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Susan Piripi, Jaime Hustace, Katelyn R. Carney, Jerry R. Heidel,
Christiane V. Löhr¹

Abstract. Two cases of pulmonary vascular anomaly in unrelated adult alpacas (*Vicugna pacos*) are described. In the first case, a 9-year-old intact male alpaca presented at Oregon State University Veterinary Teaching Hospital with bilateral epistaxis and died the subsequent day following severe hemorrhage from the mouth and nostrils. At necropsy, a tortuous vascular lesion was identified in the right cranial lung lobe, associated with hemorrhage into airways. In the second case, a 2-year-old female alpaca presented with postpartum anorexia, opisthotonus, and recumbency. In this second case, a similar vascular lesion was identified in the right cranial lung lobe but without associated hemorrhage. Histopathological examination of the lesion in both cases revealed numerous dilated, irregular blood vessels with marked variation in wall thickness within vessels, surrounded by foci of extramedullary hematopoiesis. Diagnoses of locally extensive pulmonary vascular anomalies (arteriovenous malformations) were made.

Key words: Alpacas; arteriovenous fistula; epistaxis; histopathology; *Vicugna pacos*; lung.

In the first case, a 9-year-old intact male alpaca (*Vicugna pacos*) was presented at Oregon State University Veterinary Teaching Hospital (OSUVTH; Corvallis, OR) in 2009 with a history of sudden-onset significant bilateral epistaxis and bleeding from the mouth. The animal was unobserved at the time of the hemorrhage, and the owner was unsure whether a traumatic event may have been involved. On arrival at OSUVTH, a clinical examination revealed no abnormalities other than dried blood around the muzzle and distal limbs. Vital parameters were normal other than mild dehydration, and careful thoracic and tracheal auscultation revealed no signs of respiratory distress at that time. Blood was drawn for standard hematologic and serum chemistry panels, revealing a mild, nonregenerative anemia ($9.91 \times 10^6/\mu\text{l}$, reference [ref.] interval: 10.1–17.3/ μl) with a moderate mature neutrophilia (24,294/ μl , ref. interval: 4,711–14,686/ μl), hyperglycemia (181 mg/dl, ref. interval: 88–151 mg/dl), hypoproteinemia (4.7 g/dl, ref. interval: 5.1–6.9 g/dl), hypokalemia (3.5 mEq/l, ref. interval: 4.1–6.3 mEq/l), hypocalcemia (7.5 mg/dl, ref. interval: 8.4–10.4 mg/dl), mild hypocholesterolemia (11 mg/dl, ref. interval: 12–68 mg/dl), and mild elevation of blood urea nitrogen (BUN; 35 mg/dl, ref. interval: 13–28 mg/dl). The next day, the animal sustained a spontaneous, severe episode of hemorrhage from the mouth and nostrils accompanied by dyspnea, followed by death.

At necropsy, extensive blood staining was present on the face, ventral neck, and lower limbs, and clotted blood was present in both nasal passages and the mouth. The lungs were heavy and mottled red, most profoundly in the cranioventral lobes. The dorsomedial portion of the right cranial lobe contained an extensive superficial network of tortuous vessels

covering approximately 10 cm \times 10 cm and extending up to 2 cm into the underlying parenchyma (Fig. 1). A large ante-mortem blood clot occluded the associated bronchus. The forestomachs contained approximately 1 liter of blood-tinged fluid. No gastric ulcers were grossly appreciable, although the mucosa of C2 was diffusely reddened and edematous.

Histopathological examination of lung from the site of the vascular abnormality revealed multiple, irregular, anastomosing blood vessels, with diameters ranging from 150 μm to 5 mm, and wall thickness ranging from 10 μm to 800 μm , the latter chiefly due to variation in thickness of the tunica media, the thickest component of the vascular wall in most areas (Figs. 2, 3A). The tunica media of these vessels often contained fibrin, and occasional small foci of mineralization were present within the vascular wall, predominantly within the tunica media, but occasionally within the media or adventitia. Occasional thrombi, both immature and organizing, were present within vessels, sometimes containing large, filamentous bacteria (postmortem invaders). Many alveoli and bronchioles contained blood, and there were multifocal interstitial accumulations of macrophages with brown-pigmented globules (hemosiderophages), lymphocytes at various stages of maturity, megakaryocytes, and occasional nonsegmented

From the College of Veterinary Medicine, Oregon State University, Corvallis, OR.

¹Corresponding Author: Christiane Löhr, Veterinary Diagnostic Laboratory, College of Veterinary Medicine, Oregon State University, 134 Magruder Hall, PO Box 429, Corvallis, OR 97339-0429. christiane.loehr@oregonstate.edu

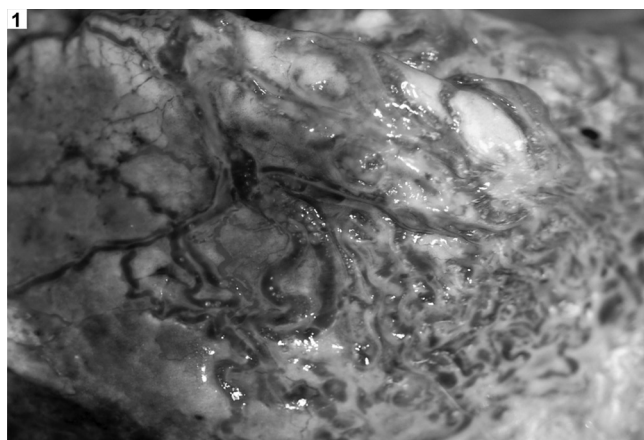


Figure 1. Lung with vascular anomaly; adult alpaca (case 1). View is of the dorsomedial aspect of the right cranial lung lobe, with the cranial direction to the left and the caudal direction to the right. Prominent, tortuous blood vessels form a dense network visible at the pleural surface.

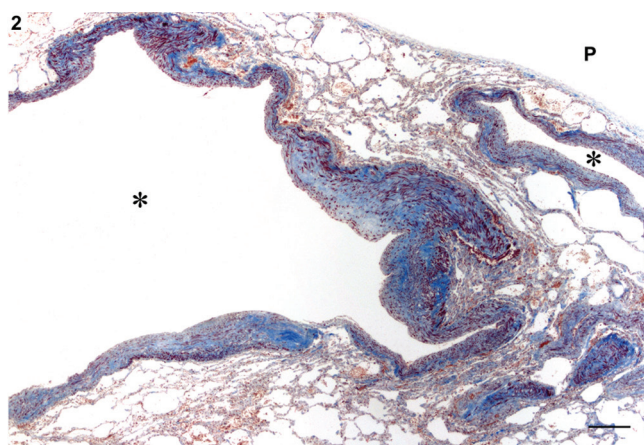


Figure 2. Lung with vascular anomaly; adult alpaca (case 1). Vascular walls contain variable fibrous thickenings and disorganization of smooth muscle. Trichrome stain: muscle stains (dark) red; collagen stains (lighter) blue. Bar = 200 μ m. * = vascular channels; P = pleural surface.

eosinophils (extramedullary hematopoiesis [EMH]) in the lung. Trichrome staining of the abnormal pulmonary vasculature revealed variably disorganized smooth muscle within thicker areas of vessel walls, along with sporadic nodular foci of increased collagen density (Fig. 2). Verhoeff elastin stain demonstrated similarly disorganized elastin deposition within the media of larger vessels within the lesion. Additionally, the thin layer of flattened cells lining the lumens of abnormal vessels showed immunoreactivity for von Willebrand factor (dilution 1:400^a), and the tunica media of the same vessels showed immunoreactivity for smooth muscle actin (dilution 1:30^a). Normal pulmonary vasculature also present within sections served as positive

internal controls for endothelial cells and smooth muscle. A diagnosis of pulmonary vascular anomaly was made. The lesion was considered mostly likely to have developed from a pulmonary arteriovenous malformation, although this could not be confirmed postmortem due to an inability to demonstrate shunting of blood from the venous to the arterial circulatory system.

Lesions identified in other areas and tissues consisted of moderate multifocal alveolar emphysema with bulla formation, testicular atrophy with interstitial cell hyperplasia, moderate eosinophilic–lymphoplasmacytic gastroenteritis, and increased bone marrow hematopoietic activity.

Death in case 1 was due to hypovolemic shock as sequela to rupture of a pulmonary vascular anomaly resulting in extensive hemorrhage into the lung. The hematologic profile, along with hypoproteinemia and hypoalbuminemia, were consistent with the recent blood loss, and hypocalcemia was likely secondary to hypoalbuminemia. The mild elevation of BUN may reflect pre-renal azotemia due to the mild dehydration reported clinically, but may also indicate digestion of swallowed blood. Hyperglycemia could at least partly be attributed to stress, but may also be secondary to anorexia. Although decreased feed intake was not reported, hyperglycemia in conjunction with mild hypocholesterolemia and hypokalemia is suggestive of anorexia in herbivores. The mature neutrophilia was likely due to a combination of stress and inflammation.

In the second case, an unrelated 2-year-old female alpaca was presented at OSUVTH in 2009, 3 days post-partum, with a 24-hr history of anorexia, recumbency, and opisthotonus. Prior to examination, the owner had administered phenylbutazone and ceftiofur (dosages unknown). Clinical examination revealed no additional abnormalities, and blood was drawn for standard hematologic and serum chemistry panels. Additionally, an endometrial swab for cytology and bacterial culture was obtained. The animal was treated with 2 liters of intravenous electrolyte replacer^b and 1,300 mg of thiamine; however, the alpaca's condition deteriorated rapidly, and euthanasia was performed that day. Hematology and serum chemistry revealed a moderate mature neutrophilia (18,242/ μ l, ref. interval: 4,711–14,686/ μ l), markedly elevated creatine kinase (23,000 U/l, ref. interval: 43–750 U/l), elevated aspartate transaminase (1,265 U/l, ref. interval: 127–298 U/l), mild hypernatremia (156 mEq/l, ref. interval: 142–154 mEq/l), mild hypokalemia (3.9 mEq/l, ref. interval: 4.1–6.3 mEq/l), moderate hypermagnesemia (3.67 mg/dl, ref. interval: 1.4–2.2 mg/dl), mild elevation of BUN (31 mg/dl, ref. interval: 13–28 mg/dl), elevated β -hydroxybutyrate (5.05 mg/dl, ref. interval: 0.12–0.75 mg/dl), and elevated non-esterified fatty acids (0.55 mEq/l, ref. interval: <0.24 mEq/l). The endometrial cytology revealed mixed inflammation with the possibility of sepsis, and a very light growth of *Staphylococcus* spp. was isolated.

At necropsy, there was marked pulmonary edema, and the lateral aspect of the right cranial lung lobe contained a network

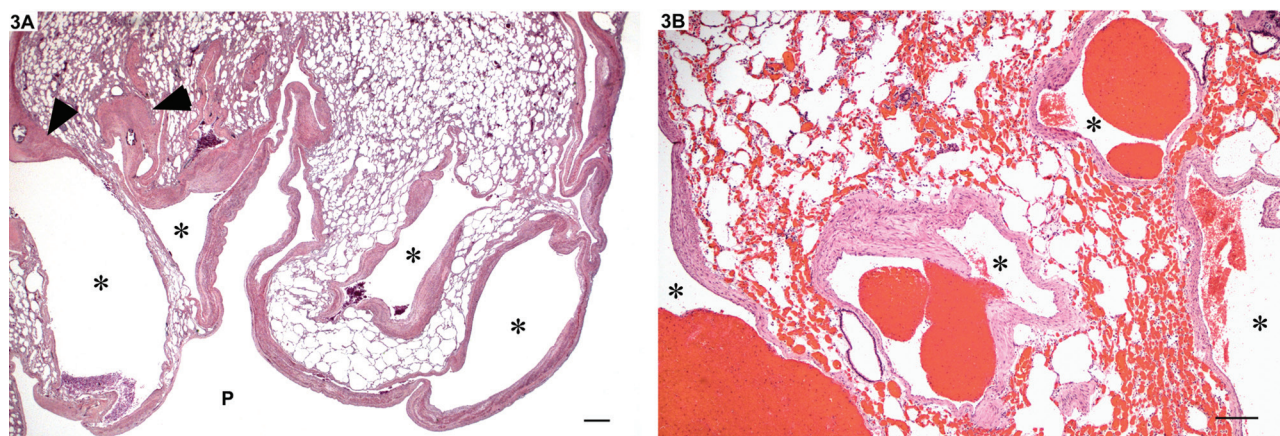


Figure 3. Lung with vascular anomaly; alpacas. Irregular vascular channels (*) vary markedly in thickness. Arrowheads indicate foci of mineralization in case 1; P = pleural surface. Hematoxylin and eosin stain. **A**, case 1, bar = 500 μ m. **B**, case 2, bar = 200 μ m.

of tortuous vessels covering approximately 10 cm \times 5 cm and extending up to 1 cm into the underlying parenchyma. Additional gross lesions included moderately severe segmental enteritis, a single endometrial cyst, and acute focal corneal ulceration.

Histopathological examination of the lung from the site of the vascular abnormality revealed multiple large-diameter (up to 4 mm), irregularly shaped blood vessels (Fig. 3B). The thickness of the vascular walls varied from 10 μ m to 300 μ m, often changing over a very short distance. The main component of the abnormal vascular walls was a disorganized tunica media, variability that contributed most to changes in vessel wall thickness. In thicker areas of larger vessels, trichrome staining revealed variably disorganized smooth muscle, and occasional foci of increased collagen density. Occasional vessels contained small fibrin thrombi, and the adjacent parenchyma contained scattered hemosiderophages and foci of EMH. A diagnosis of pulmonary vascular anomaly was made, and localized arteriovenous malformation was suspected, but as in case 1, shunting of blood from the venous to the arterial circulation could not be proved. Lesions identified in other areas and tissues consisted of severe, acute, diffuse pulmonary congestion and edema, locally extensive eosinophilic enteritis, and very mild, focal granulomatous encephalitis involving the brainstem.

A cause of death could not be identified with certainty in case 2; however, a combination of metabolic disease and possibly intravenous fluid overload inducing pulmonary edema were thought to be the most likely candidates. The pulmonary vascular anomaly was considered to be an incidental finding. The serum chemistry profile is consistent with muscle damage due to recumbency (elevated creatine kinase and aspartate transaminase). Hypokalemia with elevated β -hydroxybutyrate and non-esterified fatty acids is consistent with the history of anorexia and resultant negative energy balance. The hypernatremia and elevated BUN are suggestive of dehydration, although serum creatinine was not significantly elevated.

While dehydration is not supported by the absence of polycythemia and hyperproteinemia, the potential for mild to moderate anemia and hypoproteinemia being masked by dehydration was considered a viable possibility in this case. The hypermagnesemia is an unusual feature that can occur with renal failure in herbivores. While renal disease cannot be completely ruled out, the azotemia was very mild in this case and there were no other lesions to support renal failure.

Spontaneous nonneoplastic pulmonary vascular anomalies are rarely reported in veterinary species, and none has previously been described in camelids. A spontaneous case with similar pathological findings to the case presented herein was described in a dog,⁷ and both pulmonary arteriovenous anastomoses and tortuosity of subpleural bronchial vessels have been induced in sheep following prenatal surgical creation of a superior cavopulmonary anastomosis.⁶ Although vascular shunts could not be confirmed in either case presented herein (e.g., by employing antemortem pulmonary angiography,¹ computerized tomography, or arterial blood gas measurement¹¹), arteriovenous malformations were considered to be the most likely underlying lesions. Additionally, the composition of the abnormal vascular walls (i.e., predominantly tunica media rather than tunica adventitia) supports an arterial rather than a venous or capillary origin of the lesion. While it cannot be determined with certainty in the cases reported herein that the vascular lesions did not consist of heavily modeled veins (e.g., due to chronic venous hypertension unrelated to shunts), there were no identifiable neoplastic, inflammatory, or degenerative lesions that could explain the localized vascular changes.

Pulmonary arteriovenous malformations (PAVMs) are well described in human beings. The lesions have numerous synonyms, including pulmonary arteriovenous fistula, pulmonary arteriovenous aneurysm, pulmonary angioma, arteriovenous angiomas, cavernous hemangioma, and pulmonary hamartoma. Pulmonary arteriovenous malformations are usually congenital and sometimes linked with hereditary hemorrhagic

telangiectasia,^{2,8,11} which is associated with mutations in several genes, including *endoglin*,⁵ *ACRVLI/ALK1*,³ and *SMAD4*.¹ In some cases, a bulbous aneurysm of the affected vessels occurs. In other cases, as in the ones described herein, the site of anastomosis is not grossly apparent. Affected human beings may live years before an episode of hemorrhage or other complication (e.g., thromboembolism or bacteria bypassing the normal pulmonary capillary bed and lodging in other organs) announces the presence of the lesion.^{4,10} The pathogenesis of PAVMs is not well understood, and current hypotheses include both intrinsic vascular defects and progressive remodeling of vessels in response to blood flow dynamics.² Microscopically, PAVMs consist of endothelium-lined vascular channels whose walls are variably thickened by fibrous tissue and elastin, and can occasionally contain mural thrombi and calcifications.⁹ The aforementioned vascular changes are consistent with those identified in the 2 current cases, supporting the diagnosis of vascular anomaly due to PAVM.

While the signalment and presenting complaints in each of the 2 cases were utterly different, the gross and histologic appearance of the vascular lesions within the lungs was strikingly similar. The presence of pulmonary EMH may be due to chronic hematopoietic stimulation secondary to recurrent hemorrhage. The variable nodular, collagenous protrusions into the lumens of abnormal vessels are likely the result of chronic thrombosis followed by recanalization and vascular remodeling. It is interesting to speculate that, given enough time, the smaller lesion in the younger alpaca may have developed to the point of causing spontaneous hemorrhage to match that in the older animal.

Sources and manufacturers

- a. Catalog no. A0082, catalog no. M0851; Dako North America Inc., Carpinteria, CA.
- b. Normosol®-R, Hospira Inc., Lake Forest, IL.

Declaration of conflicting interests

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