

Case Report

## Spontaneous necrotizing sialometaplasia of the submandibular salivary gland in a Beagle dog

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**Abstract:** A single mass was found on the left submandibular salivary gland at necropsy of a 15-month-old male commercially bred laboratory Beagle dog from a control dose group from a repeat toxicity study. Microscopically, the mass was composed of a well-demarcated area of coagulative necrosis surrounded and separated from the normal salivary gland tissue by a thick fibrovascular capsule. Necrosis was admixed with areas of hemorrhage, fibrin, edema, fibrinoid necrosis of the vascular tunica media, and thrombosis of small and large vessels. Within the necrotic tissue, there was marked ductal hyperplasia, and squamous metaplasia of duct and acinar epithelium. The mass was diagnosed as necrotizing sialometaplasia of the submandibular gland. Hyperplastic ductal elements and squamous metaplasia can be mistaken microscopically with squamous cell carcinoma. Therefore, pathologists should be aware of this lesion as to avoid errors in the diagnosis of this benign pathologic condition. (DOI: 10.1293/tox.2015-0018; *J Toxicol Pathol* 2015; 28: 177–180)

**Key words:** Beagle dog, necrotizing sialometaplasia, submandibular salivary gland

Necrotizing sialometaplasia (NSM) is a benign self-limiting inflammatory lesion of the salivary glands characterized histopathologically by ischaemic lobular coagulative necrosis of sero-mucinous glands and, squamous metaplasia of ducts and acini. NSM may simulate, both clinically and histologically, malignant lesions such as squamous cell carcinoma. The first case in humans was described in 1973<sup>1</sup>, and it was defined as a reactive necrotizing inflammatory process involving the minor salivary glands of the hard palate. Since then in humans numerous cases of NSM have been reported, predominantly affecting the palatal minor salivary glands. In animals NSM is rare; naturally occurring cases have been reported dogs and cats<sup>2–5</sup>, and one spontaneous case has been reported in a rabbit<sup>6</sup>. In laboratory animals, NSM has been induced experimentally in rats by arterial ligation of the submandibular salivary gland<sup>7</sup> or by local anaesthetic injections in the palate<sup>8</sup>. The first cases in dogs were described in 1979, and these were characterized by ischaemic necrosis, capsular fibrosis and regenerative hyperplasia of surviving ductal epithelium<sup>9</sup>. Since then in dogs a number of cases of NSM have been reported, predominantly in small breeds<sup>4</sup>. A literature search revealed that spontaneous NSM in the Beagle dog has not been reported. In the present report, the pathological features of a

case of NSM affecting the submandibular salivary gland in a Beagle dog are described.

A 15-month old male Beagle dog from a control dose group was housed and maintained for an 8-week toxicity study. The animal was purpose bred for laboratory use and was obtained from Harlan, UK. Dogs were housed in groups of 3 by sex in custom designed dog pens with an area of at least 2.25 m<sup>2</sup> for each dog, at a temperature of 15–24°C and a minimum of 10 air changes per hour and a twelve-hour light/dark cycle. Each dog was given 300 g/day of standard Certified Canine Diet No. 5007 (PMI Nutrition International, Inc), and purified water ad libitum. The dogs were maintained in accordance with the UK Animals (Scientific Procedures) Act 1986, which conforms to the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, Council of Europe).

All animals were observed for clinical signs twice a day (in the morning and afternoon) until termination of the study. At the termination of the study, a detailed necropsy was done. A 27 × 20 × 12 mm single mass was identified on the left submandibular salivary gland. The mass was mottled and firm, and smooth on cut surface. There were no other significant gross findings. The mass together with the mandibular lymph node (local draining lymph node) and standard study protocol tissues were obtained, fixed in 10% buffered formalin, and processed and stained with hematoxylin and eosin for histopathological examination. The submandibular salivary mass was further examined by periodic acid–Schiff (PAS) stain. An additional section was stained with a polyclonal rabbit anti-cow cytokeratin (Wide Spectrum Screening, Carpinteria, CA, USA). Tissue sections were incubated with primary antibody. Bound primary

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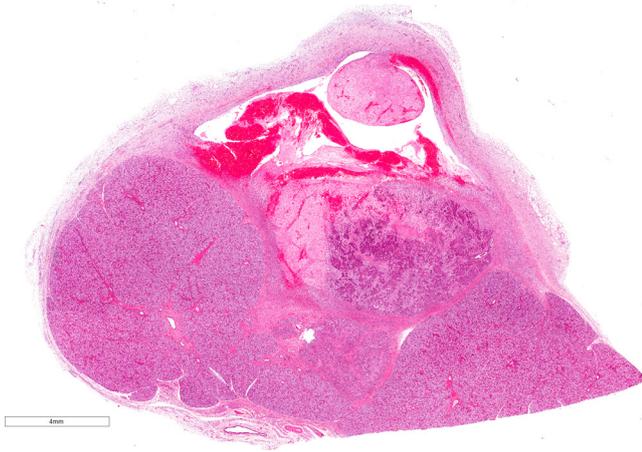
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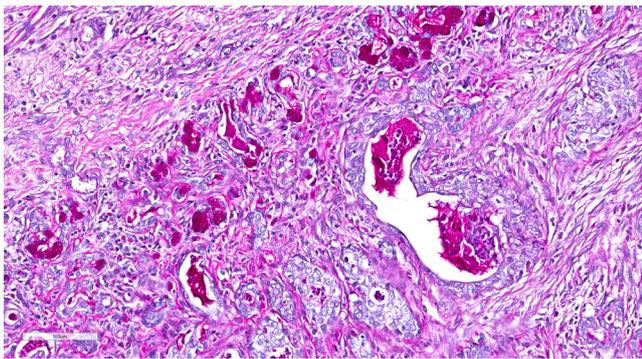
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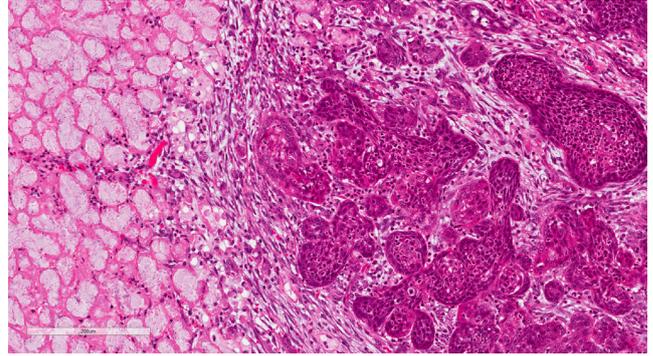
**Fig. 1.** Necrotizing sialometaplasia. Sub-gross appearance. Extensive coagulative necrosis of acini, haemorrhage and glandular hyperplasia of acini separated from viable tissue by a thick fibrovascular capsule. Hematoxylin and eosin stain. Bar = 4 mm.



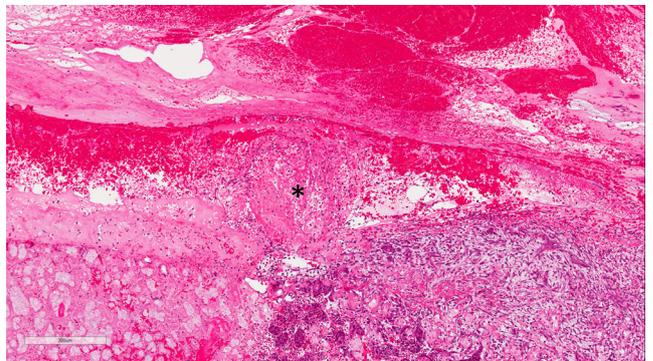
**Fig. 3.** Necrotizing sialometaplasia. Hyperplastic and metaplastic ducts surrounded by reactive fibrosis, and some duct lumens are filled with degenerate neutrophils and Periodic acid-Schiff (PAS) positive secretory product. Periodic acid-Schiff (PAS) stain. Bar = 100 µm.

antibody was detected using the Dako Envision visualization system with diaminobenzidine chromogen substrate and counterstained with hematoxylin.

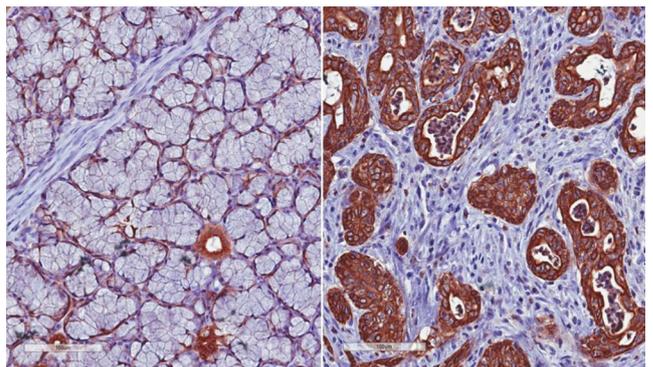
Microscopically, the mass was composed of a well-demarcated area of coagulative necrosis (Fig. 1) surrounded and separated from the normal salivary gland tissue by a thick fibrovascular capsule. Coagulative necrosis of the acinar epithelium was admixed with areas of hemorrhage, fibrin and edema. Multifocally within the necrotic tissue, there was ductal hyperplasia and squamous metaplasia of duct and acinar epithelium (Fig. 2). Hyperplastic and metaplastic ducts were surrounded by reactive fibrosis, and some duct lumens were filled with degenerate neutrophils and Periodic acid-Schiff (PAS) positive secretory product (Fig. 3). There was fibrinoid necrosis and thrombosis of small and large vessels in the necrotic areas (Fig 4). Immunohisto-



**Fig. 2.** Necrotizing sialometaplasia. Coagulative necrosis of acini, hyperplasia and metaplasia of duct and acinar epithelium. Hematoxylin and eosin stain. Bar = 200 µm.



**Fig. 4.** Necrotizing sialometaplasia. Fibrinoid necrosis and thrombosis (\*) of a large vessel in the necrotic areas. Hematoxylin and eosin stain. Bar = 300 µm.



**Fig. 5.** Necrotizing sialometaplasia. Cytokeratin had stronger cytoplasmic immunoreactivity in the metaplastic squamous epithelium (right) compared to the normal glandular epithelium (left). Immunohistochemical stain for cytokeratin, diaminobenzidine chromogen and counterstained with hematoxylin. Bars = 100 µm.

chemically, cytokeratin had stronger cytoplasmic immunoreactivity in the metaplastic squamous epithelium compared

to the normal glandular epithelium (Fig. 5). The right submandibular salivary gland, and the parotid and sublingual glands were normal. No vascular lesions or other histological abnormalities were found in the other tissues examined.

In dogs, NSM has been reported in a number of small breeds of dogs, primarily terriers<sup>4</sup>, and has not been reported in the Beagle dog. In dogs, NSM commonly affects the submandibular salivary gland; however, one case in which the parotid salivary gland was affected has been described<sup>10</sup>. In humans, any salivary gland can be affected, but most of the cases have been reported in the oral cavity<sup>11</sup>. The most common clinical presentation of NSM in dogs is nausea, dysphagia, and pain in the mandibular region<sup>4,9</sup>. On physical examination, swelling of the salivary gland or an ulcerated mass may be observed<sup>10</sup>. In contrast, no clinical signs were observed in the present case. Most likely the enlargement of the salivary gland did not compress the esophagus and larynx sufficiently to cause clinical signs or to be noticed on clinical examination. In humans, NSM presents in the majority of cases as a painful ulcerated lesion, however the symptoms and clinical appearance may vary<sup>12,13</sup>.

The exact etiology and pathogenesis NSM is not known. The most widely accepted theory explaining the etiology of NSM is injury of the blood vessels, leading to ischemia and infarction of the salivary gland acini<sup>14</sup>. In this case there was no evidence of trauma. In one dog with bilateral lesions, which had vasculitis and thrombosis in the affected gland, IgG and C3 were demonstrated immunohistochemically, suggesting an immune-mediated mechanism<sup>15</sup>. Immune-mediated vasculitis usually affects several organs. In the present case vascular lesions (fibrinoid necrosis and thrombosis) were localized to submandibular gland, suggesting that the ischemia was not a result of immune-mediated vasculitis.

Five stages have been proposed in the pathogenesis of NSM: infarction, sequestration, ulceration, reparation and healing<sup>16</sup>. In the present case different stages (infarction, sequestration and reparation) were observed. In humans, coagulative necrosis of the acini and squamous metaplasia of the salivary ducts are observed in early lesions and reactive fibrosis during the late stage of NSM<sup>11</sup>. Pseudoepitheliomatous hyperplasia could develop during the healing process of ulceration. In the present case the infarct was limited in its extent and no pseudoepitheliomatous hyperplasia or ulceration of the overlying epithelium was present.

Definitive diagnosis of NSM is by histopathology. The repair of ductal epithelium and acini by hyperplastic ductal elements and squamous metaplasia can be mistaken microscopically with squamous cell carcinoma. Preservation of lobular architecture of the gland, lobular infarction, presence of mucin in metaplastic ducts and the absence atypical nuclei in the metaplastic squamous epithelium was used to differentiate NSM from squamous cell carcinoma<sup>1</sup>. Squamous cell carcinomas of the salivary glands are very rare in laboratory Beagles. The most common spontaneous salivary gland lesions of commercially bred laboratory Beagle dogs are focal lymphocyte infiltrates and focal acinar cell

atrophy<sup>17,18</sup>, and these lesions can be easily distinguished from NSM.

In humans, NSM is a self-limiting lesion and does not require any specific treatment other than follow-up<sup>7</sup>. In dogs, the paucity of published information makes it difficult to draw conclusions regarding the typical clinical course, treatment and prognosis of NSM. Surgical removal of the affected gland has led to minimal improvement<sup>4</sup>, and recurrence<sup>10</sup>, or nonrecurrence<sup>3</sup>.

In conclusion, we present a case report of a laboratory Beagle dog with a spontaneous NSM of the submandibular salivary gland. Pathologist should be cognizant of this condition and should be careful to differentiate it from malignancy or regard it as a test article-related finding.

**Disclosure of Potential Conflicts of Interest:** There are no conflicts of interest.

## References

1. Abrams AM, Melrose RJ, and Howell FV. Necrotizing sialometaplasia. A disease simulating malignancy. *Cancer*. **32**: 130–135. 1973. [[Medline](#)] [[CrossRef](#)]
2. Kelly DF, Lucke VM, Denny HR, and Lane JG. Histology of salivary gland infarction in the dog. *Vet Pathol*. **16**: 438–443. 1979. [[Medline](#)]
3. Spangler WL, and Culbertson MR. Salivary gland disease in dogs and cats: 245 cases (1985–1988). *J Am Vet Med Assoc*. **198**: 465–469. 1991. [[Medline](#)]
4. Brooks DG, Hottinger HA, and Dunstan RW. Canine necrotizing sialometaplasia: a case report and review of the literature. *J Am Anim Hosp Assoc*. **31**: 21–25. 1995. [[Medline](#)] [[CrossRef](#)]
5. Brown PJ, Bradshaw JM, Sozmen M, and Campbell RH. Feline necrotizing sialometaplasia: a report of two cases. *J Feline Med Surg*. **6**: 279–281. 2004. [[Medline](#)] [[CrossRef](#)]
6. Villano JS, and Cooper TK. Mandibular fracture and necrotizing sialometaplasia in a rabbit. *Comp Med*. **63**: 67–70. 2013. [[Medline](#)]
7. Dardick I, Jeans MT, Sinnott NM, Wittkuhn JF, Kahn HJ, and Baumal R. Salivary gland components involved in the formation of squamous metaplasia. *Am J Pathol*. **119**: 33–43. 1985. [[Medline](#)]
8. Shigematsu H, Shigematsu Y, Noguchi Y, and Fujita K. Experimental study on necrotizing sialometaplasia of the palate in rats. Role of local anesthetic injections. *Int J Oral Maxillofac Surg*. **25**: 239–241. 1996. [[Medline](#)] [[CrossRef](#)]
9. Kelly DF, Lucke VM, Lane JG, Denny HR, and Longstaff JA. Salivary gland necrosis in dogs. *Vet Rec*. **104**: 268. 1979. [[Medline](#)] [[CrossRef](#)]
10. Kim HY, Woo GH, Bae YC, Park YH, and Joo YS. Necrotizing sialometaplasia of the parotid gland in a dog. *J Vet Diagn Invest*. **22**: 975–977. 2010. [[Medline](#)] [[CrossRef](#)]
11. Imbery TA, and Edwards PA. Necrotizing sialometaplasia: literature review and case reports. *J Am Dent Assoc*. **127**: 1087–1092. 1996. [[Medline](#)] [[CrossRef](#)]
12. Samit AM, Mashberg A, and Greene GW Jr. Necrotizing sialometaplasia. *J Oral Surg*. **37**: 353–356. 1979. [[Medline](#)]
13. Lamey PJ, Lewis MA, Crawford DJ, and MacDonald DG.

- Necrotising sialometaplasia presenting as greater palatine nerve anaesthesia. *Int J Oral Maxillofac Surg.* **18**: 70–72. 1989. [[Medline](#)] [[CrossRef](#)]
14. Suckiel JM, Davis WH, Patakas BM, and Kaminishi RM. Early and late manifestations of necrotizing sialometaplasia. *J Oral Surg.* **36**: 902–905. 1978. [[Medline](#)]
  15. Mawby DI, Bauer MS, Lloyd-Bauer PM, and Clark EG. Vasculitis and necrosis of the mandibular salivary glands and chronic vomiting in a dog. *Can Vet J.* **32**: 562–564. 1991. [[Medline](#)]
  16. Anneroth G, and Hansen LS. Necrotizing sialometaplasia. The relationship of its pathogenesis to its clinical characteristics. *Int J Oral Surg.* **11**: 283–291. 1982. [[Medline](#)] [[CrossRef](#)]
  17. Hottendorf GH, and Hirth RS. Lesions of spontaneous sub-clinical disease in Beagle dogs. *Vet Pathol.* **11**: 240–258. 1974. [[Medline](#)] [[CrossRef](#)]
  18. Sato J, Doi T, Wako Y, Hamamura M, Kanno T, Tsuchitani M, and Narama I. Histopathology of incidental findings in beagles used in toxicity studies. *J Toxicol Pathol.* **25**: 103–134. 2012. [[Medline](#)] [[CrossRef](#)]