Comparative Medicine
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Vol 52, No 2
April 2002
Pages 167-170

Stromal Decidualization of Endometriosis in the Rhesus Macaque (*Macaca mulatta*): A Case Report

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During exploratory laparotomy, a 10-year-old female rhesus macaque was found to have a 6.0 × 9.5 × 2.0-cm multichambered, yellow, cystic mass cranial to the uterus, from which large amounts of opaque, white fluid were discharged into the abdominal cavity. The animal was euthanized, and the body was submitted for gross and histologic evaluation. Sections of the mass examined microscopically consisted of sheets of polygonal to round cells, with well defined cell borders and moderate amounts of eosinophilic cytoplasm. Scattered throughout these cells were few, variably sized glandular structures composed of columnar to cuboidal epithelium. Glandular epithelial cells were positive for keratin, and the sheets of polygonal cells were positive for vimentin and negative for keratin and CD 68. Gross and histologic appearance, immunohistochemical findings, and history of medroxyprogesterone acetate injections were compatible with a diagnosis of stromal decidualization of endometriosis. Subsequent biopsies of similar lesions in other rhesus macaques in the colony being treated with medroxyprogesterone acetate for endometriosis revealed comparable histologic findings.

In May 2000, a 10-year-old colony-bred female rhesus macaque (*Macaca mulatta*) was examined in response to a clinical finding of neutrophilic leukocytosis. Previous pertinent clinical and research history included three cesarian sections and multiple follicle aspirations after administration of human recombinant follicle-stimulating hormone. In February 2000, the macaque had tested negative for cerpithocene herpesvirus 1 (antibody -based enzyme linked immunosorbent assay), simian immunodeficiency virus, type D retrovirus (SRV), and simian T-lymphotrophic virus (antibody-based enzyme immunoassays followed by immunoblot [western] analysis if equivocal or positive results), and tuberculosis (intradermal tuberculin test). At the time of physical examination the animal was menstruating. The uterus was moderately enlarged, firm, and irregularly shaped. Tentative diagnostic possibilities included endometriosis or adenomyosis, and ultrasonography was performed. Numerous fluid-filled structures were associated with the body of the uterus, and aspiration of these structures yielded a dark red to brown, opaque, thick fluid, consistent with endometrial cysts. Because the animal was being used in a study at the time, further diagnostics were not performed. Animal care and experimentation were conducted in accordance with all relevant local, state, and national regulations, using protocols approved by the appropriate institutional Animal Care and Use committees.

In June 2000, the macaque was reported to be lethargic and inappetent during menstruation, and ketoprofen (analgesic) was administered intramuscularly (i.m.) at a dosage of two milligrams per kilogram daily or twice daily as needed. The monkey was released from the study a week after menstruation began, and 150 mg of medroxyprogesterone acetate (MPA; Upjohn & Pharmacia, Kalamazoo, Mich.) was given i.m. to better ameliorate the clinical signs of endometriosis.

At tuberculosis testing in August 2000, the animal had gained 0.7 kg. Results of the physical examination were normal, except for a 4-cm-diameter, roughly spherical, caudal intra-abdominal mass that was assumed to be endometriosis.

In September 2000, menstruation occurred, and MPA administration was repeated at the same dosage. In October 2000, the animal became inappetent again and began menstruating. The MPA was repeated at an increased dose of 250 mg, and butorphanol was given i.m. as an analgesic at a dose of 10 mg daily.

In December 2000, the animal was released from a final study. Exploratory laparotomy was scheduled to attempt to permanently control the endometriosis by removing the ovaries. On opening of the abdomen, a flaccid, 6.0 × 9.5 × 2.0-cm multichambered, yellow, cystic mass was detected cranial to the uterus. Large amounts of opaque, white, viscous fluid were discharged into the abdominal cavity from the cavitations in the mass. The ovaries could not be visualized. Due to poor prognosis for full recovery, the animal was euthanized, and the body was submitted to the pathology service for necropsy.

At necropsy, the animal was in normal nutritional condition (7.05 kg). The only gross lesion found was the previously described cystic mass. The cystic structure had adhesions to the anterior wall of the uterus, as well as to the omentum, peritoneum, urinary bladder, and large intestine. The ovaries were assumed to be entrapped within the cystic structure.

On histologic examination of routinely processed, hematoxylin and eosin-stained sections, the mass was found to be principally composed of sheets of polygonal to round cells, with well defined cell borders and moderate amounts of eosinophilic cytoplasm (Fig. 1, A-C). Scant, fibrovascular stroma was present.

Received: 10/30/01. Revision requested: 12/27/01. Accepted: 1/10/02.
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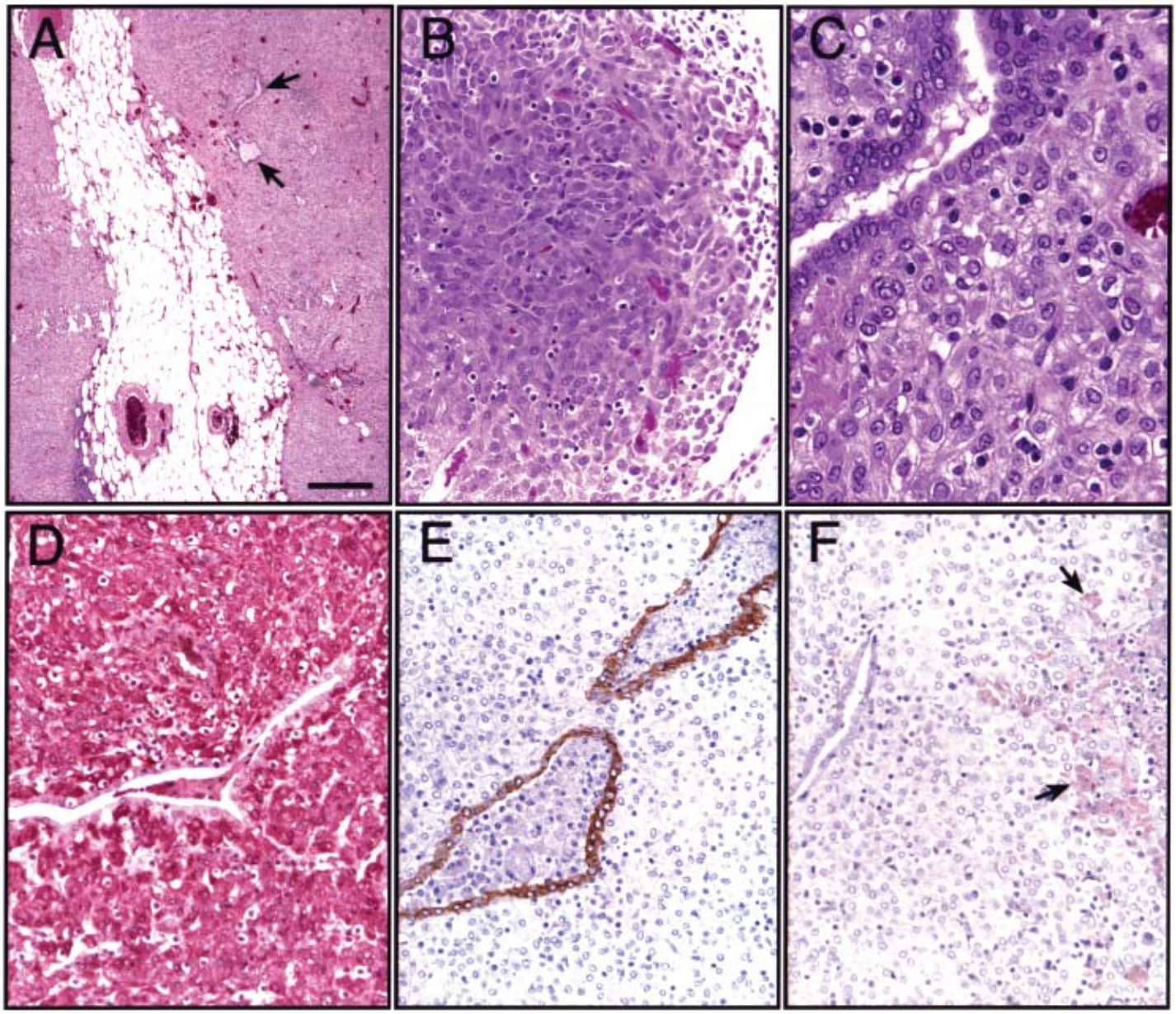

Figure 1. Photomicrographs of sections from the uterus of the rhesus macaque. (A) Staining with hematoxylin and eosin (H&E) at low magnification (bar = 250 mm). Glandular structures (arrows) were embedded in sheets of polygonal to round cells. Central area of adipose tissue was most likely of omental origin. (B) Higher magnification of area of stromal proliferation devoid of glands. Cells are round to spindle shaped. H & E stain; bar = 50 mm. (C) Focus of stromal cells with distinct cell borders. Notice glandular structure in upper left corner. H & E stain; bar = 25 mm. (D) Immunohistochemical staining for vimentin with fuchsin and a hematoxylin counterstain demonstrating broad cytoplasmic positivity of the stromal cells (bar = 50mm). (E) Immunohistochemical staining for keratin (AE1) with diaminobenzadine and a hematoxylin counterstain. Notice staining of glandular epithelial cells with lack of staining in surrounding stroma. Glandular lumen contains numerous macrophages (bar = 50 mm). (F) Immunohistochemical staining for CD with fuchsin and a hematoxylin counterstain. Macrophages with positive cytoplasmic staining are surrounding an area of liquifactive necrosis (arrows). Gland is present on the left side of the photomicrograph (bar = 50 mm).

Nuclei were round to oval, with finely vesicular chromatin and none or one round nucleolus. Mitoses were rare, with fewer than one observed per five 40× high-power microscopic fields. The cells extended to the edges of the sections examined.

Scattered throughout the mass were few, variably sized, glandular structures composed of columnar to cuboidal epithelium (Fig. 1A, arrows). The lumen of these structures occasionally contained necrotic cellular debris accompanied by macrophages. Multiple small foci of liquifactive necrosis were present throughout the sections, and these frequently were surrounded by macrophages. Inflammatory infiltrates of lymphocytes, plasma cells, or neutrophils also were present in small numbers. Some sections contained foci of adipose tissue.

To better characterize the polygonal cells, immunohistochemical staining was performed. Staining for vimentin (No. N1583, DAKO, Carpinteria, Calif.) and CD 68 (macrophage marker; No. N1577, DAKO) was done by use of the DAKO LSAB2 System according to the manufacturer's instructions. For digestion/retrieval, the DAKO Target Retrieval Solution was applied at 95°C for 20 min for vimentin and for 40 min for CD 68. For keratin

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staining, which included multiple cytokeratins (No. N1589, DAKO), AE1 (No. 1199 099, Boehringer Mannheim, Roche Diagnostics, Indianapolis, Ind.), and Lu-5 (No. CMO-43C, Biocare Medical, Walnut Creek, Calif.), the DAKO EnVision+ System was used according to manufacturer's instructions, with proteinase-K as the chosen pretreatment.

On formalin-fixed sections, the polygonal cells stained positive for vimentin (Fig. 1D), but negative for keratin (Fig. 1E) and CD 68 (Fig. 1F; arrows indicate CD 68-positive macrophages). On the basis of clinical history, gross and histologic appearance, and immunohistochemical staining, a diagnosis of stromal decidualization of endometriosis was made.

Later, biopsies were done on abdominal masses from 11- and 16-year-old rhesus macaques. Both animals had been treated with MPA for various durations. Both animals had gross lesions of voluminous serosal and peritoneal plaques composed of material that varied from soft to firm and light red to yellow-white. The histologic changes and immunohistochemical staining pattern were identical to those described for the first monkey.

Discussion

Endometriosis is a common diagnosis in Old World nonhuman primates, and case reports in literature of the disease in cynomolgus and rhesus macaques are numerous (1). At the Wisconsin Regional Primate Research Center (WRPRC), the overall prevalence of endometriosis in female rhesus macaques necropsied from 1980-1995 was 20%. Monkeys younger than 10 years old were not found to have the disease. Associated risk factors included exposure to estradiols and undergoing hysterotomy (2).

The WRPRC has a large colony of aging rhesus macaques, and several protocols allow extensive geriatric medical care prolong quality life. As a part of such protocols, treatment to alleviate the acknowledged clinical abnormalities and physical discomfort associated with endometriosis (e.g., inappetence, increased somnolence and anemia) is routinely performed. Treatment of these animals is dependent on whether the reproductive tract needs to be left intact and if surgery is a viable option. If oophorectomy is allowed, and the ovaries can be visualized surgically, this procedure is preferred. If the reproductive tract cannot be surgically altered, due to protocol or inability to surgically isolate the structures, medical management is a reasonable alternative. In humans, medical management of endometriosis includes administration of non-steroidal anti-inflammatory drugs, estrogen-progestin combinations, progestogens, pituitary-ovarian axis suppressants (danazol), gonadotropin-releasing hormone agonists, and antiprogestins (3). In nonhuman primates in a research setting, long-term daily administration of medications is frequently impractical, therefore making long-acting, injectable progestogens, such as MPA, an attractive treatment modality. There also is evidence that MPA may be as or more effective than oral contraceptives for treatment of pelvic pain associated with endometriosis (4, 5). Adverse effects, such as decreased high- density lipoprotein concentration, depression, bloating, and weight gain, reported in women being treated with MPA, have not caused clinical problems in macaques. A report of pyometra in a rhesus monkey following MPA therapy is of concern, and animals should be monitored for vaginal discharge and/or uterine enlargement (6).

Decidualization of the stroma of the uterus is a complex process that has yet to be fully elucidated. Results of recent studies in the estrogen receptor-α knockout mouse suggest that progesterone and mechanical stimulation of the stromal cells encourage terminal differentiation into decidual cells (7). The morphologic change in shape and size of stromal cells that decidualize is associated with extensive organelle development, especially those involved in protein synthesis and secretion (8). Immunophenotypes for human decidua, extra-uterine decidual reactions, and cultured endometrial stromal cells exposed to progesterones or progesterone-estrogen combinations are similar, indicating a consistency in cellular reaction despite location (9, 10). Therefore, with regard to the lesions of endometriosis, the amount of exogenous or endogenous progesterone is probably the most important factor in decidualization.

The gross and histologic appearance of endometriosis that has undergone a decidual reaction can mimic other processes. The moderate to massive increase in the size of stromal cells can create a mass lesion where a typical, flat, firm focus of endometriosis previously existed. In this instance, the clinical veterinarian considered an intra-abdominal abscess or neoplastic proliferation in the differential diagnoses during exploratory laparotomy. Such conditions may carry a poorer prognosis than does endometriosis. In human cases mimicking malignancy, immunohistochemical analysis was important in ascertaining the definitive diagnosis (11, 12). The histologic features of the decidualized stromal cells may be similar to those of epithelial cells or macrophages, or a composite of both. Glandular structures may or may not be present in biopsy specimens, making definitive diagnosis more difficult. Positive staining for vimentin, coupled with lack of staining for keratin or CD 68 (macrophage stain), aids in confirmation of stromal decidualization. If uterine tissue is available, histologic findings of the endometrial lining should be similar to those revealed by biopsy of endometriosis.

As human lifespan increases, aging research and the need for animal models of diseases and conditions common to geriatric patients also increases (13). Typical species used in aging experiments include macaques and baboons, both of which have regular menstrual cycles and are at risk for development of endometriosis (14). Veterinary clinicians may choose medical management of endometriosis to alleviate discomfort, decrease anemia, or prevent life-threatening sequella such as hemoabdomen (15). Clinicians and pathologists should become familiar with the appearance of endometrial lesions before and after treatment to prevent misdiagnosis and unnecessary intervention.

Acknowledgments

We thank Michael Goldschmidt, Jackie Ferracone, and Amanda G. Trainor for their assistance with immunohistochemical analysis, Clay Glennon for digital microscopy assistance, and the veterinary technicians and animal care staff for their care and assistance with these monkeys.

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