Comparative Medicine
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Vol 67, No 1
February 2017
Pages 51–55

Case Report

Shope Fibroma in the External Ear Canal of a Domestic Rabbit

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A 5-y-old, intact, 2.5-kg female domestic rabbit was presented because of blood spatter on the wall of its cage and the toenails of its right hind limb. Physical examination revealed a red, gelatinous mass that spanned the width of the right vertical ear canal. Radiographic images revealed a soft-tissue opacity at the base of the right ear, which was superimposed over the tympanic bulla and extended to the pinna. A CT scan revealed that the soft-tissue mass was within the vertical and horizontal portions of the right external ear canal and extended to the level of the tympanic membrane, with no bony involvement. An incisional biopsy of the mass and subsequent histopathology revealed heterophilic inflammation with bacteria, necrosis, and no evidence of neoplasia. The patient died during anesthesia for removal of the mass at 1 mo after the initial presentation. Necropsy with histopathology of the mass was consistent with Shope fibroma virus in light of the presence of typical intracytoplasmic eosinophilic inclusions. Electron microscopy of paraffin-embedded tissue revealed electron-dense intracytoplasmic structures within neoplastic cells consistent with the diagnosis of *Leporipoxvirus*. To our knowledge, this report is the first description of Shope fibroma virus invading the external ear canal of a domestic rabbit. Given the results of this case, Shope fibroma should be considered in rabbits presenting with abnormal tissue in the ear canal.

Abbreviations: SFV, Shope fibroma virus

The rabbit Shope fibroma virus (SFV) was first identified in wild eastern cottontails (*Sylvilagus floridanus*) in 1932 and has since been classified as a *Leporipoxvirus* belonging to the family *Poxviridae*.[2,4,15,19] The virus is endemic in wild rabbit populations throughout North America and Canada, with high prevalence along the east coast.[8,11,20] Numerous wild mammals in Virginia, including weasels (*Mustela frenata noveboracensis*), opossums (*Didelphis virginiana*), woodchucks (*Marmota monax*), white-footed mice (*Peromyscus leucopus noveboracensis)* voles (*Microtus pennsylvanicus*), a flying squirrel (*Glaucomys volans*), and a chipmunk (*Tamias striatus fisheri*), were inoculated with a strain of SFV that had been isolated from an infected wild cottontail, but none of experimentally infected animals developed lesions or became clinically ill.[7] In domestic rabbits (*Oryctolagus cuniculus*), SFV is typically considered a viral infection of minimal clinical significance.[11] A collective study done on cutaneous neoplasms in domestic rabbits stated that the most common skin tumors, in descending order of frequency, are basal cell tumors, spindle cell sarcomas, collagenous hamartomas, squamous papillomas, and mammary gland adenocarcinomas.[9] In contrast, a retrospective study from the University of Pennsylvania reported that SFV was diagnosed in 10% of all cutaneous neoplasms presented over a 16-y-period and stated that SFV was the third most common diagnosis for cutaneous neoplasms in pet rabbits.[21]

SFV is spread through the bite of an infected arthropod vector, either a flea or mosquito, and the prevalence of the disease is highest in autumn when the number of arthropods in the environment is at its peak.[11,21] Fibromas in domestic rabbits are described as mucoid in appearance and manifest as a freely moveable soft-tissue swelling at the site of inoculation, which most often is located on the haired portion of the head, limbs, and pinna.[11,15] On rare occasions, SFV has been reported to affect ocular structures and cause keratitis.[10] Histologically, the lesion initially manifests as acute inflammation with localized fibroblastic proliferation. As the fibroma progresses, fibroblasts proliferate until a distinct tumor is formed, and eosinophilic inclusions can be observed in tumor cells.[6] After a few months of disease progression, areas of necrosis occur within the fibroma, and the entire lesion may slough.[8] Here we describe a case of SFV that invaded the external ear canal of a domestic rabbit.

Case Report

A 5-y-old, 2.52-kg, intact female domestic rabbit was presented to the Kansas State Veterinary Health Center because blood spatter was observed on the wall of its cage. The rabbit was housed indoors and had free roam of the house while under supervision. Its daily diet consisted of 80% timothy hay, 1/4 cup pelleted rabbit feed, supplemental leafy greens, and carrots as intermittent treats. Abnormalities on physical examination included moderate

Received: 25 Feb 2016. Revision requested: 07 Apr 2016. Accepted: 18 Aug 2016.
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obesity, delayed left pupillary light reflex, a large gelatinous mass at the opening of the right vertical ear canal, and a slight amount of blood on the toenails of the right hindfoot.

Two days after initial presentation, the patient was anesthetized for further diagnostics. The rabbit was premedicated with midazolam (1 mg/kg IM; Versed, Akorn, Lake Forest, IL) followed by anesthetic induction with isoflurane by face mask. Warm lactated Ringers solution (50 mg/kg) with vitamin B complex was administered subcutaneously. A complete physical examination of the anesthetized rabbit was performed, and the mass in the right vertical ear canal was found to fill the entire width of the canal. The right ear was clipped and gently scrubbed with a dilute chlorhexidine solution, and a blood sample collected from the lateral saphenous vein was placed in heparin. The CBC and biochemical analyses were unremarkable except for hyperglycemia (188 mg/dL; reference range, 75 to 150 mg/dL).[16] An incisional biopsy of the aural mass was performed, followed by histopathologic examination and whole-body radiography and CT. After the procedures, midazolam anesthesia was reversed by using flumazenil (0.05 mg/kg IM; Romazicon, Mylan, Rockford, IL).

Two-view whole-body radiographs revealed a mass of soft-tissue opacity at the base of the right ear and extending into the pinna (Figures 1 and 2). This soft-tissue opacity was superimposed with the tympanic bulla, which was otherwise unremarkable. The lung fields contained increased soft-tissue opacity, consistent with atelectasis secondary to anesthesia, and the abdomen was unremarkable in appearance.

A whole-body CT study was performed by using a 16-slice scanner (GE Brightspeed, General Electric, Waukesha, WI) and standard protocol (slice thickness, 1.25 mm; 120 kV; 17 mA), with the patient positioned in sternal recumbency. A homogenous, soft-tissue mass filled the entire right external ear canal and extended to the level of the external acoustic meatus (Figure 3). The mass was distinct from and hypoattenuated to the cartilage of the pinna. The pinnal cartilage was intact except at the dorsal aspect of the base of the ear, where additional soft tissue mass was visible and extended dorsally and rostrally from the cartilage (Figure 4). The middle ear and tympanic bulla were unremarkable. The remainder of the skull and the torso yielded no other significant findings.

Given the location of the lesion and the involvement of the external ear canal, total ear-canal ablation was proposed. The purpose of this procedure was to remove the mass by dissecting the vertical tract of the ear canal from the pinna and the horizontal tract to the level of the tympanic bullae.[3] However, during preparations for surgical removal of the mass, the rabbit underwent respiratory arrest and died.

Necropsy examination revealed a red, friable mass ($2 \times 2 \times 4.5$ cm), which occluded the external auditory meatus of the right ear and extended to the horizontal-vertical ear canal junction (Figure 5). On cut section, the mass was slightly firm and solid, with peripheral necrosis. Histopathology revealed that the external ear mass expanded the dermis, elevated the overlying epidermis, and filled the space of the ear canal (Figure 6 A). The mass was a well-demarcated, unencapsulated, densely cellular neoplasm composed of interlacing streams and fascicles of neoplastic spindle cells (Figure 6 B). The neoplastic spindle cells had indistinct borders, a moderate amount of eosinophilic cytoplasm, and round to elongated nuclei with finely stippled chromatin.

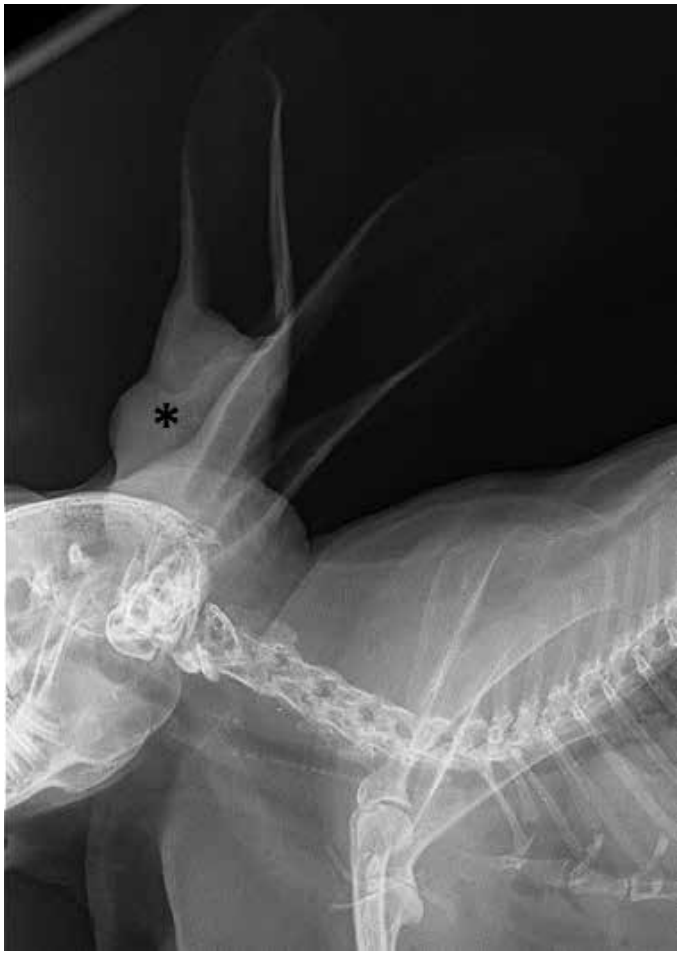

Figure 1. This radiograph of a domestic rabbit in right lateral recumbency demonstrates a mass of soft-tissue opacity associated with the right pinna (*). The mass was later diagnosed as Shope fibroma. The cranial thorax visible to the right of the image is unremarkable.

Moderate anisokaryosis and anisocytosis were noted. Scattered throughout the spindle cell proliferation and more pronounced at the periphery were areas of hemorrhage and necrosis, with moderate heterophilic infiltration, few aggregates of lymphocytes, occasional multinucleate giant cells (Figure 6 C), and small numbers of hemosiderophages. The mass showed mild hyperplasia of the epidermal and follicular epithelium with occasional intracytoplasmic eosinophilic inclusion bodies and frequent ballooning degeneration of keratinocytes (Figure 6 D). There were also multifocal ulceration of the aural epidermis with underlying dermal hemorrhage and infiltration by large numbers of heterophils, moderate numbers of lymphocytes, and numerous bacterial colonies. Given the gross appearance of the mass and the results of histopathology, a presumptive diagnosis of SFV was reached.

Paraffin-embedded tissues were examined for viral particles by using electron microscopy. Neoplastic neutrophils contained multiple intracytoplasmic electron-dense structures (Figure 7). The structures were spherical to elongate, 80 to 100 nm in diameter, 100 to 200 nm in length, and often had a knobby, irregular outer surface. These features are consistent with poxviruses and supportive of the diagnosis of *Leporipoxvirus*.

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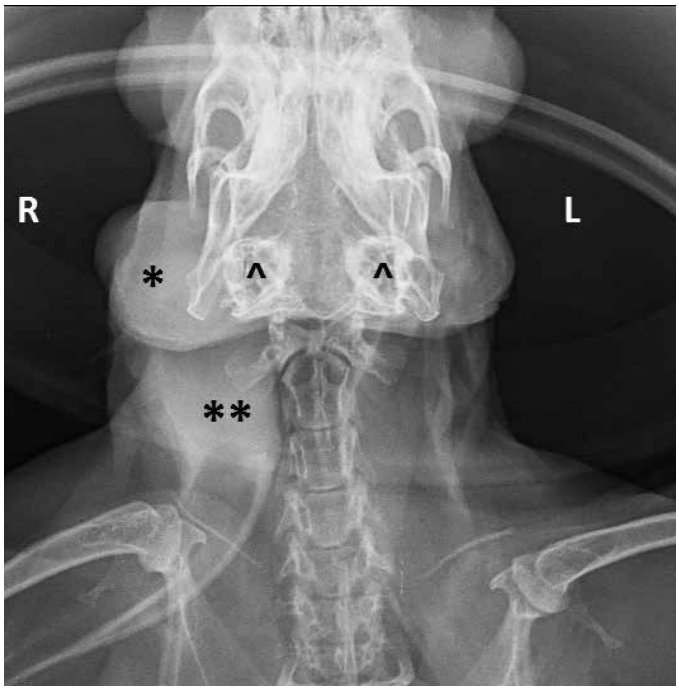

Figure 2. This dorsoventral radiograph demonstrates the soft-tissue mass (*) at the base of the right ear and extending into the right pinna (**). The mass was later diagnosed as Shope fibroma. The left and right tympanic bullae (^) are unremarkable. The rostral aspect of the head is at the top of the image.

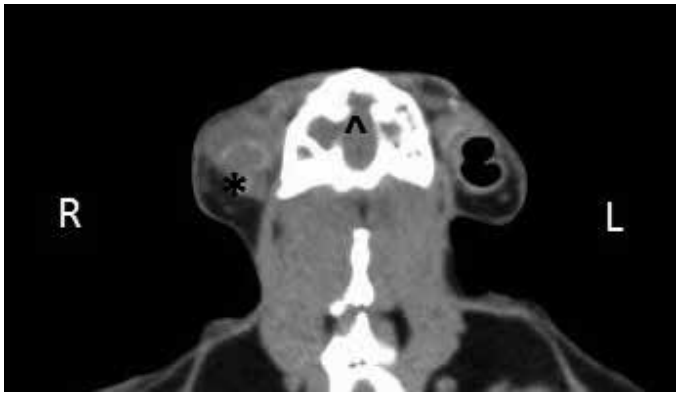

Figure 3. A transverse CT image at the level of the occipital bone and cerebellum (^) shows a mass of soft-tissue density that fills the right external ear canal (**) and extends dorsally to the margins of the pinnal cartilage. The mass was later diagnosed as Shope fibroma. The normally aerated left external ear canal is visible for comparison. The cervical spine extends toward the bottom of the image.

Discussion

Shope fibroma virus, hare fibroma virus, myxoma virus, and squirrel fibroma virus are the 4 viruses that belong to the genus *Leporipoxvirus*, family Poxviridae, and are characterized by cross-reactivity between agents, intracytoplasmic viral replication, and localized infection of skin upon inoculation.[18] SFV is spread from the bite of an infected flea or mosquito, and the resulting lesion is a confined, freely moveable cutaneous mass.[12-14] The virus replicates in the head of multiple species of mosquitos found in North America, and the highest risk of disease transmission occurs during

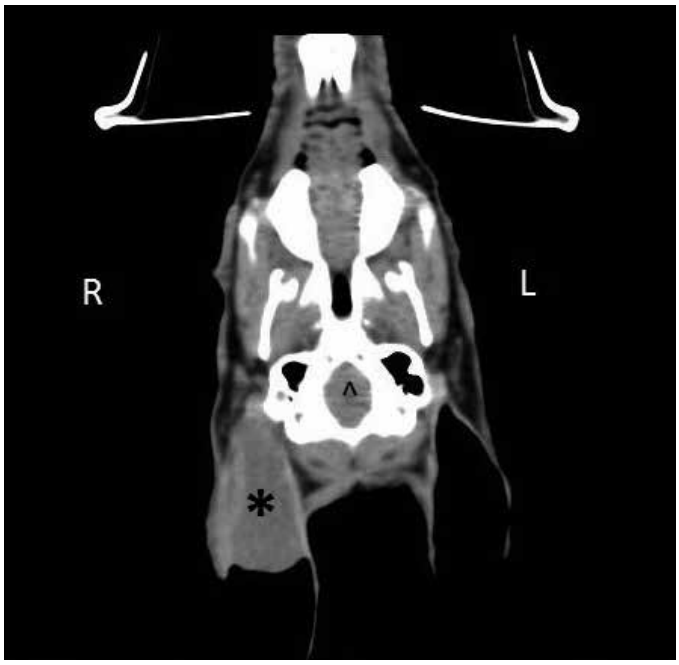

Figure 4. A dorsal planar reconstruction image at the level of the tympanic bulla reveals a soft-tissue mass that fills the right external ear canal (**). The mass, later diagnosed as Shope fibroma, extends to the level of the external acoustic meatus. The normally aerated tympanic bullae are visible on either side of the cerebellum (^). The rabbit's nose, surrounded by an anesthetic mask, is at the top of the image.

Figure 5. Postmortem examination of the domestic rabbit revealed a Shope fibroma in the external ear and extending to the horizontal ear canal and to the tympanic membrane.

autumn, when the mosquito populations are at their peak.[11,14] Mosquitoes can transmit the virus as long as 2 wk after feeding on the fibroma of an infected rabbit, and the fibroma itself is transmissibly infectious for as long as 10 mo.[12,14] The severity of the disease varies, depending on the age of the infected rabbit. Intradermal injections of 320 domestic rabbits with infectious doses of SFV caused viremia-induced mortalities in rabbits in 6 d or less, whereas rabbits that survived 14 d or longer developed immense primary tumors at the site of inoculation.[22]

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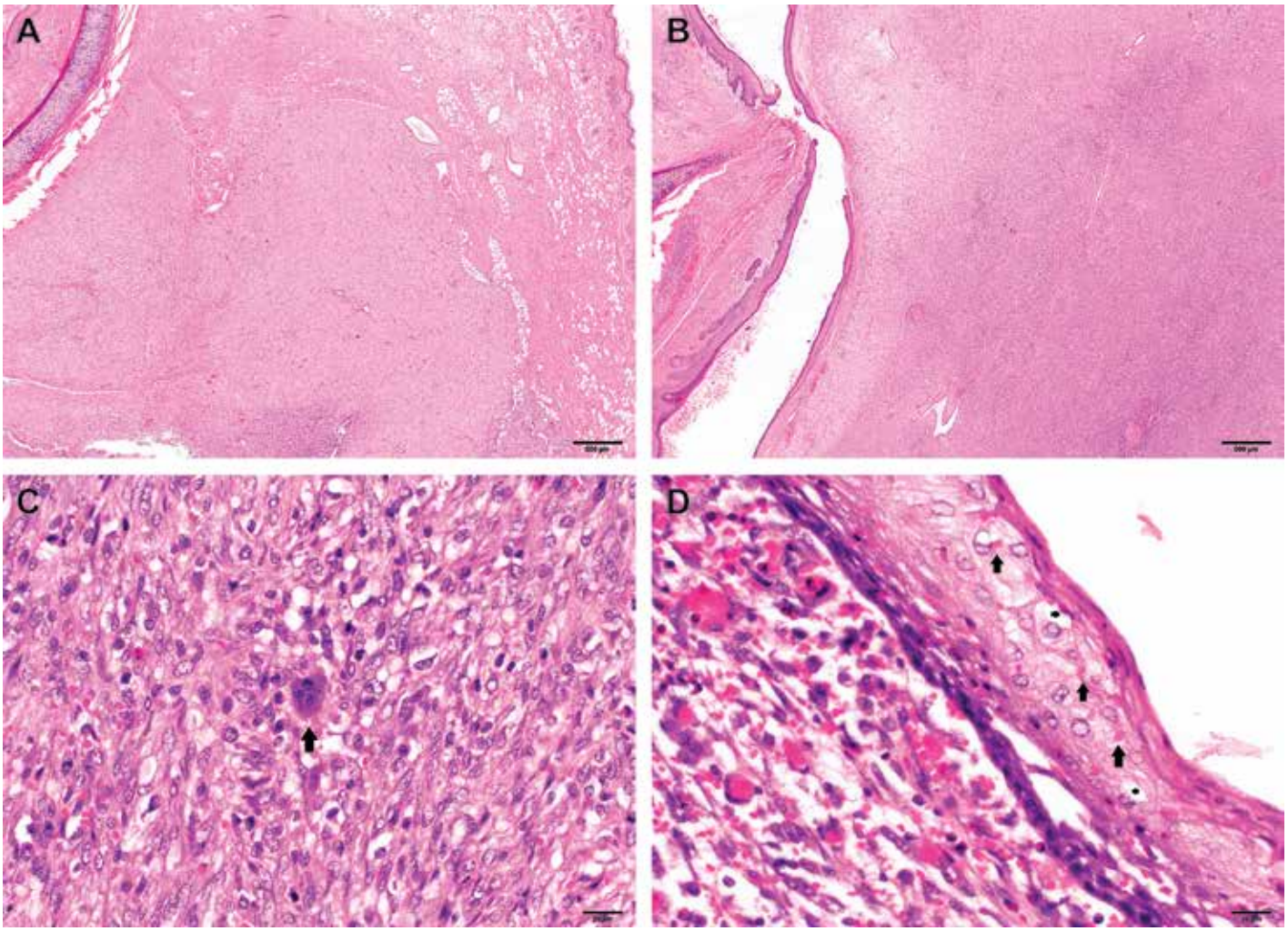

Figure 6. (A) Photomicrograph of a Shope fibroma in the external ear canal of a domestic rabbit**.** The mass is composed of a spindle-cell population (arrow), which expands the dermis, elevates the overlying dermis, and fills the ear canal. Normal cartilage of the canal is present at the upper left. Hematoxylin and eosin stain; bar, 500 µm. (B) Photomicrograph. The ear canal (left) is compressed by a mass of tightly arranged spindle cells. Hematoxylin and eosin stain; bar, 500 µm. (C) Photomicrograph of the mass in the external ear canal demonstrates neoplastic spindle cells, including multinucleate cells (arrow), admixed with hemorrhage and small numbers of heterophils. Hematoxylin and eosin stain; bar, 20 µm. (D) Photomicrograph of the external ear mass shows the epidermis has ballooning degeneration (*) and intracytoplasmic inclusion bodies (arrow) typical of those seen with Shope fibroma virus. Hematoxylin and eosin stain; bar, 20 µm.

The rabbit we describe here presented with an aural mass, located entirely within the ear canal. This presentation is in contrast to previously reported cases in domestic rabbits, in which the virus most commonly caused lesions on the thin-haired portions of the body, such as the feet, legs, and nasal area.[7,17] A rare case of aberrant SFV formation affected the eyes of a domestic rabbit, where it caused keratitis and corneal lesions.[10] The progression of SFV is well documented, regardless of the location of the lesion. In adult cottontails, the fibroma is confined to the skin surrounding the inoculation site and begins to grow 1 wk after inoculation. Resistance to reinoculation occurs 4 to 6 d after primary inoculation, and the antibodies formed at this time persist for the life of the fibroma.[18]

In the rabbit we present, an inflammatory lesion was seen in the early stages of tumor development, followed 1 mo later by lymphocyte concentration at the base of the tumor, marked spindle-cell proliferation, necrosis, and eosinophilic inclusions in the tumor cells. Typical early pathologic changes in cases of SFV include acute inflammation that progresses to fibroblast proliferation with mononuclear and polynuclear leukocyte infiltration.[5] Fibroblasts continue to proliferate until a distinct tumor is formed.[8,11] As we observed in the current case, histopathologic changes that can occur during tumor development include intracytoplasmic inclusion bodies in tumor cells, lymphocyte accumulation at the base of the tumor, and mononuclear lymphocyte cuffing of vessels surrounding the tumor.[6,15] These cutaneous fibromas can persist for long periods in the presence of circulating antibodies, with peak virulence in the late stages of tumor development (as long as 142 d after inoculation). The epidermis can become necrotic and slough, and the lesion may regress naturally in 1 to 2 mo.[8,17] Alternative ways to diagnose SFV include electron-microscopic detection of poxvirus particles, transmission to susceptible rabbits, isolation of RK13 cell monolayers, and molecular techniques.[18]

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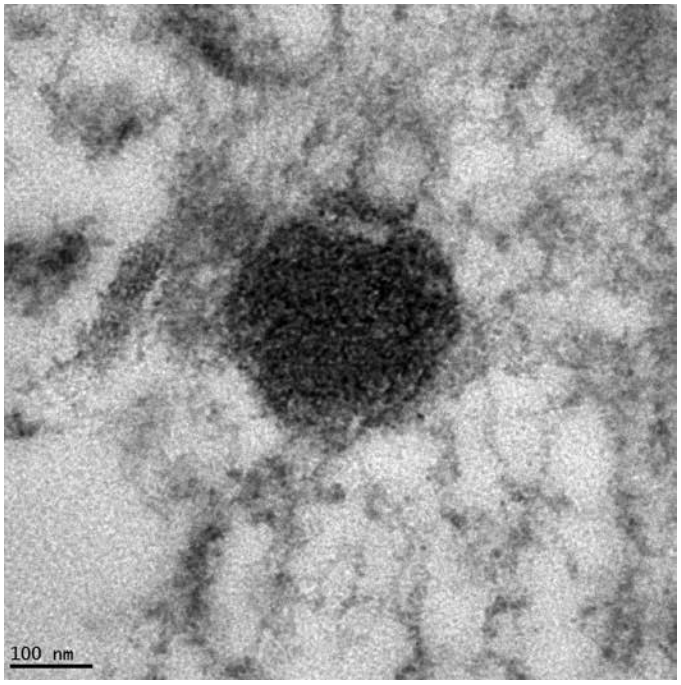

Figure 7. Transmission electron microscopy of a paraffin-embedded section of the mass from the rabbit's external ear canal**.** The spherical intracytoplasmic electron-dense structure with an irregular outer surface and located within a neoplastic cell is consistent with poxvirus and supportive of the diagnosis of *Leporipoxvirus.* Bar, 100 nm.

The treatment of SFV in domestic rabbits is largely based on supportive care and antibiotic administration to prevent secondary infection.[8] A 1-y live vaccine (Nobivac Myxo-RHD, MSD Animal Health, Milton Keyenes, United Kingdom) that provides cross-immunity for both SFV and myxoma virus has been created but is not available in the United States.[20] Nodule formation at the site of vaccination can occur, especially when the vaccine is administered intradermally and may correlate with the serologic response.[4] No association between serologic response and injection technique emerged when subcutaneous and intradermal vaccine administration were compared.[1] Prevention recommendations for SFV include arthropod control, enclosure screening, and restriction of contact with wild rabbits, especially in areas where the virus is endemic.[5]

The diagnosis of SFV in the rabbit we present was based on the clinical appearance, histopathology, and electron microscopic analysis of the aural mass. This case report alerts clinicians that SFV should be considered as a differential diagnosis in rabbits that present with abnormal tissue or a mass within the ear canal as well as in those manifesting the typical appearance on the haired skin of the feet, legs, and face.

Acknowledgments

We thank Drs Dalen Agnew and Steve Bolin (Diagnostic Center for Population and Animal Health, Michigan State University) and Dr Alicia Withrow (Center for Advanced Microscopy, Michigan State University) for assistance with sample preparation for transmission electron microscopy and the analyses themselves.

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