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Case Report

Bilateral Cataract in a Cynomolgus Monkey

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Abstract: Severe bilateral cataract was found in a 7 year-old naïve female cynomolgus monkey (*Macaca fascicularis*) 3 months before necropsy. During macroscopic examination, severe opacity and thinning of the lens were observed in both eyes. Histopathology revealed that the lens nuclei and majority of cortex lens fibers had disappeared and become excavated, while the lens fibers in the subcapsular area were swollen and distorted. Other observations included atrophy and vacuolation in the lens epithelial cells and proliferation of spindle cells and collagen fiber beneath the anterior capsule of the right eye. Immunohistochemical staining of these spindle cells revealed the presence of vimentin, cytokeratin and α-smooth muscle actin (α-SMA), which were considered to be derived from lens epithelial cells. This is a rare case of spontaneous, bilateral, hypermature cataract in a cynomolgus monkey. (DOI: 10.1293/tox.24.69; J Toxicol Pathol 2010; **24**: 69–73)

Key words: cynomolgus monkey, histopathology, hypermature cataracts

Cataract is a common eye disease characterized by complete or partial loss of lens transparency. Various factors such as increasing age, exposure to ultraviolet light, trauma, atopic dermatitis, diabetes and genetics are thought to be related to the pathogenesis of cataract[1–7]. The incidence of cataract in macaques is known to increase with age, similar to age-related cataract in humans[8,9]. However, all previously reported cases of spontaneous cataract in the cynomolgus monkey have been mild and have lacked histopathological descriptions.

In this case report, we describe the histopathological changes in a 7 year-old naïve female cynomolgus monkey (*M. fascicularis*) with severe bilateral cataract. The cynomolgus monkey had been imported from China (Guangxi Grandforest Scientific Primate Co., Ltd., Guangxi, China) and used for breeding. All procedures involving the animal were approved by the Animal Care and Use Committee of Shin Nippon Biomedical Laboratories, Ltd. and performed in accordance with the standards published by the National Research Council, USA (Guide for the Care and Use of Laboratory Animals, NIH OACU), and the National Institutes of Health Policy on Human Care and Use of Laboratory Animals, USA. The room the monkey was housed in was maintained at a temperature range of 23°C to 29°C, with the humidity levels between 35 and 75%, 15 air changes/h and artificial illumination for 12 h/day (06:00 to 18:00). The monkey was housed in an individual, stainless steel cage (Taiyo Stainless Co., Ltd., Kagoshima, Japan) and provided with approximately 108 g of solid food (Teklad Global Certified 25% Protein Primate Diet; Harlan Sprague Dawley Inc., Madison, WI, USA) daily at approximately 15:00. The quality of the water provided met the water quality standards of the Japanese Waterworks Law, and the water was available ad libitum from an automatic supply system (Edstrom Industries, Inc., Waterford, WI, USA).

Bilateral cataract was detected 3 months before necropsy. Ophthalmology was not photographed, and blood sampling was not performed. Before necropsy, the animal was weighed and anesthetized with an intravenous injection of sodium pentobarbital (Tokyo Chemical Industry Co., Ltd., Tokyo, Japan) solution (64.8 mg/mL, 0.4 mL/kg) into the cephalic vein of the forearm. The eyes, pancreas, liver, kidneys, lung, heart, brain and bone marrow (sternal and femoral) were fixed in a 10% neutral buffered formalin, embedded in paraffin, sectioned and stained with hematoxylin and eosin (HE). In addition, the eyes were stained with Periodic Acid Schiff (PAS), Congo red and Masson's Trichrome. Immunohistochemical staining was also performed for vimentin (Dako Japan, Kyoto, Japan), pancytokeratins (AE1/AE3, M3515, Dako Japan), α-SMA (α-smooth muscle actin) and CD68 (Dako Japan, Kyoto, Japan).

During macroscopic examination, severe opacity and thinning (right, approximately 2 mm thick; left, approxi-

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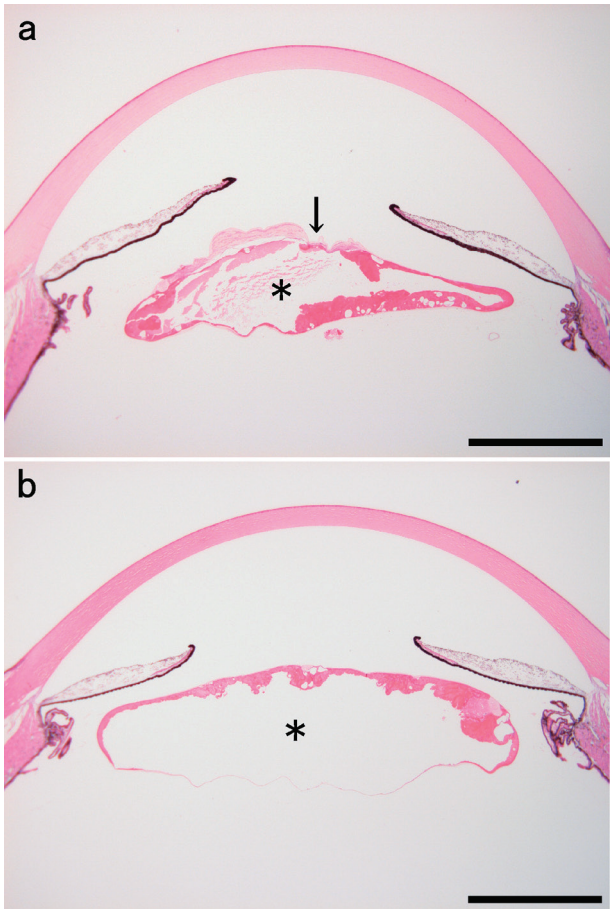


Fig. 1. Histopathological findings (lens, right and left eyes). The majority of lens fibers had disappeared and become excavated (*). The lens capsule (arrow) at the anterior pole of the right eye was partially distorted (arrow). Vacuoles of various sizes were diffusely observed in the lens fibers. (a) Right eye. (b) Left eye. HE stain. Bar = 2 mm.

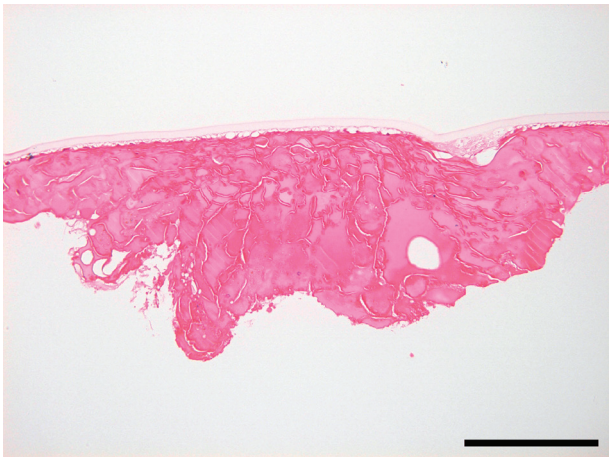


Fig. 2. Histopathological findings (anterior pole of lens, left eye). The majority of lens fibers in the subcapsular area had become swollen and distorted. Remnants of cell nuclei were observed in the lens fibers. Mineralization of the lens fibers was not observed. HE stain. Bar = 200 µm.

mately 1.5 mm thick) of the lens were observed in both eyes. No gross abnormality was observed in any other organ.

Histopathological examination showed that the lens nuclei and most of the cortex lens fibers had disappeared and become excavated (Figs 1a and b). The lens capsule at the anterior pole of the right eye was partially distorted. Cellular infiltration or adhesion of the lens to the ciliary body or iris was not observed. No abnormalities were observed in the cornea or retina. Most of the lens fibers in the subcapsular area of the lens cortex of both eyes were swollen and distorted (Fig 2). Vacuoles of various sizes were also diffusely observed in the lens fibers, and remnants of cell nuclei were observed in the lens fibers at the anterior and posterior poles of each eye. Mineralization of the lens fiber was not observed, and there were no Congo red-positive deposits in the lens fibers or lens epithelial cells.

Lens epithelial cells had atrophied and contained vacuoles in their cytoplasm (Fig 3a). Immunohistochemistry showed that these lens epithelial cells were positive for vimentin and cytokeratin, but most of them were negative for α-SMA (Fig 3b, c, d). In the anterior pole of the right eye, beneath the lens capsule and adjacent to the lens epithelium (Fig 4a), a proliferation of spindle cells was observed with abundant collagen fibers (Fig 4a, 5a). The lens capsule, which stained positive for PAS, was intact, with no observed rupture of the lens capsule (Fig 4b) and no continuity between the lens capsule and the spindle cells. These spindle cells were positive for vimentin, cytokeratin and α-SMA (Fig 5b, c, d). The expression of α-SMA was also observed in lens epithelial cells adjacent to the spindle cells (Fig 5d). In the left eye, between the lens capsule and the epithelium, collagen fibers had accumulated without α-SMA-positive spindle cells (Fig 6). CD68-positive macrophages were not observed in either lens, and no histopathological changes were observed in the pancreas, liver, kidneys, lung, heart, brain or bone marrow.

Cataracts are classified by both location (e.g., anterior subcapsular, posterior subcapsular, nuclear and cortical) and stage of development (e.g., incipient, immature, mature and hypermature). In cortical cataracts, lens fibers appear disorganized, degenerated or swollen, with marked liquefaction and reduction of lens volume in a hypermature cataract[10,11]. Histopathological changes in this monkey's eyes were characterized by marked intralenticular cavitation, with the remaining lens fibers severely degenerated. These findings suggest that the liquefaction of degenerated lens fibers and ejection of liquefied tissue during specimen preparation (fixation or embedding) caused the intralenticular cavitation. Therefore, the histopathological features of this monkey's eyes are consistent with the features of hypermature cortical cataract in humans. Cataracts in both humans and the rhesus monkey are known to accompany

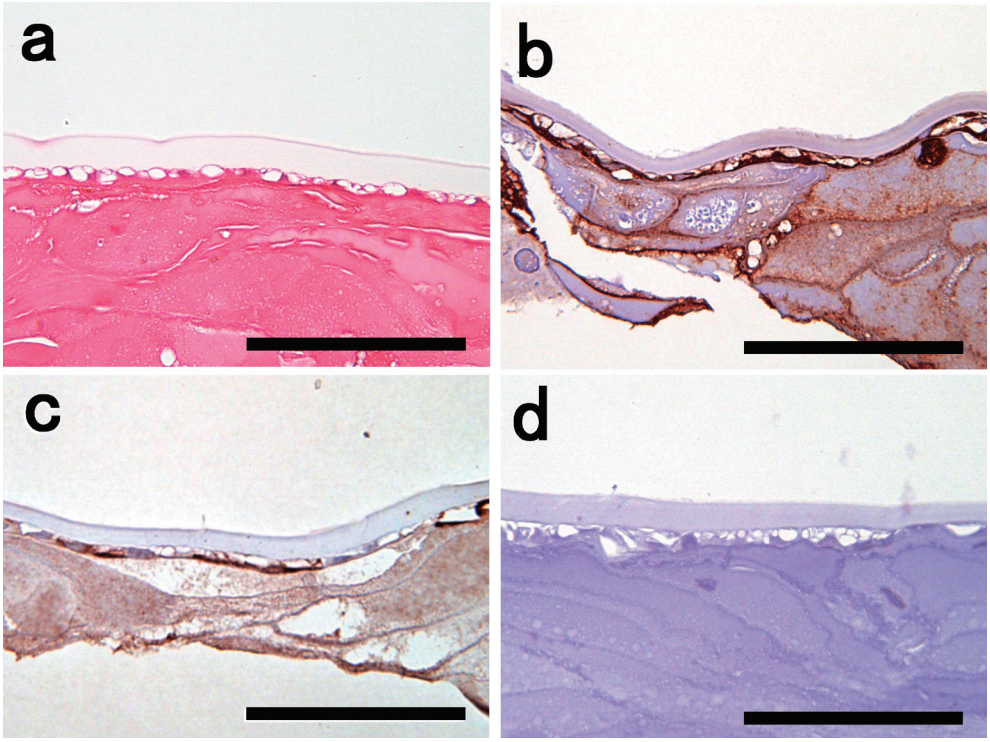
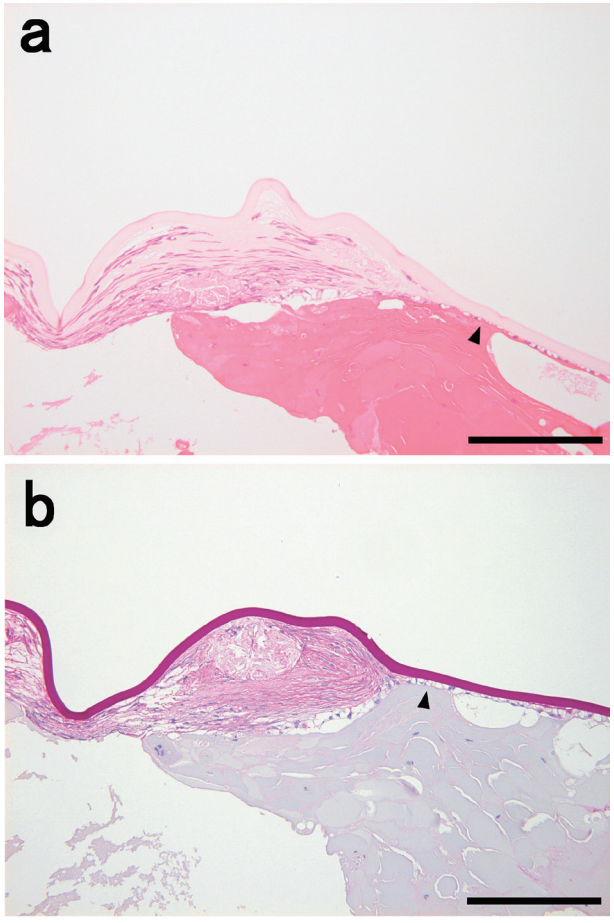


Fig. 3. Histopathological findings and immunohistochemical staining (lens epithelial cells). Lens epithelial cells were atrophied with vacuoles in their cytoplasm. (a) HE stain. Lens epithelial cells were positive for (b) vimentin and (c) cytokeratin, but negative for (d) α-SMA. Bar = 100 μm.



vacuolation or loss of lens epithelial cells[12,13]. Atrophy and vacuolation in the lens epithelial cells were also found in this monkey and were considered to be secondary because of the marked changes in the lens fibers. No inflammation or uveitis was observed in any portion of the monkey's eyes, which contrasts with the anterior uveitis caused by hypermature cataracts in dogs[11,14]. On the other hand, amyloid formation in the lens fiber cells derived from γ-crystallins causes inherited cataract in γ-crystallin mutant mice, and this process may contribute to the development of senile cataract[15,16]. In this case, Congo red staining did not reveal any evidence of amyloid formation associated with cataracts.

Lens opacity is caused by the proliferation of spindle cells with extracellular matrix containing collagen fibers, in anterior subcapsular cataracts or after cataract surgery in humans[17–22]. Lens epithelial cells transdifferentiate into myofibroblast-like cells and express vimentin, cytokeratin and α-SMA[21,22]. Spindle cells were associated with lens epithelial cells in this case, but because no perforation of the lens capsule was observed, it is unlikely that these

Fig. 4. Histopathological findings (beneath the anterior capsule, right eye). A proliferation of spindle cells with abundant collagen fibers was observed beneath the lens capsule and adjacent to the lens epithelium (arrow head). (a) HE stain. (b) PAS stain. Bar = 200 μm.

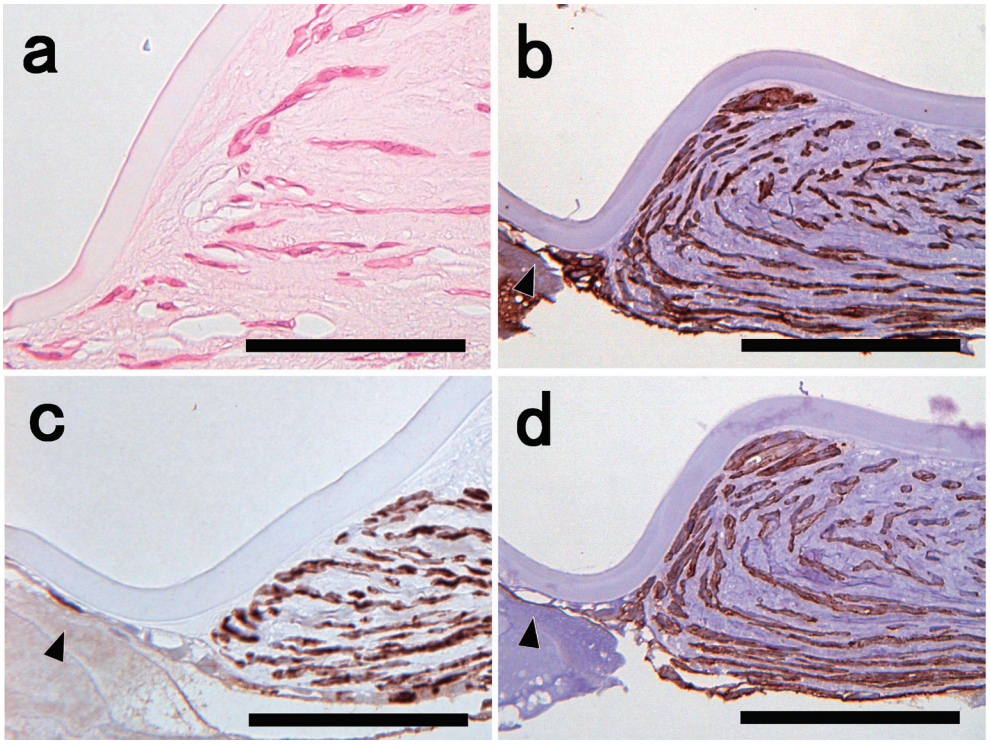


Fig. 5. Histopathological findings and immunohistochemical staining of the spindle cells (beneath the anterior capsule, right eye). (a) HE stain. Spindle cell proliferation beneath the anterior capsule of the right eye and adjacent to the lens epithelial cells (arrowheads) was positive for (b) vimentin, (c) cytokeratin and (d) α-SMA. Bar = 100 μm.

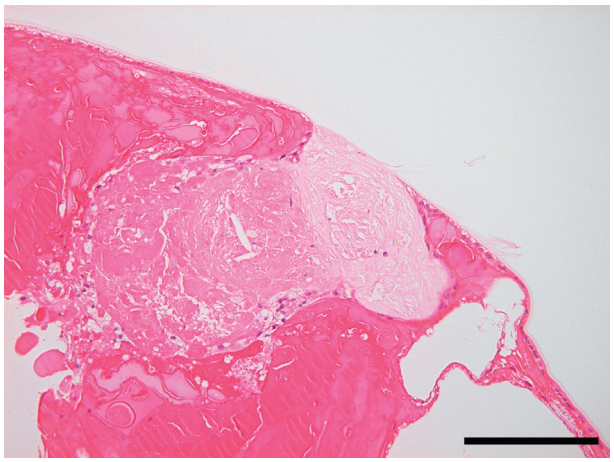


Fig. 6. Histopathological findings (beneath the lens capsule, left eye). Accumulation of collagen fibers without spindle cells was observed between the lens capsule and epithelium. HE stain. Bar = 200 μm.

spindle cells had infiltrated from outside the lens. The histopathological and immunohistochemical features of cataracts in humans are the same as in this monkey. Considered together, the spindle cell proliferation in the right eye in this case was likely derived from lens epithelial cells. Distortion of the lens capsule may also have been caused by these myofibroblast-like lens epithelial cells. CD68-positive macrophages were not observed between the spindle cells, although in secondary cataracts in humans, macrophage infiltration has been reported in association with spindle cell proliferation[22]. The morphogenesis of a fibrous mass in the subcapsular area of the left eye was unclear because it lacked cellular components; however, it may have been the final stage of myofibroblast-like cell proliferation.

Considering the monkey's age, this case cannot be considered as senile cataract[23]. Various factors including aging, genetics, underlying diseases such as diabetes and ocular trauma may be related to the development of a cataract[1–7]. Although the blood chemistry of this monkey was not examined, it is unlikely that an underlying disease, such as diabetes, caused the cataract, since the only histopathological abnormality was found in the eyes. Likewise, ocular trauma was not evident in macroscopic examination or histopathology. Therefore, genetic factors may have contributed to the development of cataract in this cynomolgus monkey.

This was a rare case of spontaneous hypermature cataract with marked liquefaction of the lens fibers in both eyes of a cynomolgus monkey.

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