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Phacoclastic Endophthalmitis Induced by *Encephalitozoon cuniculi* in a Lionhead Rabbit in Korea

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Abstract : An 8-month-old female rabbit was presented with a white intraocular mass in the right eye. Slit-lamp biomicroscopy showed a white mass behind the iris, accompanied by rubeosis iridis and aqueous flare. Ocular B-scan ultrasonography revealed hyperechoic material within the anterior chamber connected with cataractous lens in the right eye. Signs deteriorated despite treatment, and enucleation was performed. Histopathologically, phacoclastic endophthalmitis due to *Encephalitozoon cuniculi* infection was confirmed. This was the first report of a client-owned rabbit affected with *E. cuniculi*-associated phacoclastic uveitis. Serological detection of anti-*E. cuniculi* antibodies should be considered to prevent potential zoonotic risk.

Key words **:** cataract, *Encephalitozoon cuniculi*, lens induced uveitis, phacoclastic endophthalmitis, zoonotic pathogen.

Introduction

Encephalitozoon cuniculi is an obligatory intracellular, spore-forming, microsporidian pathogen (4,5,7). Infections with *E. cuniculi* have been observed in a wide range of mammalian hosts, including carnivores and horses (1,5), and while *E. cuniculi* is an opportunistic pathogen of immunocompromised humans, the main host for this organism is the rabbit, which has been increasingly affected by this pathogen (5,6).

Encephalitozoonosis is a common condition in laboratory rabbits with an incidence ranging from 5 to 75% (3,4). In rabbits, *E. cuniculi* affects the central nervous system, kidneys, and eyes (1,5). Ocular manifestations of encephalitozoonosis have rarely been reported in Korea. The purpose of this case report is to present the case of a pet rabbit affected with phacoclastic uveitis and to discuss the best method for the successful management of *E. cuniculi*-induced phacoclastic uveitis in rabbits.

Case

An 8-month-old, female Lionhead rabbit was referred for a white intraocular mass in the right eye (OD), which was detected 2 weeks previously. The rabbit was housed indoors with dry rabbit pellets in good condition. At first presentation, moderate conjunctival hyperemia and chemosis accompanied by blepharospasm was observed in the OD. Intraocular pressure (IOP) values measured by rebound tonometry (TonoVet; iCare; Helsinki, Finland) were 10 mmHg OD and 12 mmHg OS. Pupillary light reflex was absent in the OD due to the posterior synechia and iris bombe, though palpebral and dazzle reflexes were normal. Neuro-ophthalmic examinations were normal OS. The pupil was fixed and contracted (miosis), and rubeosis iridis and iris bombe were observed, especially in the 4-8 o'clock position in the iris of the OD (Fig 1A and B). In addition, a white mass was noticed in the ventral portion of the pupil and behind the iris, connected with the anterior lens capsule in the 4-8 o'clock position, with moderate aqueous flare in the OD. Ocular B-scan ultrasonography revealed hyperechoic material within the anterior chamber and immature cataract with no other abnormalities in the posterior segment in the OD (Fig 1C). On full ophthalmic examinations, abnormalities were identified only in the OD, while the OS was normal (Fig 1D-F). Severe uveitis and cataract in the OD was diagnosed, and the iris of the OD was non-responsive to repeated administration of mydriatics including 1% tropicamide (Mydriacyl®; Alcon; Fort Worth, TX, USA), 2.5% phenylephrine (Mydfrin®; Alcon), and 1% atropine (Isopto Atropine®; Alcon), and thus the miosis and synechia remained unsolved. Septic uveitis due to *Pasteurella* spp., iridal abscess, iris neoplasia, and phacoclastic uveitis due to *Encephalitozoon cuniculi* were considered. As the age of this rabbit was young and the iridal and lenticular findings were typical for *E. cuniculi*, with the absence of clinical respiratory symptoms, this rabbit was treated for a presumptive diagnosis of *E. cuniculi* induced phacoclastic uveitis. Topical instillation of 0.03% flurbiprofen eye drop TID (Ocufen®; Allergan; Irvine, CA, USA) and oral fenbendazole 20 mg/kg PO SID (Panacur®; Intervet/Schering-Plough Animal Health; Union, NJ, USA) were prescribed. The serological detection of antibodies was recommended, but refused by the owner for financial reasons.

One week later, no significant change was observed. Three

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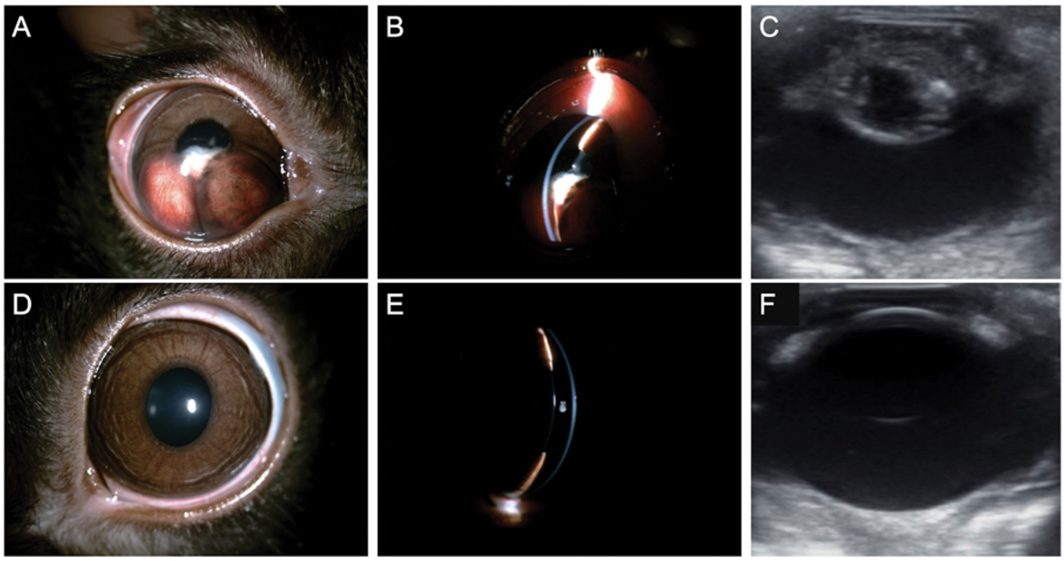

Fig 1. Initial presentation and ocular ultrasonographic images. (A-C) Right eye. (D-F) Left eye. Compared with the normal left eye, the right eye showed a white mass in the ventral portion of the pupil, behind the iris. Ocular B-scan ultrasonography revealed hyperechoic material within the anterior chamber connected with the anterior lens capsule with immature cataract in the right eye.

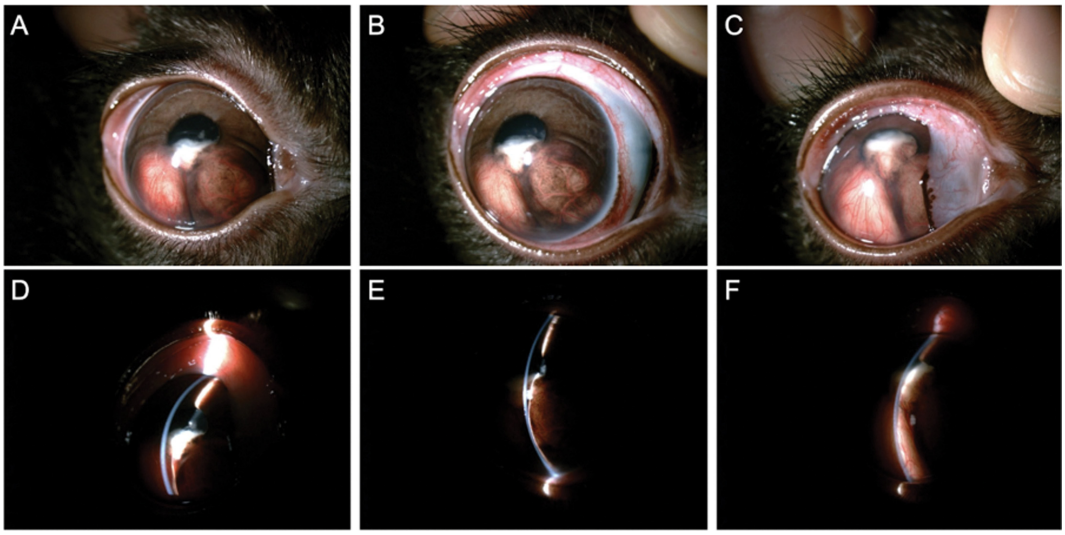

Fig 2. Chronological slit lamp biomicroscopy of the right eye. (A and D) Initial presentation. (B and E) One week later, no significant change was observed. (C and F) Three weeks later, the white intraocular mass grew large enough to cover the pupil.

weeks later, the owner complained that the intraocular mass was growing despite the treatment (Fig 2). Mild conjunctival hyperemia and severe aqueous flare of the OD remained uncontrollable. Iris bombe worsened, and neuro-ophthalmic reflexes were decreased. Enucleation of the OD was performed to relieve the pain due to intractable uveitis and potential glaucoma resulting from the intraocular mass. Complete blood count, serum biochemical analysis, and thoracic radiographic imaging revealed no significant systemic abnormalities, with no clinical signs of renal failure. There were also no clinical symptoms related to neurological signs. The rabbit was premedicated with enrofloxacin 5 mg/kg SQ (Baytril®; Bayer Animal Health, Leverkusen, Germany), midazolam 0.5 mg/kg IV (Midazolam Injection®; Bukwang Pharm., Korea), and hydromorphone 0.05 mg/kg IV (Dilid Injection®; Hana Pharm., Korea). General anesthesia was induced using propofol 5 mg/kg IV (Provive 1%®; Myungmoon Pharm., Korea), and administration of isoflurane (Ifran Solution®; Hana Pharm., Korea) was maintained. The enucleated eye was fixed in 10% neutral buffered formalin and was then sent for histopathological examination.

Fibrinosuppurative and granulomatous phacoclastic endophthalmitis and phakitis with anterior lens capsule rupture and intralenticular *E. cuniculi*, along with secondary chronic glaucoma, were histopathologically confirmed (Fig 3). Associated with the anterior lens capsule, adjacent to the rupture, there are several accumulations of round to oval 2-3 μm organisms containing a basophilic nucleus with a central clearing consistent with *E. cuniculi* (Fig 4). Postoperatively, this rabbit was medicated with enrofloxacin 5 mg/kg PO SID and carpforen 2 mg/kg PO SID (Rimadyl®; Pfizer; Ann Arbor, MI, USA) for 5 days, and the surgical wound healed

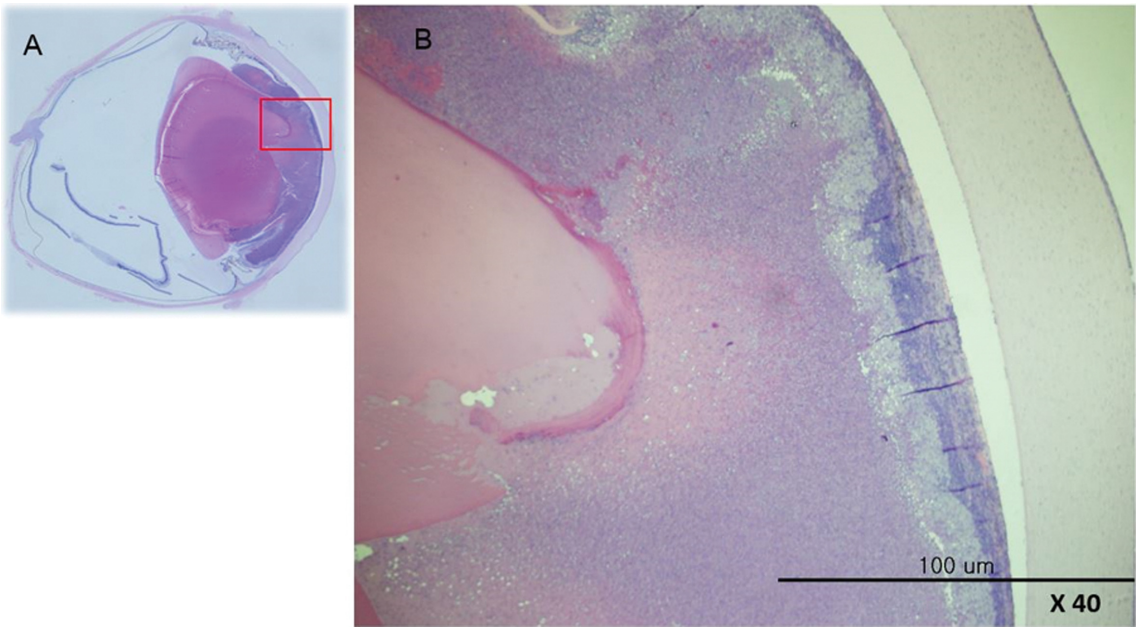

Fig 3. Histopathological images from the enucleated right eye. (A) Subgross image. (B) Magnification of ×40, hematoxylin and eosin stain. The area of the red rectangle in (A) shows the ruptured anterior lens capsule and an intense inflammatory infiltrate mixed with the liquefied lens fibers within the anterior chamber. Numerous macrophages and multinucleated giant cells with abundant finely granular amphophilic cytoplasm line the anterior chamber.

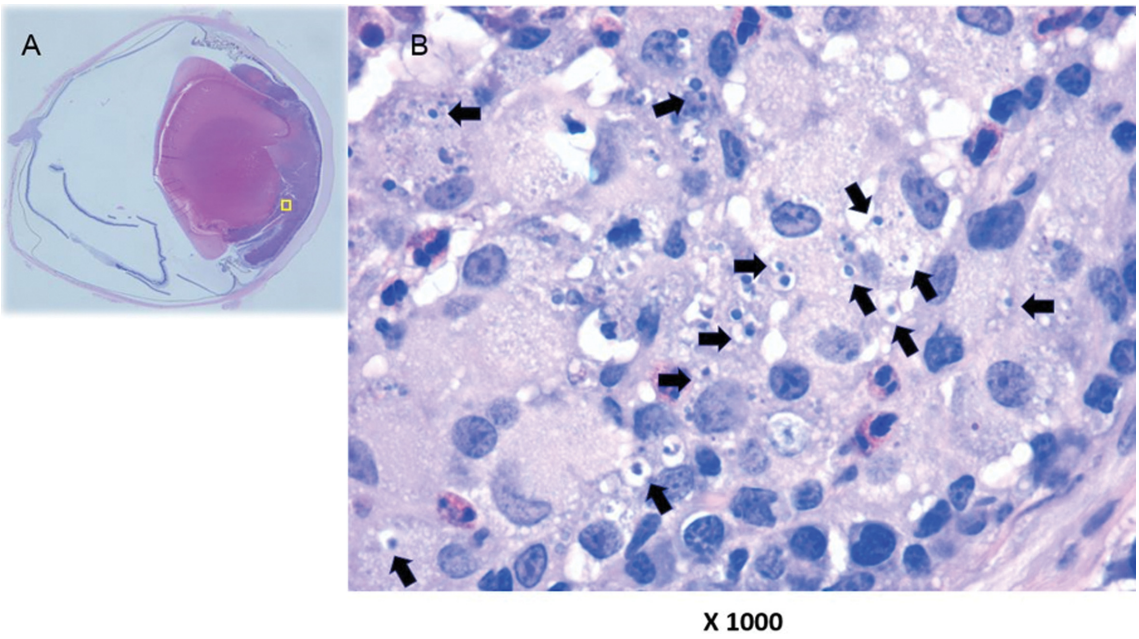

Fig 4. Histopathological demonstration of *E. cuniculi* organisms. (A) Subgross image. (B) Magnification of ×1000. The area of the yellow rectangle in (A) shows *E. cuniculi* microorganisms (black arrow), which are gram- and GMS-positive and Ziehl Nielsen-negative. Adjacent to the ruptured lens capsule, several accumulations of round to oval organisms (size 2-3 μm) containing a basophilic nucleus with a central clearing consistent with *E. cuniculi* were observed.

without apparent inflammation.

Discussion

E. cuniculi-associated phacoclastic uveitis has been observed in rabbits with no sex predilection (3,4,8). It was suggested that this organism replicates within lens fibers, causing spontaneous lens capsule rupture, resulting in phacoclastic lens-induced uveitis, as in this case (4,8). The lens fibers are completely enveloped by a thick avascular lens capsule; therefore *E. cuniculi* might enter into the lens through the richly vascularized thin capsule of the tunica vasculosa lentis in rabbit cubs during early life (4). The lens capsule rupture induces granulomatous uveitis through the released lens anti-

gens into the anterior chamber (8). An inflammatory response to the *E. cuniculi* antigen itself and an autoimmune reaction could play important roles (4).

Encephalitozoonosis is a sub-clinical, asymptomatic disease in lagomorphs. Because it is caused by a zoonotic pathogen, immunocompromised human beings are at a risk of opportunistic *E. cuniculi* infection (7). *E. cuniculi* is a life-threatening pathogen in different species, including humans, monkeys, foxes, dogs, and cats (4). Rabbits are known to be the main host for *E. cuniculi*, which is transmitted through the inhalation of spores, ingestion of contaminated foods with infected urine, or transplacental infection (5,9). When *E. cuniculi* infection leads to clinical symptoms, neurological signs, renal failure, and ocular signs can manifest according to the predilection organ affected, which can ultimately lead to death (5,9). When this disease is diagnosed post-mortem, granulomatous meningoencephalitis (GME), interstitial nephritis, and phacoclastic uveitis are the predominant histopathological alterations (5).

Encephalitozoonosis is a common neurological disease in rabbits (5). However, differential diagnosis of signs of neurological or renal diseases from other causes, is difficult (5). Asymptomatic rabbits show high rates of infection (37-68%) across countries. Moreover, healthy seropositive rabbits may increase the zoonotic risk (9). Antibodies to *E. cuniculi* have also been found in one animal caretaker and spores have been found in the urine of a seropositive caretaker and a clinically affected rabbit (7). In a study on the prevalence of *E. cuniculi*, 42/163 (25.8%) of asymptomatic rabbits in Korea were seropositive (9).

A definitive diagnosis in vivo for encephalitozoonosis is difficult but essential for the determination of possible zoonotic risks and for the application of specific treatment (2,5). A tentative diagnosis is often obtained by a combination of neurological or ophthalmologic clinical signs, by serological examinations, and by excluding other diseases (5). In the early stage of *E. cuniculi* infection, occurring at an early age or in the presence an immunosuppressive primary disease, spores are rarely found in the absence of specific antibodies; therefore, a negative antibody titer cannot always exclude the infection (5). However, while even nested PCR of urine or cerebrospinal fluid from rabbits with seroconversion is not reliable, conventional PCR of eyes with phacoclastic uveitis is highly (100%) sensitive (2). In this case, intralenticular *E. cuniculi* organisms was identified by histopathology. A client-owned rabbit affected with *E. cuniculi*-associated cataract and phacoclastic uveitis accompanied by spontaneous lens capsule rupture was first reported in this study, even though the seroprevalence of *E. cuniculi* in pet rabbits was previously reported in Korea (9). Considering the potential zoonotic risk, the existence of apparently healthy seropositive rabbits indicates the need for screening examinations of detecting anti-*E. cuniculi* antibodies.

In a previous study that examined rabbits serologically for antibodies against *E. cuniculi*, 14.6% of 144 seropositive rabbits with clinical signs suffered from phacoclastic uveitis (6). Along with uveitis, most of the affected rabbits showed cataract or intraocular mass. Unilateral lesions have been reported much more frequently than bilateral lesions, even though the ocular lesions are caused by systemic infection (6). In a feline study, it was reported that all 11 European shorthair cats with cataract and uveitis showed serologically positive antibody titers for *E. cuniculi*, and *E. cuniculi* DNA was also detected by PCR in 18/19 lens and 10/19 aqueous humors (1). That study shows that, compared with rabbits, cats seem to present bilateral cataracts more frequently, and suggested a vertical route of infection due to inconsistency in serology results between companion cats and littermates (1). In some pet shops in Korea, both rabbits and cats are raised and sold in the same place. Further studies aimed at studying the seroprevalence of *E. cuniculi* in cats in Korea are also required.

Few controlled studies have evaluated treatment options for rabbits, and hence protocols for the treatment of this disease have not been yet established (5). However, for *E. cuniculi*-associated phacoclastic uveitis, treatment methods included: for preserving vision, phacoemulsification as promptly as possible to remove lens materials including microsporidia, followed by symptomatic treatment for uveitis; enucleation if phacoemulsification is challenging due to pupillary obstruction by granulomatous inflammation associated with the ruptured lens capsule; before and after these surgeries, specific systemic medical treatment for *E. cuniculi* was provided (1,3,4,8).

Conclusion

Uveitis accompanied by a white mass in the anterior chamber could be considered as indicative of infection of *E. cuniculi* in rabbits. Early diagnosis could be essential for treatments (other than enucleation) for preserving vision and the eyeball and for preventing potential zoonotic risk.

Acknowledgment

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