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CASE REPORT

Companion or pet animals

Bartonella henselae mitral valve endocarditis associated with multi-resistant *Enterococcus faecalis* bacteraemia in a cat

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Abstract

Feline infective endocarditis is a difficult condition to detect and diagnose early, with a poor long-term prognosis. This case report describes the clinical, laboratory, instrumental and histological findings in a 12-year-old cat with *Bartonella henselae* endocarditis associated with multi-resistant *Enterococcus faecalis* bacteraemia. The latter pathogen recently emerged as deadly nosocomial bacteria in humans and is considered a common cause of infective endocarditis. The prolonged corticosteroid therapy administered in the cat probably played a role in the onset of *B. henselae* endocarditis and *E. faecalis* intestinal translocation and bacteraemia. Echocardiography remains the tool of choice to suspect infective endocarditis, as it can detect vegetative lesions consistent with this condition. Feline infective endocarditis should always be considered as a differential diagnosis in cats, especially when there are signs of systemic disease, a history of prolonged corticosteroid treatment or concomitant infections.

KEYWORDS

Bartonella henselae, cat, echocardiography, endocarditis, *Enterococcus faecalis*

BACKGROUND

Infective endocarditis (IE) in small animals is a serious valve disease with a poor long-term prognosis.[1–3] The disease is caused by invasion of the vascular endothelium or endocardium by an infectious agent, in most cases a bacterial one. IE is considered an infrequent disease in dogs but rare in cats,[3–5] although increasing numbers of cases have been reported in recent years, probably due to an increased diagnostic attention by veterinarians or due to the availability of diagnostic instruments such as echocardiography.[2,3]

CASE PRESENTATION

A 12-year-old, neutered, female shorthair cat had a 1-month history of dysorexia and weight loss. The cat was under long-term treatment with prednisone (1.5 mg/kg orally [PO] twice a day) at the time of presentation to treat presumed infiltrative enteropathy.

Because of the worsening of clinical conditions, the patient was referred to the Veterinary Medical Teaching Hospital, University of Bari, Italy. On physical examination, the cat was found to be mentally depressed, dehydrated, hypothermic with pale mucous membranes. The body condition score was 2/5, with bodyweight of 3.35 kg. Its respiratory rate was 48 breaths per minute, and it was dyspnoeic with discordant breathing. Its heart rate was 180 beats per minute. No heart murmur or abnormal rhythm was detected on auscultation. The temperature was 36.0°C.

A complete blood count was performed showing a severe microcytic (mean cell volume 37.5 fL; reference interval [RI]: 39–55 fL), normochromic, non-regenerative anaemia (haematocrit 11%; RI: 30.0%–45.0%) and leukocytosis (WBC 35.6 K/μL; RI: 5.50–19.5/μL) characterised by neutrophilia with left shift (83% neutrophils; 6% bands). The chemistry panel revealed an increase of bilirubin (0.67 mg/dL; RI: 0.14–0.25 mg/dL) and a severe increase of serum amyloid (143.7 μg/mL; RI: 0.1–0.5 μg/mL).

Abdominal ultrasound examination revealed splenomegaly, hepatomegaly with decreased echogenicity of both organs; a mild enteropathy suggestive of inflammatory disease without abdominal effusion, hypoechogenic lymph nodes and diffuse increase in peritoneal echogenicity.

Thoracic ultrasound examination demonstrated the presence of a moderate amount of thoracic effusion. Thoracentesis was performed. The non-corpuscular citrine yellow thoracic fluid was compatible with a modified transudate

(specific gravity of 1.018; protein 2 g/dL; few leukocytes WBC 2.55 K/μL).

Lateral and dorsoventral thoracic radiographs were taken after thoracentesis to evaluate heart and lung conditions, but the persistence of a small amount of effusion precluded a thorough radiographic evaluation of the heart and lungs.

An echocardiography examination was performed; it revealed dilatation of the left atrium and an independently hyperechoic oscillating lesion attached to both mitral valve leaflets (Figure 1a,b). A moderate mitral regurgitation was documented on colour flow Doppler examination. Signs of volumetric overload of the left ventricle were present. The aortic valve appeared to be normal, with no evidence of valvular insufficiency. No alterations were documented at the myocardial level. In the differential diagnosis, the mitral oscillating lesion was suggestive of an infective vegetative lesion, neoplasia or, less probably, rupture of the tendinous cord.

Therefore, due to strong echocardiographic suspicion of IE, samples for blood cultures and *Bartonella* spp. detection were collected. A sample of blood (2.5 mL) was aseptically collected before starting the antimicrobial treatment, from the saphenous vein by using a citrate vial. Blood was divided into two aliquots, for aerobic and anaerobic culture. For aerobic culture, the haemo-aerobic culturing, Brain Heart Infusion broth with PABA, SPS (Liofilchem) was inoculated and incubated at 37°C in aerobic condition for 48 hours. The broth was subcultured into Columbia Blood Agar (CBA), MacConkey Agar (MCK) and Mannitol Salt Agar (Liofilchem) for 24 hours. For anaerobic culture, a vial of Haemo-anaerobic Culturing Schaedler broth with Vit K, PABA (Liofilchem) was inoculated and incubated at 37°C in anaerobic condition for 48 hours. The broth was plated into CBA for 48 hours. From both culturing, a consistent number of grey-white non-haemolytic smooth colonies with a diameter of 2–3 mm was observed in CBA medium after 24 hours. The microorganism was initially identified with Gram stain, oxidase, catalase and API tests (Biomerieux). The isolate was identified as *Enterococcus faecalis* by using the API Strep system. To confirm the identification, the isolate was subjected to 16S rRNA PCR and sequencing. The universal primers BV5 and AV6 were used to amplify the 16S rRNA gene.[6] The primers were: BV5 5′-ATTAGATACCCYGGTAGTCC-3′ (tm 55°C) and AV6 5′ ACGAGTGACGACARCCATG-3′ (tm 69.8°C). Cycling conditions were as follows: 95°C, 10 minutes; 35 cycles of (94°C, 30 seconds; 57°C, 30 seconds; 72°C, 30 seconds); 72°C, 8 minutes. Reaction conditions (50 μL) were as follows: 50 ng template DNA; 50 mM KCl; 10 mM Tris−HCl; pH 8.3; 1.5 mM Mg^{2+}; 0.2 mM dNTPs; 40 pmol of each primer, 5 U of Taq DNA polymerase (AmpliTaq Gold, Thermo Fisher). PCR-amplified products (300 bp) were purified by using enzymes QIA-quick PCR Purification Kit (Qiagen), and sequence analysis was performed using the MiSeq NGS (Illumina) technology. All sequences were analysed with the Geneious Prime10.1 Software and compared with reference sequences available on the BLAST database (https://blast.ncbi.nlm.nih.gov/Blast.cgi). Purified genomic DNA was subjected to WGS using the Nextera XT library preparation workflow (Illumina), and 2 × 250-nucleotide paired-end reads were generated on an Illumina MiSeq instrument. De novo genome assembly was performed using SPAdes v.3.12.[7] The analysis of the sequences confirmed the isolation of *Enterococcus faecalis*, with an identity score of 99%. The isolate was tested for antimicrobial susceptibility with the Kirby–Bauer method, and the results were interpreted according to the Clinical and Laboratory Standards Institute criteria.[8] The isolate was found to be resistant to enrofloxacin (5 μg), moxifloxacin (5 μg), norfloxacin (10 μg), trimethoprim-sulfamethoxazole (25 μg), nalidixic acid (30 μg), tetracycline (30 μg), amikacin (30 μg), gentamicin (30 μg), ceftriazone (0 μg), cefotaxime (30 μg), ceftazidime (30 μg), clindamycin (10 μg), aztreonam (30 μg), clarithromycin (15 μg), streptomycin (10 μg), erythromycin (5 μg), kanamycin (30 μg), and susceptible to amoxicillin (30 μg), amoxicillin + clavulanic acid (30 μg), nitrofurantoin (300 μg), chloramphenicol (30 μg) and rifampicin (30 μg).

LEARNING POINTS/TAKE-HOME MESSAGES

- Echocardiography was the basic tool to suspect infective endocarditis even in the absence of heart murmur.
- Blood cultures and molecular tests allowed to diagnose *Enterococcus faecalis* infection associated with *B. henselae* infective endocarditis; aetiological diagnosis is crucial for targeted treatment.
- *Enterococcus faecalis* may have contributed to the clinical course of the disease in this cat.
- An early diagnosis is desirable to avoid fatal outcome.

For *Bartonella* spp. detection, an EDTA blood sample and pleural effusion sample were subjected to DNA extraction using the DNeasy Tissue Kit (Qiagen) according to the manufacturer's instructions. All DNA samples were subjected to molecular screening using *Bartonella* genus-specific quantitative real-time polymerase chain reaction (qPCR) assay targeting the transfer-mRNA *ssr*A (*ssr*A) gene.[9] For species identification, all the positive samples were further analysed by a cPCR targeting the *pap*31 gene.[10] Based on the combined results of qPCR and cPCR assays, *Bartonella henselae* DNA was detected in both blood and pleural effusion samples.

The cat was initially treated with oxygen, furosemide (0.5–1 mg/kg/h CRIev) and empirically with ampicillin/sulbactam (20 mg/kg intravenously thrice a day) plus enrofloxacin (5 mg/kg subcutaneously daily) before results of blood cultures and PCR. Twelve hours after hospitalisation, the cat developed aortic thromboembolism (AT). At the physical examination, the cat was hypothermic, with no pulse on the right hindlimb. Thereafter, considering the general conditions and the sudden deterioration of clinical signs, euthanasia was carried out, and the owner consented to perform a postmortem examination.

An echo-guided ago-aspiration from the mitral proliferative lesion was performed immediately postmortem, and the material used for cytological examination revealed the presence of numerous coccoidal bacteria (Figure 2a).

At the postmortem examination, the heart presented dilatation of the left atrium and granular yellowish outgrowths on the mitral valve (Figure 2b). The left kidney was hypotrophic and pale compared to the right one, which was hyperaemic. The liver appeared hypertrophic with a nutmeg aspect. The spleen was increased in volume.

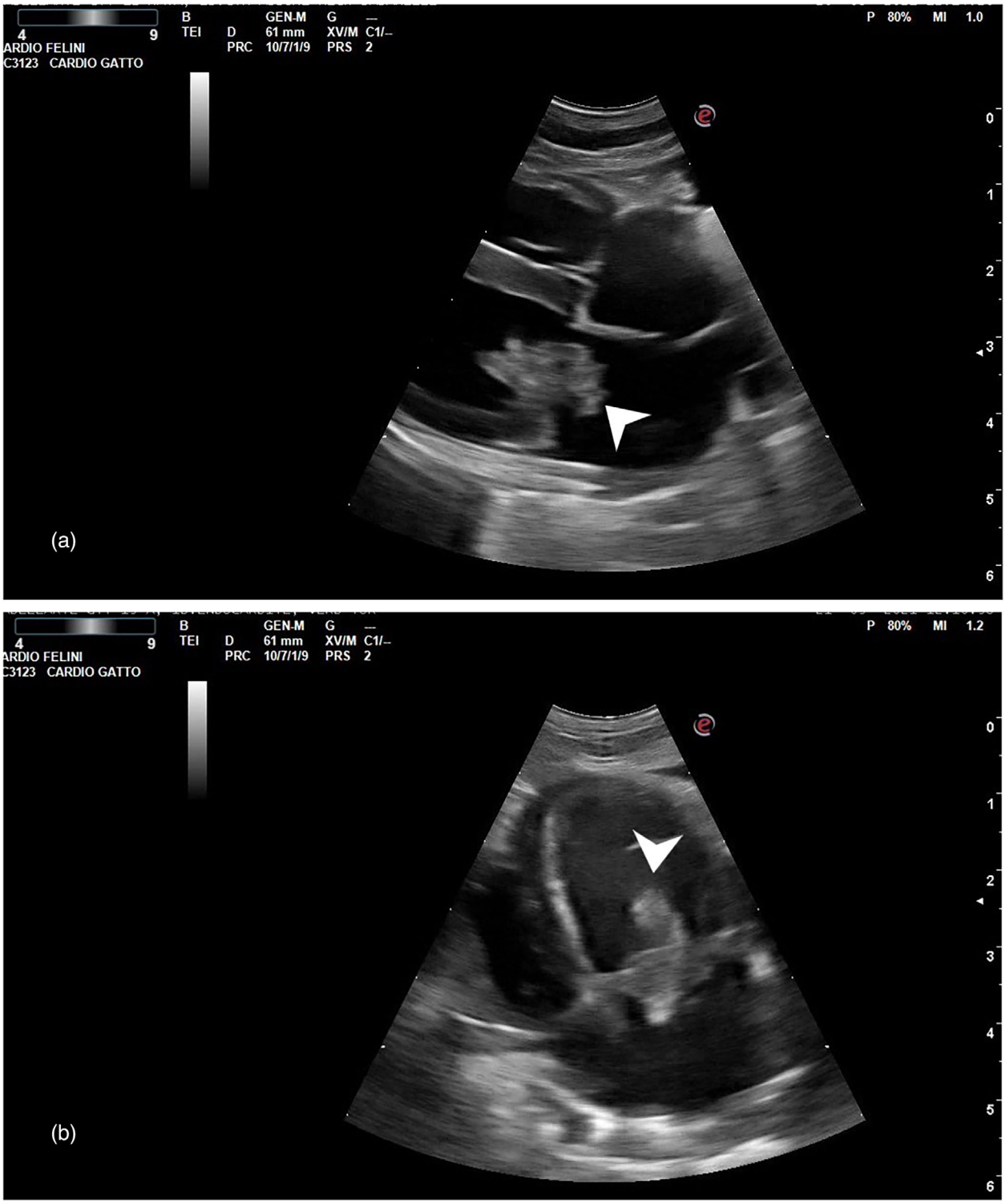

FIGURE 1 (a) Right parasternal long-axis B-mode scan: presence of a thickened, irregular, hyperechogenic lesion adhered to the mitral valve (arrow). (b) Left parasternal apical four-chamber view: presence of an irregular, oscillating hyperechogenic lesion adhered to the mitral valve (arrow).

Histological examinations of heart, kidney, jejunum, spleen and liver samples were subsequently performed. Three sections of the heart were examined and confirmed a severe vegetative bacterial valvular endocarditis with epi-myocarditis: in multiple areas, both on the valve surface and in its centre, there were large deposits of fibrin, and multiple aggregates of coccoid bacteria were found within the deposited fibrin. Heart samples were characterised by a severe inflammatory infiltrate (90% neutrophils, minimal % macrophages and rare plasma cells) that tended to reach the adjacent myocardium, where it resulted in cardiomyocytes degeneration (myocardial necrosis) and sub-epicardial tissue (Figure 2c). The intestine had abundant inflammatory infiltrate (mainly characterised by lymphocytes) in its section, from mucosa to serosa. The right kidney showed severe tubular vacuolar degeneration with glomerular congestion, compatible with a picture of a congestive/degenerative nephrosis, and the left one was characterised by moderate chronic tubular-interstitial inflammation. Liver findings were suggestive of cholestasis with mild biliary proliferation samples showed focal areas of hepatic necrosis,

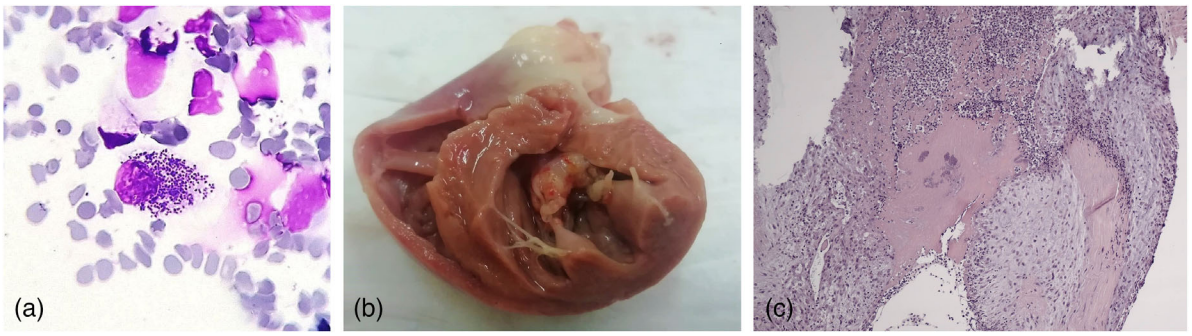

FIGURE 2 (a) Cytological preparations of the mitral proliferative lesion sampled by ultrasound-guided needle aspiration. Numerous coccoidal bacteria are evident in the macrophage cytoplasm. (b) Cardiac section at the level of the papillary muscles: yellowish granular proliferative lesion adhered to the mitral valve. (c) Histological section of the mitral valve: widespread proliferation of reactive fibroblasts; presence of large deposits of eosinophilic amorphous material (fibrin) in multiple areas; presence of multiple aggregates of coccoid bacterial colonies in the deposited fibrin; and presence of severe inflammatory infiltrate (90% neutrophils).

hypertrophic hepatocytes, multifocal feathery degenerations with an accumulation of brownish pigment in the cytoplasm and focal phenomena of macro-vesicular lipidosis. Triads appear surrounded by mild fibrosis and minimal biliary ductal proliferation. The spleen showed follicular hypertrophy.

Spleen and liver samples were also subjected to molecular investigation for *Bartonella* infection, as previously described for the blood sample and the pleural effusion. *B. henselae* DNA was detected in both specimens, thus supporting a systemic infection.

Molecular investigation for *E. faecalis* on thoracic effusion, spleen and liver was performed as previously described for blood sample and was negative.

DISCUSSION

Feline IE is uncommonly reported and has only been featured in a few case reports and two case series[3,5,11–20]; in contrast, the clinical course of IE in dogs has been widely described.[1,21,22] The prevalence of IE in cats is about 0.007%,[3,23] much lower than that of canine patients (0.05%–6.6%).[24] Though this might be due to a lower prevalence of IE in cats, it is also possible that the disease is underdiagnosed in this species.[3]

Bacteria cultured from the blood or valvular tissue of cats with IE have included similar pathogens to dogs such as *Staphylococcus*, *Streptococcus*, *Enterococcus* and *Escherichia coli*.[1,3,5,11,19,20,24,25] As in dogs, *Bartonella* species appear to be the most common cause of feline IE.[1,3,5,13,14,17,18] *Bartonella* spp. are gram-negative, haemotropic and pleomorphic bacteria. They are fastidious, facultative intracellular and arthropod-transmitted bacteria that have emerged as important pathogens in domestic animals and people.[26-29] The cat is the primary but not sole reservoir for *B. henselae*, the causal agent of human cat scratch disease.[13,27] Even though cats are usually considered to be healthy carriers of *B. henselae*,[30] infected cats rarely develop clinical signs.[2,26,30] Evidence suggests that *Bartonella* spp., in particular *B. henselae*, can cause endocarditis and myocarditis in cats, as reported for dogs and human patients.[1,3,5,13,14,17,18,30] Some factors that could influence the appearance of disease manifestations include virulence differences among *Bartonella* spp. and strains, differences in the host immune response, concurrent infectious or non-infectious diseases, immunosuppression and malnutrition.[27]

Bartonella spp. infection (ongoing infection or exposure) is diagnosed by using specialised microbiological culture techniques, molecular methods (PCR), immunohistochemistry and serology.[31] The most employed sample to diagnose *Bartonella* spp. ongoing infection by PCR or culture is peripheral blood. However, also oral swabs, lymph nodes or other tissue samples or aspirates can be used for this purpose. Serological tests can be employed to confirm prior or ongoing infection, but due to poor sensitivity, serology is of more limited value for predicting bacteraemia in animals potentially sick.[32] Besides, similar to dogs and humans, there are sick bacteremic cats that do not have detectable *Bartonella* spp. antibodies, for different reasons, including early infections.[14] Moreover, *Bartonella* spp. can be visualised in biopsied tissues by using different stains including Warthin–Starry staining.[18]

In our case report, the combined results of molecular tests (qPCR and cPCR performed on blood, pleural effusion, liver and spleen) and heart postmortem cytological and histological examination support the diagnosis of IE caused by chronic *B. henselae* infection.

In cats experimentally infected with *B. henselae* by blood transfusion, histopathological lesions revealed peripheral lymph node hyperplasia, splenic follicular hyperplasia, lymphocytic cholangitis/pericholangitis, lymphocytic hepatitis, lymphoplasmacytic myocarditis and interstitial lymphocytic nephritis.[33] In the cat of the present case report, the histopathological findings of heart, spleen, liver and kidney samples are compatible with those previously described in literature.

In addition, the bacteraemia caused by multi-resistant *E. faecalis* in the cat probably contributed to the worsening of the outcome. Enterococci are gram-positive facultative anaerobic bacteria, aligned as cocci in short chains. Enterococci, including *E. faecalis*, are a part of the normal microbial flora in the gastrointestinal tracts of humans and animals.[34,35] These bacteria can cause urinary, intra-abdominal, wound and pelvic infections, as well as bacteraemia and IE in different species.[34–39] *E. faecalis* is the predominant clinical pathogen responsible for more than 90% of human enterococcal IE,[39,40] and it is the third most common cause of IE in humans.[39] In veterinary medicine, only one case of IE, caused by these pathogens, has been reported in a 5-month rottweiler puppy.[25] A bacterial culture, qRT-PCR, or Warthin–Starry staining on the pathological valve was not performed in our patient, so a coexistence of *B. henselae* and *E. faecalis* in the valve cannot

be totally excluded. Indeed, the follicular hypertrophy of the spleen and the deposition of fibrin and necrosis in the valve leaflets are consistent with chronic and persistent infection by *B. henselae*, as the cat is the primary host and reservoir of this pathogen.[27] In addition, the structural damage of the valve leaflets may have favoured colonisation of the valve itself by the opportunistic bacterium *E. faecalis* of intestinal origin, contributing to the fatal outcome. Molecular investigations excluded the presence of this bacterium in both the hepatic and splenic samples, hypothesising the involvement of *E. faecalis* as a secondary infection on chronic infection by *B. henselae*.

The origin of *E. faecalis* bacteraemia can be various but involves frequently the gastrointestinal and urinary tracts.[37–39,41–43] The gastrointestinal tract is the suspected port of entry of *E. faecalis* in this domestic cat, accredited by histologically diagnosed lymphocytic enteritis.

Clinical signs of IE in cats are often vague, including lethargy, anorexia and weakness,[3] as exhibited by the cat in this report. Cats with IE commonly show respiratory distress, whereas in dogs it is less frequent.[1,3,21,22] The respiratory distress is often a reflection of the high prevalence of congestive heart failure (pulmonary oedema, pleural effusion, pericardial effusion or a combination of these), as reported in previous feline cases.[3,5,11,15,16] Left apical heart murmur is a very common finding in cats with IE during thoracic auscultations, but is not necessarily present.[3,5,15] This could be one of the reasons why endocarditis is underestimated in cats. In the cat of this case, although mitral regurgitation was present on echocardiographic evaluation, a heart murmur was not audible. Other common disorders evaluated in cats with IE are locomotor abnormalities (paresis, lameness or pain) caused by the occurrence of aortic AT or immunological phenomena.[2,3] The cat of this report showed right hindlimb paresis 1 day after the first presentation. Femoral pulse was absent, and the paw was cold and pale, suggestive of AT.

In cats with *B. henselae* infection, complete blood count, serum biochemical profiles and urinalysis findings are frequently normal; however, laboratory abnormalities reported with some frequency in sick cats include anaemia, eosinophilia, hyperproteinemia, hyperglobulinemia, neutropenia and thrombocytopenia.[44] In our case, we only found severe anaemia as a laboratory alteration. The severe non-regenerative anaemia could be caused by the IE itself. In fact, in human medicine, anaemia is reported as one of the most frequently encountered laboratory abnormalities related to IE.[45] The two main pathological mechanisms leading to non-regenerative anaemia are ineffective erythropoiesis, as a result of cytokine abnormalities seen in various states of inflammation, and decreased red blood cell lifespan, like in blood cell oxidative damage.[45] Anaemia is also frequently encountered in feline IE.[3,20]

The echocardiographic examination is an important instrument for the diagnosis of IE in humans and animals.[21,46] The mitral vegetative lesion found in our cat was similar to findings reported in previous feline IE reports.[3,5,12–16] Except for two reported feline cases where IE affects the tricuspid valve,[5,16] vegetative lesions appear to affect the aortic and mitral valves exclusively.[3,5] The independent, hyperechoic and oscillating mitral lesion found in the patient of this report was more consistent with vegetative endocarditis and less likely with other differential diagnoses of similar echocardiographic features as rupture of tendinous cord, a sterile thrombus or neoplasia, more commonly described in dogs.[47,48] Furthermore, myxomatous mitral valve degeneration, which could be a further differential diagnosis in dogs, is uncommon in cats,[47] so it was not considered a possible cause of the significant valvular changes in this case. Other findings at echocardiography examination were mitral insufficiency, suspected to be a consequence of modified valve, and left atrium dilatation for the volumetric overload. Myocardial alterations were not detected on echocardiographic examination, although a picture of myocarditis was found on histological examination.

Diagnosis of IE in humans utilises the Modified Duke's Criteria.[48] Physical examination findings, diagnostics and history are categorised as major or minor criteria. Combinations of major and minor criteria help to differentiate definitive from probable endocarditis or reject the diagnosis. This algorithm has also been proposed for veterinary patients.[2] Palerme et al.[3] proposed a modification of Duke's criteria for the antemortem diagnosis of IE in cats. Based on these Modified Duke's Criteria, the cat in this report fulfilled at least one major criteria (a vegetative echocardiographic lesion) and three minor criteria (vascular phenomena, presence of moderate mitral insufficiency in the absence of primary myocardial disease and microbiological evidence).

The prolonged corticosteroid therapy administered in the cat of this report probably played an important role in the onset of *B. henselae* endocarditis and *E. faecalis* intestinal translocation into the bloodstream. Indeed, prolonged steroid administration has been postulated to enable bacterial adherence to valvular structures in the heart,[38,49] as well as leading to a state of immunosuppression that predisposes to the spread and multiplication of opportunist pathogens. The combination of *B. henselae* infection, advanced age, co-infection with multi-resistant bacteria, exogenous corticosteroids administration may all have contributed to the development of severe disease and cat's death.

The antimicrobial therapy is the mainstay of IE treatment, but there is no standardised antibiotic protocol for the treatment of bartonellosis in cats or dogs.[50] Use of an antibiotic capable of crossing lipid membranes and reaching high intracellular concentrations such as amoxicillin, azithromycin, doxycycline and enrofloxacin is recommended.[51] In a recent clinical case, the combined use of marbofloxacin and azithromycin for 6 weeks was reported as a successful treatment in a cat with *B. henselae* endocarditis.[14]

Enterococci infections remain problematic, as they are difficult to eradicate from host tissues because of natural and acquired resistance to many antimicrobials. Reference antibacterial chemotherapy of enterococci infections consists of an association of penicillin or ampicillin with aminoglycosides.[52] However, aminoglycosides (e.g., amikacin) are potentially toxic and are only recommended for a short time. Concomitant therapy with furosemide is contraindicated because it may increase nephrotoxicity, so the use of these antibiotics in animals with IE and chronic heart failure is limited.[53] The resistance of enterococci to adverse environmental conditions has led to the emerging role of these bacteria in nosocomial infections in veterinary medicine as well as in human medicine.[34,35,52,53]

Although feline IE is uncommon, it should always be considered as differential diagnosis in cats, especially when there

are signs of systemic disease, a history of prolonged steroid therapy or concurrent infections.

AUTHOR CONTRIBUTION

Paola Paradies and Antonella Colella: conceptualisation, methodology. Paola Paradies and Antonella Colella: data curation, writing—original draft preparation. Paola Paradies, Grazia Greco, Antonella Tinelli and Marco Cordisco: investigation. Paola Paradies and Grazia Greco: supervision. Paola Paradies, Antonella Colella, Grazia Greco and Marco Cordisco: writing—reviewing and editing

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CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

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