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Idiopathic endocardial fibroelastosis in a foal with biventricular heart failure

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Summary: A six-month-old foal was initially presented with recurrent, progressive respiratory symptoms over a period of three months. During fixation for medical treatment of a suspected bacterial infection of the respiratory tract, the horse developed acute circulatory failure and was referred to an equine clinic. Cardiac auscultation revealed holosystolic murmur centered around the mitral valve, whilst thoracic auscultation and radiography revealed pulmonary edema and a highly enlarged cardiac silhouette. The foal collapsed during echocardiographic examination and was humanely euthanized. At necropsy, the heart was enlarged with severe dilation of all four chambers and the endocardium was markedly thickened and diffusely opacified. Histopathologically, the endocardium was also severely thickened to up to 601 μm by a significantly increased amount of collagen fibers and discontinuous and irregularly arranged elastic fibers, consistent with severe endocardial fibroelastosis (EFE). In contrast, five control horses with a median age of six months lacking cardiac alterations had a mean left ventricular endocardial thickness of 29.8 $\pm$17.3 μm with few, regularly arranged collagen and elastic fibers. Further pathological findings included pulmonary edema and fibrosis, detection of hemosiderin-laden macrophages in the alveoli, vascular and perivascular fibrosis, as well as ascites and were consistent with biventricular heart failure. Idiopathic EFE has very rarely been described in young horses and other animals and its intravital diagnosis is very difficult. However, EFE should be considered as a differential diagnosis in foals with acute or chronic congestive heart failure. As in the present case, therapeutic approaches have to date always been unrewarding in animals and therefore, prognosis is generally considered poor.

Keywords: Congestive heart failure, congenital heart defect, horse

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Introduction

The normal endocardium in horses macroscopically appears as a translucent and shiny, thin layer, histopathologically consisting of few collagen fibers and continuous, regularly arranged elastic fibers. Pathological thickening and opacification due to excessive, endocardial deposition of both collagen fibers and discontinuous and irregularly arranged elastic fibers is consistent with endocardial fibroelastosis (EFE) (*Belgrave* et al. 2002, *Cushing* 2013, *Hughes* et al. 1984). Traditionally, two forms of EFE have been recognized: 1) Primary or congenital EFE in the absence of other obvious cardiac malformations and 2) secondary EFE as a sequela of a preceding cardiovascular disorder (*Belgrave* et al. 2002, *Cushing* 2013). However, current literature contradicts the formation of EFE being congenital, i.e. primary, and argues that all cases of EFE are secondary to cardiac stress and therefore should not be considered a discrete disease (*Lurie* 2010). Hence, the term "idiopathic EFE" rather than "primary EFE" is proposed, if no underlying cause can be identified.

EFE has been reported as a rare cardiac disorder in several mammalian species including cattle (*Gopal* et al. 1986, *Scarratt* et al. 1987), sheep (*Dennis* et al. 1968), cats (*Tidholm* et al. 2015, *Eliot Jr* et al. 1958, *Rozengurt* 1994, *Zook* et al. 1981), dogs (*Tidholm* 1997, *Bentley* 1999), and tigers (*Rodriguez* et al. 2017), as well as in humans (*Lurie* 2010). In horses, EFE has so far been only reported in three case reports and as a single mention in a systematic study concerning sudden death in race horses (*Belgrave* et al. 2002, *Cushing* 2013, *Hughes* et al. 1984, *Lyle* et al. 2011). These four equine cases involved young horses between four months and four years of age in which further cardiac disorders were absent, suggesting idiopathic EFE. Further knowledge of EFE in horses is warranted, to which this current case report contributes to. Clinical and post-mortem examination findings in a six-month-old colt foal with EFE associated with biventricular heart failure are described.

Case report

A six-month-old colt foal displayed recurrent, progressive respiratory symptoms including tachypnoea, nasal stridor with discharge, crackles in the cranial lung, as well as exercise intolerance over a period of three months. Microbiological examination of a nasal swab revealed the presence of Streptococcus zooepidemicus. Although the rectal temperature had always been within reference limits, a bacterial infection of the upper respiratory tract and lung was suspected and the foal was treated with bromhexine (Equilysin®[1]; 0.3 mg/kg bwt, PO, q12h) and antibiotics, initially consisting of trimethoprim/sulfadiazine (Synutrim® 72%[2]; 30 mg/kg bwt, PO, q12h). However, the clinical symptoms of the foal were recur-

rent. Treatment with antibiotics per os led to diarrhea, thus, the antimicrobial treatment was changed to procain benzylpenicillin (Procain Penicillin G®[3]; 15 mg/kg bwt, IM, q24h). Within a few minutes after fixation and penicillin administration, the foal developed hyperexcitability, moderate tachycardia, tachypnoea, and mild hyperthermia. Since anaphylactic shock was suspected, therapy with dexamethason[4] (0.06 mg/kg bwt, IV) and intravenous fluids (NaCl 0.9%®[5]) was immediately initiated, and the foal was referred to the equine clinic.

At admission, clinical signs included tachycardia (84 bpm), tachypnoea (36 breaths per minute), and normothermia. Cardiac auscultation revealed holosystolic murmur (grade III/VI) with points of maximum intensity centered around the mitral valve. Pulmonary auscultation and radiographs (Fig. 1) were suggestive of pulmonary edema. Additionally, thoracic radiographs revealed an enlarged cardiac silhouette (cardiomegaly) with dorsal displacement of the trachea. Endoscopic examination of the upper respiratory tract was unremarkable. Two-dimensional echocardiography suggested dilation of all four chambers and thickening of the left atrioventricular valve (AVV). The foal collapsed during examination and it was impossible to visualize atrioventricular regurgitation by color flow Doppler imaging. The foal was humanely euthanized due to poor prognosis and submitted to necropsy.

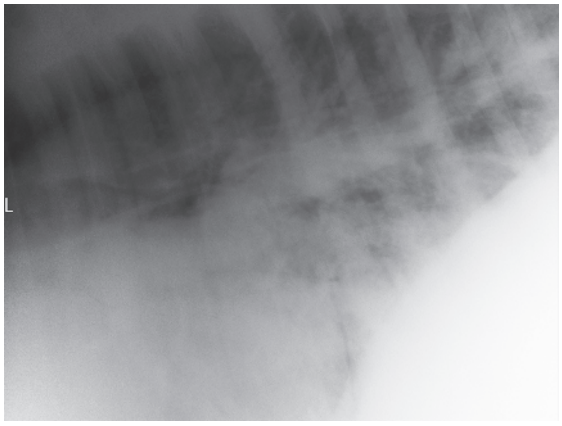

Fig. 1 Lateral radiographic projection of the caudoventral lung field of the six-month-old foal. An alveolar-interstitial lung pattern, enlarged cardiac silhouette, and dorsal deviation of the trachea were evident, suggestive of pulmonary edema and cardiomegaly.

At post-mortem examination, all four chambers of the heart were moderately to severely dilated (Fig. 2A) with a relative wall thickness proportion of 1:1.8:1.7 (right ventricle wall to septum to left ventricle wall, reference value 1:3:3) and a relative heart weight (heart weight relative to body weight) of

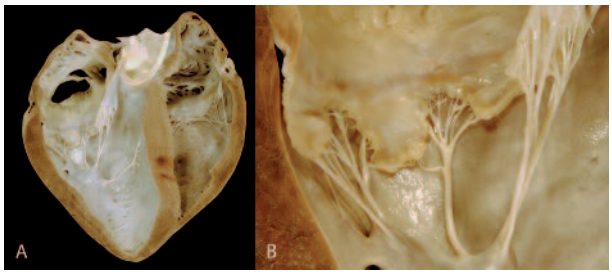

Fig. 2 Macroscopic images of the foal's heart affected by endocardial fibroelastosis. All four chambers of the heart were moderately to severely dilated and the endocardium was thickened and opacified (A). The left AVV was comprised of three shortened and peripherally thickened cusps (B).

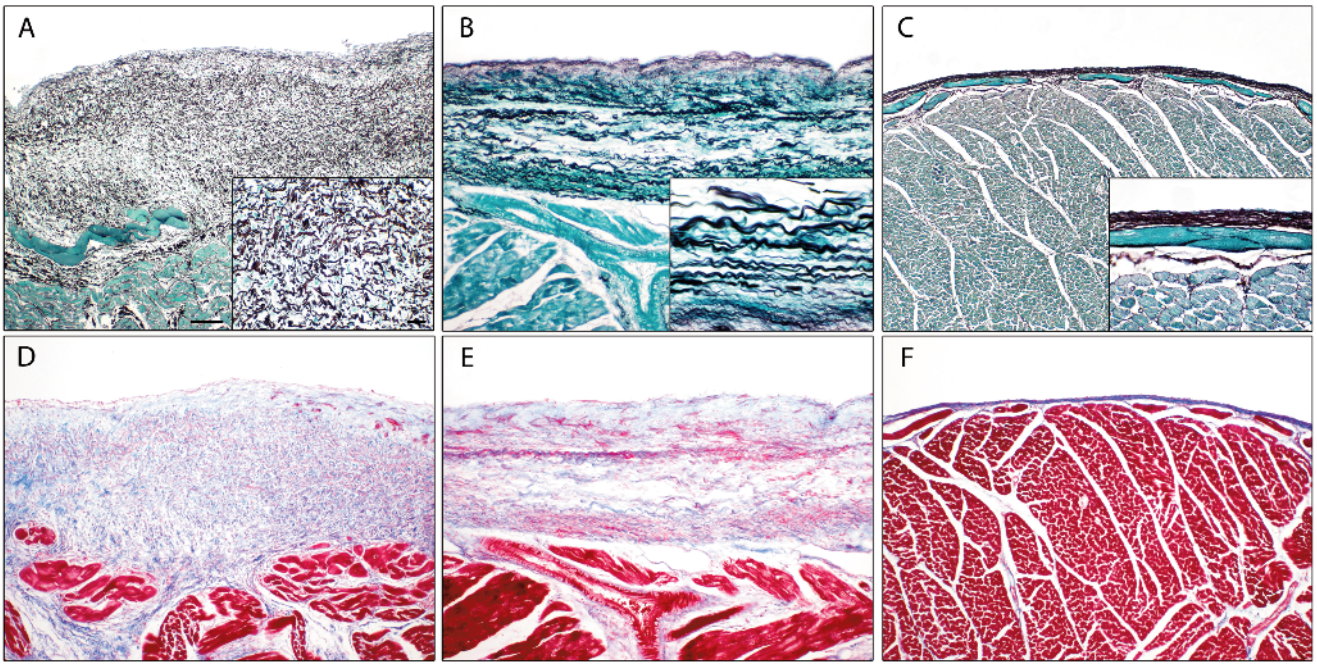

Fig. 3 Histopathology of endocardial fibroelastosis in the presented foal (A, D), endocardial fibrosis, as the most important histopathological differential diagnosis for a grossly thickened and opaque endocardium, in an eight-year old mare (B, E), and unaltered endocardium of a control horse (C, F). The endocardium of the foal was severely thickened to up to 601 μm by discontinuous and irregularly arranged, elastic fibers (A and inset) and mainly loosely packed collagen fibers (D). Findings were consistent with endocardial fibroelastosis. Contrarily, the endocardium of the mare displayed scattered but continuous and regularly arranged elastic fibers (B and inset) and was moderately thickened by collagen fibers (E), consistent with endocardial fibrosis. The control horse had a thin endocardium with sparse amounts of continuous, parallel, and slightly woven elastic fibers (C and inset) as well as a thin layer of collagen fibers (F). (A – C) Grocott silver staining (elastic fibers in black). Bar = 100 μm; insets: bar = 20 μm. (D - F) Azan staining (collagen fibers in blue). Bar = 100 μm.

1.12% (reference range 0.6–1.0%). The left and, to a lesser degree, the right cardiac ventricle and atrium, as well as the left AVV had pronounced, whitish, superficial opacification and thickening of the endocardium (Fig. 2A and 2B). The left AVV consisted of three major cusps, which were severely shortened, contracted, and peripherally thickened (Fig. 2B). Histopathological thickness measurements of the left and right ventricular endocardium ranged from 293.3 to 601.0 μm (mean: 400.0 ± 107.0 μm) and 96.8 to 155.1 μm (mean: 120.7 ± 20.9 μm), respectively. Ventricular and valvular endocardium had moderate to severe deposition of loosely pakked, irregularly oriented, and discontinuous elastic fibers as detected by Grocott silver staining (Fig. 3A and inset). Additionally, Azan staining revealed an increased amount of loosely arranged collagen fibers within the affected endocardium (Fig. 3D). Deposition of elastic and collagen fibers partially also involved the subendocardial tissue with degeneration of adjacent myocytes and Purkinje fibers. A severe, diffuse endocardial fibroelastosis (EFE) with involvement of the left AVV and subsequent biventricular dilation was diagnosed.

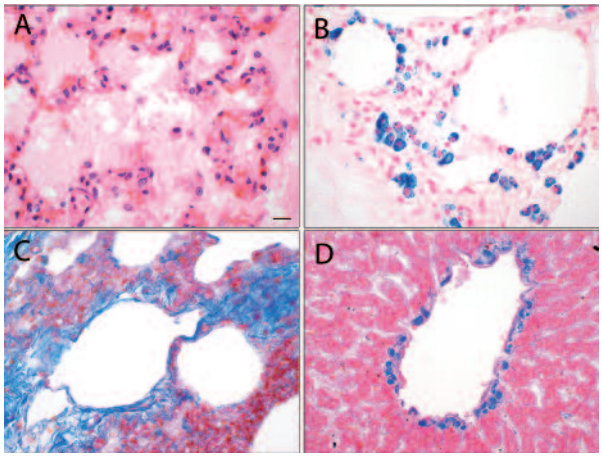

Fig. 4 Histopathology of endocardial fibroelastosis, consistent with chronic biventricular heart failure. (A) The alveoli of the lungs were filled withhomogeneous, pale pink material, consistent with severe, diffuse, alveolar edema. HE staining; bar = 20 μm. (B) Several hemosiderin-laden macrophages (so called heart failure cells) were detected in the alveoli by Turnbull's blue staining (hemosiderin in blue). Bar = 20 μm. (C) Additionally, severe, multifocal, interstitial fibrosis of the lung and (D) moderate, multifocal fibrosis of central hepatic veins were detected by Azan staining (collagen fibers in pale blue). Bar = 20 μm.

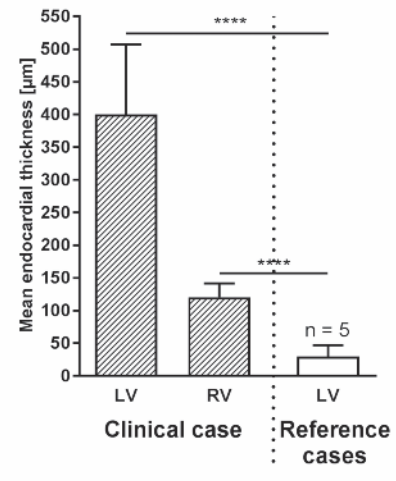

Fig. 5 Endocardial thickness in μm measured by histopathology in the presented case of a six-month-old foal versus five reference cases of a median age of six months (range: four to twelve months) devoid of cardiac disorders. Error bars indicate the standard deviation. An unpaired t-test revealed significant (****$p < 0.001$) differences between the endocardium of the foal's left ventricle (LV) or right ventricle (RV) and of the LV of the reference cases.

The foals lung was poorly retracted and of firm consistency due to severe, chronic, diffuse, alveolar edema, accompanied by moderate, diffuse congestion (Fig 4A). Histologically, moderate, multifocal, interstitial fibrosis was confirmed by Azan staining (Fig. 4C). Turnbull's blue staining was used to detect ferrous iron(III)s and revealed moderate to severe, multifocally distributed amounts of hemosiderin-laden macrophages (Fig. 4B). Additionally, approximately 500 ml of a clear, serous fluid were present in the abdominal cavity and liver and spleen had moderate, congestive hyperemia. In nearly all organs examined, histopathology including Azan staining revealed severe vascular and perivascular fibrosis within the tunica media and in proximity of blood vessels. Furthermore, the liver had mild, acute, multifocal hemorrhage, whilst the central veins displayed moderate, multifocal perivascular fibrosis (Fig. 4D). These findings are consistent with biventricular heart failure resulting from EFE and consecutive valvular insufficiency.

Reference cases

Reference tissues were obtained from five horses that had been autopsied in routine pathological diagnostics. Only tissues devoid of macroscopical and histopathological evidence of cardiac disease were included. The age of the horses ranged from four to twelve months (median: six months). In all reference cases, the endocardium macroscopically appeared as a thin, translucent layer. Microscopically, the endocardium displayed only sparse quantities of collagen fibers (Fig. 3F), continuous, regularly arranged and slightly undulated elastic fibers (Fig. 3C), and an average left ventricular thickness of 29.8 ± 17.3 μm. The endocardium of the left and right ventricle of the present case was significantly ($p > 0.001$; unpaired t-test) thicker compared to the left ventricular endocardium of five reference cases (Fig. 5). In general, the endocardium is thicker in the left heart side compared to the right heart side in healthy animals. Therefore, it is not ideal but acceptable to compare endocardial thickness of the left heart side of reference cases with a thickened right ventricular endocardium.

Discussion

The aetiology of EFE is still poorly understood in animals. Although current literature hypothesizes that all cases of EFE are secondary to cardiac stress (*Lurie* 2010), an underlying cardiac disorder resulting in secondary EFE has not been described in animals to date. Consistently, all four previously reported (*Belgrave* et al. 2002, *Cushing* 2013, *Hughes* et al. 1984), as well as the present case were devoid of an underlying cardiac disorder, consistent with idiopathic EFE. In some feline breeds, i.e. Burmese and Siamese, and in an inbred colony of specific-pathogen-free domestic cats, an inheritance was proposed (*Eliot Jr* et al. 1958, *Rozengurt* 1994, *Zook*

et al. 1981). A case report of two tigers from one litter affected by EFE suspected either an inheritance or a maternal combination vaccination with modified live canine distemper and parvovirus to be causative of EFE. Other reports hypothesized an impaired cardiac lymph flow as underlying cause of idiopathic EFE in cats and dogs (*Miller* et al. 1963, *Zook* et al. 1981). In humans, numerous cardiac disorders such as congenital malformations, cardiomyopathies, infectious myocarditis, and lysosomal storage disease have been found to be associated with secondary EFE but the exact underlying mechanism remains speculative to date (*Lurie* 2010).

Most animals reported in current literature have typically become clinically apparent a few months after birth, as in the present case of the foal, and either died spontaneously during exercise (*Hughes* et al. 1984, *Lyle* et al. 2011) or following clinically apparent acute or chronic congestive heart failure (*Belgrave* et al. 2002, *Hughes* et al. 1984, *Cushing* 2013). Affected are either only one – in most cases the left – heart side (*Belgrave* et al. 2002, *Bentley* 1999, *Hughes* et al. 1984, *Rozengurt* 1994, *Tidholm* 1997, *Dennis* et al. 1968, *Scarratt* et al. 1987) or both heart sides with differing severity (*Hughes* et al. 1984, *Cushing* 2013) and may also include the AVV, as seen in this case. Accordingly, symptoms and clinical findings represent those of congestive left-sided, right-sided, or biventricular heart failure. The foal presented here was initially considered suffering from a bacterial infection of the upper respiratory tract and lung. However, during post-mortem examination, inflammation of the respiratory tract was not evident. The pathological finding of a chronic, pulmonary edema supports the notion that the respiratory symptoms were caused by EFE. After treatment with procaine benzylpenicillin, anaphylactic shock was suspected. Nonetheless, considering the diagnosis of EFE, cardiogenic shock resulting from extensive stress due to handling and drug administration is considered more likely. Similarly, Hughes and Howard (*Hughes* et al. 1984) reported hyperexcitability after treatment with procaine penicillin in a case of left ventricular EFE in a horse. Also, *Bentley* (1999) described sudden, stress-related cardiovascular failure post-vaccination in a dog with EFE.

Besides EFE, differential diagnosis of foals with clinical findings specific for heart failure should include congenital heart defects, despite their prevalence generally being considered low in horses, i.e. accounting for only 3.5 % of all lethal congenital abnormalities in fetuses or newborn foals (*Crowe* et al. 1985). Most common congenital heart defects include the ventricular septum, valvular defects, and tetralogy of Fallot (*Hall* et al. 2010, *Crowe* et al. 1985). In contrast to these, intravital diagnosis of EFE is almost impossible in animals, as clinical tests including sonography do not reliably reveal subtle endocardial changes (*Belgrave* et al. 2002, *Coumbe* 2002). A definitive diagnosis of EFE should always be based on histopathology of the endocardium. Intravital, left-ventricular endomyocardial biopsies are performed in human medicine but are rarely justified in equine medicine. Therefore, a thorough post-mortem examination including detailed histopathological examination is essential for the diagnosis of left ventricular EFE (*Coumbe* 2002). A right-ventricular endomyocardial biopsy technique has been recently described for horses (*Decloedt* et al. 2016) and may have the potential for intravital diagnosis of right ventricular EFE. However, as discussed above, the involvement of the right heart side has only been infrequently reported in animals. Histopathologically, endocardial thickening due to increased amounts of discontinuous and irregularly arranged elastic fibers in combination with increased amounts of collagen fibers is conclusive for EFE. However, current literature is lacking reference values for normal endocardial thickness in foals. *Belgrave* et al. (2002) measured an endocardial thickness of 50 μm in the apparently unaffected right heart side of a horse affected by left-sided EFE. However, as discussed above, both heart sides are often affected, rendering an endocardial thickness comparison within the animal itself not ideal. A single additional control horse of unknown age in a study by *Cushing* (2013) yielded a left-ventricular, endocardial thickness of 80–100 μm, whilst the five present control horses with a median age of six months yielded solely 29.8 ± 17.3 μm. Histopathologically, EFE needs to be differentiated from subendocardial fibrosis, which is defined as focal to diffuse, excessive deposition of subendocardial collagen fibers. In contrast to EFE, however, the elastic fibers here remain unaltered, i.e. continuous and regularly arranged.

All previous therapeutic approaches to EFE in foals (*Davis* et al. 2002, *Jesty* et al. 2006) and other animal species have so far been unrewarding. The foals either died spontaneously (*Lyle* et al. 2011, *Hughes* et al. 1984) or were humanely euthanized due to the severity and progressive nature of the disease (*Cushing* 2013, *Belgrave* et al. 2002). Also in the present case, the foal was humanely euthanized due to repeated, acute circulatory collapse before a specific treatment for cardiac failure could be initiated. In general, congestive heart failure in horses has a grave prognosis (*Davis* et al. 2002). In contrast to veterinary medicine, prenatally diagnosed EFE has been successfully treated by dexamethasone in human medicine (*Raboisson* et al. 2005, *Pises* et al. 2009)

In conclusion, EFE is a rare cardiac disorder affecting young horses. The six-month-old foal presented here developed progressive respiratory symptoms, likely caused by chronic pulmonary edema, which were initially considered to be due to bacterial infection. Subsequently, the foal developed acute onset of biventricular heart failure, which was initially interpreted as anaphylactic shock. A pathological examination of the heart revealed severe, idiopathic EFE of the left and right ventricular and left AVV endocardium, resulting in congestive, biventricular heart failure, including chronic pulmonary edema. Considering the diagnosis of EFE, the respiratory symptoms and the acute circulatory failure are assumed to be associated with cardiac insufficiency.

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Conflict of interest statement

The authors state no conflict of interest.

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