Epideimiologic, clinicopathologic, and diagnostic findings in pet rabbits with myxomatosis caused by the California MSW strain of myxoma virus: 11 cases (2022–2023)

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OBJECTIVE
To determine epidemiologic features of naturally occurring myxomatosis in domestic rabbits in California and to characterize clinicopathologic and diagnostic findings.

ANIMALS
11 client-owned rabbits, Oryctolagus cuniculus subsp domesticus.

CLINICAL PRESENTATION
A prospective study of pet rabbits with myxomatosis seen at an exotic animal specialty clinic in Santa Cruz county, California, was conducted between January 1, 2022, and December 31, 2023. Rabbits were included in the study if they had bilateral blepharedema and were PCR positive for myxoma virus.

RESULTS
All infected rabbits had spent time outdoors. Common clinical signs included bilateral blepharedema (11/11), anogenital edema (10/11), rectal temperature ≥39.7 °C (5/9), and sudden death (4/11). Eyelid biopsies from all rabbits (11/11) were positive for myxoma virus by qualitative PCR followed by Sanger sequencing (100% nucleotide identity to strain MSW, also known as California/San Francisco 1950 [Genbank accession KF148065]). Most rabbits had keratinocytes containing eosinophilic intracytoplasmic viral inclusions in biopsies of edematous skin (8/11) and lymphocyte necrosis in the spleen (10/11). Immunohistochemistry identified myxoma virus in samples of skin, heart, lung, ileum, spleen, and lymph node.

CLINICAL RELEVANCE
Clinical signs of myxomatosis caused by the MSW strain of myxoma virus are distinctive but subtle. Cases occur regularly in the Santa Cruz and San Jose regions of California. As infection with this virus is almost 100% fatal and no vaccine is available in the US, owners of domestic rabbits in endemic areas should keep their pets indoors or behind mosquito screens. Myxomatosis is a reportable disease in the US, and the appropriate state or federal agencies should be contacted when outbreaks occur.

Keywords: myxomatosis, rabbit, California, myxoma virus, epidemiology

Myxoma virus is a poxvirus in the genus Leporipoxvirus that is naturally carried by New World cottontail rabbits in the genus Sylvilagus. There are 2 distinct lineages of myxoma virus: the South American strains endemic to South and Central America, which are carried by the tapeti (Sylvilagus brasiliensis), and the North American (or California) strains endemic to Baja California and the west coast of the US, which are carried by the brush rabbit (Sylvilagus bachmani). While both myxoma virus lineages cause only transient and harmless cutaneous fibromas in their native hosts, they cause the virulent systemic disease myxomatosis in European rabbits (Oryctolagus cuniculus), the rabbit species commonly kept as pets or used as a food source.1,2

Clinical signs of nodular myxomatosis caused by South American myxoma virus strains tend to be florid, with multiple protuberant skin masses, marked swelling of the eyelids and anogenital region, and mu-
Clinical signs of atypical myxomatosis (amyxomatous myxomatosis) caused by South American myxoma virus strains are primarily characterized by edematous blepharitis, seromucoid blepharoconjunctivitis, and respiratory distress. In contrast, clinical signs of myxomatosis caused by California strains are less conspicuous, causing only mildly edematous eyelids and genitals, and deaths occur earlier in the course of disease. The MSW strain of myxoma virus (MSW), also known as the California/San Francisco 1950 strain, is the most virulent strain of myxoma virus known, with a mean survival time of 6.5 to 8.5 days and a mortality rate of almost 100% in domestic rabbits. Rabbits infected with MSW can die prior to the development of clinical signs. Those that survive for longer develop mild to moderate blepharedema with variable conjunctival discharge that is thin and cloudy rather than mucopurulent. Anogenital edema appears later in the course of infection and may be absent at the time of death. Genetic analysis of myxoma viruses shows that California strains contain more copies of virulence genes than do South American strains, which may account for the more acute and lethal nature of the disease. All myxoma virus strains possess an array of immune-modulating proteins, which cause immunosuppression in European rabbits, and secondary bacterial infections are common.

Myxomatosis in North America is limited to the brush rabbit’s native habitat, which extends from the Columbia River in Oregon to the north, the Sierra Nevada and Cascade mountains to the East, and the tip of the Baja California peninsula to the south. Myxomatosis was first reported in California in 1931 by Kessel et al., who described outbreaks in Santa Barbara, Ventura, and San Diego counties. Scientific reports since then have also described cases in San Mateo, Santa Clara, Humboldt, and San Luis Obispo counties. Outbreaks of myxomatosis have also been described in western Oregon in 1976 and 2003 and in Baja California in 1993. The most recent scientific report of naturally occurring myxomatosis in California was in 1965. Myxomatosis is considered a reportable disease by the California Department of Food and Agriculture, USDA APHIS, and Los Angeles county. The brush rabbit is the sole carrier of myxoma virus in the US because other North American lagomorphs, including cottontail rabbits and hares, are incapable of transmitting the disease. Myxoma virus can spread from brush rabbits to domestic rabbits via biting insects, direct contact, and contaminated fomites. Mosquitoes are likely the primary mode of viral transmission, and multiple species of mosquito can carry the virus. Outbreaks of myxomatosis in North America have a seasonal nature, with most cases occurring in the late summer and fall, and the locations of outbreaks tend to vary from one year to the next.

Because the clinical signs of myxomatosis are distinctive and nearly pathognomonic, initial diagnosis is largely based on physical exam findings. If classic symptoms of myxomatosis are not present before the rabbit dies, or if a definitive diagnosis is desired, confirmation of the disease can be made by laboratory testing. As infections with virulent strains of myxoma virus have mortality rates approaching 100% and infected rabbits experience suffering prior to death, humane euthanasia is often recommended. No vaccine against myxomatosis is approved in the US, although effective vaccines are available in Europe.

Methods

Case selection and historical information

A prospective study of client-owned domestic rabbits (O cuniculus subsp domesticus) examined at the Exotic Pet Clinic of Santa Cruz in California was performed between January 1, 2022, and December 31, 2023. Rabbits that presented with clinical signs of myxomatosis, including bilateral blepharedema, pyrexia, anogenital edema, and sudden death, were tested for myxoma virus by use of PCR. All rabbits that tested positive for myxoma virus were included in the study. Owners of symptomatic rabbits that arrived at the clinic alive were informed of the grave prognosis, and humane euthanasia was discussed. Owner consent was secured for each rabbit in the study.

Information gathered on each rabbit included breed, date of birth, sex, spay/neuter status, whether the rabbit spent time outdoors, whether the owner had had other rabbits die recently, whether there were wild cottontail rabbits near the owner’s home, whether the rabbit had received recent veterinary care, whether the owner was aware of the risks of myxomatosis, and whether the owner had noted mosquitoes near their home or ectoparasites on their pet.

As myxomatosis is a reportable disease in California, a Public Records Act request was made to the California Department of Food and Agriculture on December 11, 2023, requesting data on myxomatosis cases reported during the previous 20 years.

Physical examination and antemortem diagnostic testing

Rabbits in the study that arrived alive had a comprehensive physical examination performed, including a body condition score measured with a 9-point scoring system, with 5 being ideal. They were then sedated with hydromorphone 0.2 mg/kg IM and midazolam 0.5 mg/kg IM, and blood was drawn from a lateral saphenous vein or central ear artery. Following collection, blood films were made
and the remaining blood placed into a 0.5-mL tube containing EDTA and a 0.80-mL tube containing lithium heparin and a gel medium. A CBC and chemistry panel were promptly run on benchtop hematology and chemistry analyzers (Vetscan; Zoetis), and blood smears were stained with a rapid differential stain kit and evaluated under a microscope. Ventrodorsal and right lateral thoracic and abdominal radiographs were taken and subsequently evaluated by a board-certified radiologist. Rabbits whose owners had elected euthanasia subsequently received additional sedation with an IM injection of 10 mg/kg ketamine and were humanely euthanized with an IV injection of a pentobarbital and phenytoin mixture given to effect.

Necropsy and postmortem diagnostic testing

Postmortem eyelid biopsies taken from all rabbits in the study and conjunctival swabs taken from a subset of rabbits in the study were submitted for poxvirus screening by conventional PCR followed by Sanger sequencing. Nucleic acids were extracted by use of a DNEasy kit (Qiagen), and PCR utilizing degenerate pan-Chordopoxvirinae primers (265F/464R) targeting the DNA-dependent polymerase gene was performed as previously described. Bands of the appropriate size as visualized by gel electrophoresis were extracted and submitted for bidirectional commercial Sanger sequencing. The prevalence of myxomatosis was calculated by dividing the number of rabbits PCR positive for myxoma virus by the total number of rabbits examined at the Exotic Pet Clinic of Santa Cruz during the study period. All cases that tested positive for myxoma virus were reported to the California Department of Food and Agriculture.

Necropsies were performed on each rabbit, and tissues were collected for histopathology. Samples of eyelids, genital skin (if edematous), liver, kidneys, spleen, stomach, duodenum, ileum, cecal appendix, colon, reproductive organs (if present), heart, lungs, lymph nodes, and brain were collected from most rabbits; brain tissue was not collected in a subset of rabbits due to the owner’s request for a cosmetic necropsy. Tissues were fixed in neutral-buffered 10% formalin, routinely processed, embedded in paraffin, sectioned at 5 μm, and stained with H&E stain. Immunohistochemistry (IHC) for myxoma virus was performed on samples of skin, heart, lung, ileum, spleen, and lymph node with the Dako Link48 automated immunohistochemistry system (Agilent) following a standard protocol. Myxoma virus antigen was detected with a monoclonal rabbit myxomatosis antiserum (dilution 1:50; Churchill Applied Biotechnology Ltd), followed by a labeled streptavidin-biotin detection system (Agilent) with 3,3′-diaminobenzidine chromogen. Sections were counterstained with Mayer hematoxylin.

Statistical analysis

Descriptive statistics were calculated for signalment, clinical signs, clinical findings, concurrent diseases, diagnostics test results, and postmortem findings. Median and range are reported for continuous data results.

Results

Patient inclusion

A total of 1,955 rabbits were examined at the Exotic Pet Clinic of Santa Cruz during the 2-year study period. Eleven rabbits met the criteria for inclusion in the study, representing a prevalence of 0.6%. Two rabbits (2/11) died shortly before arrival at the clinic, and 2 of the rabbits that arrived at the clinic alive were moribund (2/9) and died shortly after being examined. Owners elected humane euthanasia for the remaining 7 rabbits (7/9). An additional rabbit that had clinical signs consistent with myxomatosis was subsequently excluded from the study due to a diagnostic sample being lost during transport.

History, signalment, and clinical presentation

Five mixed-breed rabbits, 2 lionhead rabbits, 1 Holland lop rabbit, 1 Dutch rabbit, 1 Flemish giant rabbit, and 1 mini rex rabbit were included in this study. Six of the rabbits were female (2/6 spayed), and 5 of the rabbits were male (4/5 neutered). The median age at diagnosis was 2 years (range, 3 months to 5 years). All rabbits presented on an emergent basis with presenting complaints that included swollen eyes (7/11), hyporexia (6/11), lethargy (6/11), rapid or labored breathing (2/11), sneezing (1/11), eye discharge (1/11), or sudden death (2/11). None of the rabbits were owned by clients new to the clinic who were unaware of the risk of myxomatosis, and 2 of the rabbits were owned by clients with whom the risk of myxomatosis had been previously discussed. Six of the rabbits were evaluated in 2022 and 5 of the rabbits in 2023; 4 presented to the clinic in September, 4 in October, 2 in August, and 1 in February. Figure 1 contains case locations.

Owners reported that 9 of the rabbits lived outdoors exclusively and 2 of the rabbits spent time both indoors and outdoors. Three of the owners had had ≥ 1 other pet rabbit die recently for unknown reasons. Five of the owners had noticed mosquitoes near their homes, and 5 of the owners had noticed cottontail rabbits near their homes. None of the owners had noticed fleas or ticks on their pets, and none of the rabbits were on medications to prevent ectoparasites.

One of the rabbits in the study had received veterinary care 6 days prior due to the owner’s concerns regarding lethargy, hyporexia, and swollen eyes. On physical examination, the rabbit was noted to be febrile with a rectal temperature of 40.3 °C (104.5 °F), had bilateral blepharedema with erythematous conjunctiva, a swollen and edematous anogenital region, and swollen lips. A tentative diagnosis of allergic reaction was made, and the pet was discharged on PO enrofloxacin and meloxicam. The owner reported no improvement with these treatments.
Public records of myxomatosis in California, 2015 to 2023

On January 29, 2024, the California Department of Food and Agriculture provided a list of the myxomatosis cases reported between January 1, 2015, and December 31, 2023. The agency stated that information on myxomatosis cases reported prior to 2015 was not available. The report included 2 cases from 2017 (Monterey and Ventura counties), 1 case from 2018 (Sonoma county), 14 cases from 2019 (Monterey, San Benito, San Mateo, Santa Clara, Santa Cruz, and Ventura counties), and 5 cases from 2020 (Santa Clara and Santa Cruz counties). Also included were 2 cases from 2022 (Alameda and Santa Clara counties), 1 of which was a case from this study, and 8 cases from 2023 (Alameda, Santa Clara, Santa Cruz, and San Mateo counties), 5 of which were cases from this study.

Physical examination findings

The median body weight of the rabbits in the study was 2.35 kg (range, 0.82 to 5.96 kg), and the mean body condition score on a 9-point scale was 6 (range, 5 to 7). Physical examination findings (Figure 2) for the rabbits that presented alive included edematous eyelids with erythematous conjunctiva (9/9), edematous genitals (8/9), edematous lips (5/9), edematous ears (5/9), generalized subcutaneous edema (2/9), lethargy (7/9), mild dehydration (2/9), serous to cloudy eye discharge (3/9), serous nasal discharge (2/9), dyspnea (3/9), tachypnea (4/9), harsh bronchovesicular sounds (2/9), cyanotic mucous membranes (1/9), diarrhea (1/9), and flea dirt (1/9). Behavioral evidence of pain was not noted in any of the rabbits. Five of the rabbits were febrile with rectal temperatures ≥ 39.7 °C (≥ 103.5 °F; 5/9), 3 were normothermic with rectal temperatures ≥ 37.4 °C and ≤ 39.6 °C (≥ 99.3 °F and ≤ 103.3 °F; 3/9), and a single rabbit was hypothermic with a rectal temperature ≤ 37.3 °C (< 99.1 °F; 1/9). No ectoparasites were noted on any of the rabbits.

Clinical, hematologic, and biochemical findings

A CBC and chemistry panel were performed in 8 of the 9 rabbits that arrived at the clinic alive; the remaining rabbit in this group died before a blood sample could be drawn. Decreased Hct was noted in 5 rabbits (5/8; range, 25.5% to 34.3%), leukocytosis in 2 rabbits (2/8; range, 12.78 to 26.34 K/µL), and
leukopenia in 3 rabbits (3/8; range, 1.27 to 2.82 K/µL). All rabbits had low platelet counts (8/8; range, 24 to 111 K/µL); clumping of platelets was noted in 1 rabbit (1/8). Lymphocytosis was noted in 1 rabbit (1/8; 25.55 K/µL) and lymphopenia in 1 rabbit (1/8; 1.23 K/µL). Monocytosis (0.62 K/µL) and heterophilia (7.01 K/µL) with toxic changes were noted in 1 rabbit without subsequent evidence of bacterial infection (1/8). One rabbit that was subsequently diagnosed with appendicitis had pancytopenia and bacteremia (1/8). Most of the abnormal findings on chemistry panels were mild, including increased ALP (2/8; range, 140 to 157 U/L), increased ALT (6/8; range, 111 to 300 U/L), increased total bilirubin (1/8; 0.4 mg/dL), increased BUN (2/8; range, 39 to 48 mg/dL), decreased phosphorus (1/8; 1.5 mg/dL), increased creatinine (1/8; 1.9 mg/dL), increased sodium (1/8; 158 mmol/L), and decreased total protein (3/8; range, 4.6 to 4.8 g/dL). Glucose was mildly elevated in 2 rabbits (2/8; range, 171 to 172 mg/dL). The rabbit with bacteremia had a markedly decreased glucose (18 mg/dL) and increased potassium (> 8.5 mmol/L). Total calcium levels were decreased in 5 rabbits (5/8; range, 7.6 to 11.9 mg/dL).

Molecular screening
Qualitative PCR testing was performed on eyelid biopsies from all rabbits, and all samples (11/11) produced an amplicon of the correct size confirmed to be myxoma virus (100% nucleotide identity to the MSW or California/San Francisco 1950 [Genbank accession KF148065]) by bidirectional Sanger sequencing and analysis. Polymerase chain reaction testing on conjunctival swabs was performed on the first 5 rabbits in the study; however, only one of the swabs was positive for myxoma virus (identical sequence to the corresponding biopsy sample), and this testing was subsequently discontinued.

Diagnostic imaging
Abdominal and thoracic radiographs were performed on all rabbits that arrived at the clinic alive (9/11). Four of these rabbits had soft tissue swelling present in the axillary regions consistent with subcutaneous fluid accumulation (4/9), 1 of which also had a small amount of subcutaneous gas present in the axillary region (1/9); sepsis was not noted in the rabbit with subcutaneous gas. Anogenital swelling was present in 7 rabbits (7/9) and absent in 1 rabbit (1/9); 1 case did not have the anogenital region fully included in the field of collimation. Mild to moderate cardiomegaly was observed in 3 of the rabbits (3/9), and a mild to severe pulmonary interstitial pattern was noted in 3 of the rabbits (3/9); only one of the rabbits with cardiomegaly (moderate) also had an interstitial pattern (mild). Four of the rabbits...
had findings consistent with rabbit gastrointestinal stasis syndrome, including reduced cecal volume, reduced gastric volume with ingesta retracted from the stomach wall, and increased cecal and intestinal gas (4/9). The remaining radiologic findings were unremarkable or incidental.

Postmortem examination

All rabbits in the study had edematous eyelids (11/11), and most had edematous genitals (10/11). Fewer of the rabbits had edematous lips (6/11), noses (2/11), or ears (3/11). Generalized subcutaneous edema was noted in 2 rabbits (2/11), 1 of which also had moderate amounts of clear thoracic and peritoneal fluid (1/11). Postmortem hemorrhage from body orifices was noted in 3 rabbits, 2 of which had hemorrhage from the nose (2/11) and 1 of which had hemorrhage from the vulva (1/11); 1 rabbit also had purpura of the skin, conjunctiva, and small intestinal serosa. The heart was grossly unremarkable in most rabbits (9/11) but was dark purple or enlarged in the remaining 2 rabbits (2/11). The lungs were abnormally wet and dark red with foam on cut surface in 6 rabbits (6/11) and unremarkable in the remaining 5 rabbits (5/11). Two rabbits had pale kidneys with capsular depressions (2/11), and 1 rabbit had 2 liver cysts filled with clear fluid (1/11). The cecal appendix was swollen and pale with a thickened wall and serosal petechiae in a single rabbit subsequently diagnosed with appendicitis (1/11). The spleen, stomach, duodenum, colon, lymph nodes, and brain were grossly unremarkable in all rabbits (11/11).

Histopathology and IHC findings

Histopathology of the skin of the eyelids and ano-genital region showed edematous to myxomatous stroma admixed with undifferentiated mesenchymal stellate to spindle cells (myxoma cells), hyperplastic epidermis, cells within the granular layer with increased keratohyalin granules, and epithelial cells with ballooning degeneration or hypereosinophilic cytoplasm in all samples (11/11; Figure 3). Most but not all of these samples also had rare keratinocytes containing eosinophilic intracytoplasmic inclusions (8/11). Some skin samples also showed scattered hemorrhage (6/11). Conjunctiva of the eyelids and genitals displayed mild hyperplasia and no eosinophilic intracytoplasmic inclusions. A majority of rabbits had myxoma cells and myxomatous stroma similar to that described in the skin present multifocally within the heart (7/11), with the location of these changes varying among the interstitium of the myocardium and the epicardium of the atria and ventricles. In 1 rabbit, both mitral valves and pulmonary arterial valves were likewise expanded by myxomatous stroma and myxoma cells (1/11). Similarly, scattered...
areas of pulmonary interstitium expanded by myxoma cells and myxomatous stroma were noted in some rabbits (4/11), while the remaining rabbits had scattered areas of the interstitium expanded by edema and inflammatory cells (7/11). Lymphocyte necrosis was noted in various lymphoid tissues, including the spleen (10/11), cecal appendix (5/11), thymus (1/1), and lymph nodes (4/4). Changes to the kidneys included infiltration with mild numbers of lymphocytes, histiocytes, and plasma cells accompanied by rare myxomatous stroma and stellate cells (1/11) or edema (1/11). Histopathology of the brain was either unremarkable or showed mild cuffing of vessels with lymphocytes within the cerebral gray matter (4/9); one of these rabbits also showed these changes in the thalamus and brainstem (1/9).

One rabbit had a severe lymphocytic to heterophilic appendicitis (1/11) with loss of the overlying epithelium and colonies of bacteria within the lumen of the glands. Another rabbit (1/11) had sepsis with bacteria present in the liver, kidneys, uterus, ovary, myocardium, lungs, stomach, duodenum, pancreas, colon, and cecal appendix. In the remaining rabbits (9/11), no abnormalities were noted in the stomach, duodenum, or colon and no abnormalities were noted in the reproductive organs when present (4/5).

Immunohistochemistry detected myxoma virus in all organs with microscopic lesions of myxomatosis (Figure 4). Myxoma virus was widely detected in scattered individual and clustered epithelial cells within the epidermis and hair follicle epithelium, and immunolabeling highlighted the previously described intracytoplasmic inclusion bodies. Positive labeling was also observed in myxoma cells, macrophages, fibroblasts, endothelial cells, adipocytes, and some lymphocytes in the dermis. In the spleen and lymph nodes, myxoma virus was in macrophages, lymphocytes, and dendritic cells, particularly within lymphoid follicles. Myxoma virus was also detected in macrophages and dendritic cells within the pulmonary interstitium and bronchus-associated lymphoid tissue, in areas of myxoid interstitium within the myocardium, and in the lamina propria and Peyer patches of the ileum.

Figure 4—Rabbits with the MSW strain of myxomatosis with virus detected by immunohistochemistry within characteristic microscopic lesions. 3,3'-Diaminobenzidine chromogen, hematoxylin counterstain. A—Positive labeling of epithelial cells in epidermis and hair follicles within epidermis and inclusion bodies (inset). Bar = 240 µm. B—Positive labeling in scattered keratinocytes within epidermis and inclusion bodies (inset). Bar = 120 µm. C—Macrophages positive for myxoma virus in a depleted lymph node. Bar = 240 µm. D—Macrophages (inset) positive for myxoma virus within myxomatous interstitium of the myocardium. Bar = 240 µm. E—Positive labeling in scattered macrophages within an edematous myocardial valve. Bar = 580 µm. F—Alveolar macrophages positive for myxoma virus within the lungs. Bar = 240 µm.
Discussion

Naturally occurring myxomatosis caused by the MSW strain (California/San Francisco 1950) \(^8\) of the myxoma virus occurs regularly in the greater San Jose and Santa Cruz regions of California. Domesticated rabbits that spend time outdoors are at greater risk of acquiring the disease, as mosquitoes are the primary mode of transmission. Most of the cases recorded in this study occurred between August and October, as has been noted previously, \(^24\) and their location varied somewhat from one year to the next. It is likely that the number of cases brought to veterinarians underestimates the number of cases occurring, as sudden death can be the first sign noted. \(^1,3\) The prevalence of myxomatosis in outdoor rabbits is likely higher than the 0.6% reported here, as most rabbit owners in our area keep their pets indoors.

The clinical signs of myxomatosis noted in this study are largely unchanged from those caused by the same strain of virus isolated in 1950 and those described in an outbreak in 1959. \(^3,6,9\) Bledaredema, edema of the anogenital region, and sudden death still occur consistently. The presence of fever is variable, as rabbits can become hypothermic prior to death. \(^9\) Rabbits that survive this phase can develop respiratory distress, sepsis, and edema of the lips, nose, and ear bases. Bloody discharge from external orifices occurs postmortem, as can be seen with rabbit hemorrhagic disease. \(^1,5\) One exception is that the muscle tremors and convulsions previously noted with MSW were not seen in this study; this may be an artifact caused by the study’s small sample size. \(^1,3,9\)

The largely consistent clinical signs and virulence of MSW over the past 60 to 70 years present a contrast to the rapidly evolving myxoma virus strains present in Europe and Australia, where the presence of wild populations of European rabbits has resulted in rabbits becoming less susceptible to disease and viral strains becoming less virulent. \(^40,41\)

When atypical myxomatosis (amyxomatous myxomatosis) first occurred in Europe, the muted cutaneous response consisting of edema rather than nodules led to conjecture that the disease was caused by a California strain of myxoma virus. \(^4,5\) Genetic analysis subsequently showed that these strains were instead mutations of the South American Lausanne strain introduced into France in 1952. \(^4,5\) The copious ocular discharge and extensive lung lesions typical of atypical myxomatosis were not noted in this study. \(^4,42\)

The histopathology and IHC results noted in this study were typical of poxviruses, with hyperplasia of the epidermis, intracytoplasmic inclusions in keratinocytes, and high expression of viral antigen in affected skin. \(^28\) As not all of the skin biopsies exhibited viral intracytoplasmic inclusion bodies, additional testing with PCR or IHC may be needed to confirm the presence of myxoma virus. Depletion of lymphocytes from lymph nodes, spleen, and thymus noted in this study has been previously reported with California myxomatosis, as has necrotizing appendicitis. \(^7,9,16\) The widespread presence of myxoma virus in the skin, lymph nodes, spleen, and lung has also been previously noted with MSW infections. \(^9\) The presence of virus in the myocardium has not been previously reported with MSW infections and may contribute to the patients’ deaths.

Rabbits infected with South American strains of myxoma virus tend to have decreased leukocyte and lymphocyte counts early in the disease and increased heterophil and monocyte counts later in the disease. \(^12,43\) This may account for the wide variability in WBC numbers found in our study. The immunosuppressive effects of the myxoma virus further complicate matters, as secondary bacterial infections can also be involved. \(^7,10,11\) A tendency toward mild anemia was also noted in our study.

While most of the changes noted on chemistry panels in these rabbits were mild and nonspecific, the presence of low total plasma calcium levels in more than half of the rabbits is intriguing. Low ionized calcium levels are common in critically ill cats and dogs \(^44\) and have been associated with azotemia and a poor outcome in rabbits. \(^45\)

The rabbits in the present study developed varying amounts of cutaneous and subcutaneous edema, some of which was visible on radiographs. Most rabbits displayed the unusual finding of mild to severe anogenital swelling on radiographs, and nearly half also had increased soft tissue density in their axillae. Care should be taken when evaluating these findings in rabbits, as increased density in the axillae could be easily dismissed as having occurred due to the administration of subcutaneous fluids. Similarly, the subcutaneous gas noted under the skin in 1 rabbit could have been misinterpreted as iatrogenic. Myxomatosis should be a rule-out for rabbits with cardio-megalgy or a pulmonary interstitial pattern if clinical signs and history are consistent. The presence of radiographic changes associated with rabbit gastrointestinal syndrome is nonspecific and occurs with many diseases.

Myxomatosis in Europe can be diagnosed in a number of ways, including clinical signs, PCR testing of conjunctival swabs and tissue samples, IHC, and serology. \(^5,12,46–48\) Our study showed that myxomatosis in the US can also be tentatively diagnosed on the basis of clinical signs, as all rabbits suspected of having myxomatosis tested positive on PCR of eyelid biopsies. Immunohistochemistry also proved a useful way to demonstrate the presence of MSW in tissues. Antemortem conjunctival swabs, however, were not an effective means of diagnosis in this study, as only 1 in a subset of 5 rabbits tested was positive on PCR. As antibodies against the MSW strain of myxoma virus were not detected prior to death in 1 study \(^6\), and a similar result was noted in a study \(^5\) of a virulent amyxomatous strain, serology may not be useful antemortem test against this disease either. Further research on finding an effective antemortem test for the MSW strain of myxomatosis is indicated.

As no vaccine against myxoma virus is approved for use in the US and the mortality rate of California strains of myxomatosis approaches 100%, prevention of the disease is of paramount importance. The seasonal nature and patchy distribution of myxomatosis...
outbreaks have resulted in most rabbit owners being unaware or dismissive of the disease until they experience its devastation. Veterinarians in endemic areas should advise rabbit owners to keep their rabbits indoors or at least behind mosquito screens. If sudden deaths or clinical signs of myxomatosis are noted in rabbits with outdoor access, all remaining rabbits should be brought indoors immediately and ill rabbits quarantined. Poxviruses are stable in the environment and can be spread by fomites but are highly sensitive to chemical disinfection.21 All cages and cage furnishings that have come into contact with infected rabbits should therefore be immediately disinfect ed and owners advised to disinfect their hands between rabbits. A similar protocol of isolation and disinfection should be used in veterinary clinics when a suspected case occurs.

This study investigated cases of myxomatosis seen by a single veterinary clinic in Santa Cruz county, California. There is unfortunately no reason to believe that cases are limited to this area. Previously published cases and unpublished cases known to the author show that myxomatosis can and likely does occur along the west coasts of California and Oregon on a regular basis. Moreover, a lack of education regarding the disease likely results in frequent misdiagnosis, as was seen with one of the rabbits in the present study. Myxomatosis is a reportable disease in California and the US, and veterinarians are encouraged to report all cases to the relevant agencies. Without accurate data on myxomatosis in the US, vaccine manufacturers will underestimate the need for a vaccine and be reluctant to produce one.

Cases of myxomatosis in southern California, Oregon, and Mexico are caused by different strains of myxoma virus than the one described in this study, and variations in clinical signs can be expected.24 A report4 of outbreaks in southern California in 1930 reported that rabbits developed mucopurulent discharge from the eyes and nose and rabbits that survived for over a week developed cutaneous nodules on the face. A 1977 report5 of an outbreak in rabbits in western Oregon described a single rabbit that developed copious mucopurulent ocular discharge and a chronic form of myxomatosis from which it eventually recovered, and a 2003 report7 from this state reported necrotizing hemorrhagic appendicitis in nearly 50% of cases. A report17 from Baja Peninsula in Mexico in 1993 described a nodular form of the disease characterized by respiratory symptoms. Further investigations into these distinct myxoma virus strains would be helpful to our understanding of the disease.

The intent of this article was to demonstrate the endemic nature of myxomatosis in California. Myxomatosis should be suspected in any rabbit with edema of the eyelids and anogenital region, and a definitive diagnosis is best achieved via PCR of swollen eyelids. Myxomatosis is a reportable disease, and cases should be reported to the appropriate state and federal agencies. It is our hope that improvements in diagnosing and tracking this lethal disease will lead to the development of a vaccine in the US.

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