The Journal of Veterinary Medical Science

NOTE

Pathology

Persistent hyperplastic primary vitreous in two piglets

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J. Vet. Med. Sci.
81(3): 357–360, 2019
doi: 10.1292/jvms.18-0321

Received: 12 June 2018
Accepted: 27 December 2018
Published online in J-STAGE: 15 January 2019

ABSTRACT. Two Large Yorkshire piglets were diagnosed as persistent hyperplastic primary vitreous (PHPV). In case 1, the white cord-like structure extending from optic disc to lens was observed in the normal-sized right eye. Case 2 showed buphthalmos of the right eye. The internal structure of the right eye was unclear due to bleeding, but a white cord-like structure was slightly observed. In both cases, histological examinations revealed the fibrovascular cord-like structure in hyaloid vitreous. The retina was detached, and dysplastic nervous tissue was observed in anterior vitreous. Immunohistochemistry using various neural markers suggested that dysplastic nervous tissue was derived from the detached neural retina. By the characteristic macroscopic and histopathological features, both cases were diagnosed as PHPV. To our knowledge, this is the first report of swine PHPV.

KEY WORDS: macrophthalmia, persistent hyperplastic primary vitreous, pig, retinal dysplasia

Persistent hyperplastic primary vitreous (PHPV) is a rare congenital disorder caused by subinvolution of the hyaloid artery and primary vitreous during fetal life [10]. Clinically, PHPV appears as unilateral microphthalmos and cataract [10]. And at autopsy, a fibrovascular, cord-like structure is observed near the posterior lens capsule and anterior vitreous [10]. In animals, PHPVs were mainly reported in dogs. It is regarded as hereditary in the Bouvier des Flandres, Staffordshire bull terrier, Doberman pinscher [8], and Miniature Schnauzer [6], and non-hereditary in the Siberian Husky [9], and Bloodhound [4]. PHPVs were also reported in cats [1], llama [5] and alpaca [7]. However, swine PHPVs were not reported to date. The purpose of this report is to describe the pathological state of PHPV in two piglets.

Two Large Yorkshire piglets (Case 1 and Case 2) were maintained in Swine and Poultry Research Center (Shizuoka, Japan). For anesthesia, the animals received intramuscular injections of 0.1 ml/kg Dormicum (Astellas Pharma Inc., Tokyo, Japan) and 10 mg/kg Ketamine (Fujita Pharmaceutical Co., Ltd., Tokyo, Japan) by a licensed senior veterinarian. After a veterinarian confirmed the unconscious state, they were euthanized by exsanguination and necropsied for diagnosis. For histopathological examination, both eyes were fixed in Davidson's fluid, and then tissues were embedded in paraffin wax. Paraffin-embedded samples were cut into 2-μm sections and stained with hematoxylin and eosin (H&E), Periodic acid-Schiff (PAS) and Masson's trichrome (MT). Immunohistochemistry was conducted with anti-glial fibrillary acidic protein (GFAP) mouse monoclonal antibody (clone: 5C10, Novus Biologicals, Littleton, CO, U.S.A.), anti-neurofilament-light (NF) mouse monoclonal antibody (clone: DA2, Novus Biologicals), anti-synaptophysin (SYN) rabbit polyclonal antibody (Novus Biologicals), anti-NeuN mouse monoclonal antibody (clone: 1B7, Novus Biologicals), anti-S100 rabbit polyclonal antibody (Thermo Fisher Scientific, Fremont, CA, U.S.A.), and anti-neuron specific enolase (NSE) rabbit polyclonal antibody (Spring Bioscience, Pleasanton, CA, U.S.A.).

Case 1: From 70-day-old, male piglet showed microphthalmos in the left eye, and gait abnormality was observed. No macroscopic findings other than ocular lesions were observed. Among ten litters, it was the only one with developmental abnormality. At 105-day-old, it was euthanized due to poor prognosis. At necropsy, the diameter of the left eye was 1.5 cm and it was smaller than the right one (2.2 cm in diameter). The cornea of the left eye showed opaque. After fixation, the sagittal section of both eyes was examined. In the left eye, the tunica thickened, the intraocular space became narrower, and a brittle black-green structure occupied (Fig. 1a). Though the lens could not be observed, the whitish irregular cord-like structure was buried in a black-green structure. In the right eye, a whitish cord-like structure connected from the optic disc to the lens (Fig. 1b). Histologically, in the right eye, the cord-like structure represented fibrovascular tissue in hyaloid vitreous (Fig. 2a) and consisted of directional connective tissue and blood vessels (Fig. 2b). The dysplastic nervous tissues with rosette formation were shown

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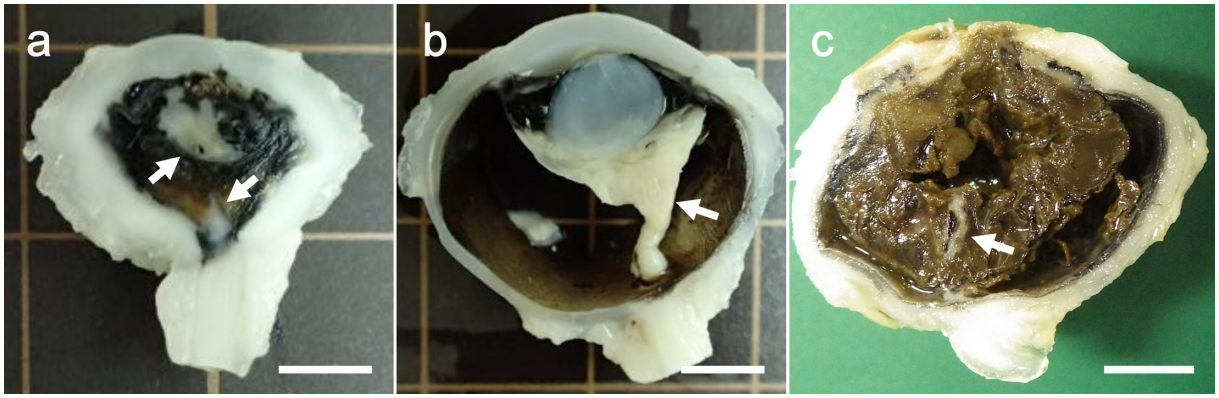

Fig. 1. Macroscopic feature of eyes. (a) Left eye in case 1. Intraocular space was narrowed and occupied by a black-green structure. Whitish irregular structure was observed within a black-green structure (arrows). The lens could not be observed. (b) Right eye in case 1. Whitish cord-like structure bridges optic disc and the posterior capsule of the lens (arrow). (c) Right eye in case 2. Severe intraocular hemorrhage was observed, and whitish cord-like structure (arrow) extended from the optic disc. Bars=5 mm.

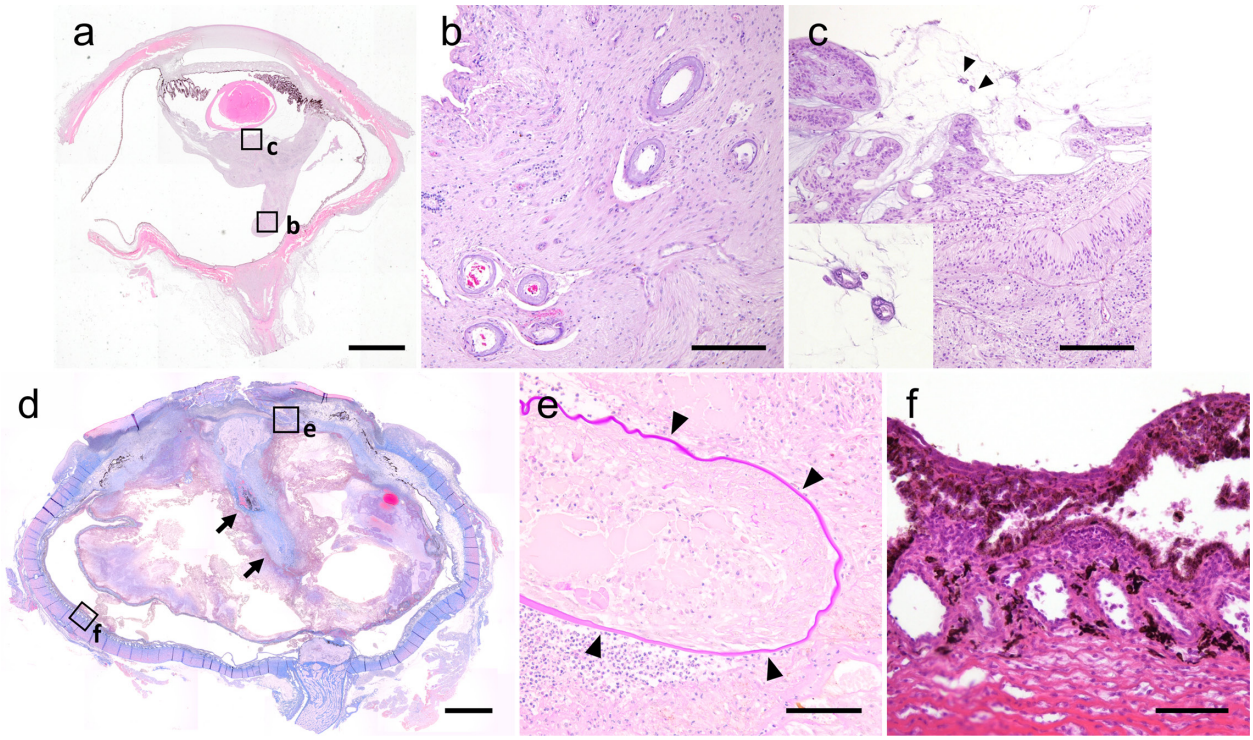

Fig. 2. Histological feature of the right eye in case 1 (a–c) and the right eye in case 2 (d–f). (a) The cord-like structure was observed between optic disc and optic lens. H&E. Bar=3 mm. (b) Abundant connective tissue and arteries were shown in the structure. H&E. Bar=100 μm. (c) Dysplastic nervous tissues were observed in anterior vitreous. In the vicinity of the cord-like structure, small-diameter vitreous artery-like blood vessels were observed (arrowheads). Insert: high magnification image of small-diameter vitreous artery-like blood vessels. H&E. Bar=100 μm. (d) The cord-like structure was observed between optic disc and ruptured optic lens (black arrows). Around the structure, severe hemorrhage was observed. Cornea and conjunctiva showed ulceration. MT. Bar=3 mm. (e) Granulomatous inflammation with lenticular debris was observed. Arrowheads indicate the lens capsule. PAS. Bar=100 μm. (f) The neural retina was detached and duct-like structures formed by cuboid retinal pigment epithelial cells and dilatation of choroidal vessels were observed. H&E. Bar=100 μm.

in the anterior region of the cord-like structure (Fig. 2c). In the tunica, most neurosensory retina was detached, and dilatation of choroidal vessels were observed. In the vicinity of the cord-like structure, a remnant of small-diameter vitreous artery-like blood vessels were observed (Fig. 2c). In the left eye, most of the vitreous body area was replaced by severe fibrosis with prominent infiltration of hemosiderin-laden macrophages (macroscopically dark structures). On the optic disc and in the anterior vitreous, dysplastic nervous tissues with rosette formation were observed (macroscopically whitish structures). Ciliary epithelium showed

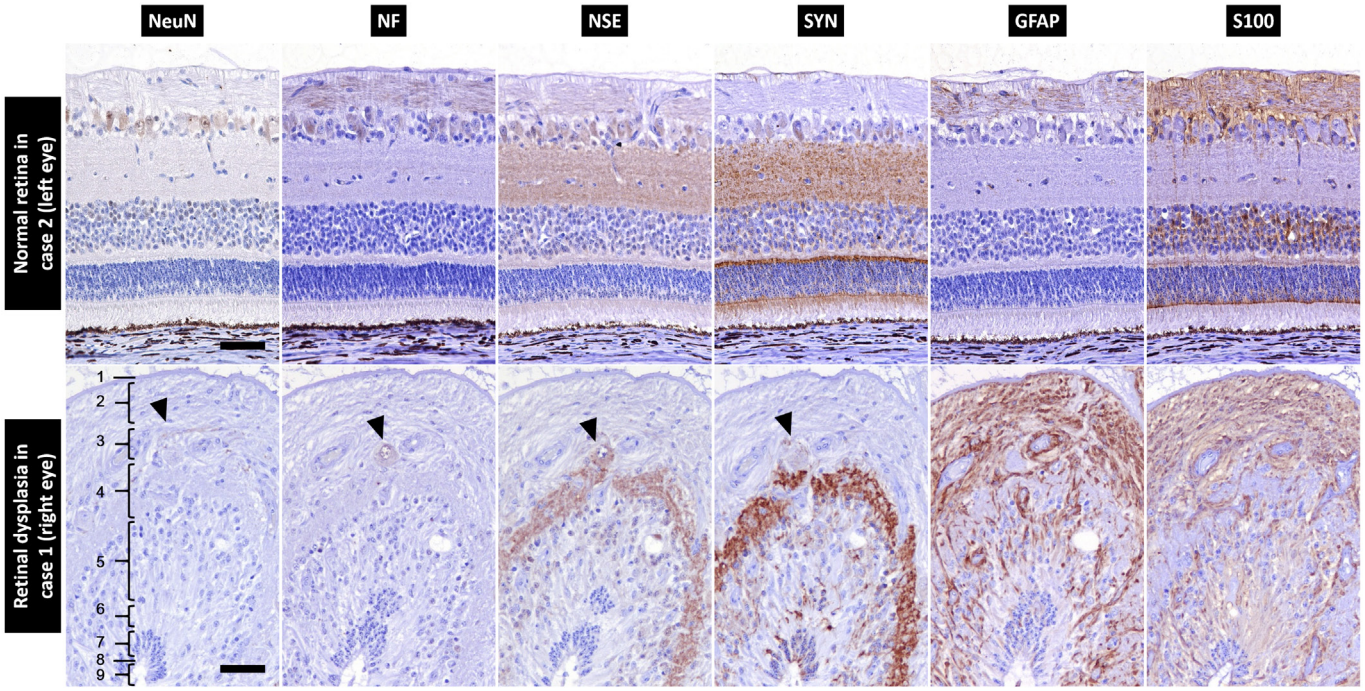

Fig. 3. Immunohistochemistry of normal retina and dysplastic nerve tissue. Each cell layer constituting the dysplastic nerve tissue showed similar reactions to the normal retina, suggesting that dysplastic nervous tissue was derived from the detached neural retina. In the dysplastic retina, GFAP-positive cells were observed across the whole area, indicating proliferative reactive astrocytes. Arrowheads indicate the positive reaction of ganglion cells. The layers considered to correspond are numbered as follows: 1, inner limiting membrane; 2, nerve fiber layer; 3, ganglion cell layer; 4, inner plexiform layer; 5, inner nuclear layer; 6, outer plexiform layer; 7, outer nuclear layer; 8, external limiting membrane, 9, photoreceptor layer of rods and cones. The NF- and NSE-positive reaction were not observed in the nerve fiber layer (2) of dysplastic nerve tissue, indicating the loss of nerve fibers. Bars=50 μm.

papillary hyperplasia. In the tunica, detachment of most neurosensory retina, duct-like structures formed by pigmented retinal cells, and dilatation of choroidal vessels were observed. The arrangement of the collagen fibers in the sclera was uneven, and fibroblast proliferation was observed. Choroid and sclera of left eye were greatly thickened compared with right one. Immunohistochemical features were shown in Fig. 3. Each cell layer constituting the rosette showed positive reactions similar to normal retina except for GFAP. On the other hand, in the anti-GFAP immunohistochemistry, only the nerve fiber layer was positive in the normal retina, whereas in the dysplastic nervous tissue, the positive reaction was observed across the whole area. Furthermore, in anti-NF and -NSE immunohistochemistry, the positive reaction of the nerve fiber layer found in the normal retina was not seen in the dysplastic nervous tissue.

Case 2: A newborn female piglet showed buphthalmos in the right eye. Its parents were different from case 1's ones. Among 5 litters, it was an only example of the developmental abnormality. It couldn't close the right eye and showed gait abnormality. At 3-day-old, it was euthanized due to the poor prognosis. At necropsy, right orbit had expanded due to the expansion of the eyeball. The right eye was 2.4 cm in diameter, which was larger than left one (diameter 1.9 cm). The sclera of right eye discolored to a pale yellow, and cornea showed ulceration with crusting. Right optic nerve and left optic tract showed hypoplasia in half to two-thirds of correspondent ones. After fixation, the sagittal section of both eyes was examined. Although the internal structure of the right eye was unclear due to intraocular bleeding, a whitish cord-like structure extending from the optic disc was recognized (Fig. 1c). Macroscopically, the lens could not be observed. In the other organs including the left eye, there were no abnormal findings. Histologically, fibrovascular cord-like structure bridged between optic disc and ruptured optic lens. The cord-like structure consisted of directional connective tissue, blood vessels and moderate infiltration of hemosiderin-laden macrophages. MT staining showed abundant connective tissue in the structure (Fig. 2d). There were severe hemorrhage and hemosiderosis around the structure. On the optic disc and in the anterior vitreous, dysplastic nervous tissues with rosette formation were observed. In the lens, fragmentation of lens fibers and granulomatous inflammation with lenticular debris were observed. PAS staining showed lenticular debris within the lens capsule (Fig. 2e). Cornea and conjunctiva showed ulceration with severe purulent inflammation with fibrosis. Iris and iridocorneal drainage angle were indiscernible due to the necrosis and inflammation. In the tunica, detachment of neurosensory retina, duct-like structures formed by retinal pigment epithelial cells, and dilatation of choroidal vessels were observed (Fig. 2f). Choroid and sclera of the right eye were greatly thickened compared with left one. On the other hand, there were no histological findings in the left eye. In immunohistochemistry, dysplastic nervous tissues showed similar reactivity to case 1.

Based on the macroscopic and histopathological features of the fibrovascular cord-like structure from the optic disc to the

vitreous body, the right eye of case 1 and the right eye of case 2 were diagnosed as PHPV. Furthermore, retinal detachment and dysplasia, and hypoplastic optic nerve also supported the diagnosis of PHPV [10]. In the veterinary field, PHPVs were mostly reported in Canidae [8]. This is the first report of PHPV in swine.

In some cases of PHPV, the fibrovascular tissue may connect with posterior lens capsule and exfoliate, leading to rupture of the posterior lens capsule and lens-induced endophthalmitis [2]. Granulomatous inflammation with lenticular debris observed in case 2 may be diagnosed as lens-induced endophthalmitis caused by PHPV during the developmental period. Perhaps, case 2 showed macrophthalmia by glaucoma associated with endophthalmitis.

In both eyes of case 1 and the right eye of case 2, retinal dysplasia was observed instead of normal retina. In the lesion forming the rosette, a neural retinal-like layered structure was observed and exhibited immunohistochemical results similar to the neural retina. As a result of immunohistochemistry, it was suggested that dysplastic nervous tissue was derived from the detached retina, though nerve fibers in the nerve fiber layer were lost. GFAP-positive astrocyte was increased throughout the area, suggesting the progression of glial scarring.

In the left eye of case 1, the cord-like structure could not be observed, but the other histological findings such as duct-like structures of pigmented retinal cells, retinal dysplasia, damaged lens and intraocular bleeding were remarkably similar to the right eye of case 2. The severe scleral fibrous thickening accompanying fibroblast proliferation found in the left eye of case 1 was considered to be due to chronic endophthalmitis. It is possible that case 1 had developed bilateral PHPV, and the histopathological feature of the left eye in case 1 showed the different stage of that of the right eye in case 2. Furthermore, a duct-like structure of pigmented retinal cells might be involved in the exacerbation of porcine PHPV.

The PHPVs are generally reported to accompany the microphthalmia. On the other hand, microphthalmia was never reported in PHPVs of animals except for Canidae [1, 5, 7]. Interestingly, case 2 in this study showed macrophthalmia. Because the right orbit was dilated, macrophthalmia of case 2 is considered congenital. In most species, including pigs, congenital macrophthalmia is a rare disorder [3]. Vitamin A deficiency was known as the cause of swine macrophthalmia [11], but it is unlikely because littermates were healthy. In case 1, PHPV was observed in the normal sized eye. From these cases, microphthalmia may not necessarily be a diagnostic criterion for PHPV in the field of veterinary medicine.

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