Bilateral Ovarian Cysts Originating from Rete Ovari i in an African Green Monkey (Cercopithecus Aethiops)

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ABSTRACT. Ovarian cyst is common incidental finding in humans and many animals and includes follicular cysts, cystic rete ovarii and mesonephric duct cysts. Ovarian cyst is often associated with reproductive disorders in humans and animals. We found accidentally bilateral cystic masses in ovaries in an African green monkey. Grossly, the left and right ovarian cystic masses were single unilocular cystic structures measuring 0.6 and 1.8 cm in diameter, respectively. Histologically, both cysts were thin-walled structures that arose from the center of the ovary and displaced ovarian tissue peripherally. The cysts were lined by a single layer of nonciliated low cuboidal epithelium. Immunohistochemically, epithelial cells in the cysts were positive for cytokeratin, and the stromal cells were positive for smooth muscle actin but negative for vimentin. These results suggest that these ovarian cysts in an African green monkey are cystic rete ovarii. To our knowledge, this is the first report of cystic rete ovarii in African green monkeys and may be of value in relation to research of the pathogenesis and treatment of ovarian cyst.

KEY WORDS: African green monkey, cystic rete ovarii, ovarian cyst.


Cysts in and around the ovary are common incidental findings in humans and arise from rete ovarii, embryonic remnants like the mesonephric duct and cycling ovarian structures [4]. Follicular cysts, involving Graafian follicles or corpus lutea usually result from disturbance of gonadotrophin release. But, other cysts are mostly nonfunctional. The precise causes of these nonfunctional ovarian cysts have not yet been fully elucidated [4, 9]. Ovarian cysts in women are often associated with reproductive disorders like polycystic ovary syndrome (PCOS) [6]. They have been also reported in many animals, including dogs, cats, cattle, horses, pigs and monkeys [1, 11, 12]. Among monkeys, ovarian cysts in macaques such as rhesus and cynomolgus monkeys have been well documented in previous reports [3, 12]. But there are few reports of ovarian cyst in the African green monkey. In this report, we found and examined immunohistochemically ovarian cysts in an African green monkey to elucidate their origin. A 17-year-old, 3.25 kg, female African green monkey was euthanized for a scientific experiment, and bilateral cystic masses in the ovaries were found accidentally during necropsy. The monkey had no history of menstruation after the last menstruation on February 24th, 2007 and no clinical symptom like abdominal pain. The monkey had been imported from the Tsukuba Primate Research Center, Japan, in 2003 and had been housed in the current facility for seven years. The monkey was not treated with hormone-associated substances after importation. This monkey was kept in an indoor individual cage and fed commercial monkey chow (Harlan Laboratories, Madison, WI, U.S.A.) supplemented daily with various fruits and was supplied water ad libitum. Environmental conditions were controlled to provide a temperature of 24 ± 2°C, a relative humidity of 50 ± 5%, 100% fresh air at a rate of ≥12 room changes per hour, and a 12:12 hr light:dark cycle. All housing and experiments were performed in accordance with the Korea Research Institute of Bioscience and Biotechnology (KRIIBB) Institutional Animal Care and Use Committee Guidelines (Acceptance No. KRIIBB-AEC-10047).

At necropsy, the cystic masses of the left and right ovaries were comprised of single unilocular cystic structures measuring 0.6 and 1.8 cm in diameter, respectively (Fig. 1). Both of cysts were filled with clear fluid, and the inner surfaces of them were smooth and whistish. No other organs had obvious macroscopic lesions. Cystic tissues were resected and fixed in 10% neutral buffered formalin, processed routinely and embedded in paraffin. Tissue sections 3 µm in thickness were cut and stained with hematoxylin and eosin (H&E). Serial sec-
tions were processed by deparaffinization, rehydration and blocking of endogenous peroxidase. Those sections were examined immunohistochemically by the avidin-biotin-peroxidase complex (ABC) procedure (Vectastain Elite ABC Kit; Vector Laboratories, Burlingame, CA, U.S.A.). Pre-treatment of tissues with heat-induced epitope retrieval was performed. Primary antibodies in this study were used with monoclonal mouse anti-human cytokeratin antibody (Dako, DakoCytomation, Carpinteria, CA, U.S.A.), monoclonal mouse anti-human vimentin antibody (Dako) and monoclo- nal mouse anti-human smooth muscle actin antibody (Dako). Nonspecific mouse IgG1 (Dako) was used as a control. All sections were incubated with primary antibody diluted 1:100 at 4°C overnight and incubated with anti-mouse biotinylated secondary antibody (Dako) for 30 min at room temperature, followed by incubation with avidin-peroxidase conjugate for one hour at 37°C. Staining was developed in 0.05% 3,3′-diaminobenzidine solution (Dako).

Histologically, both cysts were thin-walled structures that arose from the center of the ovary. The ovarian parenchyma, which contained mostly corpus lutea, was displaced periph- erally by the cysts. They are separated from the ovarian tissues by fibrotic tissues (Fig. 2A). They were lined by a single layer of low cuboidal epithelium, but cilia were not apparent (Fig. 2B and 2C). Spindle-shaped cells were observed in the subepithelial layer (Fig. 2B), and flattened cells were rarely detected in the epithelium of the cyst (Fig. 2C). No inflam- matory infiltrates were present (Fig. 2).

Immunohistochemically, epithelial cells in the cysts were positive for cytokeratin (Fig. 3A) but negative for vimentin (Fig. 3C). Stromal cells were positive for smooth muscle ac- tin (Fig. 3B) but negative for vimentin (Fig. 3C). The negative control with nonspecific IgG1 also showed no positive

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**Fig. 1.** Gross findings of ovarian cysts in an African green monkey. Ovarian cysts that include transparent fluid are observed bilaterally. C, cervix; Ov, ovary; Ovi, oviduct; U, uterus. Bar=1 cm.

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**Fig. 2.** Histological features of ovarian cysts. (A) The cysts in the left ovary are thin-walled structures and press the ovarian tissue peripherally. H&E. Bar=500 µm. (B) The lining cells of cysts comprise a single layer of low cuboidal epithelium. H&E. Bar=10 µm. (C) Flattened cells are rarely detected in the epithelium of the cysts. H&E. Bar=10 µm.
labeling with all three markers (Fig. 3D).

In humans, ovarian cysts have been investigated in relation to reproductive disorders like PCOS, which is caused by chronic anovulation and associated with amenorrhea, hyperandrogenism, anorexia, hirsutism, obesity and diabetes mellitus type 2. In animals, the association of ovarian cysts with reproductive disorders has been studied to prevent economical loss in farm animals like cattle and pigs [2, 10]. On the other hand, ovarian cyst in the guinea pig as a disease model of PCOS has been reported previously [8]. In cynomolgus monkeys, mesonephric duct cysts are reported to be the most frequent cysts [3], whereas, in rhesus monkeys, cystic rete ovarii are the most common cysts, followed by mesonephric duct cysts and then follicular cysts [12]. But, there is no report describing the incidence of ovarian cyst in African green monkeys.

In many cases of ovarian cysts, it may be difficult to identify the origin of the cyst, because the location of the cyst often becomes unclear, as an expanded cyst can lose its distinctive structure under pressure [5, 13]. The cells lining cysts also lose their original structure with the expansion of the cysts [1]. Therefore, immunohistochemistry can be useful in differentiating different types of ovarian cysts. Cytokeratin is a marker for epithelium-originating cells, vimentin is a marker for mesenchymal cells, and smooth muscle actin is a marker for smooth muscle cells. Follicular cysts are lined by multiple layers of granulosa cells, which are immunohistochemically positive for cytokeratin, vimentin and smooth muscle actin. A cystic rete when arises in the center of the ovary is dilated, often containing multilocular structures, and is typically positive for cytokeratin and vimentin but negative for smooth muscle actin. However, it often shows positive staining variably for vimentin and smooth muscle actin in some cases [12]. Rete ovarii can be distinguished from mesonephric tubules, because rete ovarii are lack of layers of smooth muscle. Inclusion cysts can be differentiated from other cysts, because it is lined by flattened to cuboidal mesothelial cells [7]. Mesonephric duct cysts are lined by a single layer of ciliated cuboidal epithelium that shows positive staining for cytokeratin and strong staining for smooth muscle actin but variable staining for vimentin [12]. In the present case, the cilia of the epithelium were not apparent and not surrounded by smooth muscle layers. These ovarian cysts were immunohistochemically positive for cytokeratin and smooth muscle actin but negative for vimentin. These results were consistent with a cystic rete ovarii case in

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Fig. 3. Immunohistochemistry of the cells lining cysts for cytokeratin (A), smooth muscle actin (B) and vimentin (C). (A) Epithelial cells were positive for cytokeratin. Bar=100 µm. (B) Stromal cells were positive for smooth muscle actin. Bar=100 µm. (C) Epithelial and stromal cells were negative for vimentin. Bar=100 µm. (D) The negative control with nonspecific IgG1 also showed no positive labeling with all three markers. Bar=250 µm.
a rhesus monkey [7] and suggest that these ovarian cysts in the African green monkey were cystic rete ovarii.

Laboratory African green monkeys are used as human surrogates for pharmacokinetic research, human disease research and organ transplantation. So, there are many concerns about reproductive disorders in relation to breeding in the laboratory environment. But, there is no literature about the relation of ovarian cyst with reproductive disorders in monkeys. However, compared with the case of human-like PCOS, reproductive disorders in the monkey could be involved in developmental problems or hormone-associated changes in the ovary, since both are physiologically similar. Thus, researchers should monitor ovarian cysts in relation to reproductive disorders in the laboratory environment.

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REFERENCES


