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NOTE

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Intraocular extraskeletal osteosarcoma in a rabbit (*Oryctolagus cuniculus*)

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ABSTRACT. An 8-year-and-9-month-old male, lop-eared rabbit (*Oryctolagus cuniculus*) presented with gradual enlargement of the left eye to 4 × 4 × 4 cm and exophthalmos. The animal died 3 months later, and necropsy was performed. On gross pathology, the intraocular tissue was effaced and occluded by a hard, light-gray mass. Histologically, the mass comprised spindle-shaped to angular cells arranged in interlacing bundles with abundant production of osteoid, bone and cartilage, consistent with osteosarcoma. Limited cases of intraocular neoplasm have been reported in pet rabbits. To the best of our knowledge, this represents the first pathologic documentation of intraocular osteosarcoma in a rabbit.

KEY WORDS: eye, intraocular osteosarcoma, neoplasm, rabbit

Osteosarcoma is a neoplasm of malignant osteoblasts producing osteoid and immature bone [14]. In rabbits (*Oryctolagus cuniculus*), several cases of osteosarcoma have been reported. This neoplasm can occur in various bones or joints, such as the glenohumeral joint, intertarsal joint, sacrococcygeal joint, and rib [7–9, 13]. Extraskeletal osteosarcoma is a mesenchymal tumor with production of osteoid primarily occurring in tissues other than bones or joints. In dogs and cats, this tumor has been reported in various tissues such as skin and mammary gland [14]. In rabbits, occurrences of extraskeletal osteosarcoma have been reported in the lip, oral cavity and skin [11, 12, 16]. Primary intraocular osteosarcoma has been reported on rare occasions in dogs, cats and an umbrella cockatoo (*Cacatua alba*), but no previous reports have described this pathology in rabbits [3, 5, 6, 15, 18]. This report describes both the clinical history and pathologic findings of intraocular extraskeletal osteosarcoma in a pet rabbit.

This case involved an 8-year-and-9-month-old male, lop-eared rabbit weighing 1.9 kg. Medical history for this animal included hypermature cataract at 3 years and 1 month old, glaucoma and posterior lens luxation of the left eye at 4 years and 1 month old and glaucoma of the right eye at 5 years and 11 months old. Three months before its death, the rabbit showed gradual enlargement of the left eye and exophthalmos at 8 years and 6 months old. On physical examination, a mottled white-to-pink mass was identified in the left eye. Exophthalmos progressed, and the rabbit died with signs of respiratory failure. Cosmetic necropsy was performed in the Laboratory of Veterinary Pathology at Nihon University.

On gross examination, the left eye showed marked protrusion from the orbit and measured 4 × 4 × 4 cm. The corneal surface of the eye was diffusely covered by a thick, dry, brown-to-red layer of crust (Fig. 1). At enucleation, no connection was apparent between the eye and this overlying orbital tissue or cranial bone. When the eye was bisected after fixation and decalcification, the intraocular tissue had been effaced and occluded by a hard, light-gray bony mass (Fig. 2). Other representative gross findings included hemothorax, multiple pulmonary masses, and a rubbery cutaneous mass. The pulmonary masses were tan to gray, soft, spherical and up to 1 cm in diameter. No significant gross lesions were observed in the bone tissue, but we could not preserve bone tissues for histopathology due to the cosmetic necropsy.

On histopathologic examination, tissue samples were removed and fixed in 10% neutral-buffered formalin solution. The left eye was decalcified in Plank-Rychlo solution (Muto Pure Chemicals, Tokyo, Japan) for about 72 hr. After trimming, representative tissues were embedded in paraffin, sectioned at a thickness of 5 μm, and stained with hematoxylin and eosin. Histologically, the intraocular mass represented highly cellular, invasive neoplasm, effacing almost all intraocular tissues (Fig. 3). The neoplasm comprised spindle-shaped to angular cells arranged in interlacing bundles with abundant eosinophilic fibrous matrix and significant production of osteoid, bone and cartilage (Figs. 4 and 5). The neoplastic cells contained small amounts of eosinophilic cytoplasm with indistinct cell borders. Nuclei were medium-sized, round to oval with coarsely stippled chromatin and distinct nucleoli. Anisocytosis and anisokaryosis were moderate, and 20 mitoses were seen per 10 high-power fields (400×) (Fig. 6). Although the neoplasm had invaded caudally over the sclera, no evidence suggested invasion to the orbital tissue or optic nerve, and

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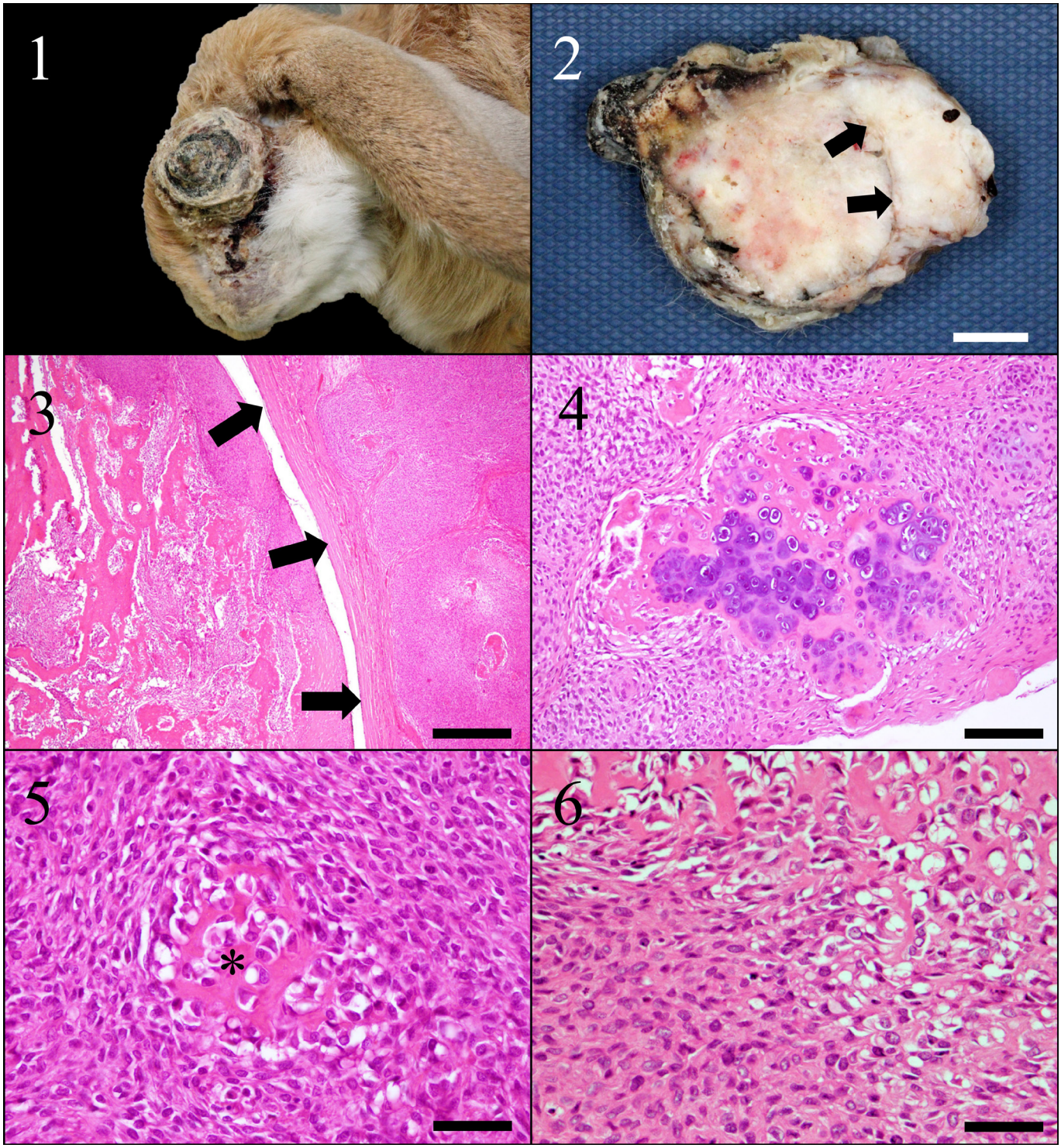

Fig. 1. Gross appearance at necropsy. The left eye is markedly enlarged. The cranial aspect of the eye, suggesting the cornea, is protruded and diffusely covered by a thick layer of crust.

Fig. 2. Gross appearance of the left eye. In cross-section, the intraocular tissue is completely effaced and occluded by a hard, light-gray mass. Arrows: pre-existing sclera. Bar=1 cm.

Fig. 3. The intraocular mass comprises a highly cellular neoplasm with production of abundant amorphous osseous matrix between neoplastic cells. These cells have invaded caudally over the sclera. Arrows: pre-existing sclera. Hematoxylin and eosin stain. Bar=500 μm.

Fig. 4. Neoplastic cells have produced a small amount of cartilaginous matrix. Hematoxylin and eosin stain, Bar=100 μm.

Fig. 5. Abundant production of lacy strands of osteoid, surrounded by neoplastic cells. Asterisk: osteoid. Hematoxylin and eosin stain, Bar=50 μm.

Fig. 6. The neoplasm comprised spindle-shaped to angular cells arranged in interlacing bundles. The neoplastic cells showed moderate pleomorphism. Hematoxylin and eosin stain, Bar=50 μm.

no metastatic lesions to other organs were noted. The histologic findings of this neoplasm were consistent with a diagnosis of osteosarcoma. Other significant lesions are shown below. In the right eye, the retina was diffusely thinned, with degeneration of ganglion cells and vacuolization of the interstitium. At the level of pigmented epithelial cells, the retina was detached, with hypertrophy of the pigmented epithelial cells. Findings from the right eye were consistent with glaucoma and retinal detachment. Pulmonary masses were highly cellular, with invasive neoplasm effacing the pulmonary tissue. The neoplasm comprised polygonal cells arranged in nests and packets irregularly divided by fine fibrous connective tissue. The neoplastic cells showed moderate amounts of eosinophilic granular cytoplasm, with distinct cell borders. Nuclei were small and round with coarsely stippled chromatin and distinct nucleoli. Anisocytosis and anisokaryosis were mild to moderate. Cytoplasmic granules stained black with Grimelius stain. The pulmonary masses were diagnosed as neuroendocrine carcinomas. The cutaneous mass was a highly cellular, expansile neoplasm. The neoplasm comprised cuboidal to polyhedral cells arranged in cords and nests, divided by abundant fibrous connective tissue. These cells contained small amounts of eosinophilic cytoplasm and showed distinct cell borders. Nuclei were small, round to oval-shaped, with finely stippled chromatin and small nucleoli. The cells showed minimal atypia. A diagnosis of trichoblastoma was made.

The neoplasm of the left eye was histologically consistent with osteosarcoma based on cellular morphology and the abundant production of osteoid, cartilage and bone. Gross and histologic findings suggested no association of the neoplasm with bone tissue of the skull, so the lesion was diagnosed as primary intraocular extraskeletal osteosarcoma. No metastatic lesions of the intraocular neoplasm were found. The cause of death was considered to be respiratory failure due to the pulmonary neoplasm and hemothorax.

In rabbits, primary intraocular osteosarcoma has not previously been reported in the English literature, although three cases of intraocular sarcoma have been described [1, 10]. In those reports, the authors suggested that the morphologic features and biologic behaviors of the neoplasms resembled those of feline post-traumatic ocular sarcoma (FPTOS) [1, 10]. FPTOS is a very aggressive tumor, with a pathogenesis that appears to involve prior history of ocular trauma or severe, chronic ocular disease [17]. Cats with FPTOS have histories such as trauma, chronic uveitis, cataract, phthisis bulbi and intraocular surgery involving the lens [4, 17, 18]. The period from these clinical event to occurrence of neoplasm is from several months to 10 years [17]. The neoplasm occurs within the eye surrounding the lens, then intraocular structures such as the lens, anterior uvea, retina, and choroid are effaced, with occlusion of intraocular spaces by the neoplasm [4, 17]. Furthermore, FPTOS sometimes shows local invasion to the adjacent sclera, optic nerve, and brain [4, 17]. Histopathologically, rupture of the lens capsule is found in almost all cases [2, 4, 17]. This neoplasm commonly comprises proliferation of spindle-shaped cells with morphologic features of spindle-cell sarcoma. The spindle cell-variant of the neoplasm has been considered to arise from neoplastic transformation of lens epithelium following lens rupture [4]. Some of these neoplasms are crystalline alpha A-immunopositive [19]. This neoplasm has been hypothesized to represent undifferentiated sarcoma arising from myofibroblasts [19]. A multipotent stem cell origin has also been suggested [4]. In one study, 387 of 560 FPTOS cases were consistent with this pattern. In addition, 41 of 560 FPTOS cases were osteosarcoma or chondrosarcoma [17]. The origin of the neoplastic cells in the osteosarcoma/chondrosarcoma variant remains unclear [17]. Lens rupture occurred in almost all cases [2]. To the best of our knowledge, this represents the first pathologic documentation of intraocular osteosarcoma in a rabbit.

In the present case, no history of trauma was elicited. In addition, the lens was completely effaced by the neoplasm, so evaluation of the lens including the presence of lens rupture could not be performed histologically. However, the case potentially showed some clinical resemblance to FPTOS, given the history of hypermature cataract of the left eye for more than 2 years before starting to show enlargement and exophthalmos. Also, an ocular lesion that resembled FPTOS has been described in a rabbit [4]. In that report, the animal showed phacoclastic uveitis and lens capsule rupture associated with encephalitozoonosis [4]. Although encephalitozoonosis was not confirmed clinically or histologically in the present case, previous uveitis by encephalitozoon infection remains a possibility. Furthermore, the biologic behavior of the neoplasm, as a locally extensive growth pattern, also resembled FPTOS. From these clinical and pathologic features, this case was considered to resemble an osteosarcoma variant of FPTOS. However, determining the cell origin of the neoplasm in this case was difficult. Limitations in the present case included the unavailability of immunohistochemical evidence due to prolonged decalcification. As a prospective study, collection of similar cases and immunohistochemical analyses using stains such as crystalline alpha A and vimentin may provide useful insights [19].

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