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Case Report

Mandibular Fracture and Necrotizing Sialometaplasia in a Rabbit

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A 7-mo-old female New Zealand white rabbit presented with hemorrhage of the gingiva surrounding a loose lower right incisor. Antemortem conventional radiographs revealed only a small bone fragment adjacent to the left mandible's body. In light of a provisional diagnosis of mandibular fracture, the rabbit was euthanized. Postmortem radiographs of the disarticulated mandible demonstrated mandibular symphyseal fracture and comminuted fracture of the ramus and body of the left mandible. According to histopathology, the left submandibular salivary gland had necrotizing sialometaplasia, a nonneoplastic condition of the salivary glands that is caused by ischemic infarction. Although rabbits have been used as animal models of mandibular fracture and necrotizing sialometaplasia, no nonexperimental case of such conditions had been reported previously.

Abbreviation: NS, necrotizing sialometaplasia.

Rabbits, a common laboratory animal species, are susceptible to diverse injuries. Here, we present a case report of a rabbit with mandibular fracture and necrotizing sialometaplasia (NS) of the left submandibular salivary gland. Although rabbits have been used to study different aspects of mandibular fracture, such as pathophysiology,[18] and healing and management,[23,31,35] a literature search revealed that spontaneous mandibular fractures in rabbits have not been reported. In contrast, jaw fractures account for 1.5% to 3% of all fractures in dogs[27,34] and for 15% to 23% in cats.[26,27] In addition, the case we present is the first documented nonexperimental case of NS, a nonneoplastic condition of the salivary glands that is caused by ischemic infarction,[17] in a rabbit.

Case Report

A 7-mo-old female New Zealand White rabbit was used for an IACUC-approved protocol at an AAALAC-accredited research facility. The rabbit colony was housed in a vivarium that was not SPF for *Bordetellea bronchiseptica*, but *Pastereulla multocida* is a controlled pathogen. Rabbits were singly housed in stainless steel cages (Harford Metal Products, Aberdeen, MD), enriched with devices like hanging plastic keys and balls, and were fed with a fixed formula rabbit diet (2031 Teklad Global High-Fiber Rabbit Diet, Harlan Laboratories, Madison, WI) supplemented with alfalfa hay once daily. Animal rooms were maintained in constant environmental conditions (61 to 72 °F [16.1 to 22.2 °C]; relative humidity, 30% to 70%; 12:12-h light:dark cycle).

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The rabbit initially presented with moderate hemorrhage on the gingiva around a loose lower right incisor. For the next 3 d, meloxicam (0.2 mg/kg SC once daily) was given for analgesia, and the rabbit was eating, drinking, urinating, and defecating normally. On day 4, no further hemorrhage was noted, but the rabbit started to have decreased appetite. It was sedated with ketamine (50 mg/kg) to facilitate oral cavity examination; the right lower incisor was slightly movable. Supportive treatment was initiated and included subcutaneous administration of fluids, meloxicam (0.2 mg/kg SC once daily) and metoclopramide (0.3 mg/kg SC twice daily), and oral supplementation with Nutri-Cal (Vétoquinol, Fort Worth, TX) and Critical Care diet (Oxbow Animal Health, Murdock, NE). On day 7, the rabbit was sedated again for radiographs of the cranium; findings were within normal limits. On day 11, oral cavity examination revealed malocclusion with the left upper central incisor, causing ulceration of the left lower lip. The left upper central and right lower central incisors were trimmed. On day 12, reevaluation of the radiographs revealed a small bone fragment adjacent to the body of the left mandible. In light of a provisional diagnosis of mandibular fracture, the rabbit was euthanized (150 mg/kg IV; Euthasol, Vedco, St Joseph, MO).

At necropsy, the mandibular symphysis was fractured, and the left mandible had a comminuted fracture of the ramus and body (Figure 1). The left submandibular salivary gland was enlarged and pale, with a rough surface. The mandibles were harvested and immersed in a fixative decalcifier (Formical 4, Decal Chemical, Tallman, NY). In addition, tissues from other major organs were collected and fixed in 10% buffered formalin. Fixed tissues were embedded in paraffin, sectioned at 6 µm, and processed and stained with hematoxylin and eosin.

The left mandible had moderate to severe nascent fibroplasia surrounding bone fragments and infiltrating skeletal muscles. Numerous small, angular (atrophic) myofibers and small basophilic

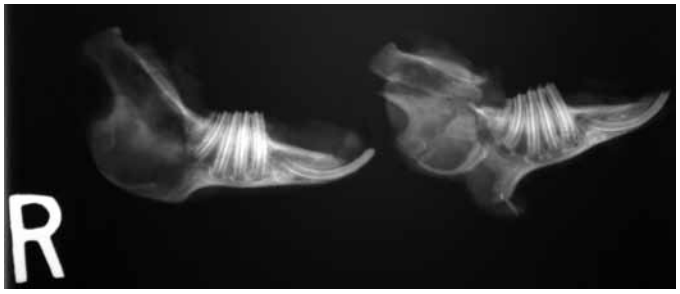

Figure 1. Postmortem lateral radiograph of the 2 disarticulated mandibles. The left mandible (right side of the radiograph) had a severe comminuted fracture of the ramus and body.

myocytes with central nuclei (myocyte regeneration) were present. Scattered bone fragments contained periosteal radiating perpendicular spicules of woven osteoid lined by plump osteoblasts in a moderately cellular fibrovascular matrix (periosteal reaction). Approximately 75% of the left submandibular salivary gland was characterized by focally extensive severe coagulative necrosis (infarction) consisting of shrunken glandular and ductular epithelial cells with hypereosinophilic cytoplasm and karyolytic nuclei ('ghost cells'; Figure 2 A and B). A thin capsule of nascent fibroplasia surrounded the gland. One margin of the salivary gland had a focally extensive area of multiple irregular and branching solid ductular structures composed of stratified cuboidal epithelium with prominent spinous processes (desmosomes) and occasional keratinization (squamous metaplasia) in a loose and edematous nascent fibrovascular matrix (Figure 2 A and C). Cells had scant to moderate amounts of faintly basophilic cytoplasm, a high nuclear-to-cytoplasmic ratio, vesicular chromatin, and 1 to 2 prominent nucleoli per cell. Mitoses were frequent, with moderate anisocytosis and anisokaryosis. Low to moderate numbers of heterophils infiltrated the glands and stroma.

Discussion

The rabbit we present in this report did not experience any documented injury from cage manipulanda, animal handling, or any of such circumstances. However, we suspect that the rabbit might have caught its incisors between cage bars and tried to free itself. Because rabbits have proportionally strong muscle mass in their hindquarters and relatively fragile bones, the struggle may have caused the left mandibular and symphyseal fracture. Such incidents involving the incisors may be more likely when incisor malocclusion and overgrowth are present. However, this rabbit had no such incisor anomaly prior to presentation, and the malocclusion observed during examination might have resulted from mandibular misalignment after the fracture. No underlying disease was present to cause a pathologic fracture in the presented rabbit, as is known to occur in dogs and cats with periodontal disease, oral neoplasia, and metabolic diseases.[21]

Diagnosing mandibular and maxillary fractures requires careful oral examination and imaging of veterinary subjects, usually under general anesthesia. Conventional skull radiography can be helpful but may be confusing, because overlaying bones and tissues may obscure the lesions. For example, only a small fragment of the mandibular body was readily apparent on the rabbit's antemortem radiograph. Noninvasive ultrasonic inspection has been used as well to diagnose fracture and monitor its healing.[8] However, dental radiography[6,15] and computed tomography[1] are

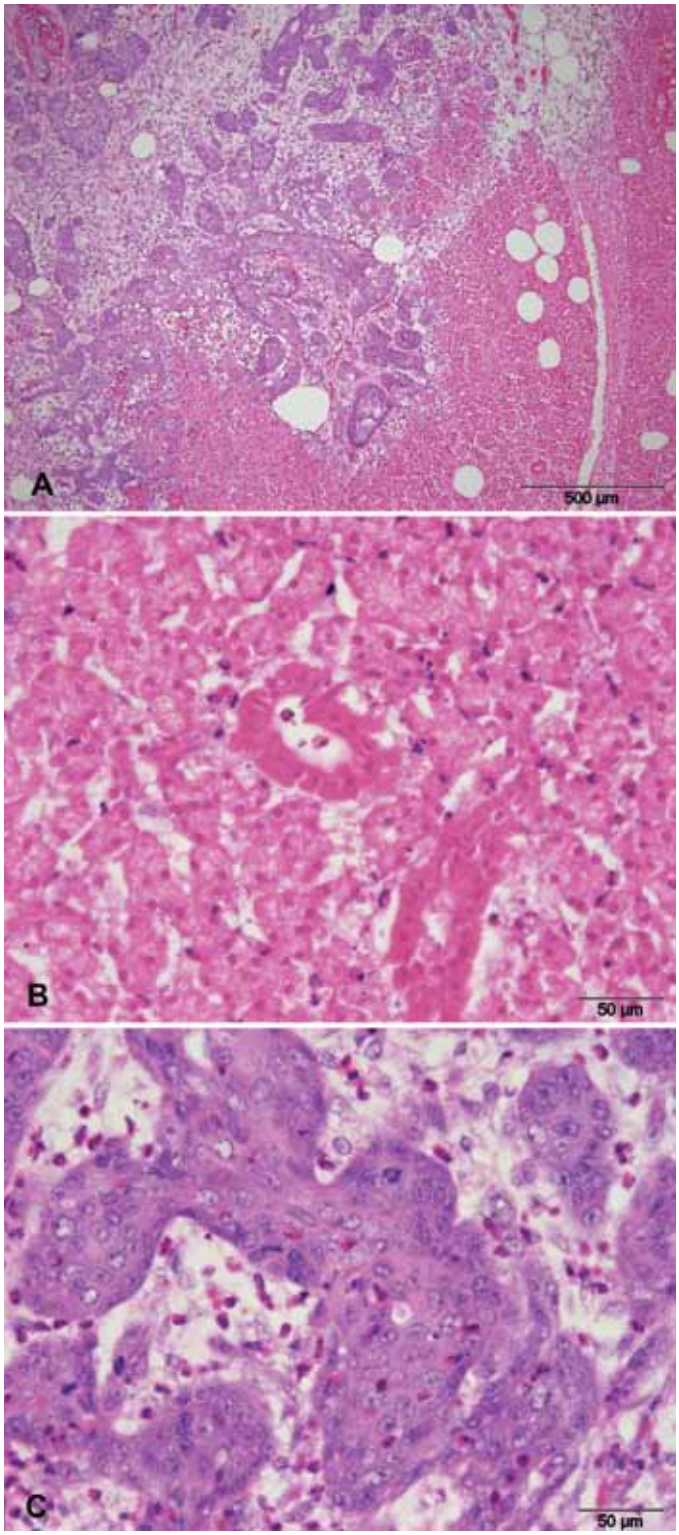

Figure 2. Left submandibular salivary gland. (A) Infarction (lower right) with ductal squamous metaplasia (upper left); bar, 500 µm. (B) Coagulative necrosis of the left submandibular salivary gland with hypereosinophilic ghost cells; bar, 50 µm. (C) Atypical hyperplasia and squamous metaplasia of the ductal epithelium with periductal fibrosis; bar, 50 µm. Hematoxylin and eosin stain.

far more effective tools for diagnosing mandibular and maxillary fractures.

The primary goals of mandibular fracture repair are to allow a rapid return to function, maintain proper occlusion, establish effective stabilization, and avoid additional trauma to the soft tissues and teeth.[22] Surgery and treatment usually depends on factors including fracture line orientation, degree of bone fragmentation, presence of contamination, and regional blood supply compromise. Most research studies on mandibular fractures in rabbits reported successful treatment with internal rigid fixation with titanium miniplates and screws.[12,16,33] In addition, a resorbable plating system has been used that incorporates a copolymer of polyglycolic acid and poly-l-lactic acid that degrades in the body via hydrolysis.[16] To improve fracture healing, other studies have combined internal fixation with other treatments, including low-intensity pulsed ultrasound,[10] electrical stimulation,[23] and intravenous injection of zoledronic acid, a synthetic analog of inorganic pyrophosphate, which is an endogenous regulator of bone mineralization.[32] In dogs and cats, the most popular repair methods still involve interdental wiring using surgical wires.[8] In some cases, intraoral acrylic splints may be used with interdental wiring to stabilize the fracture.[21] As a last resort, partial mandibulectomy may be recommended in cases wherein the blood supply is damaged severely and extensive bone fragmentation is present, as was the case for this rabbit. Regardless of the method, mandibular and maxillary fractures and symphyseal separations must be repaired meticulously to precisely align the jaws to prevent malocclusion. Other problems associated with surgical intervention include nonunion, malunion, osteomyelitis, and soft tissue infection.

NS has been reported only rarely in animals. Naturally occurring cases have been reported in dogs[4,20,30] and cats;[5,30] most of these cases involve unilateral infarction of the mandibular salivary glands. In one canine case, the parotid gland was affected.[20] Furthermore, NS has been induced experimentally in rats by injection of local anesthetic into the palate[29] and by ligation of blood vessels supplying the gland.[9] In rabbits, NS has occurred in the submandibular glands after photodynamic therapy of the mandible[25] and in the parotid glands after instillation of a resorbable protein solution into the excretory ducts.[28] In humans, any salivary gland may be affected, but unilateral NS of the palatine glands is most common.[3]

We surmise that when the rabbit injured its mandible, the blood supply to the submandibular salivary gland was compromised, leading to infarction. Similarly, trauma-induced vascular compromise, especially after surgical procedures,[9] is the most commonly implicated cause of human NS.[4] In comparison, the underlying cause of canine and feline NS is usually unknown, but some reports have implicated ischemia and vasculitis with thrombosis.[4,19,24] In one dog with bilateral lesions, an immune-mediated mechanism was demonstrated by IgG- and C3-positive immunohistochemistry of the salivary gland vasculitis.[24]

The primary diagnosis of NS is by histopathology.[7] Four features differentiate NS from other salivary gland lesions and include lobular necrosis of salivary tissue, squamous metaplasia conforming to ductal or acinar outlines, preservation of salivary lobular morphology, and variable inflammation and granulation tissue.[2] In addition, although squamous metaplasia in NS has a benign behavior, it may lead to misdiagnosis as mucoepidermoid or squamous cell carcinoma[13] and to inappropriate treatments, such as radical surgery and chemotherapy.[4,11] In humans, immunohistochemistry showing focal to absent immunoreactivity for p53, low immunoreactivity for MIB1 (Ki67), and presence of 4A4/p63- and calponin-positive myoepithelial cells has been used as an adjunct diagnostic tool.[7] In the current case, the rabbit's left submandibular gland was enlarged, as is typical for NS. However, the enlargement was neither apparent on the antemortem radiographs nor palpated during physical examination. Although commonly seen in dogs with NS,[4] clinical signs including ptyalism, lip smacking, gulping, dysphagia, and vomiting were not observed in our rabbit. Perhaps the enlarged gland did not press sufficiently on the rabbit's larynx and esophagus to cause these signs. In addition, rabbits are unable to vomit, due to the limiting ridge in their stomachs.

In humans, NS resolves spontaneously, and therefore treatment is unnecessary.[13] In dogs and cats, sialectomy of the affected gland has led to minimal, if any, improvement,[4] and NS recurrence[20] or nonrecurrence.[5,30] Consistent with their use as antiemetics in cancer chemotherapy in human patients,[14] anticonvulsants like phenobarbital have been used successfully to control progressive retching and vomiting in canine cases.[3] The left submandibular gland of the presented rabbit could have been removed, but its quality of life would not be improved without repair of the mandibular fracture.

In conclusion, we present a case report of a rabbit with mandibular fracture and NS. Clinicians should be cognizant of these conditions, and their correct diagnosis by careful oral and neck examination and imaging is paramount for effective clinical management.

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