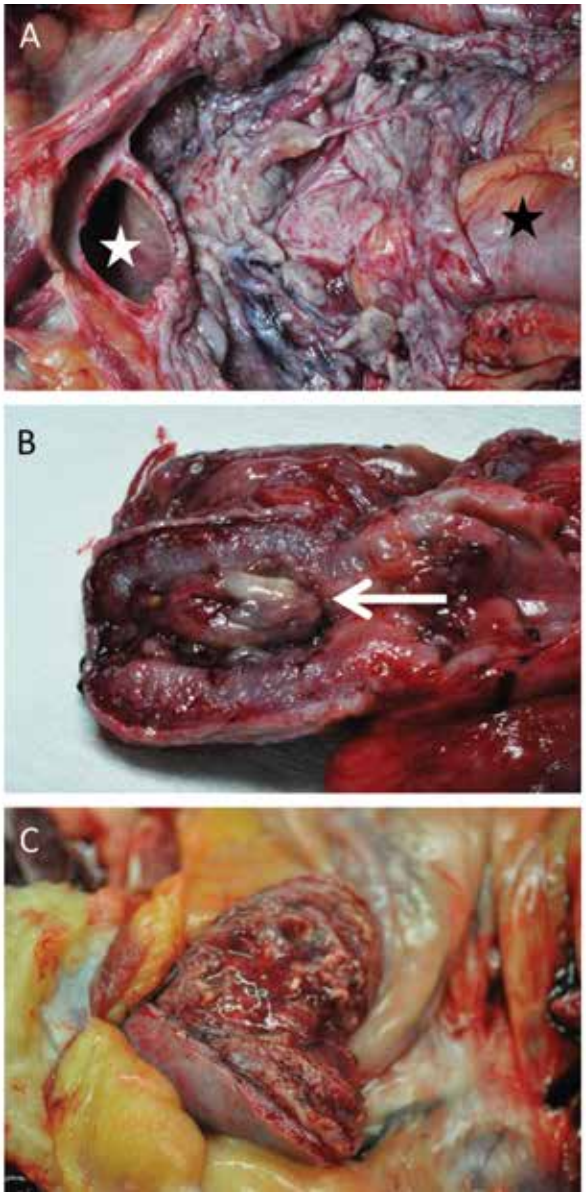

Figure 1. (A) Case 1. Within the caudal peritoneal cavity, the abdominal serosa contains extensive multifocal to coalescing, cream-colored, nodular to linear, flat lesions that enclosed the uterus, ovaries, bladder (white asterisk) and distal rectum (black asterisk). (B) Case 1. The uterus contains a focal intraluminal mural mass (arrow) accompanied by endometrial hemorrhage and thickening. (C) Case 2. The uterine endometrium is diffusely and markedly thickened with an irregular yellow to brown surface covered by small amount of blood and yellow–brown fluid.

with one of these diverticles. Approximately 10 mL of serosanguinous fluid was noted in the peritoneal cavity. On cytologic examination of this fluid, abundant degenerate neutrophils and macrophages packed with intracytoplasmic rods were present, and bacterial culture of the peritoneal cavity was positive for *Escherichia coli* and *Pseudomonas aeruginosa*. The uterus contained a 2 cm × 2 cm × 2 cm intraluminal mural mass, accompanied by endometrial hemorrhage and thickening (Figure 1 B). A gross diagnosis of septic peritonitis secondary to a breached intestinal barrier was made. No gross rupture of the intestine was noted,

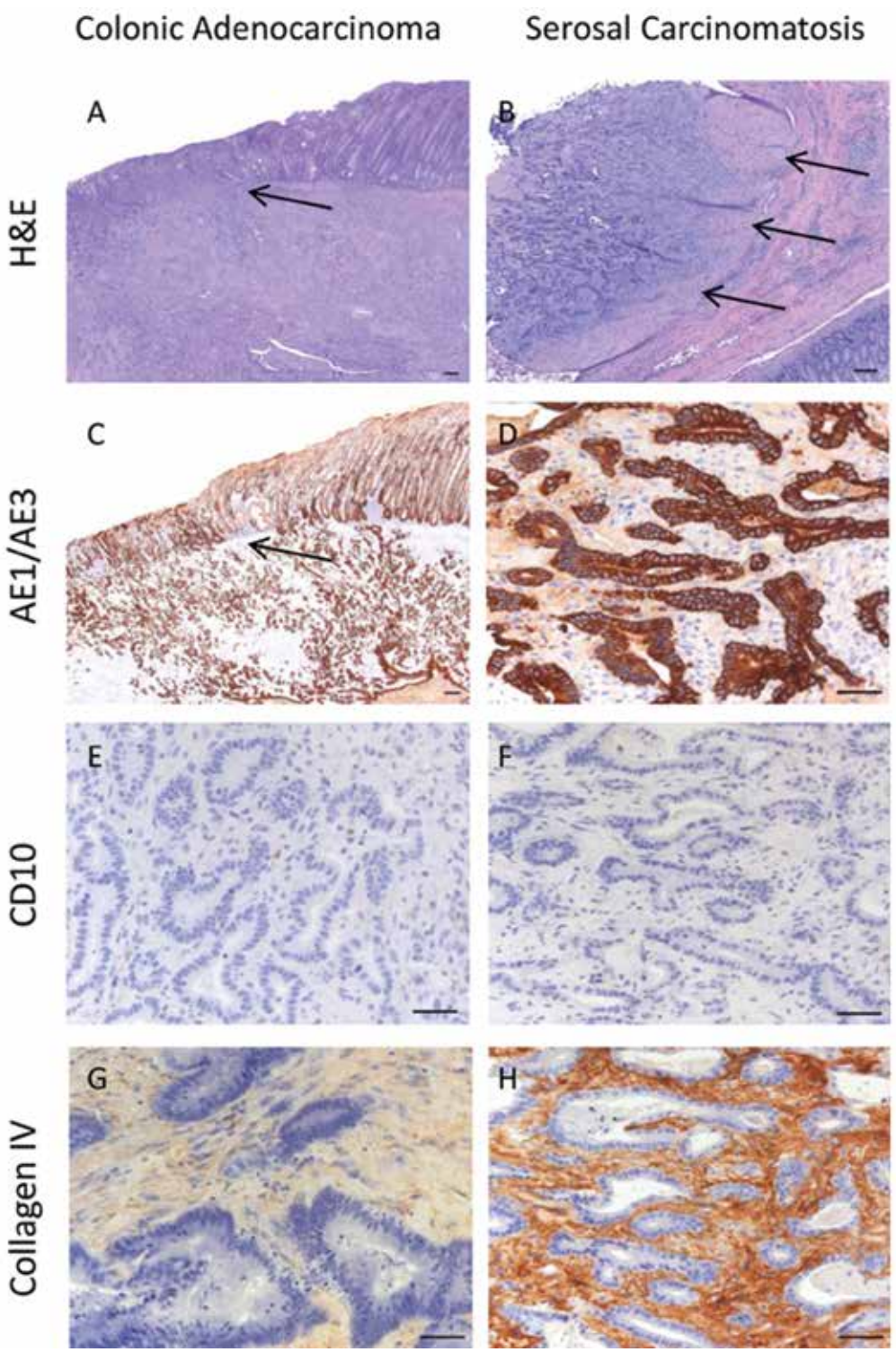

Figure 2. Histopathology and immunohistochemical features of (A, C, E, G; same site) the colonic adenocarcinoma and (B, D, F, H; same site) a metastatic focus of colonic adenocarcinoma from case 1. (A) The primary tumor is an invasive, transmural colonic adenocarcinoma, which extends through the basement membrane (arrow). Hematoxylin and eosin stain; scale bar, 200 µm. (B) A metastatic focus of colonic adenocarcinoma is present on the serosal surface of the large intestine (arrows), distinct from the primary tumor. Hematoxylin and eosin stain; scale bar, 200 µm. (C) Neoplastic glands of the primary colonic carcinoma are strongly positive for cytokeratin AE1/AE3 immunostain. The arrow indicates the comparable site in panel A. Scale bar, 200 µm. (D) Similarly, neoplastic glands of the focus of serosal carcinomatosis are strongly positive for cytokeratin AE1/AE3 immunostain. Scale bar, 50 µm. (E) Within the primary colonic carcinoma and (F) metastatic focus of carcinomatosis, both neoplastic epithelium and stroma are negative for CD10 immunostain. Scale bar, 50 µm. Collagen IV staining is immunopositive in stroma but not epithelial cells within the (G) primary carcinoma and (H) focus of serosal carcinomatosis. Scale bar, 50 µm.

and microscopic rupture due to diverticulosis or focal intestinal neoplasia accompanied by carcinomatosis was considered to be likely. Hyperplastic, neoplastic, and inflammatory processes were all considered to be possible etiologies for the uterine mass.

Tissue samples were fixed in 10% buffered formalin, processed routinely for sectioning, and then stained with hematoxylin and eosin. On histopathologic examination, the small nodule found grossly in association with one of the colonic diverticles was an invasive transmural colonic adenocarcinoma, which extended into adjacent segments of the colon (Figure 2 A). Neoplastic cells formed tubules and acini and expressed the typical cytologic features of an anaplastic and invasive adenocarcinoma. Metastatic foci with similar morphology were found within the liver, mesentery and on the serosal surfaces of the urinary bladder, uterus, and small and large intestine (Figure 2 B). The original neoplastic mass and its metastatic foci shared identical immunohistochemical profiles. As expected, neoplastic glands of both the primary colonic carcinoma and serosal colonic carcinomatosis were strongly positive (cytoplasmic staining) for cytokeratin AE1/AE3 (1:100; Thermo Fisher Scientific, Waltham, MA; Figure 2 C and D). Both neoplastic epithelium and stroma were negative for CD10 (1:30; Thermo Fisher Scientific; Figure 2 E and F). Collagen IV (1:800; Abcam, Cambridge, MA) was immunopositive in stromal but not epithelial cells within both the primary tumor and carcinomatous foci (Figure 2 G and H).

Examination of the abdominal serosa revealed extensive nodular lesions with histopathologic morphology distinct from that of the carcinomatous foci (Figure 3 A). These additional lesions consisted of nests of spindloid to large polygonal cells with abundant, often granular, cytoplasm and variably sized nuclei. Mitoses were not noted. Cells were embedded in varying amounts of collagenous or eosinophilic stroma (Figure 3 A, inset) and resembled those within the uterine endometrium. Microscopic examination of the uterine mass revealed extensive decidualization within the endometrium and within the mass that had been identified grossly (Figure 3 B). The endometrium was diffusely thickened by sheets of densely packed, round to polygonal cells, with variably distinct cell borders, moderate amounts of pale eosinophilic highly vacuolated or granular cytoplasm, and centrally placed round to oval nuclei with finely stippled chromatin and one basophilic nucleolus (decidual cells; Figure 3 B inset). A continuum of differentiation from a spindloid phenotype within the deepest aspect of the endometrium to a polygonal phenotype within the superficial 1/2 to 2/3 of the endometrium was evident. This same continuum was noted in serosal decidual foci. The stroma of both the endometrial and uterine serosal decidual reactions were strongly positive by periodic acid–Schiff (PAS) and Masson trichrome staining (Figure 3 C through F), implying a basement membrane component to the stroma that was elaborated by decidual cells. In addition, cytoplasmic granules of large polygonal decidual cells in both locations were PAS-positive. Decidual cells were immunopositive for smooth muscle actin (SMA; 1:1500; Neomarkers, Fremont, CA) and in both the endometrial decidual reaction and serosal decidual foci; the intensity of immunostaining for SMA decreased as decidual cells evolved from spindloid to polygonal morphology (Figure 3 G and H). Immunohistochemically, decidual serosal foci presented a distinctly different pattern from that demonstrated by neoplastic colonic carcinomatous foci. In contrast to colonic epithelium, the endometrial and serosal decidual reactions were negative for AE1/AE3 (Figure 4 A and B) and positive for CD10 (Figure 4 C and D). CD10 immunostaining of decidual cells was primarily membranous and occasionally cytoplasmic. In general, both tissues exhibited weaker staining for CD10 than did normal endometrial mucosal stromal cells. With collagen IV, strong (primarily membranous) immunostaining of decidual cells of both the endometrial and uterine serosal decidual reactions was evident (Figure 4 E and F). These reactions confirmed the mesenchymal (stromal) origin of decidual cells in both the endometrium and serosal nodules.

The addition of immunostains for vimentin (1:100, Thermo Fisher Scientific) and cytokeratin 5/6 (1:160; Dako, Carpinteria, CA) completed the immunohistochemical comparison of the endometrial decidual reaction, uterine serosal decidual reaction, primary colonic adenocarcinoma and a metastatic serosal focus of colonic adenocarcinoma (Table 1). The mesenchymal origin of the endometrial decidual reaction and serosal decidual foci was confirmed by positive vimentin immunostaining. There was some sporadic positive cytoplasmic staining of stromal cells (but not epithelial cells) for vimentin within the focus of colonic serosal carcinomatosis. All tissues tested were negative for cytokeratin 5/6.

Within the remaining endometrium, there was frequent atrophy of endometrial glands, and the remaining glands exhibited mild to marked cystic glandular dilation with intraluminal amphophilic fluid admixed with neutrophils and necrotic cell debris. There was multifocal implantation of endometrial glands into the underlying myometrium (adenomyosis), as well as several small foci of endometriosis in the uterine broad ligament (multiple glands lined by a single layer of cuboidal to columnar epithelial cells embedded within endometrial stroma). Because many of the sites of ectopic peritoneal deciduosis were also the sites of colonic adenocarcinoma metastasis, there was considerable intermixing of the neoplastic and deciduotic cell populations, particularly on the serosal surfaces of the abdominal organs, accounting for the plaque-like appearance grossly.

Case 2. A 23-y-old female intact rhesus macaque (*Macaca mulatta*) was obtained from Charles River Laboratories in China in 1988 for use in cognitive function testing at Yale University. In July 2003, she was reported to the veterinary staff for prolonged, heavy cycling and decreased appetite. Analgesics (50 mg ibuprofen PO twice daily) for pain associated with cycling were initiated, without marked improvement of her clinical signs. A few days later, she was reported to be very pale but active and alert. Physical examination revealed mild paleness and a firm, irregular uterus. CBC and serum chemistry analyses revealed a microcytic, hypochromic nonregenerative anemia. In light of the clinical and hematologic findings, a presumptive diagnosis of endometriosis was made. Temporary iron supplementation was initiated, and the macaque was started on monthly leuprolide (1.88 mg IM). Her clinical condition improved over the next month and remained stable for several years. Leuprolide was continued until June 2008, when she began to receive medroxyprogesterone acetate (40 mg IM) once monthly; this treatment was continued until her euthanasia for chronic cardiac disease (August 2011). The macaque tested seronegative annually for *Macacine herpesvirus 1*, measles virus, SIV, simian T-cell leukemia virus types I and II, and *Mycobacterium tuberculosis*.

On gross examination, the uterus was diffusely enlarged, with a purple to red and congested serosal surface. On cut surface, the endometrium was diffusely and markedly thickened (maximal diameter, 1.5 to 2.0 cm), with an irregular yellow to brown surface covered by small amount of blood and yellow–brown discharge

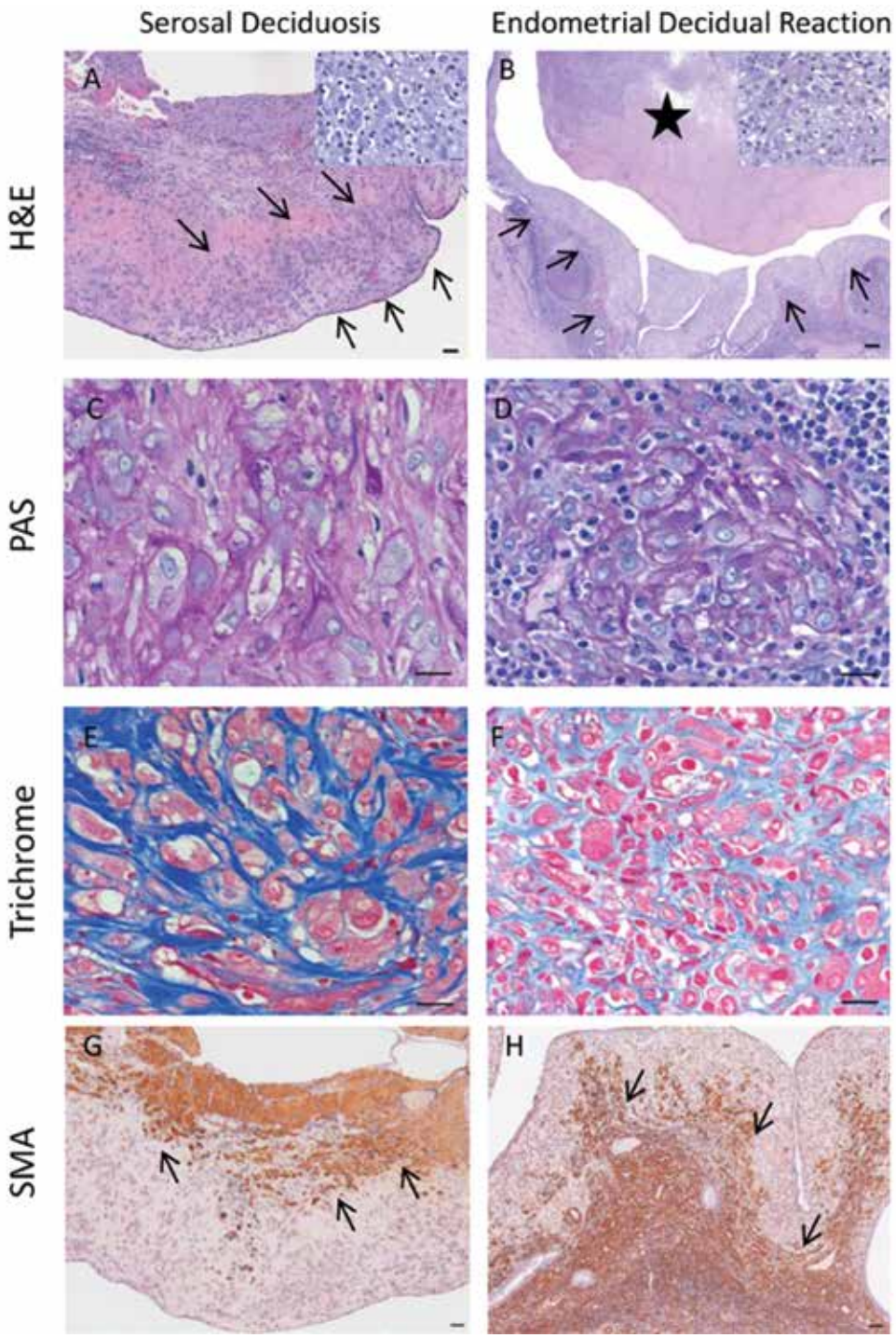

Figure 3. Histopathology and immunohistochemical features of the (A, C, E, G; same site) serosal and (B, D, F, H; same site) endometrial decidual reaction from case 1. (A) The abdominal serosa contains extensive nodular lesions (arrows) with morphology distinct from those of the carcinomatous foci noted above. Inset, Nodules consist of nests of spindloid to large polygonal cells with abundant, often granular cytoplasm, and variably sized nuclei. Cells are embedded in varying amounts of collagenous or eosinophilic stroma and resemble those within the uterine endometrium. Hematoxylin and eosin stain; scale bar: 50 µm (main image), 20 µm (inset). (B) The uterine displays a band of extensive endometrial decidualization (arrows), continuous with a similarly decidualized partly necrotic endometrial mass (asterisk). Inset, Decidual cells are round to polygonal, with variably distinct cell borders, moderate amounts of pale eosinophilic highly vacuolated or granular cytoplasm and centrally placed round to oval nuclei with finely stippled chromatin and a single basophilic nucleolus. Hematoxylin and eosin stain; scale bar: 200 µm (main image), 20 µm (inset). The stroma of both the (C) endometrial decidual reaction and (D) uterine serosal decidual reaction are strongly periodic acid–Schiff-positive. Scale bar, 20 µm. (E, F). The stroma of both the (E) endometrial and (F) uterine serosal decidual reactions are strongly positive with Masson trichrome stain. Scale bar, 20 µm. Decidual cells were immunopositive for smooth muscle actin (SMA) in both the (G) endometrial and (H) serosal decidual foci. Intensity of immunostaining for SMA decreased as decidual cells evolved from spindloid to polygonal morphology (G, H: arrows). Scale bar, 50 µm.

(Figure 1 C). No gross lesions consistent with endometriosis were noted at gross examination.

Histopathologic examination of the uterus revealed marked diffuse endometrial decidualization. The endometrium was expanded (maximum, 5 times normal) by sheets of densely packed polygonal decidual cells with morphology similar to that noted in case 1. There was multifocal necrosis, hemorrhage and marked neutrophilic infiltrate, primarily on the surface and within the upper 1/3 of the decidual proliferation. Endometriosis was not noted with histopathologic examination of any organ. A similar immunohistochemical pattern to that for Case 1 was identified. Decidual cells in the uterus of case 2 were immunopositive for CD10, SMA, and vimentin but negative for pancytokeratin AE1/AE3 (data not shown).

Discussion

Here we describe 2 cases of marked uterine decidualization in rhesus macaques under treatment with medroxyprogesterone acetate for endometriosis. In addition, case 1 demonstrated extensive extrauterine decidualization in multiple serosal sites, the diagnosis of which was complicated by the presence of carcinomatosis originating from colonic adenocarcinoma.

In humans, ectopic (extrauterine) decidua were first described in 1887, and peritoneal serosa decidual reactions were first observed in 1917.[7,20] In general, the peritoneal location in women is considered rare and is thought to result from progesterone-induced metaplasia of the pluripotential subserosal stromal cells from hormones produced during pregnancy.[6,7,14,18,22,28,29,38] Often the lesion will be microscopic; if visible grossly, there may be yellow, gray, brown, or red nodules or plaques on the peritoneal surface.[6,20] Histologically, decidual cells generally are found under the mesothelium in the subcoelomic mesenchyme or within adipose tissue.[6,7,38] Decidual cells typically occur in small clusters but can form confluent sheets or polyploid projections, occasionally admixing with smooth muscle cells.[6-8,38] Histologically, decidual cells are large, polygonal, and cytoplasm-rich and often display 2 or more nuclei.[6,13,27,30,35] Immunohistochemically, extrauterine mesenchymal cells that have undergone a decidual reaction are closely similar to their counterparts in the endometrial stroma[16] and therefore stain positively for common mesenchymal markers such as vimentin, desmin, and muscle-specific actin, as well as progesterone receptor, α1-antitrypsin, and α1-antichymotrypsin.[6,7,14,16,20,22] Furthermore, they may be focally positive for estrogen receptor and cytokeratin.[14,20,28]

Decidualization of stromal endometriosis has been previously described to occur in a macaque that was treated for endometriosis for 6 mo (2 doses of intramuscular medroxyprogesterone acetate, 150 and 250 mg, given 3 mo apart).[33] The cited macaque had a cystic mass cranial to the uterus; histologically the mass was composed of sheets of polygonal cells with distinct cell borders and moderate amounts of eosinophilic cytoplasm, which are very similar cellular features to those of the decidual population noted in the 2 cases we present here.[33] Immunohistochemically, the decidual population in the previous macaque was positive for vimentin and negative for cytokeratin.[33] Despite the similarities with the previously reported case, a unique finding in our report is the concurrent presentation of serosal decidualization and carcinomatous in case 1. The macaque presented in case 1 had an adenocarcinoma within the proximal colon, with metastasis to the liver, omentum, mesentery, and the serosa of multiple abdominal organs. Intestinal adenocarcinoma is the most common malignant neoplasm of aged rhesus macaques (that is, usually 13 y or older) and most often affects the distal ileum, ileocecal valve region, or proximal colon.[26,34] These neoplasms typically are very aggressive and invasive locally, with extension to the serosa and mesentery, but are slow to metastasize.[26,34] In our case 1 macaque, the foci of decidualization frequently were admixed with and embedded within metastatic foci of colonic adenocarcinoma, resulting in extensive plaque-like serosal lesions. By using immunohistochemical staining, the epithelial or mesenchymal origin of metastatic colon carcinoma or decidualized foci was differentiated clearly. The most helpful markers in our macaques were AE1/AE3 (pancytokeratin), CD10, and collagen IV.

AE1/AE3 (catalog no. MS343; Thermo Fisher Scientific) is a pancytokeratin stain that recognizes the acidic and basic subfamilies of cytokeratins and can be used to detect most cells of epithelial origin. Accordingly, AE1/AE3 positively and strongly stained the neoplastic glands within the primary and metastatic colonic carcinoma in case 1. However, AE1/AE3 did not stain the decidual cells, because they are stromal—not epithelial—in origin. Conversely, CD10 is expressed by normal endometrial stromal cells and a wide range of normal and neoplastic human cells.[25,32] In the normal endometrial stroma, AE1/AE3 has been reported to exhibit cytoplasmic immunolocalization; but in endometrial stromal tumors, where it also exhibits strong positive staining, the stain has been found to be localized to the apical surface in syncyntiotrophoblasts.[32] In addition, CD10 expression is typically absent or faint in decidual cells. Consistent with that observation, case 1 exhibited positive staining of the decidual cells of the endometrial and serosal decidual reactions. However, in both of our cases, the CD10-positive staining of the decidual reactions was weaker than that noted in the normal endometrial mucosa of the monkey. As expected, the colonic tissue did not stain positively with CD10. In the decidual reaction (endometrial and serosal), collagen IV antibody immunostained the actual decidual cells themselves, whereas in the carcinoma and focus of carcinomatosis, it stained the stroma surrounding and supporting the neoplastic cells; this finding is not surprising considering that collagen IV is an integral component of basement membranes.[36] Differential diagnoses to consider for extrauterine decidual reactions in light of findings from gross or histologic examinations in women are peritoneal tuberculosis, metastatic malignant melanoma, and deciduoid mesothelioma.[6,14,18,20,28] Of these, we eliminated the first 2 according to routine histopathology and then performed immunohistochemical staining for cytokeratin 5/6 to rule out deciduoid mesothelioma.[6,14,20]

The 2 macaques that we describe here were being treated for a presumptive clinical diagnosis of endometriosis for approximately 8 and 10 y prior to death; this treatment is the likely cause of the uterine decidualization seen at postmortem examination. Endometriosis is seen only in those species that menstruate and is a common diagnosis in Old World nonhuman primates, with an incidence of 25% to 30% in some colonies of sexually mature female rhesus and cynomolgus macaques.[1-3,5,9,10,15,17,23,33] Because exposure to ovarian hormones is required for the development of clinical disease, ovariectomy or ovariohysterectomy is often the ideal treatment for endometriosis, because it removes the primary source of estrogen.[1,10] However, if the case is mild or if surgery is not an option because of the degree of fibrosis or adhesions or because the animal is on a research protocol that does

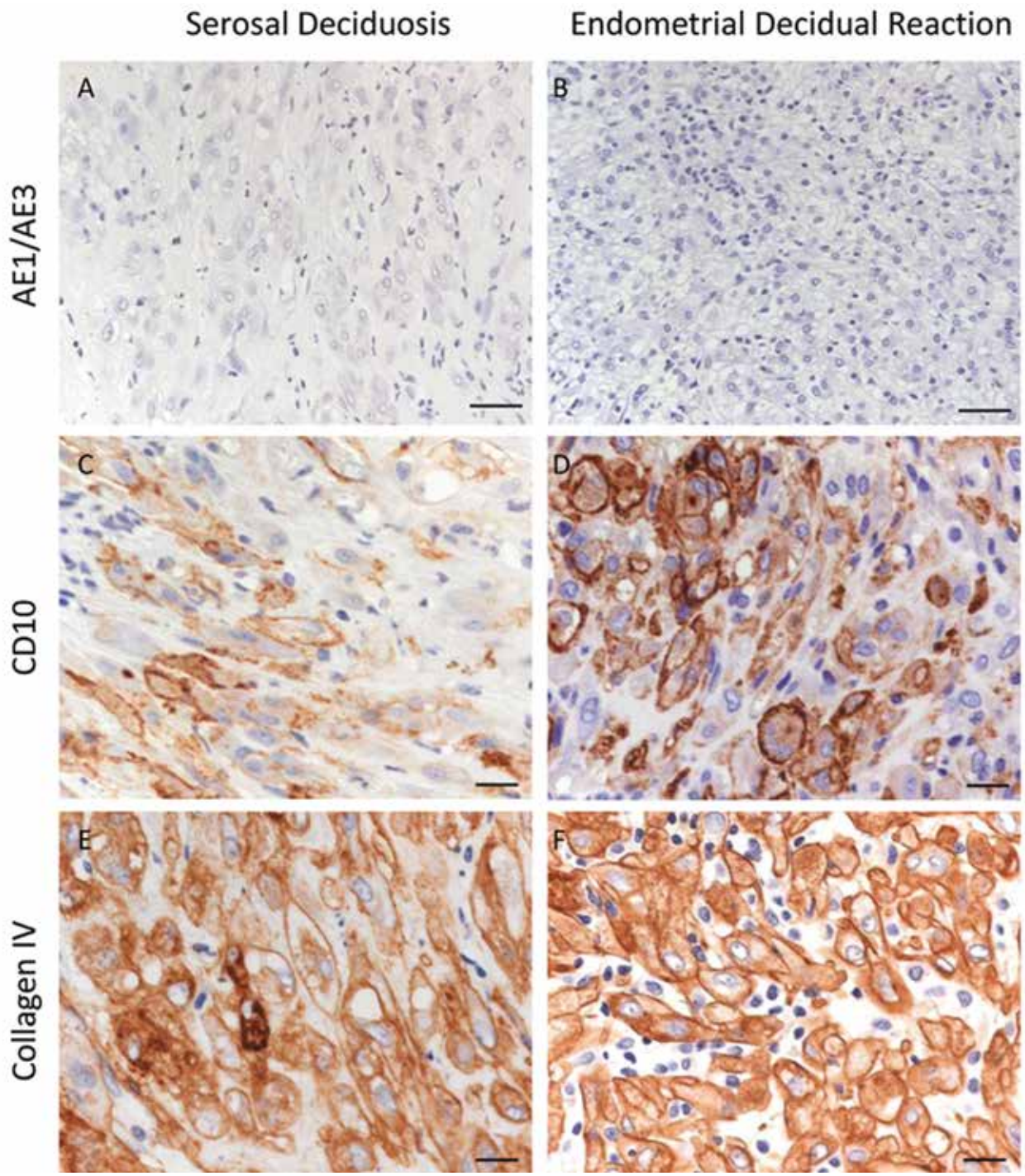

Figure 4. Additional immunohistochemical features of the (A, C, E) serosal and (B, D, F) endometrial decidual reactions from case 1. (A, B) The serosal and endometrial decidual reactions are immunonegative for AE1/AE3. Scale bar, 50 µm. Decidualized stromal cells within the serosal and endometrial decidual reactions displaymembranous immunoreactivity for (C, D) CD10 and (E, F) collagen IV. Scale bar, 20 µm.

not allow such a manipulation, medical treatment may be considered.[1,10,11,19,23,33] Potential treatments to suppress estrogen secretion or to stop the endometrium's response include gonadotropin-releasing hormone (GnRH) agonists and antagonists, progestins and antiprogestins, estrogen–progestin combinations, aromatase inhibitors, and pituitary–ovarian axis suppressants, often in combination with various antiinflammatories for pain control.[1,4,10,23,33]

In addition to symptomatic treatment with analgesics, both of our macaques initially were treated with monthly leuprolide, a GnRH agonist.[1,10,21,23] The purpose of GnRH agonists is to inhibit pituitary stimulation of ovarian function, thereby suppressing estradiol production and its subsequent effect on endometrial cells.[15,23] In one report, continuous infusion of a GnRH agonist for 6 mo led to dramatic improvement in 4 rhesus macaques

Table 1. Comparison of the immunohistochemical staining profiles of the primary colonic adenocarcinoma, a metastatic serosal focus of colonic adenocarcinoma, normal endometrial mucosa, endometrial decidual reaction, and uterine serosal decidual reaction from case 1

	Colon				Uterus			Serosa
	Mucosa		Serosa (carcinomatosis)		Normal endometrial mucosa		Endometrial decidual reaction	Serosal deciduosis[a]
	Epithelium	Stroma	Epithelium	Stroma	Epithelium	Stroma		
AE1/AE3	++	–	++	–	++	–	–	-
CD10	–	–	–	–	–	++	+	+
Collagen IV	–	+	–	++	–	++	++	++
SMA	–	++	–	++	–	++	+/++	+
Vimentin	–	–	–	+	–	–	+	+/++

++, strong staining; +, weak or sporadic staining; –, no staining; SMA, smooth muscle actin
[a]Serosal deciduosis: decidualized foci were present on the serosal surface of the uterus, urinary bladder and large intestine.

with spontaneous endometriosis, with a marked decrease in lesion size, secretory activity of the ectopic endometrial tissue, and overall increase in body weight, confirming previous reports that GnRH agonists were effective treatment for mild to moderate endometriosis.[21] In addition, the authors stated that clinical improvement was maintained for least 4 mo after treatment, and they emphasized that a main advantage of a GnRH agonist over progestational steroid treatment for endometriosis is the earlier resumption of menstrual cycles after termination of treatment.[21] However, this drug has not been used widely in nonhuman primates because of its high cost,[10] which was the reason for its discontinuation in both of the cases we present here.

Medroxyprogesterone acetate is a synthetic progestogen that is currently the most commonly used medical treatment for endometriosis in nonhuman primates.[10] Medroxyprogesterone acetate suppresses estrogen secretion and then, via its progestin effects on the uterus, causes an initial decidualization of endometrial tissue followed by suppression of endometrial proliferation and eventual atrophy.[1,4,10,23,33] The intramuscular depot injectable formula, which we used in our animals, is long-acting and designed to suppresses cycling and ovulation for at least 3 mo, causing the physical evidence and clinical signs of the disease to subside.[4,10] The most commonly published dose for treatment of endometriosis is 150 mg IM every 3 mo.[10,33] Alternatively, a dose of 40 mg IM monthly, as was given to our 2 animals, has been used.[24] Because ectopic decidualization can occur in women experiencing physiologic levels of progesterone accompanying pregnancy, serosal and uterine decidualization in our macaques most likely resulted from exogenous medroxyprogesterone acetate. It is unclear whether the decidual reactions seen induced discomfort in these animals. Furthermore, it is difficult to speculate on which of the commonly used doses is best, except to say that the 150-mg dose regimen appears to suppress cycling adequately for 3 mo. To our knowledge, this report is the first to describe both extensive serosal decidualization in a nonhuman primate as well as concurrent serosal decidualization and carcinomatosis accompanying the much more commonly diagnosed colonic carcinoma. In addition, it is important to consider that endometriotic foci can undergo marked decidualization with the effects of progesterone, much like the endometrium does. These foci closely resemble ectopic decidua grossly and histologically, so it also is necessary to differentiate deciduosis from foci of decidualized endometriosis.[6,18,22,28,29]

Acknowledgments

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References

1. **Abee CR, Mansfield K, Tardif S, Morris T, editors.** 2012. Nonhuman primates in biomedical research. Volume 2: diseases. Waltham (MA): Academic Press.
2. **Arnold DL, Nera EA, Stapley R, Tolnai G, Claman P, Hayward S, Tryphonas H, Bryce F.** 1996. Prevalence of endometriosis in rhesus (*Macaca mulatta*) monkeys ingesting PCB (Aroclor 1254): review and evaluation. Fundam Appl Toxicol **31:**42–55.
3. **Assaf BT, Miller AD.** 2012. Pleural endometriosis in an aged rhesus macaque (*Macaca mulatta*): a histopathologic and immunohistochemical study. Vet Pathol **49:**636–641.
4. **Benagiano G, Pera A, Primiero FM.** 2000. The endometrium and hormonal contraceptives. Hum Reprod **15 Suppl 1:**101–118.
5. **Bertens APMG, Helmond FA, Hein PR.** 1982. Endometriosis in rhesus monkeys. Lab Anim **16:**281–284.
6. **Bolat F, Canpolat T, Tarim E.** 2012. Pregnancy-related peritoneal ectopic decidua (deciduosis): morphological and clinical evaluation. Turk Patoloji Dergisi **28:**56–60.
7. **Buttner A, Bassler R, Theele CH.** 1993. Pregnancy-associated ectopic decidua (deciduosis) of the greater omentum. An analysis of 60 biopsies with cases of fibrosing deciduosis and leiomyomatosis peritonealis disseminata. Pathol Res Pract **189:**352–359.
8. **Cline JM, Wood CE, Vidal JD, Tarara RP, Buse E, Weinbauer GF, de Rijk EPCT, van Esch E.** 2008. Selected background findings and interpretation of common lesions in the female reproductive system in macaques. Toxicol Pathol **36:**142S–163S.
9. **Coe CL, Lemieux AM, Rier SE, Uno H, Zimbric ML.** 1998. Profile of endometriosis in the aging female rhesus monkey. J Gerontol A Biol Sci Med Sci **53:**M3–M7.
10. **Cruzen CL, Baum ST, Colman RJ.** 2011. Glucoregulatory function in adult rhesus macaques (*Macaca mulatta*) undergoing treatment with medroxyprogesterone acetate for endometriosis. J Am Assoc Lab Anim Sci **50:**921–925.
11. **Dore M, Lagace A.** 1985. Spontaneous external endometriosis in a gorilla (*Gorilla gorilla*). Can Vet J **26:**347–349.
12. **Dwivedi A, Bansode FW, Setty BS, Dhar JD.** 1999. Endometrial steroid receptors during decidualization in rhesus monkey (*Macaca mulatta*): their modulation by antioestrogen CDRI-85/287. Hum Reprod **14:**1090–1095.
13. **Gellersen B, Brosens IA, Brosens JJ.** 2007. Decidualization of the human endometrium: mechanisms, functions, and clinical perspectives. Semin Reprod Med **25:**445–453.
14. **Gradauskas A, Cincikas J, Daunoravicius R, Mickys U, Mazarevicius G, Sataite I, Jotautas V, Rutkauskaite D, Strupas K.** 2012.

Ectopic decidua presenting with a sigmoid bowel perforation: a case report. J Clin Case Rep **2:**1–3.

15. **Hadfield RM, Yudkin PL, Coe CL, Scheffler J, Uno H, Barlow DH, Kemnitz JW, Kennedy SH.** 1997. Risk factors for endometriosis in the rhesus monkey (*Macaca mulatta*): a case–control study. Hum Reprod Update **3:**109–115.
16. **Heatley MK, Maxwell P, Toner PG.** 1996. The immunophenotype of human decidua and extrauterine decidual reactions. Histopathology **29:**437–442.
17. **Ito T, Sakamaki Y, Fujii E, Misawa Y, Suzuki M, Sugimoto T.** 2001. Endometriosis in a rhesus monkey. J Toxicol Pathol **14:**313–315.
18. **Kinra SLP, Sen WCA, Sharma WCJC.** 2006. Ectopic decidual reaction: a case report. Med J Armed Forces India **62:**280–281.
19. **Maginnis G, Wilk J, Carroll R, Slayden OD.** 2008. Assessment of progestin-only therapy for endometriosis in macaques. J Med Primatol **37 Suppl 1:**52–55.
20. **Malpica A, Deavers MT, Shahab I.** 2002. Gross deciduosis peritonei obstructing labor: a case report and review of the literature. Int J Gynecol Pathol **21:**273–275.
21. **Mann DR, Collins DC, Smith MM, Kessler MJ, Gould KG.** 1986. Treatment of endometriosis in monkeys: effectiveness of continuous infusion of a gonadotropin-releasing hormone agonist compared to treatment with a progestational steroid. J Clin Endocrinol Metab **63:**1277–1283.
22. **Massi D, Susini T, Paglierani M, Salvadori A, Giannini A.** 1995. Pregnancy-associated ectopic decidua. Acta Obstet Gynecol Scand **74:**568–571.
23. **Mattison JA, Ottinger MA, Powell D, Longo DL, Ingram DK.** 2007. Endometriosis: clinical monitoring and treatment procedures in rhesus monkeys. J Med Primatol **36:**391–398.
24. **McCarthy TJ, Beluhan FZ, Bardawil WA, Bennett BT.** 1989. Pyometra in a rhesus monkey secondary to prolonged therapy with medroxyprogesterone acetate. Lab Anim Sci **39:**71–72.
25. **McCluggage WG, Sumathi VP, Maxwell P.** 2001. CD10 is a sensitive and diagnostically useful immunohistochemical marker of normal endometrial stroma and of endometrial stromal neoplasms. Histopathology **39:**273–278.
26. **O'Sullivan MG, Carlson CS.** 2001. Colonic adenocarcinoma in rhesus macaques. J Comp Pathol **124:**212–215.
27. **Ramathal CY, Bagchi IC, Taylor RN, Bagchi MK.** 2010. Endometrial decidualization: of mice and men. Semin Reprod Med **28:**17–26.
28. **Rodriguez FJ, Abraham SC, Sendelbach KM, Nascimento AG.** 2006. Florid decidual reaction mimicking gastrointestinal malignancy in a primipara woman. Histopathology **49:**82–85.
29. **Sammour RN, Leibovitz Z, Shapiro I, Degani S, Levitan Z, Aharoni A, Tal J, Lurie M, Ohel G.** 2005. Decidualization of ovarian endometriosis during pregnancy mimicking malignancy. J Ultrasound Med **24:**1289–1294.
30. **Sato J, Doi T, Kanno T, Wako Y, Tsuchitani M, Narama I.** 2012. Histopathology of incidental findings in cynomolgus monkeys (*Macaca fascicularis*) used in toxicity studies. J Toxicol Pathol **25:**63–101.
31. **Slayden OD, Brenner RM.** 2004. Hormonal regulation and localization of estrogen, progestin, and androgen receptors in the endometrium of nonhuman primate: effects of progesterone receptor antagonists. Arch Histol Cytol **67:**393–409.
32. **Toki T, Shimizu M, Takagi Y, Ashida T, Konishi I.** 2002. CD10 is a marker for normal and neoplastic endometrial stromal cells. Int J Gynecol Pathol **21:**41–47.
33. **Usborne AL, Bolton IB, Slukvin I.** 2002. Stromal decidualization of endometriosis in the rhesus macaque (*Macaca mulatta*): a case report. Comp Med **52:**167–170.
34. **Valverde CR, Tarara RP, Griffey SM, Roberts JA.** 2000. Spontaneous intestine adenocarcinoma in geriatric macaques (*Macaca* sp). Comp Med **50:**540–544.
35. **Van Esch E, Buse E, Weinbauer G, Cline JM.** 2008. The macaque endometrium, with special reference to the cynomolgus monkey (*Macaca fascicularis*). Toxicol Pathol **36:**67S–100S.
36. **Veidal SS, Karsdal MA, Nawrocki A, Larsen MR, Dai Y, Zheng Q, Hägglund P, Vainer B, Skjøt-Arkil H, Leeming DJ.** 2011. Assessment of proteolytic degradation of the basement membrane: a fragment of type IV collagen as a biochemical marker for liver fibrosis. Fibrogenesis Tissue Repair **4**:22–32.
37. **Wadsworth PF, Lewis DJ, Heywood R.** 1980. The ultrastructural features of progestagen-induced decidual cells in the rhesus monkey (*Macaca mulatta*). Contraception **22:**189–198.
38. **Zaytsev P, Taxy JB.** 1987. Pregnancy-associated ectopic decidua. Am J Surg Pathol **11:**526–530.