Endometriosis in Cynomolgus Monkeys Retired from Breeding

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ABSTRACT. Twenty-seven cases of endometriosis were found in 94 female cynomolgus monkeys retired from breeding. The ages of the affected monkeys (28.7% of all the monkeys) ranged from 11 years to 23 years of age with an average of 15.3 years. There was no significant difference in the incidence of endometriosis between groups which had or had not undergone a cesarean section. Time after the last pregnancy was significantly longer in the affected monkeys than in the non-affected ones. These cases were histopathologically classified into four types; 1) pelvic endometriosis with formation of endometrial cysts (51.8% of the affected monkeys), 2) pelvic endometriosis invading other organs without formation of endometrial cysts (3.7%), 3) uterine adenomyosis (22.2%), 4) combined pelvic endometriosis and uterine adenomyosis (22.2%).—KEY WORDS: cynomolgus monkey, endometriosis.


Endometriosis, which is one of the important disorders in female reproductive organs, is characterized by ectopic growth of endometrial tissues, both endometrial epithelium and stromal tissues, in the myometrium and/or outside the uterus. The ectopic growth of the endometrial tissues limited to the myometrium of the uterus is termed adenomyosis or internal endometriosis, while the growth outside the uterus including its serosa is simply termed endometriosis or external endometriosis [2, 8]. In most cases of endometriosis, ectopic growth of endometrial tissue was limited to the peritoneal surface of the pelvic and abdominal cavities, but in some cases it metastasized to the liver, intestines, and mesenteric and pelvic lymph nodes [6, 12].

In non-human primates, both spontaneous and experimentally induced cases of endometriosis in rhesus monkeys have been reported [1, 6, 8, 12]. Several population-based studies showed a correlation between the incidence of endometriosis and factors related to age, fertility, hysterotomy and irradiation [2]. Endometriosis has been observed in baboons [7], cynomolgus monkeys [5], pig-tailed macaques [3] and African green monkeys [11].

This paper describes the histopathological findings in 27 cases of endometriosis out of 94 female cynomolgus monkeys that were reared for breeding purposes and later necropsied in our laboratory.

MATERIALS AND METHODS

Twenty-seven cases of endometriosis of cynomolgus monkeys (Macaca fascicularis) were obtained from 94 cases of female monkeys necropsied in our laboratory from 1989 to 1991 (Fig. 1). All monkeys were wild-caught and imported from Philippine, Indonesia, Malaysia about a decade ago. They were reared at Tsukuba Primate Center for Medical Science (TPC), NIH, Japan for breeding purposes and then transported to our facilities for use in the experiments for live vaccines. The ages of these monkeys were estimated by examination of the dentition at the first quarantine. During quarantine at TPC and our laboratory, the general condition of the monkeys and the values of serum blood examinations were within normal range. However, in some cases, solid masses were palpated in the region from the ventral abdomen to the pelvic cavity.

They were housed individually and given water ad libitum, and fed a commercial pelleted diet (80 g/day/monkey) and orange (100 g/day/monkey) for supplementing vitamin C. On completion of experiments or with deterioration of general conditions, they were sacrificed by exsanguination under ketamine anesthesia. Two cases died spontaneously. All cases were necropsied and representative organs including female reproductive organs were fixed in 10% neutral buffered formalin, and processed for paraffin embedding. Tissue sections were stained with hematoxylin and eosin (HE). Selected sections were stained with Gomori’s one step trichrome and...
periodic acid-Schiff. Endometriosis was diagnosed by gross and microscopic observation.

RESULTS

The age distribution of affected monkeys is shown in Fig. 1. The incidence of endometriosis was 28.7% of the necropsied animals, and the average age of the affected monkeys was 15.3 years, ranging from 11 to 23 years.

Sixteen monkeys had undergone cesarean sections once or twice, out of which 5 (31.3%) were affected with endometriosis. Out of the other 78 monkeys which had not undergone a cesarean section, 22 monkeys (28.2%) had endometriosis. There was no significant difference in the incidence of endometriosis in the two groups, but out of 5 cases with endometriosis in the former group, 4 ones underwent a cesarean section at the last pregnancy.

The average time after the last pregnancy in the affected and non-affected monkeys was 5.4 and 3.1 years, respectively, which were significantly different by Student's t-test (p<0.001). None of our monkeys had been exposed to irradiation and the incidence of endometriosis was not correlated to factors like habitat of the monkey, numbers of parturition, and drug treatment.

The 27 cases of endometriosis were histopathologically classified into four types. The first type was pelvic endometriosis with formation of cysts, 14 cases (51.9% of the affected monkeys). Ectopic growth of endometrial tissues was limited to the pelvic cavity. The uterus was always affected and had one or more cysts, 1.5 to 8.0 cm in diameter, containing brown to red-brownish materials, and were located mostly at dorsal wall near the cervix or the lateral margins of the uterus (Fig. 2). In most cases of this type, adhesion by fibrous tissues and endometrial cysts to the serosa of the colon, ovaries, urinary bladder, oviducts, omentum, and dorsal peritoneal wall was observed (Fig. 3). Adhesions sometimes caused the stricture and the distention of the urethra and/or the rectum. One monkey (No. 2735) died spontaneously due to renal and intestinal dysfunction, subsequent to these adhesions. Dissemination of endometrial tissues to the abdominal organs was not noted in any of the cases.

Microscopically, ectopic growth of endometrial tissues was found in the serosa of the uterus, urinary bladder and colon, the part of which formed the endometrial cysts. The ovaries were most frequently involved in the cysts and became atrophic due to compression by the cysts. Myometrial hyperplasia without growth of endometrial tissues in itself was also observed in 2 cases.

Ectopic endometrial tissues were similar in all cases throughout all the types consisting of endometrial epithelial and stromal cells (Fig. 4). The endometrial epithelial cells were cuboidal to low-columnar with foamy cytoplasm, which sometimes contained periodic acid-Schiff positive materials. The stromal cells had small, round to oval, hyper-
chromatic nuclei and scanty cytoplasm. Both cell types were well differentiated and showed normal features. A single layer of endometrial epithelium formed glandular structures and occasionally cysts. The endometrial cysts contained eosinophilic hyaline material with hemorrhage, some cellular debris and macrophages. The wall of the cysts consisted of the extensive fibrous tissue with proliferated blood vessels. In some cases there were no stromal cells and the papillary growth of endometrial epithelium was seen (Fig. 5).

The second type was pelvic endometriosis invading other organs without formation of cysts, found in only one case (No. 2769) (3.7%). This monkey, which died spontaneously, had undergone a cesarean section at the last pregnancy and been sterile for 8 years. At necropsy, the uterus was normal in size and appearance, but a stricture, 1 to 2 cm in length, of the rectum with firm, fibrous tissues about 10 cm proximal to the anus was observed. The left ovary was also replaced by the same tissues but the right ovary was normal. Microscopically, the firm, fibrous tissues were endometrial tissues with abundant stromal and connective tissues and absence of cysts. The endometrial tissues invaded the smooth muscle layer in the rectum (Fig. 6).

The third type, to which 6 cases (22.2%) belonged, was uterine adenomyosis, in which endometrial tissues were only found in the myometrium of the uterus (Fig. 7). Cyst formation was found in only one case of this type. Grossly, the uterus was irregularly enlarged about 4×3×4 to 6×6×5 cm, and the serosa of the uterus was smooth. No adhesions were observed. In most cases of endometrial hyperplasia, enlargement of the uterus was regular maintaining the original shape. In all cases of this type, diffuse or nodular hyperplasia of the
smooth muscles caused irregular enlargement of the uterus. There was no growth of endometrial tissues in the serosa of the uterus or other organs.

The fourth type was a complex of the first and second types. Six cases (22.2%) were included in this category.

DISCUSSION

Endometriosis of monkeys is an important problem in a breeding colony. Diseases of the uterus cause a decline in fertility, endometriosis being the most common. Many reports on this disease of rhesus monkey have presented valuable data [2, 6], but there are only a few case reports on the cynomolgus monkey. Our present report might be useful for a breeding colony of cynomolgus monkeys to decide on the age for retirement from breeding and to diagnose long-term sterile monkeys.

One reason of the high incidence (28.7%) of endometriosis in this report might be that the population examined was a high-risk group. They were more than ten years of age and supplied for the experimental study due to decreased fertility. Their average age (17.9 years) was higher than that of female animals in the breeding colony of TPC and other facilities of rhesus monkeys, which was about 8 to 10 years old [6]. Age has been known to be one of the factors which increased the prevalence of endometriosis [10]. But in rhesus monkeys averaging about 8 years of age, a relatively high incidence (36%) of endometriosis has been reported [2].

Hence, the incidence of endometriosis unlikely increases at ages higher than 10 years. The other reason was the cumulative effect. In a breeding colony of the rhesus monkey, endometriosis occurred spontaneously in less than 1% of female animals per year [9]. The size of the breeding colony in TPC was about six hundreds. Therefore, our data might be the accumulated value of the incidence during 5 to 10 years.

Many workers have reported on the pathogenesis of endometriosis in the non-human primates [1, 12]. To date, the main causes of this disease were thought to be retrograde menstruation and implantation of endometrial tissues during uterine surgery [8]. In our cynomolgus monkey cases, the incidence of endometriosis in the hysterotomy group was almost equal to that in the non-hysterotomy group. In 8 (40%) of all cases forming endometrial cysts, bilateral or unilateral oviducts were affected and endometrial cysts were most frequently formed at the lateral margins of the uterus. These results suggested that hysterotomy did not possibly increase the incidence of endometriosis and the retrograde flow of endometrial fragments via oviducts might be the main cause of extraterine implantation of endometrial tissues.

In the endometriosis of our cynomolgus monkeys,
the lesion was limited to the pelvic cavity and mostly associated with the uterus. In contrast, the endometrial tissues in the rhesus monkeys with endometriosis were often distributed to the abdominal organs, livers, small intestines, and lymph nodes. This type of endometriosis was not present in our classification. These cases of massive endometriosis mostly occurred in association with frequent irradiation and other treatment increasing the incidence [1, 12]. Irradiation, ovarian steroids and the drugs causing immunodeficiency might augment the incidence of endometriosis in rhesus monkeys [1, 4, 12, 13]. But in our cases, the monkeys had neither irradiation nor drug treatment in spite of the high incidence. Therefore, these factors might influence the severity of endometriosis rather than its incidence.

Uterine adenomyosis was often accompanied with pelvic endometriosis in our cases. Twenty (74.1%) of 27 cases had growth of endometrial tissues in the myometrium. DiGiacomo reported that 5 (35.7%) of 14 cases of endometriosis in the rhesus monkey had adenomyosis as a complication [2]. High incidence of adenomyosis might be a characteristic feature in the cynomolgus monkey.

REFERENCES