



## Diagnostic Exercise

From the Latin Comparative Pathology Group and the Davis-Thompson Foundation

# Ovine enzootic calcinosis by ingestion of *Nierembergia veitchii*

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### Clinical History:

A chronic wasting disease occurred in sheep from a flock in southern Brazil (29° 32' 16" S 53° 51' 18" O) from October 2003 to January 2004. Of a total population at risk of 460 sheep, 43 were affected, 29 died spontaneously, and 10 were euthanized. Clinical signs included weight loss, cachexia, rigid walking, retracted abdomen, and kyphosis. In some cases, terminal pulmonary edema led to oozing of abundant white foam from the nasal and oral cavities. *Nierembergia veitchii* (Fig. 1) was present in the pastures where the affected sheep were held.

### Autopsy Findings:

Twelve sheep were autopsied. Gross lesions included poor nutritional status with depletion of fat deposits and serous atrophy of the coronary and perirenal fat. There was widespread mineralization of various soft tissues, particularly blood vessels and heart (Figs. 2-4). Affected arteries and cardiac valvar and mural endocardium were rigid and had an irregular intimal surface with coalescing, hard, white plaques throughout. Similar areas of mineralization consisting of white chalky streaks were also found in the serosa of abdominal organs such as the omasum, reticulum, rumen, and uterus. Seven sheep had widespread, white, hard coalescing areas of mineralization in the lungs, which did not collapse after death (Fig. 5). Six sheep had acute pulmonary edema.

### Microscopic description:

Histologically, systemic mineralization of soft tissues characterized by fine basophilic deposits occurred in several organs. In arteries, mineralization was observed mainly in the tunica media, and there was often intimal proliferation (Fig. 6) and occasional chondroid or osseous metaplasia of the media. In seven sheep, mineralization involved the vessels of the carotid *rete mirabile*. In the myocardium and lung, foci of mineralization and osseous metaplasia occurred in cardiomyocytes and alveolar septa, respectively.

### Follow-up Questions

- *Morphologic diagnosis:*
- *Cause:*
- *Name of the condition:*
- *Differentials:*

*\*The Diagnostic Exercises are an initiative of the Latin Comparative Pathology Group (LCPG), the Latin American subdivision of The Davis-Thompson Foundation and published in cooperation with the Brazilian Journal of Veterinary Pathology. These exercises are contributed by members and non-members from any country of residence.*

*Consider submitting an exercise! A final document containing this material with answers and a brief discussion will be posted on the DTF website:*

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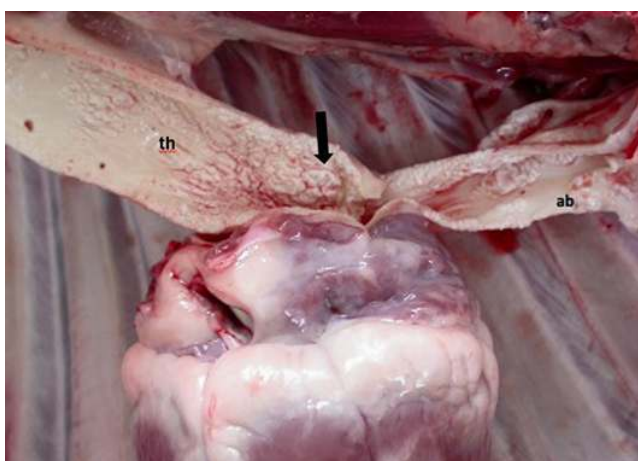
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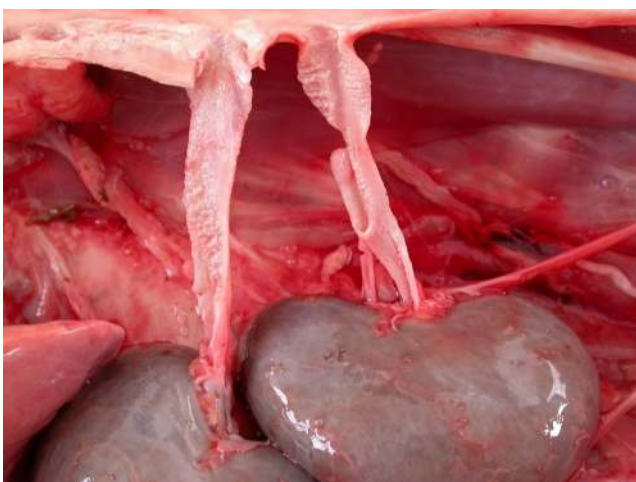
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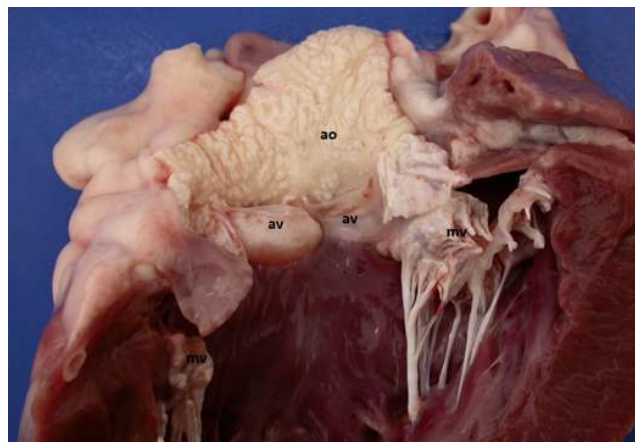
**Figure 1.** A flowering specimen of *Nierembergia veitchii* in October in southern Brazil.



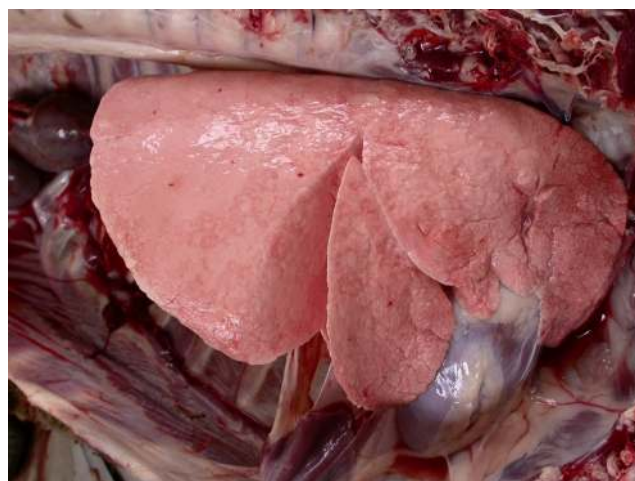
**Figure 2.** Affected sheep, thoracic (th) and abdominal (ab) and aorta. The rigid intimal surface is corrugated by coalescing, hard, white plaques (arrow).



**Figure 3.** Affected sheep renal arteries. The rigid intimal surface is corrugated by coalescing, hard, white plaques.



**Figure 4.** Affected sheep left atrium and aorta. There is mineralization of the intimal surface of the aorta (ao), aortic (av) and atrioventricular (mitral[mv]) valves. The mineralization and rigidity of the valves compromise their proper function, which likely led to the pulmonary edema and sudden death observed in some cases.



**Figure 5.** Affected sheep, lung. The lungs did not collapse and had widespread, white, hard coalescing areas of mineralization throughout the parenchyma.

## ANSWERS

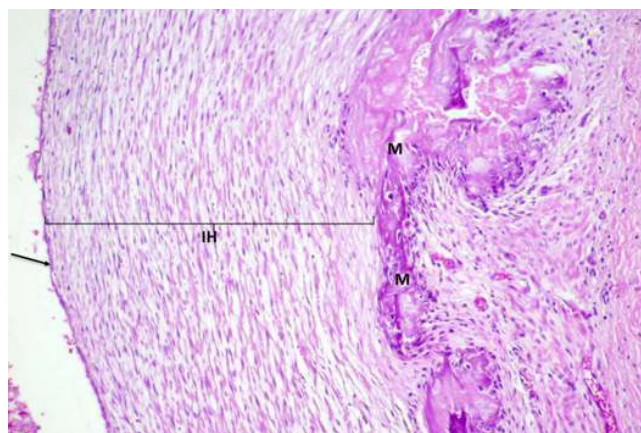
- *Morphologic diagnosis:* Systemic mineralization of soft tissues
- *Cause:* Ingestion of *N. veitchii*, a plant containing vitamin-like substance(s)
- *Name of the condition:* Enzootic calcinosis
- *Differentials:* Other calcinogenic plants containing the same toxic principle (see Table 1), iatrogenic poisoning by vitamin D, wasting diseases (e.g., paratuberculosis, gastrointestinal parasites)

## Discussion:

Enzootic calcinosis (EC) is a chronic condition characterized by abnormal calcium deposition in soft tissues, often induced by the ingestion of calcinogenic poisonous plants (Table 1) that contain high levels of 1,25(OH)<sub>2</sub>D<sub>3</sub> (calcitriol) or substances with similar biological action. EC is characterized by soft tissue mineralization, hypercalcemia, hyperphosphatemia, hypercalcitoninemia, hypoparathyroidism, osteonecrosis, and osteopetrosis (1,3, 6).

The primary species affected by EC are ruminants, particularly cattle and sheep. These animals are more likely to ingest these plants due to their grazing habits and dietary requirements, making them especially vulnerable to the toxins (4).

EC in sheep was recognized in southern Brazil in late 1960s (1) and was later attributed to the ingestion of *N. veitchii* (6). The disease affects sheep that classically develop



**Figure 6.** Affected sheep, renal artery. There is intimal hyperplasia (IH) and extensive areas of mineralization (M) of the tunica media. The contractile vascular smooth muscle cells differentiate and migrate from the tunica media to the intima through fenestrations in the internal elastic lamina, and proliferate, resulting in the IH.

a chronic disorder characterized by weight loss, stiff gait, tucked abdomen, dyspnea, kyphosis, and recumbency (1,6). Sheep ingest *N. veitchii* during the flowering period (September and October) and clinical cases are usually detected through February (1,6). Chronic cases are eventually fatal and can terminate with sudden death associated with acute pulmonary edema due to cardiac valvar compromise due to mineralization (7).

The pathogenesis of lesions induced by calcinogenic plants is complex and was recently reviewed (4). Briefly, the toxins in these plants are derived from glycosides of 1,25 (OH)<sub>2</sub>D<sub>3</sub> (calcitriol). Hydrolytic enzymes in intestinal or ruminal flora split the sugar from the glycoside, releasing the steroidal fragment, usually 1,25 (OH)<sub>2</sub>D<sub>3</sub>. This compound is absorbed directly into the intestines, causing degeneration and calcification of elastic fibers, hypercalcemia, and hyperphosphatemia. Endogenous 1,25 (OH)<sub>2</sub>D<sub>3</sub> formation is inhibited due to hypoparathyroidism, hypercalcemia, and hyperphosphatemia. The hypercalcitoninemia, hypercalcemia, and hyperphosphatemia result in osteopetrosis. Additionally, the excessive minerals are deposited in the form of hydroxyapatite oxalates in blood vessels, muscles, hyaline and articular cartilage, and other soft tissues (3). The chemical structure of the toxin in *N. veitchii* is unknown, but it has similar biologic actions as calcitriol (6).

Clinical signs are characterized by progressive weight loss, stiff gait and lameness, tucked-up abdomen, and kyphosis. Animals tend to remain recumbent due to joint pain. If they are flicked, they might fall and show evidence of cardiac and respiratory failure. The clinical course is chronic, and death may occur within 2-4 months from extreme malnutrition and cachexia. If sheep are removed from the pasture during the early stages of clinical disease, recovery may occur (5). Some signs may remain in affected animals, and in the following year, they can worsen when new cases of intoxication appear.

Gross findings include thick, hard, and inelastic arterial walls, except for the pulmonary artery, which is typically

**Table 1.** Main calcinogenic plants affecting livestock

Plant	Family	Distribution	Toxic principle	Species affected
<i>Trisetum flavescens</i>	Poaceae	Austria, Germany, and Switzerland	1,25(OH) <sub>2</sub> D <sub>3</sub>	Cattle and goats
<i>Stenotaphrum secundatum</i>	Poaceae	Jamaica	1,25(OH) <sub>2</sub> D <sub>3</sub>	Cattle, sheep, and goats
<i>Cestrum diurnum</i>	Solanaceae	Cuba and Florida, USA	1,25(OH) <sub>2</sub> D <sub>3</sub>	Horses and cattle
<i>Nierembergia rivularis</i>	Solanaceae	Uruguay	Vitamin D-like	Sheep
<i>Nierembergia veitchii</i>	Solanaceae	Brazil	Vitamin D-like	Sheep, rarely cattle
<i>Solanum glaucophyllum</i>	Solanaceae	Argentina, Uruguay, Brazil	1,25(OH) <sub>2</sub> D <sub>3</sub>	Mainly cattle. Rarely sheep and horses
<i>Solanum stuckertii</i>	Solanaceae	Argentinian Andes	Not yet determined	Goats
<i>Solanum torvum</i>	Solanaceae	Papua New Guinea	Vitamin D-like	Cattle

The distribution indicated here refers to countries where enzootic calcinosis (EC) was diagnosed, not countries where the plant occurs without the documentation of EC.

not affected. The intima of the arteries appears wrinkled and covered with mineral deposits. In addition, there is mineralization of the mitral and aortic valves and occasionally the endocardium of the left ventricle. There is also mineralization in the lungs, especially on the borders of the diaphragmatic lobes, kidneys, and uterus. Occasionally, centrilobular chronic hepatic congestion with ascites and hydrothorax may occur (5-7).

Histologically, there is edema and fragmentation of elastic fibers in arteries of several organs, with granular deposits and mineral plaque. In the lungs, besides calcification of the arteries, alveolar septa, and interlobular interstitium, there may be alveolar edema, and mineralization of the bronchial and tracheal cartilage. There is also mineralization of tendons and ligaments. Bone lesions include osteopetrosis and osteonecrosis. There is also hyperplasia of the parafollicular cells of the thyroid gland and atrophy of the parathyroid gland (5-7).

The diagnosis is based on the presence of the plant in the pasture associated with the clinical signs and pathologic evidence of widespread soft tissue mineralization. Systemic mineralization, especially in the cardiovascular and respiratory systems, is typical of EC in sheep in southern Brazil. The association of clinical signs and pathology with weed detection in pastures strengthens the diagnosis (4). Differential diagnosis must include wasting diseases such as paratuberculosis and gastrointestinal parasites (4) and iatrogenic vitamin D intoxication (2).

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