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Case Report

Aortocavitary fistula secondary to vegetative endocarditis in a rabbit

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Received 7 May 2018; received in revised form 20 August 2018; accepted 21 August 2018

KEYWORDS

Haemophilus parainfluenzae;
Periaortic infection;
Heart failure;
Atrial fibrillation;
Left-to-right intracardiac shunt

Abstract A 4-year-old intact male mini lop rabbit (*Oryctolagus cuniculus*) was presented with a 2-week history of severe progressive lethargy. A right parasternal continuous heart murmur and an irregular rhythm were detected on physical examination. Echocardiography identified vegetative aortic and tricuspid valve (TV) endocarditis. There was an aortocavitary fistula between the right sinus of Valsalva into the right ventricle, creating a left-to-right intracardiac shunt. Based on the echocardiographic findings, it was suspected that the infection originated in the aortic valve, eroded through the periannular tissue, and secondarily infected the TV. Pleural and peritoneal effusion secondary to right-sided congestive heart failure was also found during the echocardiogram. Atrial fibrillation, conducted with a left bundle branch block morphology, was identified using electrocardiography. Necropsy findings directly correlated with the echocardiographic diagnosis; marked periodontal disease was also identified. Aerobic culture of the aortic and tricuspid vegetations resulted in significant growth of *Haemophilus parainfluenzae*. *Haemophilus* spp. belong to a group of similar gram-negative coccobacillus bacteria (HACEK group), which can act as an uncommon cause of endocarditis in humans. HACEK endocarditis is most commonly associated with oral infection and/or dental

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procedures in people. This is the first case report of a rabbit with periannular complications of infective endocarditis. It remains unknown whether dental disease resulted in endocarditis in this patient.

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Abbreviations

ACF	aortocavitary fistulae
AV	aortic valve
IE	infective endocarditis
RV	right ventricle
TV	tricuspid valve

A 4-year-old male intact mini lop rabbit was presented to the University of Wisconsin-Madison, Veterinary Medical Teaching Hospital with a 2-week history of progressive lethargy. The animal did not have a history of cardiovascular disease, and dental abnormalities were suspected, based on a history of refusing to eat hay. On physical examination, the rabbit was lethargic and moderately dehydrated with pale mucous membranes. The animal had a thin body condition, weighing 1.9 kg, and his coat was unkempt. This was a noticeable change from the last evaluation 3 months prior when he weighed 2.4 kg, and he had an appropriate body condition. The rabbit was initially tachycardic on auscultation (360 beats per minute, reference 130–325 beats per minute) [1], tachypneic (100 breaths per minute, reference 32–60 breaths per minute [1], and his temperature was normal (102.9 F, reference 100.5–104 F) [1]. The heart rate slowed and was within normal limits at 260 beats per minute with further handling and sedation. The rabbit had a new grade IV/VI right parasternal continuous heart murmur, and his heart rhythm was irregular. His incisors were symmetric in length and occlusion, but there was a palpable asymmetry of the mandible, consistent with cheek tooth root abnormality. A packed cell volume was obtained, demonstrating moderate to severe anemia (21%, reference interval 35–55) [2]. A plasma biochemistry panel demonstrated mild hypoproteinemia (5.1 g/dL, reference interval 5.3–8.5 g/dL), moderately elevated liver enzymes (ALP 283 U/L, reference interval 18–128 U/L; ALT 410 U/L, reference interval 20–109 U/L), moderately elevated blood urea nitrogen (64 mg/dL, reference interval 10–32 mg/dL), moderate hypoglycemia (55 mg/dL, reference interval

100–155 mg/dL), and hyperkalemia (8.1 mmol/L, reference interval 3.5–6.2 mmol/L) [3].

A cardiac work-up was performed to evaluate the heart murmur and tachyarrhythmia. An electrocardiogram showed atrial fibrillation conducted with a left bundle branch block morphology, evidence of Ashman's phenomenon, and a ventricular response rate of 260 beats per minute (Fig. 1). A standard transthoracic echocardiogram was performed in right and left lateral recumbency using a phased-array transducer with a 10.0 MHz frequency. The right coronary cusp of the aortic valve (AV) was markedly hyperechoic and thickened, and there was an apparent vegetative lesion associated with the right coronary cusp (Fig. 2A). A defect was identified between the right coronary cusp of the AV and the right ventricle (RV) using two-dimensional (2D) imaging, and color flow Doppler revealed continuous flow across the defect (Fig. 2B and C). The AV leaflets had decreased excursion, and the right coronary cusp could be seen prolapsing into the RV. The transaortic systolic velocity was elevated at 1.80 m/s (reference interval 0.76–1.02 m/s) [4]. The tricuspid valve (TV) was diffusely thickened, and there was severe tricuspid regurgitation associated with a second vegetative lesion on the septal TV leaflet (Fig. 2A). The right atrium was subjectively moderately dilated, and the left atrium was severely dilated using the LA:Ao ratio calculated using the right parasternal short-axis M-mode (LA:Ao 2.09, reference interval 1.22–1.39) [4]. The pulmonic valve leaflets were normal in appearance, but transpulmonic velocities were mildly increased (1.05 m/s, reference interval 0.73–0.94 m/s) [4]. The transmitral inflow velocities were elevated at 1.17 m/s (reference interval 0.55–0.75 m/s) [4]. There were no A waves, consistent with the electrocardiography (ECG) diagnosis of atrial fibrillation. There was peritoneal effusion and mild pericardial effusion detected.

The owner elected for humane euthanasia due to the poor prognosis, and a full necropsy was performed. On necropsy, there was a small to moderate amount of serous, non-clotting fluid within the pericardium and thoracic cavity, respectively (Fig. 3A). The heart was grossly

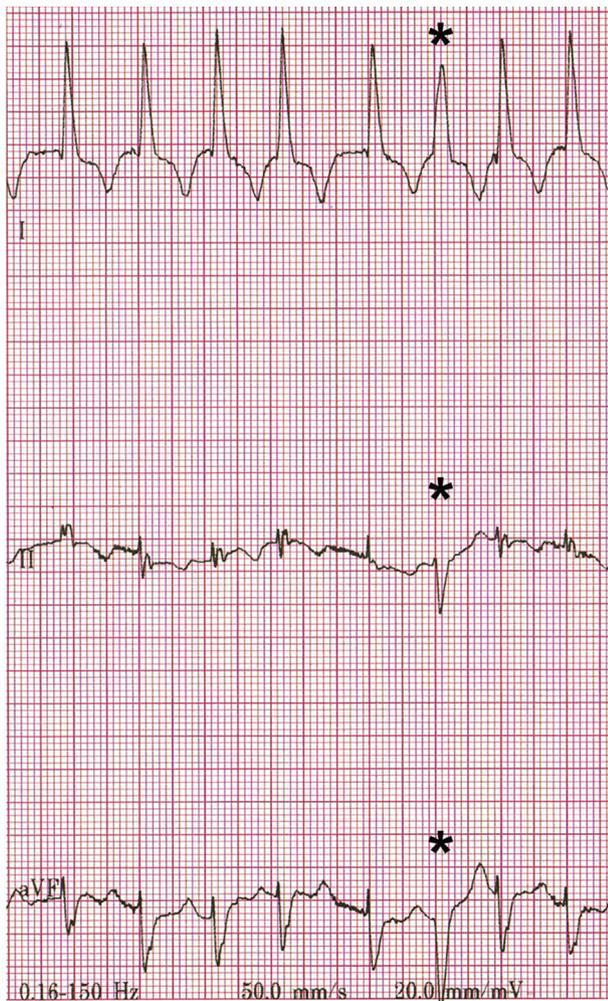


Fig. 1 Lead I, II, and aVF surface ECG recording obtained during the cardiac evaluation showing atrial fibrillation with a ventricular response rate of 260 beats per minute and a left bundle branch block morphology. There is evidence of phasic aberrant conduction (*). The aberrant impulse occurs when a long conduction cycle (R–R interval) is followed by a short conduction cycle, consistent with Ashman’s phenomenon. The aberrant impulse has a right bundle branch block morphology in leads II and aVF and a left bundle branch block morphology in lead I. These findings are consistent with concurrent right bundle branch block and left anterior fascicular block aberrancy. Paper speed = 50 mm/s; 20 mm/mV. ECG, electrocardiography.

enlarged, weighing 14.45 g or approximately 0.7% of body weight (reference 0.2% body weight in adult rabbits) [5] and characterized by severe left atrial and ventricular enlargement and moderate right atrial and right ventricular enlargement. Aortic and TV vegetative lesions with an aorta to RV fistula were confirmed. There was a tan, firm, mass-like lesion on the right coronary cusp of the AV, measuring $1 \times 1 \times 0.5$ mm (Fig. 3B). A blunt probe confirmed the communication between the

aorta and the RV (Fig. 3C). The fistula tracked from the sinus of Valsalva of the right coronary cusp of the AV, to just beneath the septal TV leaflet. There was a second tan, firm, $2 \times 2 \times 1$ mm nodular lesion on the septal TV leaflet (Fig. 3C). There was a large volume of peritoneal effusion with multifocal to coalescing pale tan regions throughout the liver (Fig. 3A), thought secondary to right sided congestive heart failure. Multiple dental abnormalities were also present, including severe malocclusions, premolar, and molar clinical crown overgrowth with marked dental attrition of the opposing quadrant, loose teeth, and impacted feed material.

Sections of the AV, interventricular septum, and TV were submitted for histopathology (Fig. 4). There were colonies of coccobacilli surrounded by moderate numbers of degenerate and viable heterophils found in all sites. Histopathological findings also included multifocal to coalescing foci of brightly eosinophilic coagulative necrosis and deeply basophilic granular mineralized material. These results were consistent with severe necrotizing and heterophilic endocarditis with mineralization and intralesional coccobacilli. Samples of the AV and TV were submitted for aerobic and anaerobic culture, which heavily grew *Haemophilus parainfluenzae* as well as minimal growth of non-hemolytic *Staphylococci* and non-hemolytic *Corynebacterium*. Histological changes within the lungs of pulmonary edema and alveolar histiocytosis with hemosiderin supported left-sided heart failure, while histologic changes of acute centrilobular to midzonal hepatocellular necrosis were consistent with ischemia. Histopathology was also performed on the right and left mandibular and maxillary premolars and molars. The results demonstrated marked diffuse gingival hyperplasia and moderate multifocal heterophilic and lymphoplasmacytic gingivitis with impacted food material, oral bacteria, and alveolar bone remodeling.

Discussion

Infective endocarditis (IE) is an uncommon disease in dogs that results in inflammation of the endothelial lining of the heart secondary to invasion of microorganisms [6]. In dogs, the AV is more commonly affected than the TV, although it is unknown if this is true for rabbits [6]. Extension of the infection into the periannular tissues is a rare complication of IE in humans and may result in abscess and/or fistulae formation [7,8]. Aortocavitary fistulae (ACF) due to IE have been reported

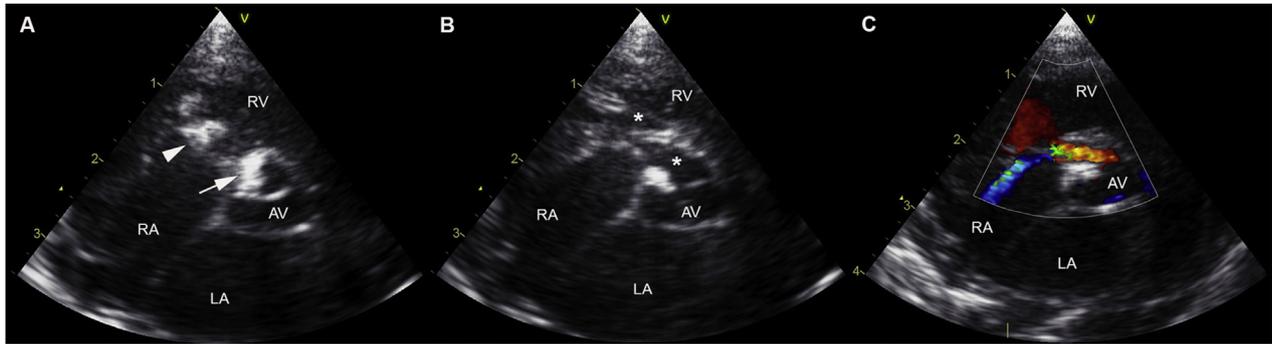


Fig. 2 2D and color-flow Doppler echocardiography of the vegetative lesions and the aortocavitary fistula. Images obtained from the right parasternal short-axis view of the heart base. (A) Hyperechoic mass-like lesions found associated with the right coronary cusp of the aortic valve (arrow) as well as the tricuspid valve (arrow head) were consistent with vegetative lesions. (B) There is a defect between the right coronary cusp of the aortic valve and the right ventricle (found between the two *). (C) Color-flow Doppler was used to identify continuous flow between the aorta and the right ventricle (red-orange flow). Tricuspid regurgitation was also identified (blue flow within the right atrium). AV, aortic valve; LA, left atrium; RA, right atrium; RV, right ventricle.

in humans, with an incidence of 2.2% [7] and as single case reports in a horse and in a dog [9,10]. Gerbode type defects, characterized by communication between the left ventricular outflow tract and right atrium, have also been reported in dogs in association with IE [11,12]. Infective endocarditis has been rarely reported in rabbits, and to the authors' knowledge, this report represents the first case of a rabbit with both IE and ACF [13,14].

Aortocavitary fistulae erode into adjacent cardiac chambers, creating intracardiac shunting that results in a volume overload and subsequent hemodynamic instability [7,8]. In this patient, it is hypothesized that the infection eroded through the right sinus of Valsalva into the RV, creating a left to right intracardiac shunt, and secondarily infecting the TV. Primary infection of TV with secondary infection of AV is considered less likely but cannot be completely ruled out. People with ACF are more likely to have moderate to severe congestive heart failure compared with people with intact periannular abscesses [7]. The rabbit had evidence of both left- and right-sided congestive heart failure. The left to right intracardiac shunt causing volume overload of the right increased pulmonary velocities, left-sided volume overload, and subsequently left-sided congestive heart failure. The right-sided heart failure observed in the rabbit was most likely caused by volume overload from severe tricuspid regurgitation, although atrial fibrillation may have contributed.

Periannular complications have been shown to increase the risk of developing certain kinds of conduction disturbances in people [7,8]. In one study, new atrioventricular block was identified as

an independent risk factor of periannular complications in people with left-sided endocarditis [8]. It is thought that this complication is a result of the infection involving the membranous interventricular septum, which contains specialized conduction tissue [15]. The rabbit was diagnosed with atrial fibrillation with a ventricular response rate that was initially rapid but appeared to be responsive to sedation. As such, the ECG findings were not consistent with 2nd or 3rd degree atrioventricular block secondary to the ACF. However, the animal did have evidence of an intra-ventricular conduction disturbance as a left bundle branch block was identified. It is unknown if this was a consequence of the ACF; however, as left and right bundle branch blocks have been reported in human patients, both with and without periannular complications of IE [8].

H. parainfluenzae is a gram-negative coccobacillus found as part of the normal flora in the oropharynx in humans [16–18]. This organism belongs to a group of similar fastidious bacteria, called the HACEK group. HACEK organisms (*Haemophilus* spp., *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*) are a rare cause of IE in humans, accounting for 1.4% and 3% of reported cases [16,17]. *Haemophilus* spp. are often isolated from dental plaques in humans, and it has been postulated that most of cases of *Haemophilus* IE are a consequence of oral disease [18]. In healthy rabbits, *Haemophilus* spp. have been cultured from the respiratory and intestinal tract [19]. *Haemophilus* spp. can act as opportunistic pathogens in rabbits, resulting in conjunctivitis or subcutaneous abscesses [20,21]. This group of

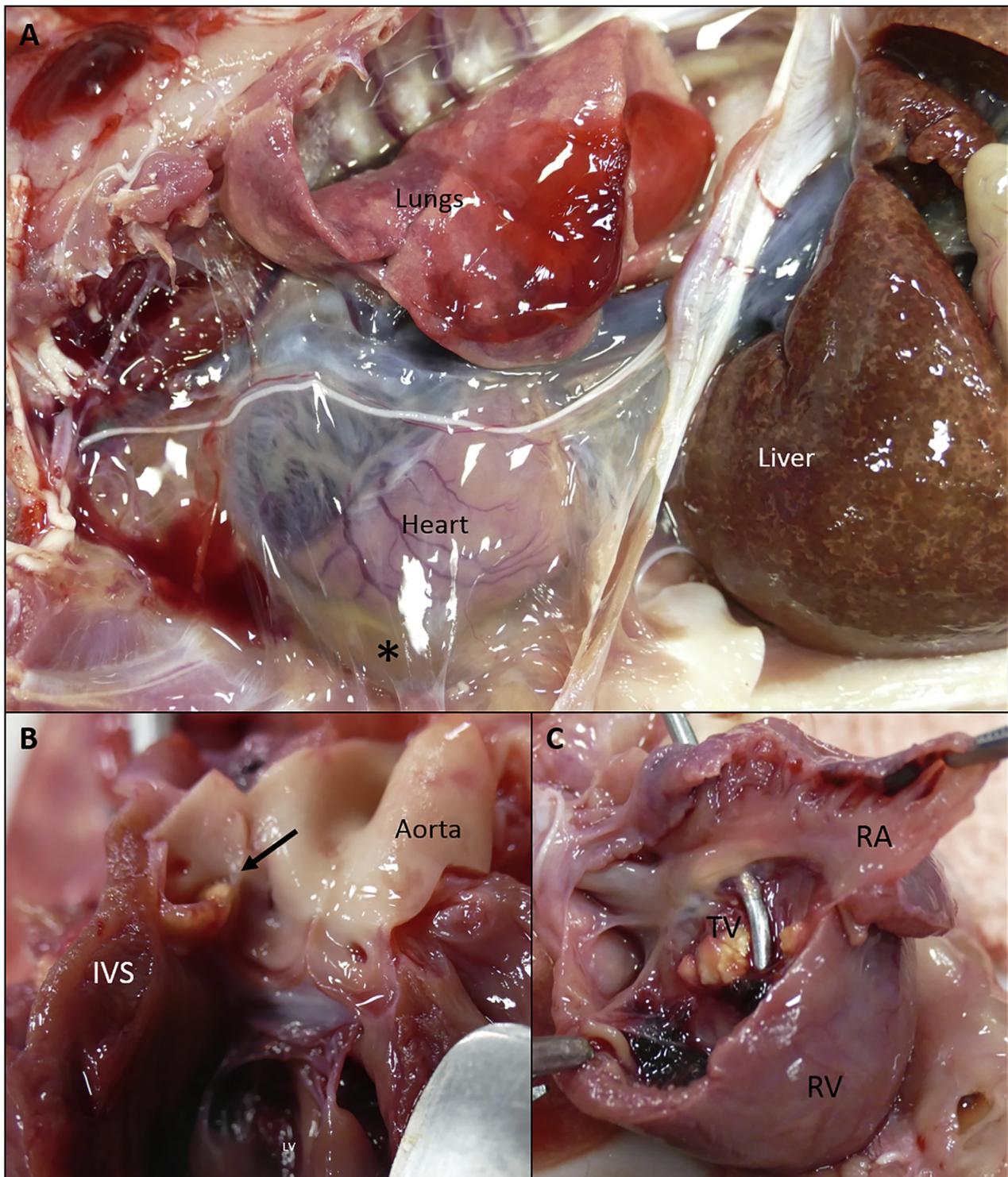


Fig. 3 (A) Gross photographs of the thoracic and abdominal cavities, (B) aortic valve, (C) and tricuspid valve. (A) Within the thoracic cavity, there is serous pericardial fluid surrounding a markedly enlarged heart. There is a small amount of serosanguinous pleural effusion remaining and partially covering the lungs, and the lungs are shrunken (compression atelectasis). The liver contains multifocal to coalescing pale regions throughout the parenchyma. (B) The right coronary cusp of the aortic valve (arrow) is expanded by a $1 \times 1 \times 0.5$ mm tan, firm, mass-like lesion. (C) The septal tricuspid valve (TV) leaflet contains a $2 \times 2 \times 1$ mm tan, firm, nodular lesion. The probe identifies the fistula between the sinus of Valsalva of the right coronary cusp of the aortic valve (AV) and the septal TV leaflet. RA, right atrium; RV, right ventricle; IVS, interventricular septum; LV, left ventricle.

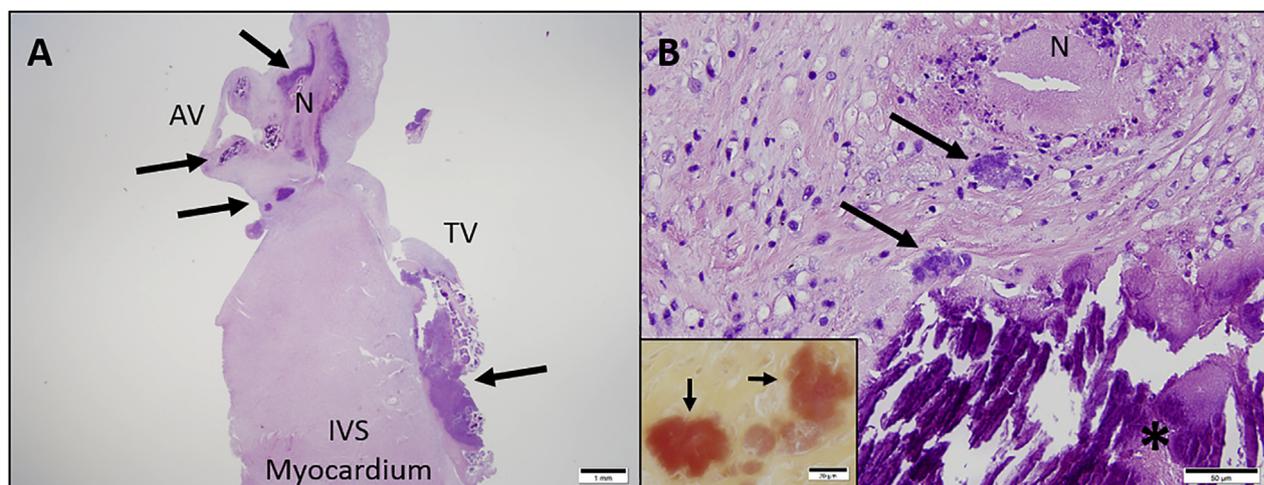


Fig. 4 Histologic photomicrographs of the heart. (A) A sagittal section through the aortic valve (AV), interventricular (IVS) myocardium, and the tricuspid valve (TV) showing thickening of both valves by eosinophilic coagulative necrosis and deeply basophilic granular material. Hematoxylin and eosin (H&E), 12.5 \times , Bar = 1 mm. (B) Higher magnification of the AV showing deeply basophilic granular mineral (*), necrosis (N), and colonies of coccobacilli (arrows). H&E, 400 \times , Bar = 50 μ m. Inset: Bacteria are red staining (Gram negative) coccobacilli. Gram stain, 600 \times , Bar = 20 μ m.

organisms have not been isolated from odontogenic abscesses in rabbits [22,23]. In the present case report, it is suspected that severe dental disease was the source of the bacteremia and subsequent IE as there was no other nidus of infection identified during necropsy. Unfortunately, samples of the patient's dental lesions were not submitted for culture, and therefore this theory cannot be confirmed as it is unknown if the dental disease was the source of *Haemophilus*.

Valvular disease has also been identified as a common risk factor for the development of bacterial endocarditis in people because endothelial damage is a critical part of the pathogenesis of IE involving any organism, as it enables bacteria to adhere and colonize the valve [6,18]. The mitral valve is the most commonly affected valve in humans with *Haemophilus* spp. endocarditis, and congenital mitral valve prolapse is the most frequent predisposing condition in these patients [18]. Congenital heart disease is a known risk factor for IE in other species as well. In dogs, subaortic stenosis has been shown to increase the likelihood of developing IE of the AV, likely related to endothelial damage resulting from turbulent blood flow in the left ventricular outflow tract [6,24]. A link has not been established between congenital heart disease and IE in rabbits. However, both congenital heart disease and IE have been reported so rarely in the pet rabbit population that such a link may exist but not yet identified.

The rabbit did not have reported abnormalities on auscultation prior to this visit. Rarely, clinically silent congenital abnormalities have been found in

association with IE, including sinus of Valsalva aneurysms in people [25] and membranous ventricular septal aneurysms in both people and dogs [26,27]. Congenital sinus of Valsalva aneurysms most commonly affect the right aortic sinus in people, and they are frequently found in combination with other cardiac congenital disease, with 54% of cases occurring concomitantly with membranous ventricular septal defects [25]. Aneurysms of the aortic sinus and ventricular septum have not been reported in rabbits. There was no definitive evidence of congenital heart disease during the echocardiogram or on necropsy in this patient, including no evidence of aneurysmal thinning or dilation of the right aortic sinus of Valsalva or the membranous ventricular septum. The transaortic systolic velocity was increased, but it is unclear if this was due to AV malformation or a result of acquired stenosis from the large vegetative lesion. As such, it is considered less likely that this patient had underlying cardiac disease that predisposed him to IE.

The clinical manifestation of HACEK endocarditis is commonly subacute because of the fact that these organisms have a low virulence, and the overall prognosis is considered excellent [16–18]. Despite this, patients with HACEK endocarditis can still develop periannular complications with similar frequency to other causes of IE with a significant negative impact on prognosis [17]. Vegetative lesions tend to be larger in patients with HACEK endocarditis in comparison to other etiologies of IE, and the risk of vascular and immunological complications is higher [16–18].

Mild, non-regenerative anemia is commonly identified in patients with IE, most likely as a consequence of chronic infection [6]. Less commonly, intravascular hemolysis resulting in regenerative anemia has been reported in both people and rabbits as a complication of vegetative IE [13,28]. The exact mechanism has not been identified and may be related to mechanical damage to the red blood cells as they pass through the affected valve or immune-mediated destruction [6,13]. The rabbit in this report had a moderate to severe anemia, and it is speculated that the severity of the anemia was greater than expected from chronic infection alone. Testing to characterize the type of anemia was not performed.

To the authors' knowledge, this case is the first report of ACF secondary to IE in a rabbit, and it also represents the first time HACEK endocarditis has been identified in this species. The presentation and course of the disease process in the rabbit presented in this report is similar in many ways to HACEK endocarditis in people. While dental disease is common in pet rabbits, it has not been reported to cause endocarditis as a sequela in this species. Additional factors that may have predisposed this rabbit to developing endocarditis were not evident.

Infective endocarditis should be considered as a differential diagnosis in rabbits with a new onset murmur. Careful interrogation of perivalvular structures using both 2D and Doppler echocardiography is recommended to identify periannular complications like ACF, particularly when there is evidence of left-sided volume overload or other consequences of arteriovenous shunts.

Conflicts of Interest Statement

None.

Acknowledgments

The authors gratefully acknowledge Dr. Rebecca L. Stepien for reviewing the manuscript.

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