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1 **Systemic mucoid degeneration of the arterial tunica intima in a young dog**

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16 Running head: Systemic intimal mucoid degeneration in a dog

17

18 **Abstract.** A 27-mo-old, spayed female mixed-breed dog was presented with left forelimb pain,  
19 which progressed to full thickness necrosis of the soft tissues of multiple limbs. Clinical imaging  
20 and postmortem examination suggested multiple large arterial thromboemboli. Histologic  
21 examination of vascular lesions revealed markedly thickened tunica intima with polypoid  
22 intraluminal projections, which partially to entirely occluded the arterial lumen. The expanded  
23 tunica intima was comprised of intimal accumulation of Alcian blue–positive matrix with  
24 scattered spindle-to-satellite cells. These cells were positive for von Willebrand factor and  
25 vimentin but negative for  $\alpha$ –smooth muscle actin, suggesting endothelial origin. Deposition of  
26 the intimal mucoïd matrix was observed in the elastic and muscular arteries associated with  
27 regional ischemic changes. Mucoïd emboli, likely from fragmentation of proliferative intimal  
28 tissue, were identified in smaller vessels supplied by affected arteries. Based on these findings,  
29 we diagnosed systemic mucoïd degeneration of the arterial tunica intima. Such systemic arterial  
30 degeneration characterized by deposition of mucoïd matrix in the tunica intima has not been  
31 reported previously in dogs, to our knowledge, and should be distinguished from  
32 thromboembolism and other degenerative vascular diseases.

33

34 **Keywords:** arterial occlusion; artery; dogs; mucoïd degeneration; thromboembolism; tunica  
35 intima.

36

37 Degenerative arterial diseases, such as arteriosclerosis, atherosclerosis, and arteriolosclerosis, are  
38 observed occasionally in older dogs. These diseases cause thickening, loss of elasticity, and  
39 luminal narrowing in arteries or arterioles as a result of proliferative and degenerative changes in  
40 the tunica media and intima.<sup>10</sup> Aside from some extensive cases of atherosclerosis, clinical  
41 consequences of degenerative arterial diseases are rarely reported in dogs. Here, we report an  
42 unusual case of systemic arterial degeneration resembling multiple arterial thromboemboli in a  
43 dog, with severe clinical consequences.

44 A 27-mo-old, spayed female mixed-breed dog was presented because of left forelimb  
45 pain and possible ataxia, and was placed on doxycycline (5 mg/kg, q12h) and prednisone (0.5  
46 mg/kg, q6h) for presumptive neurologic disease. The dog failed to respond to treatment after 6  
47 wk and was referred to Hokkaido University Veterinary Teaching Hospital (HUVTH; Sapporo,  
48 Japan). At presentation at the HUVTH, the dog had deep ulcers of the skin on the left forelimb.  
49 Hematologic and biochemistry profiles were within RIs except for some elevated liver enzyme  
50 activities (alanine aminotransferase 218 IU/L, RI: 17–78 IU/L; aspartate aminotransferase 67  
51 IUL, RI: 17–44 IU/L; alkaline phosphatase 1,165 IU/L, RI: 47–254 IU/L; gamma-glutamyl  
52 transferase 16 IU/L, RI: 5–14 IU/L), and the total T4 level was low (10.3 nmol/L, RI: 13–50  
53 nmol/L). An MRI did not identify any lesions in the brain. The patient was continued on  
54 prednisone (0.5 mg/kg, q6h), and the antibiotic was switched to minocycline (10 mg/kg, q12h).  
55 The patient returned 2 mo later because of development of full-thickness soft tissue necrosis  
56 (gangrene) with bone exposure of the right forelimb (Fig. 1), development of additional foci of  
57 dermal necrosis on the hindlimbs and nasal planum, and minimal improvement of the initial left  
58 forelimb lesions. Sonographically, the abdominal aorta contained a mildly echogenic mass that  
59 extended into both external iliac arteries. Blood flow to the hindlimbs was minimal. Computed

60 axial tomography confirmed the mass and also revealed an intraluminal mass occluding  
61 segments of the aorta, specifically the aortic arch proximal to and extending into the  
62 brachiocephalic artery. Echocardiography did not reveal any abnormalities. A presumptive  
63 diagnosis of arterial thromboembolism was made, and the dog was given anticoagulant therapy  
64 and underwent amputation of the right distal forelimb; however, 2 wk later, the dog was  
65 euthanized because of a poor prognosis.

66 At postmortem examination, the distal left forelimb was detached at the carpus as a result  
67 of ischemic necrosis of all soft tissues (gangrene). The hindlimbs, tail, and nose had multifocal-  
68 to-coalescing well-demarcated foci of alopecia, which were often ulcerated and accompanied by  
69 underlying soft tissue necrosis and bone exposure. The exposed soft tissues were dry and  
70 discolored dark gray-tan. Segments (3–6 cm long) of the abdominal aorta, brachiocephalic artery,  
71 and mesenteric artery were occluded by ill-defined, pink-to-tan soft intraluminal masses (Fig. 2).  
72 The masses could not be detached from the arterial wall. Multiple wedged-shaped, dark-red foci  
73 were identified in the spleen, kidneys, and ileum.

74 Samples of the arteries, amputated limb, and major organs were fixed in 10% neutral-  
75 buffered formalin, processed routinely, and sections stained with hematoxylin and eosin.  
76 Additional sections of the arteries, kidney, and spleen were stained with Alcian blue (pH 2.5) and  
77 Elastica van Gieson stains, and then subjected to immunohistochemistry using primary  
78 antibodies directed against von Willebrand factor (vWF; A00821, 1:500, Dako),  $\alpha$ -smooth  
79 muscle actin ( $\alpha$ -SMA; N1584, 1:2, Dako), and vimentin (IS630, 1:2; Dako). The intraluminal  
80 masses were demonstrated histologically to be markedly thickened tunica intima expanded by  
81 intimal accumulation of a hypocellular pale basophilic matrix (Figs. 3, 4) that stained deeply blue  
82 with Alcian blue stain (Fig. 3, inset). Within the mucoid matrix, spindle-to-satellite cells with

83 elongate hyperchromatic nuclei and scant cytoplasm were sparsely distributed. These cells were  
84 positive for vWF and vimentin but negative for  $\alpha$ -SMA (Fig. 5). The tunica intima was partially  
85 to circumferentially thickened, such that the lumen of the affected arteries was often obscured or  
86 markedly narrowed leaving slit-like spaces. The intimal mucoid matrix was sometimes separated  
87 from the overlying endothelium by a thin layer of collagenous connective tissue. Recanalization  
88 was occasionally observed within the connective tissues. Endothelium was morphologically  
89 normal. Focally, the intimal mucoid matrix compressed the outer vessel wall, with destruction of  
90 the internal elastic lamina and elastic fibers in the tunica media (Fig. 6). The amount of Alcian  
91 blue-positive substance in the tunica media of these arteries was similar to that of unaffected  
92 arteries. There were no apparent histologic changes in the tunica externa.

93         The same histologic changes with variable severity were observed in the following  
94 arteries: abdominal aorta, brachiocephalic artery, mesenteric artery; and medium and small  
95 muscular arteries in the nose, right forelimb, spleen, pancreas, duodenum, and kidneys. Infarcts  
96 were found in the spleen, kidneys, and ileum in fields supplied by the affected arteries. Some  
97 glomerular capillaries and splenic sheathed capillaries were occluded by pieces of Alcian blue-  
98 positive hypocellular matrix, which were morphologically similar to the proliferative intimal  
99 tissue of the large arteries but not connected to the capillary walls. Other histologic lesions in the  
100 arteries included vacuolation of the medial smooth muscle cells of the splenic trabecular arteries,  
101 and fibrinoid necrosis of the left renal interlobar and arcuate arteries. The latter lesions were  
102 accompanied by minimal infiltrates of neutrophils and macrophages. There were no apparent  
103 histologic abnormalities in the brain.

104         On the basis of these findings, we diagnosed systemic mucoid degeneration of the arterial  
105 tunica intima. Although arterial thromboembolism was suspected based on clinical imaging and

106 at postmortem examination, the intraluminal masses were demonstrated histologically to be  
107 marked expansion of the tunica intima with accumulation of hypocellular mucoid matrix. This  
108 unusual intimal mucoid deposition likely caused luminal occlusion and subsequent ischemia,  
109 manifested as infarction and necrosis. In addition, emboli morphologically similar to the mucoid  
110 intimal tissue were observed in capillaries. Such disseminated mucoid emboli might be observed  
111 in cardiac myxoma<sup>7</sup>; however, our case had no evidence of neoplasia. Other diseases that could  
112 predispose to emboli or thromboemboli, such as cardiac disease, pancreatitis,  
113 hyperadrenocorticism, necrotizing myelopathy, or massive trauma,<sup>2,6,10,14</sup> were not evident in our  
114 case. Given these findings, the mucoid emboli are considered to be products of degeneration of  
115 the intimal mucoid matrix in the upstream arteries.

116         Although fibrinoid necrosis accompanied by inflammation was observed in the left renal  
117 arteries, it is unlikely that inflammatory processes were involved in the myxoid change seen in  
118 most arteries. Chronic vasculitis can cause deposition of mucoid matrix in the vascular wall<sup>16</sup>;  
119 however, the majority of the affected arteries lacked inflammation. In contrast, the inflamed left  
120 renal arteries did not exhibit the intimal proliferation or mucoid matrix deposition noted  
121 elsewhere in this dog. Our findings suggest a distinct pathogenesis for each lesion. Hypertension  
122 is a known cause of fibrinoid necrosis with inflammation.<sup>2</sup> Although antemortem blood pressure  
123 was not obtained in our case, hypertension resulting from major arterial occlusion is a possible  
124 cause of the vascular lesion in the left renal arteries.

125         Our case has histopathologic features distinct from well-known canine degenerative  
126 cardiovascular diseases such as atherosclerosis or endocardiosis. In atherosclerosis and  
127 endocardiosis, the majority of intimal and subendocardial proliferating cells are smooth muscle

128 cells and fibroblasts, respectively,<sup>10</sup> which contrasts with immunohistochemical findings that the  
129 proliferating cells were positive for the endothelial marker vWF in our case.

130         Several degenerative arterial diseases accompanied by mucoid matrix deposition are  
131 reported in human medicine, including intimomedial mucoid degeneration (IMD), Erdheim–  
132 Gsell cystic medial necrosis (EGCMN), and mucoid intimal edema (MIE). However, the  
133 histologic features of our case are not entirely consistent with any of these diseases. The mucoid  
134 changes in IMD and EGCMN are mainly present as localized deposition in the tunica media of  
135 large arteries,<sup>1,12,17</sup> which is distinct from our case in which there was systemic mucoid  
136 deposition in the tunica intima. Some IMD patients also have mucoid matrix deposition in the  
137 tunica intima; this change is always accompanied by medial mucoid matrix deposition.<sup>1,3,5,12,15,17</sup>  
138 Furthermore, the typical consequence of IMD and EGCMN is a focal aneurysm as a result of  
139 disruption of the inner elastic lamina, rather than luminal occlusion as observed in our  
140 case.<sup>1,3,15,17,18</sup> In addition, our case had no histologic evidence suggestive of Marfan syndrome or  
141 Ehlers–Danlos syndrome, which could cause EGCMN.<sup>9,13</sup> Our case had several similarities with  
142 MIE, which has intimal mucoid deposition in arterioles and luminal occlusion as a consequence.  
143 However, our case is characterized by proliferation of vWF-positive cells, instead of the  
144 concentric proliferation of  $\alpha$ -SMA-positive myointimal cells associated with MIE.<sup>4,8</sup>

145         Given that the T4 level was below the RI, hypothyroidism cannot be excluded as a  
146 possible cause of mucinous matrix accumulation in the arteries. There is, however, no report  
147 describing mucinous accumulation of arteries in animals or humans with hypothyroidism.  
148 Furthermore, in our case, clinical imaging and postmortem examination did not reveal  
149 abnormalities in either thyroid gland or any clinical sign such as hyperkeratosis, myxedema, or  
150 hyperpigmentation that would support a diagnosis of hypothyroidism.<sup>11</sup>



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202

203           **Figures 1–4.** Systemic intimal mucoid degeneration of the arteries in a dog. **Figure 1.**  
204 Dry gangrene and bone exposure in the amputated right forelimb. **Figure 2.** Opened abdominal  
205 aorta and bifurcation of the iliac arteries. Arrows indicate the intraluminal masses from the distal  
206 abdominal aorta extending into both external iliac arteries. **Figure 3.** Transverse section of the  
207 opened abdominal aorta and a small artery supplied by the abdominal aorta. There is marked  
208 expansion of the tunica intima by an accumulation of hypocellular pale basophilic matrix.  
209 Asterisks indicate incision sites where the artery was opened at postmortem examination. H&E.  
210 Inset: the intimal extracellular matrix is strongly alcianophilic. Alcian blue stain. **Figure 4.**  
211 Higher magnification of the small artery in Fig. 3. H&E.

212           **Figures 5, 6.** Systemic intimal mucoid degeneration of the arteries in a dog. **Figure 5.**  
213 High magnification of the wall of the abdominal aorta demonstrating the proliferative tunica  
214 intima. Both the endothelium and the intimal spindle-to-stellate cells are positive for von  
215 Willebrand factor (vWF). Inset: higher magnification of vWF–positive cells (arrows).  
216 Immunohistochemistry for vWF. **Figure 6.** High magnification of a transverse section of the  
217 abdominal aorta showing the junction between proliferative tunica intima and tunica media. The  
218 internal elastic lamina and elastic fibers in the tunica media are partially disrupted. Elastica van  
219 Gieson stain.



