Received: 12 June 2017 | Revised: 23 November 2017 | Accepted: 18 January 2018

DOI: 10.1111/jvim.15074

CASE REPORT

Journal of Veterinary Internal Medicine Open Access

ACVIM American College of Veterinary Internal Medicine

Incomplete endothelialization of an intravascular implant and fatal late-onset bacterial ductal arteritis in a dog with occluded patent ductus arteriosus

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An 18-month-old male Akita Inu dog developed fever and lameness 8 months after successful transcatheter closure of a patent ductus arteriosus with an Amplatz Canine Duct Occluder (ACDO). *Corynebacterium* species were cultured from 3 blood samples. Echocardiography showed a vegetative process on the aortic valves. The dog died spontaneously 3 days after development of the initial signs. Necropsy confirmed the presence of bacterial ductal arteritis and myocarditis, and revealed an incomplete endothelialization of the intraductal metal implant. The reason for the lack of (neo)endothelialization of the ACDO remains unknown. We conclude that late-onset bacterial device-related ductal arteritis can develop in dogs where the implant is incompletely covered by a protective endothelial layer.

KEYWORDS
Amplatz, cardiac catheterization, congenital, endocarditis, infective

1 | INTRODUCTION

An 18-month-old, 29 kg, intact male Akita Inu dog was presented for transcatheter closure of a patent ductus arteriosus (PDA). Surgical ligation of the PDA was attempted 4 weeks earlier in a private veterinary referral center, but the surgical dissection of the PDA was complicated by intraoperative hemorrhage and the procedure was aborted. The hemorrhage originated from the medial side of the ductal ampulla, and it was only present during manipulation of the PDA. No sutures or any other hemostatic measures were applied. The dog fully recovered from the thoracotomy within a week.

At presentation, the owner reported exercise intolerance as the only clinical problem. The dog was bright, alert, and panting. The femoral pulse was regular and bounding with a frequency of 100/min. A grade VI/VI continuous cardiac murmur was auscultated over the left heart base. The remainder of the physical examination did not reveal abnormalities. Echocardiographic examination confirmed the presence of a left-to-right shunting PDA, and revealed severe eccentric hypertrophy of the left ventricle (normalized diastolic left ventricular internal diameter of 2.44; reference $<$1.85), a moderate systolic dysfunction of the left ventricle (normalized systolic left ventricular internal diameter of 1.47; reference $<$1.26), a normal sized left atrium (based on a left atrium to aortic ratio of 1.4; reference $\leq$1.5) and mild aortic and mitral valve regurgitations.[1] One week later, a transarterial embolization of the PDA was performed by implanting an Amplatz Canine Duct Occluder (ACDO; AGA Medical Corp, Plymouth, Minnesota) under general anesthesia according to a previously described protocol.[2,3] A surgical cut down was used to access the right femoral artery, which was ligated upon completion of the catheterization procedure with polyglactin absorbable suture material (Vicryl Plus 3-0, ETHICON, Johnson & Johnson International, c/o European Logistics Centre, Diegem, Belgium). On the angiography images, the pulmonary ostium of the PDA measured 6 mm and the ductal ampulla was 12 mm. An ACDO with a waist diameter of 10 mm was implanted according to the manufacturer's recommendation. An immediate complete occlusion of the PDA

Abbreviations: ACDO, Amplatz canine ductal occlude; PDA, patent ductus arteriosus.

was reached, which was confirmed by intraoperative angiography and transthoracic color Doppler ultrasonography according to a previously described technique.[4] The recovery from the general anesthesia was uneventful and the dog was discharged from the clinic with the prescription of carprophen (Carporal 20 and 100 mg tablet, AST B.V., Oudewater, The Netherlands; 2 mg/kg PO, q12h) for 3 consecutive days. No intraoperative or postoperative prophylactic antibiotics or heparin were administered.

Eight months after the transcatheter occlusion of the PDA, the dog underwent a physical examination by the referring veterinarian and it was subsequently routinely vaccinated. The dog was reported to be healthy and cardiac auscultation did not reveal any abnormalities either. One week after the vaccination acute onset of vomiting and a large amount of brown diarrhea appeared. The next day, progressive lethargy, decreased appetite, and stiff locomotion with stilted gait developed. The referring veterinarian observed hyperthermia (39.9°C), a heart rate of 135 beats/min and pale mucous membranes with prolonged capillary refill time. The dog received dexamethasone (1.4 mg) and antibiotic (sulfamethoxazole 200 mg and trimethoprim 40 mg) injections. The dog was referred to the authors' clinic the next day.

At presentation, the dog was lethargic, panting, and showed severe lameness of the left foreleg. The rectal temperature was 40.2°C. Hyperdynamic, regular femoral pulse with a frequency of 120/min was found. Petechial bleedings on the buccal mucous membranes were noticed. Because of panting, a reliable cardiac auscultation could not be carried out, but murmurs could not be auscultated. Echocardiogram revealed a large vegetative lesion (14 mm length) on the aortic valves and aortic valve regurgitation. The ACDO was in its original position and color Doppler examination did not reveal any shunting through the PDA. The dog was hospitalized and 3 blood samples were collected aseptically for bacterial culture by jugular venipuncture. The 3 blood samples were taken with 1-1.5 hour time intervals from various anatomical sites, and the 3 culture bottles were inoculated separately from independent venipunctures. Amoxicillin and clavulanic acid (Amoxicilline/Clavulaanzuur Sandoz 500 mg/50 mg IV injection, Sandoz B.V., Almere, The Netherlands; 12.5 mg/kg IV, q8h) and enrofloxacin (Baytril 25 mg/mL injection, Bayer B.V. Animal Health Division, Mijdrecht, The Netherlands; 5 mg/kg SC, q24h) injections were subsequently started. During the 1st day of hospitalization alternating sinus rhythm with frequent solitary ventricular premature complexes and periods of accelerated idioventricular rhythm with a frequency of 140/min were noticed on the telemetry electrocardiogram. The next day suddenly stupor developed. The dog was unable to stand and was lying in lateral recumbency with hyperextension of all 4 legs. A left sided hyphema was also noticed. The right pupil was wide and the pupil-reflex was absent. Several hours later, the dog died spontaneously.

All 3 blood culture samples were positive for a *Corynebacterium sp*. There was anemia (hematocrit 0.36 L/L, reference 0.42-0.61), thrombocytopenia (106×10^9/L, reference 144–603), and a leukocyte count (12.7×10^9/L, reference 4.5–14.6) and leukocyte differentiation within the reference range. The blood urea nitrogen, creatinine, total protein, albumin, potassium, and sodium concentrations, the prothrombin, and the activated partial thromboplastin times were within the reference ranges. Fibrinogen and D-dimer concentrations were increased (3.9 g/L, reference 1.0–2.7 g/L, and 540 ng/mL, reference <250, respectively).

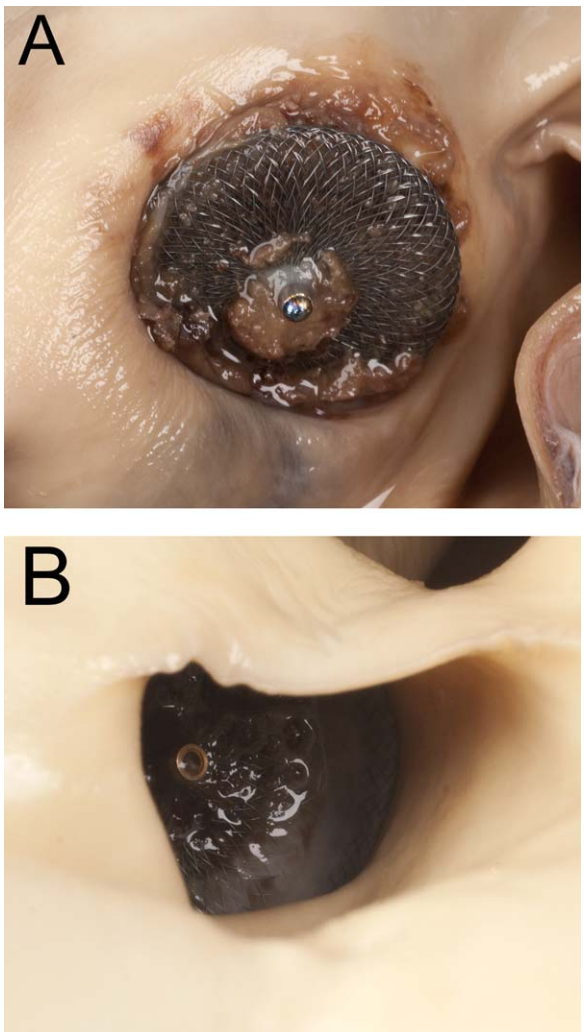

FIGURE 1 Incomplete endothelialization of an ACDO at necropsy. Formaldehyde-fixated specimen. A, The ACDO in the PDA, viewed from the pulmonary artery, is incompletely covered with endothelium. Irregular, vegetative lesions on the ACDO and on the wall of the pulmonary artery adjacent to the ACDO are the result of bacterial infection. B, The ACDO in the ductal ampulla, viewed from the aortic side. The peripheral parts of the device are covered with normal endothelium

Postmortem examination revealed incomplete endothelialization of the ACDO (Figure 1A,B). All cardiac valves looked normal on gross pathology. Histopathology revealed an acute focal purulent vasculitis of the ductal wall and an acute, moderate, multifocal purulent myocarditis with vasculitis and intralesional bacteria (Figure 2). In the cerebrum acute, multifocal, purulent embolic meningoencephalitis, and moderate, multifocal vasculitis were found along with multifocal meningeal and cerebral hemorrhages. Necropsy of the left eye revealed acute, moderate, neutrophilic cranial uveitis with purulent retrobulbar cellulitis. The lungs showed an acute, multifocal, moderate, and neutrophilic interstitial pneumonia with purulent vasculitis. The kidneys showed multifocal hyperemia and hemorrhages, as well as multifocal mild cortical necrotic

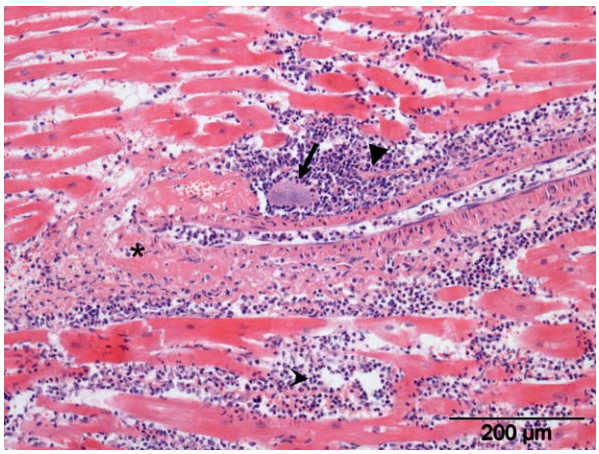

FIGURE 2 Photomicrograph of the myocardium. In the center of the image, a blood vessel can be seen in longitudinal section. The vascular wall shows a focal loss of cellular detail and hypereosinophilia (asterisk). The vascular wall and the myocardium are infiltrated with neutrophilic granulocytes (arrow heads). The arrow points to a colony of bacteria. These findings are compatible with a bacterial vasculitis and myocarditis. Hematoxylin and eosin staining

lesions infiltrated with small amount of degenerated neutrophil granulocytes.

The antemortem findings of echocardiographic visualization of a vegetative lesion on the aortic valve and 3 positive blood cultures were suggestive of a bacterial endocarditis.[5] However, the postmortem findings failed to prove the presence of an aortic valve endocarditis. Therefore, the definitive diagnosis of bacterial ductal arteritis with myocarditis was made. Sudden occurrence of the stupor was possibly the result of a cerebral thromboembolism of the suspected septic aortic valve vegetation, which was not found on necropsy on the aortic valve.[5] However, a thrombus can also be a potential alternative explanation for the echocardiographic lesion on the aortic valve, which might have been mimicking infective valvular endocarditis.

Bacterial endocarditis in dogs is a serious, potentially life-threatening condition that can develop spontaneously, but also after implantation of intracardiac or intravascular devices.[5–7] The absence of echocardiographic abnormalities on the PDA and the ACDO does not rule out the presence of bacterial arteritis and device-infection.[7] Despite the large number of dogs whose PDA is embolized with a metal implant worldwide, only a few cases have been reported with implant-related infection, of which 1 had an ACDO.[7] The single study that reports the frequency of PDA-occlusion-device-related infection in dogs described an incidence of 4.3% (2 of 47 dogs).[7] Reported incidence of infective endocarditis in dogs without intravascular/intracardiac implants in tertiary veterinary referral centers is similar: 0.1%-6.6%.[5]

The pathogenesis of cardiovascular implant/device-related bacterial endocarditis/arteritis in both human and veterinary medicine is not fully elucidated, but 3 factors are believed to play a role: the physical and chemical characteristics of the implant, pathogen virulence factors, and host response to the implant.[8] The presence of foreign material and a (transient or sustained) bacteremia are thought to play a vital role in the development of infective endocarditis.[8,9]

The physical and chemical characteristics of the implant can be important in how easily fibrinogen will attach to the surface of the implant.[8] Fibrinogen coverage of the implant will be followed by adhesion of platelets and red blood cells (ie, thrombus formation), which in certain cases can be followed by adhesion of bacteria.[8]

Regarding the role of pathogen virulence factors in the pathogenesis of implant-related infections, the presence of adherence molecules on the bacteria is essential for binding the microorganisms to the fibrinogen coating the implant. Potential injury causing denudation of the endothelium of the ductal wall by the ACDO can abolish the natural microbial resistance of the endothelium. The exposed host proteins, in turn, can also become a target of bacterial adhesion.[8] Certain bacteria such as *Staphylococcus* and *Streptococcus spp*. have adhesins on their surface, which enable their attachment to the host's extracellular matrix proteins.[8,9] These are also the most commonly encountered bacteria in implant/device-related infections.[7–10] The surface of the implanted nitinol ACDO is coated by these proteins, facilitating bacterial adherence and colonization.[5,7,8] Though the surface proteins of *Corynebacterium diphtheriae* might act as adhesins, the exact adherence mechanism and capacity of *Corynebacterium* species, which was cultured from the reported dog, remains unknown.[11,12] In addition to the adherence molecules, biofilm-formation is another important microbial virulence factor that contributes to implant-related infections. Biofilm develops on the metal surface of the implant and consists of extracellular matrix and the infective bacteria.[8] Biofilm protects bacteria from antibiotics and the host's immune system.[5,7,8]

The 3rd factor is the host's response to the implant, which can contribute to the pathogenesis of implant-related bacterial infections in 2 ways. Endothelialization of the implant is thought to be the major protective mechanism against microbial infection.[8] However, turbulent blood flow, created by the implant, can lead to regions of low shear stress in the vascular system, which in turn, increases the reactivity of endothelial cells and platelets, with an end result of thrombus formation and bacterial adherence.[8]

In addition to the above described 3 factors, procedure-related factors are thought to play a role in device infections: sterile equipment, operator experience, procedural time, and aseptic technique.[7,10] Procedural infections mostly start shortly after the surgery, typically within 30 days.[6,7,9,13–15] Because of the late-onset of clinical signs in the present dog, a possible bacteremia during surgery seems to be a very unlikely etiology. Bacterial seeding of the incompletely endothelialized ACDO resulting from a hematogenous spread is more plausible. Routine daily activities (such as chewing) might result in transient bacteremia caused by oral microflora, including *Corynebacterium sp*.[5,8,10,16] As vomiting and diarrhea preceded the onset of fever, the gastrointestinal tract might have been the port of bacterial entry. However, these gastrointestinal signs might have also been the initial signs of the developing sepsis. Because no earlier reports document late-onset arteritis after embolization of a PDA with an ACDO, device-related factors are thought to be unlikely to have contributed to the genesis of infection. A patient-related factor, such as the incomplete endothelialization of the device, however, is more likely to have contributed to the development of this unusual complication in this dog. The potential role of the

previous mechanical damage to the ductal wall during surgical dissection remains unclear.

Incomplete endothelialization of Amplatzer implants used for closing atrial septal defects in humans was thought to be the reason of development of infective endocarditis in a number of recently reported human patients.[17–22] Necropsy of the Akita revealed an ACDO that was incompletely covered with endothelial layer 8 months after implantation. Whether incomplete endothelialization has predisposed this dog for developing a bacterial arteritis is unknown, but seems to be plausible. In addition, the reason of incomplete coverage of the implant by endothelial cells remains unclear. An alternative explanation to the necropsy findings of the ACDO in the present dog can be that bacteria damaged the (neo)endothelial layer of the previously fully endothelialized ACDO. This scenario is in our opinion very unlikely, because endothelialization of the implant is thought to be the most important factor that prevents future infection.[8] Currently, it is impossible to assess whether an implanted device is fully endothelialized without its direct inspection at necropsy or at surgical removal.

The normal process of neoendothelialization of intravascular implants is well described in the literature. After the placement of an intravascular/intracardiac metal implant, a series of events take place.[23–26] First, thrombotic material (coagulum), consisting of fibrin and blood cells, develops, and seals on the surface of the implant.[25,26] This process begins directly after implantation and usually ends within 1–2 days.[25] Afterwards, proliferation of fibromuscular cells occurs, which lasts 2–3 weeks.[25] In the final phase, formation of granulation tissue, containing of extracellular matrix and fibroblasts, and new blood vessels take place.[25,26] In experimental studies, consisting of 1 lamb and 4 minipigs complete endothelialization of an atrial septal defect occluder was documented 3 month after device implantation.[27,28] Nitinol implants are usually covered with neoendothelium by 3–5 months after device placement.[24] Human guidelines tend to refer to these studies when they recommend secondary antibiotic prophylaxis for 6 months after implantation of an occlusion device.

In conclusion, we report a dog with a late-onset of acute bacterial arteritis most likely associated with incomplete endothelialization of an intravascular metal implant. Incomplete endothelialization could be—similar to humans—a predisposing factor for bacterial colonization of intracardiac and intravascular metal implants also in dogs and might contribute to the development of late-onset infective arteritis even beyond 6 months after device implantation.

ACKNOWLEDGMENTS

The authors are grateful to Mr Joop Fama, who made the postmortem photographs. The authors thank Willemijn Ekkebus for contributing to the literature study. The authors thank Dr Els Broens, Dr Mark Dirven, and Prof Dr Erik Teske for their advice during manuscript preparation.

CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Beijerink NJ, Bergmann W, Szatmári V. Incomplete endothelialization of an intravascular implant and fatal late-onset bacterial ductal arteritis in a dog with occluded patent ductus arteriosus. *J Vet Intern Med*. 2018;32:1155–1159. https://doi.org/10.1111/jvim.15074