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NOTE

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Reversible myocardial injury aggravated by complex arrhythmias in three *Toxoplasma gondii*-positive dogs

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ABSTRACT. Although *Toxoplasma gondii* represents an oft-cited cause of myocarditis in veterinary medicine, the existing literature on the pre-mortem demonstration of *T. gondii*-associated myocardial injury (MI) in dogs is scant. In this case series, we provide detailed clinical, laboratory, echocardiographic and electrocardiographic description of three *T. gondii*-positive dogs diagnosed with MI. In all cases, etiological diagnosis was based on the antibody screening test (all dogs had IgM titres ≥1:64) and MI was demonstrated by a concomitant increase of the serum concentration of cardiac troponin I (0.25–9.6 ng/ml, upper hospital limit <0.15 ng/ml). In all dogs, MI was aggravated by complex arrhythmias (ventricular in two dogs, and either ventricular and supraventricular in the remaining dog). In one case, left ventricular systolic dysfunction was also present. All dogs underwent an extensive diagnostic work-up aimed at excluding additional comorbidities, either cardiac and extra-cardiac, possibly able to contribute to MI, arrhythmias and systolic dysfunction. All dogs received appropriate antiprotozoal (i.e., clindamycin) and antiarrhythmic (i.e., amiodarone, sotalol) therapy. This was systematically followed by a simultaneous decline in *T. gondii* serology titres, normalisation of troponin level and left ventricular systolic function, and the resolution of clinical and electrocardiographic abnormalities. In light of this result, therapies were interrupted and subsequent controls ruled out any disease relapse. In these cases, the clinical and instrumental findings obtained at admission and rechecks strongly supported the clinical suspicion of toxoplasmic myocarditis.

KEY WORDS: cardiac troponin I, electrocardiography, Holter monitoring, toxoplasmic myocarditis, ventricular tachycardia

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In dogs, the term myocardial injury (MI) is conventionally used for patients in whom at least one cardiac troponin concentration, especially cardiac troponin I (cTnI), is above the upper reference limit [15, 24]. In many cases, MI represents a clinically relevant disease entity as it is frequently associated cardiac complications such as systolic dysfunction and arrhythmias. Both infectious and non-infectious diseases can cause MI in this species [6, 10, 14, 15, 17, 23, 24, 27]. Among infectious triggers, bacteria (e.g. *Bartonella* spp., *Borrelia burgdorferi*, *Ehrlichia canis*) and parasites (e.g. *Leishmania infantum*, *Dirofilaria immitis*, *Toxoplasma gondii*) represent frequent causes of canine MI, especially in adult dogs, whereas viruses seem to trigger MI more commonly in puppies (e.g. canine parvovirus, canine distemper virus) [6, 10, 14, 15, 24, 27]. Accordingly, adult dogs with MI are often tested for several bacterial and parasitic diseases, purposefully researching those which are known to be present in the country and capable of causing MI in this species [14, 27]. Among parasites, *T. gondii* represents an oft-cited trigger of cardiac involvement in companion animals. Nevertheless, clinical reports providing detailed data on cardiac abnormalities associated with this parasitic disease are extremely scant in veterinary literature [14]. Therefore, the aim of this case series is to describe the clinical, electrocardiographic, echocardiographic and laboratory findings of three *T. gondii*-positive dogs with reversible cardiac compromise.

Case 1: A 16-year-old 30-kg female mongrel dog was presented for recent onset of exercise intolerance. Past medical history was unremarkable. The dog lived indoors but had access to the outside and was current on vaccinations and parasite prevention. At admission, physical abnormalities were limited to a grade II/VI left apical systolic murmur, an irregularly irregular cardiac rhythm (heart rate 136–200 beats/min) and frequent pulse deficits. Thoracic radiographs were unremarkable (vertebral heart scale

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9.6, reference interval 9.7 ± 0.5 [1]). A stage B1 myxomatous mitral valve degeneration (MMVD) was diagnosed in light of the presence of typical irregular thickening and prolapse of mitral leaflets associated with an eccentrically-directed mitral regurgitation, without concurrent diltation of the left-sided cardiac chambers [12]. Moreover, a reduced left ventricular (LV) systolic function was found echocardiographically (Table 1). Electrocardiogram showed a sinus rhythm punctuated by multifocal ventricular premature complexes (VPCs) (minimal coupling interval 220 msec [maximal instantaneous heart rate 273 beats/min]). Further diagnostic steps aimed at excluding systemic diseases able to impair systolic function and cause ventricular arrhythmias (complete blood count, biochemistry, urinalysis and abdominal ultrasound) were unremarkable. The serum concentration of cTnI was also measured (IMMULITE 2000, Siemens, Erlangen, Germany) (9.6 ng/ml, hospital reference interval [HRI] <0.15 ng/ml) revealing myocardial injury (MI) [15, 24]. Additionally, a Holter monitoring was performed employing a commercially available software program designed for humans (Cube Holter software, Cardioline S.p.A., Milan, Italy) and validated for use in dogs [25, 26] and using a non-corrected orthogonal 3-lead system [21]. This allowed us to observe frequent VPCs often organized into complex arrhythmias, including sustained runs of polymorphic ventricular tachycardia (minimal coupling interval 200 msec [maximal instantaneous heart rate 300 beats/min]) (Fig. 1 and Table 2). Amiodarone was prescribed (loading dose 15 mg/kg orally every 24 hr for 2 weeks, maintenance dose 7.5 mg/kg orally every 24 hr), and blood samples were submitted for investigation of infections able to cause MI. The antibody screening tests for *B. burgdorferi*, *D. immitis*, *Anaplasma phagocytophilum*, *E. canis* and *L. infantum* were negative (SNAP 4Dx, IDEXX Laboratories Inc., Westbrook, ME, USA; MegaFLUO LEISH, Vetefarma S.r.l., Cuneo, Italy). Conversely, the patient's IgG and IgM titres for *T. gondii* (MegaFLUO TOXOPLASMA Gondii, Vetefarma S.r.l.) were both positive at 1/80, indicating an active infection [6]. The dog was started on clindamycin (Antirobe, Zoetis Italia S.r.l, Roma, Italy) (9.5 mg/kg orally every 12 hr). After 2 months, physical examination revealed no abnormalities apart from the heart murmur associated with MMVD, LV systolic function was normal (Table 1), cTnI was decreased (0.66 ng/ml) and the IgM and IgG were both negative. Moreover, a significant electrocardiographic improvement was documented by Holter as an almost complete disappearance of VPCs was observed (Fig. 2 and Table 2). Accordingly, therapies were interrupted and a control was planned after 1 month. At that time, cTnI was within HRI (0.14 ng/ml) and no relapse of ventricular arrhythmias were documented. The dog continued to do well for 2 years; then, the follow-up was lost.

Case 2: A 10-year-old 24-kg female Labrador was presented for two episodes of syncope over the previous week. The dog lived outdoors and was reported to hunt mice. The dog had no history of previous diseases; vaccinations and parasite prevention were not regular. At admission, clinical abnormalities included an irregularly irregular rhythm (heart rate 120–320 beats/min) and frequent pulse deficits. Thoracic radiographs and echocardiography were normal. On electrocardiogram, sinus rhythm was punctuated by multifocal VPCs (minimal coupling interval 235 msec [maximal instantaneous heart rate 255 beats/min]) and unifocal atrial premature complexes (minimal coupling interval 186 msec [maximal instantaneous heart rate 326 beats/min]). Blood was drawn for complete blood count, biochemistry and cTnI. Laboratory abnormalities were limited to an increased cTnI (0.25 ng/ml). On Holter monitoring, ventricular and atrial ectopies, either isolated and organized into complex arrhythmias, were identified (Fig. 3 and Table 2). Additional blood samples were sent for antibody screening tests for the same pathogens investigated in Case 1, and for *Bartonella* polymerase chain reaction. The dog tested positive only for *T. gondii*; an active infection was documented by the patient's IgM and IgG titres (1:80 and 1:640, respectively). Sotalol (2 mg/kg orally every 12 hr) and clindamycin (12.5 mg/kg orally every 12 hr) were prescribed. No further episodes of syncope were not noticed by the onwers after the start of medical treatment. After 2 months, the dog was clinically normal, the cTnI was within HRI (0.13 ng/ml) and the IgG titre was unchanged, while the IgM titre was halved (1:40). Therapies were interrupted and a recheck was organized within 1 month. At that time, nor physical neither electrocardiographic abnormalities were found (Table 2). The dog continued to do well for 1 year; then, she died due to acute kidney injury.

Case 3: A 10-year-old 42-kg female German Shepherd was presented for recent onset of lethargy and weakness. No other relevant medical problems were present in anamnesis. The dog lived indoors but had access to the outside and was current on vaccinations and parasite prevention. Physical evaluation revealed hyperthermia (39.8°C), a grade III/VI left apical

Table 1. Selected echocardiographic findings of the dog showing left ventricular systolic dysfunction at admission

Measurement	Formula	Case 1		Comparison intervals	References
		Admission	Control		
LA/Ao		1.35	1.35	<1.6	[22]
EPSS (mm)		8.5	5	1–6	[13]
LVIDDn	$LVIDD/[BW]^{0.294}$	1.4	1.47	1.27–1.85	[5]
LVIDSn	$LVIDS/[BW]^{0.294}$	1.14	0.99	0.71–1.26	[5]
EDVi (ml/m^2)	EDV/BSA	64	72	49.8–122.4	[28]
ESVi (ml/m^2)	ESV/BSA	39	28	13.2–38.0	[28]
SF (%)	[(LVIDD-LVIDS)/LVIDD] × 100	18	33	30–49	[28]
EF (%)	[(EDV-ESV)/EDV] × 100	39	61	57.8–82.1	[28]

BSA: body surface area; BW: body weight; EDV: end-diastolic volume; EDVi: end-diastolic volume index; EF: ejection fraction; EPSS: mitral-valve E-point-to-septal-separation; ESV: end-systolic volume; ESVi: end-systolic volume index; LA/Ao: left atrial-to-aortic root ratio; LVIDD; left ventricular internal diameter in diastole; LVIDDn; left ventricular internal diameter in diastole indexed to bodyweight; LVIDS; left ventricular internal diameter in systole; LVIDSn: left ventricular internal diameter in systole indexed to bodyweight; SF: shortening fraction.

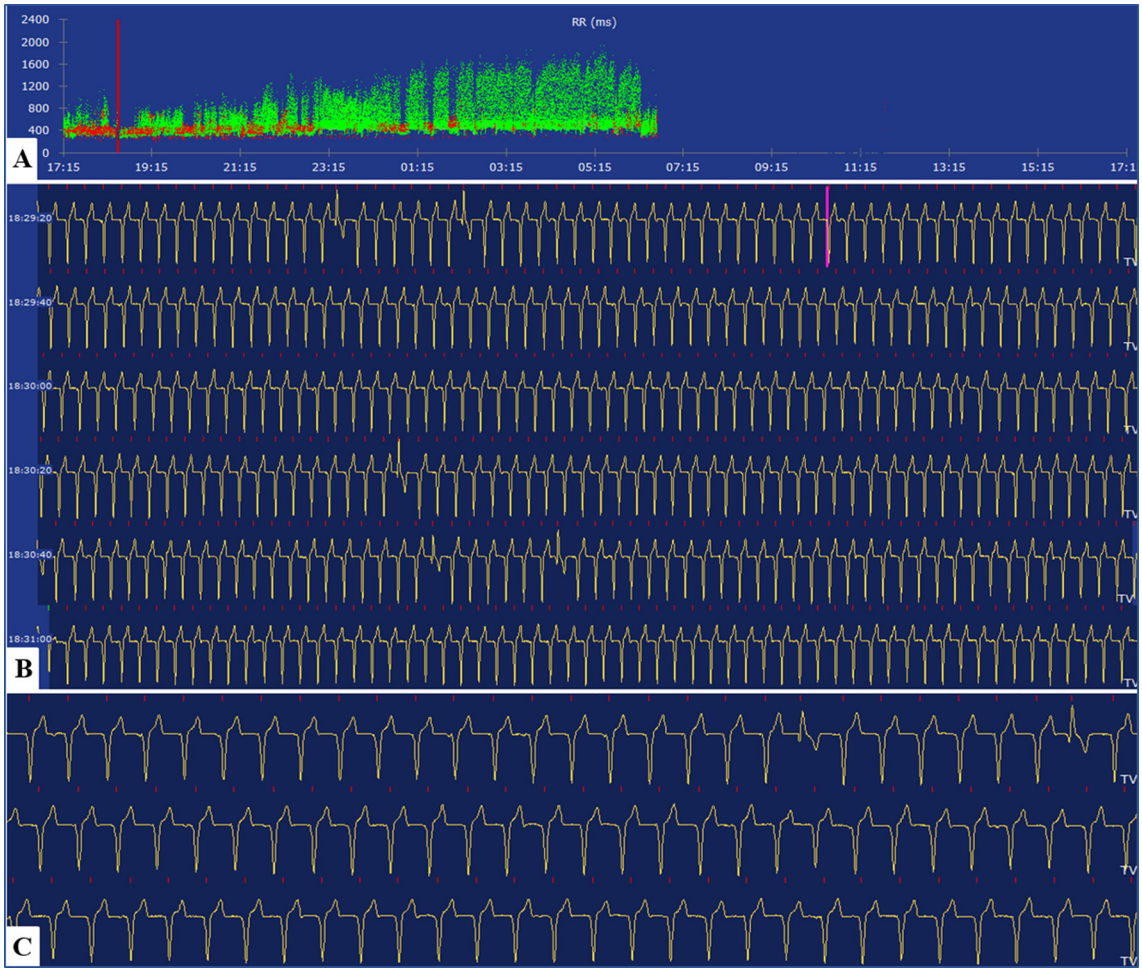

Fig. 1. Holter monitoring obtained in Case 1. The recording is limited to 13 hr and 25 min due to the premature detachment of electrodes caused by uncooperativeness of the dog. Despite this, the Holter findings were considered sufficient to justify the anamnestic and physical findings of the dog as well as to prescribe an antiarrhythmic therapy. **A**. Tachogram is presented above the selected portion of Holter recording. On tachogram, the time of day and the RR intervals are represented on the X-axis and Y-axis, respectively. Variations of the heart rate are depicted as increases and decreases of the band of RR intervals. Based on the QRS duration, the software identifies 'typical beats' (≤70 msec; i.e., sinus beats) and 'atypical beats' (>70 msec; i.e., ventricular ectopic complexes) and represents them on tachogram as green and red dots, respectively. In the case described herein, the diffuse presence of red dots with RR intervals largely <400 msec indicates frequent premature ventricular premature ectopic complexes. On both tachogram and electrocardiographic tracing, a red line indicates the moment analyzed. **B**. The selected portion of electrocardiogram shows a run of sustained ventricular tachycardia (mean heart rate 188 beats/min). Paper speed: 22.1 mm/sec. Amplitude: 5 mm/1 mV. Channel: Z axis. **C**. Close-up of a selected portion of electrocardiographic tracing aimed at providing further visual details on ventricular tachycardia. Note the presence of two different populations of ventricular ectopic complexes which are characterized by distinct morphology and polarity. Paper speed: 44.3 mm/sec. Amplitude: 5 mm/1 mV. Channels: Z axis.

Table 2. Selected electrocardiographic findings of the three cases reported herein

	Case 1		Case 2		Case 3	
	Admission	Control	Admission	Control	Admission	Control
Diagnostic technique	HM	HM	HM	HM	ECG	HM
Recording duration	13 hr, 25 min	24 hr	24 hr	24 hr	5 min	24 hr
VPCs (No.)	4,376	7	173	2	160	1
V-CPTs (No.)	1,825	0	0	0	2	0
V-TPTs (No.)	985	0	0	0	2	0
AIVR (No.)	1,486	0	2	0	0	0
VT (No.)	825	0	4	0	10	0
APCs (No.)	0	0	63	0	0	0
AT (No.)	0	0	15	0	0	0

AIVRT: accelerated idioventricular rhythm (i.e., ≥4 VPCs at a rate between 60 and 160 beats/min); APCs: isolated atrial premature complexes; AT: atrial tachycardia (i.e., ≥4 APCs at a rate >160 beats/min); ECG: electrocardiogram; HM: Holter monitoring; VPCs: isolated ventricular premature complexes; V-CPTs: ventricular couplets; V-TPTs: ventricular triplets; VT: ventricular tachycardia (i.e., ≥4 VPCs at a rate >160 beats/min).

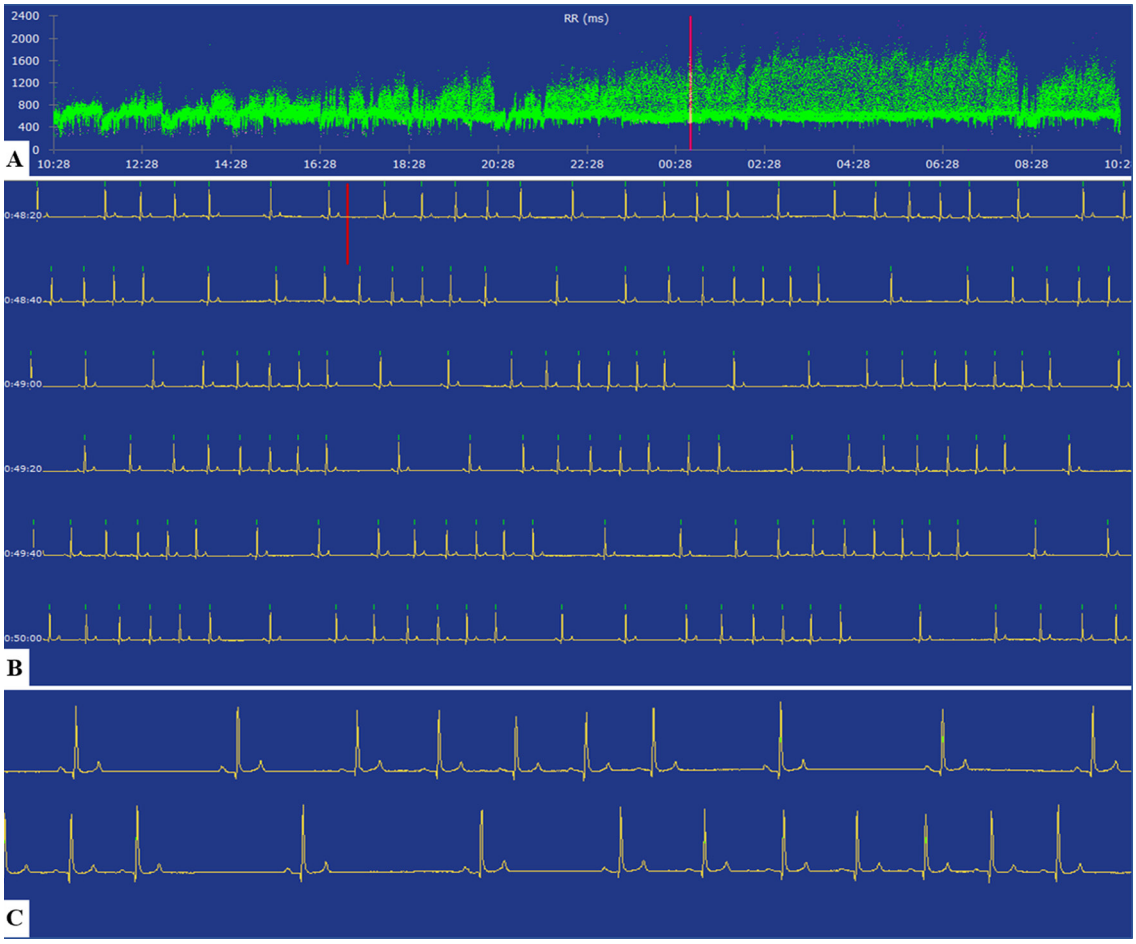

Fig. 2. Holter control obtained in Case 1. **A**. On tachogram, note the lack of red dots, indicating the disappearance of numerous ventricular arrhythmias identified at admission. **B**. The selected portion of electrocardiogram shows sinus arrhythmia (mean heart rate 80 beats/min), which represented the dominant rhythm for the entire recording. Paper speed: 22.1 mm/sec. Amplitude: 5 mm/1 mV. Channel: X axis. **C**. Close-up of a selected portion of electrocardiographic tracing aimed at providing further visual details on sinus rhythm. Paper speed: 44.3 mm/sec. Amplitude: 10 mm/1 mV. Channels: X axis.

systolic murmur, an irregularly irregular rhythm (heart rate 120–200 beats/min) and frequent pulse deficits. Echocardiography demonstrated a stage B1 MMVD with preserved left ventricular systolic function. Frequent unifocal VPCs often organized into complex arrhythmias (minimal coupling interval 320 msec [maximal instantaneous heart rate 188 beats/min]) were identified electrocardiographically (Table 2). Laboratory tests initially included complete blood count, biochemistry, a thyroid profile, cTnI and urinalysis. Clinicopathologic abnormalities indicated systemic inflammation (white blood cells 18,600/µl, HRI 5,050–16,760/µl; neutrophils 15,900/µl, HRI 2,950–11,640/µl; C-reactive protein 3.4 mg/dl, HRI <0.89 mg/dl) and MI (cTnI 0.28 ng/ml). Blood samples were then sent for antibody screening tests for the same pathogens investigated in Case 1, and for *Neospora caninum* (Test IDEXX Neospora Ab, IDEXX Laboratories Inc.). Moreover, as the dog was diagnosed with MI during a local surge of coronavirus disease 2019, an additional serum sample as well as nasopharyngeal and rectal swabs were sent for *severe acute respiratory syndrome coronavirus 2* seroneutralization (GenScript cPass™ SARS-CoV-2 Neutralisation Antibody Detection Kit, GenScript Biotech Co., Ltd., Leiden, Netherlands) and polymerase chain reaction (targeting E gene as previously described by Corman *et al*. [4]), respectively [23]. Positivity was documented exclusively for *T. gondii*; the patient's IgM and IgG titres (1:64 and 1:640, respectively) indicated an active infection. Sotalol (2 mg/kg orally every 12 hr) and clindamycin (10 mg/kg orally every 12 hr) were prescribed. After 2 months, clinical, electrocardiographic (Table 2) and clinicopathologic abnormalities were resolved (cTnI 0.03 ng/ml); moreover, the IgM was negative and the IgG titre was halved (1:320). Therapies were interrupted and no disease relapses were subsequently documented. The dog was still alive and doing well at the time of manuscript writing (7 months after MI resolution).

This report describes three *T. gondii*-positive dogs with MI predominantly complicated by arrhythmias. In these cases, the clinical and instrumental findings obtained at admission and rechecks caused the clinical suspicion of toxoplasmic myocarditis (TM) [6, 14, 16, 29]. The term MI and myocarditis are not synonyms, and the former may be a consequence of the latter. Specifically, the term myocarditis refers to inflammatory myocardial infiltration associated with cardiomyocyte damage of non-

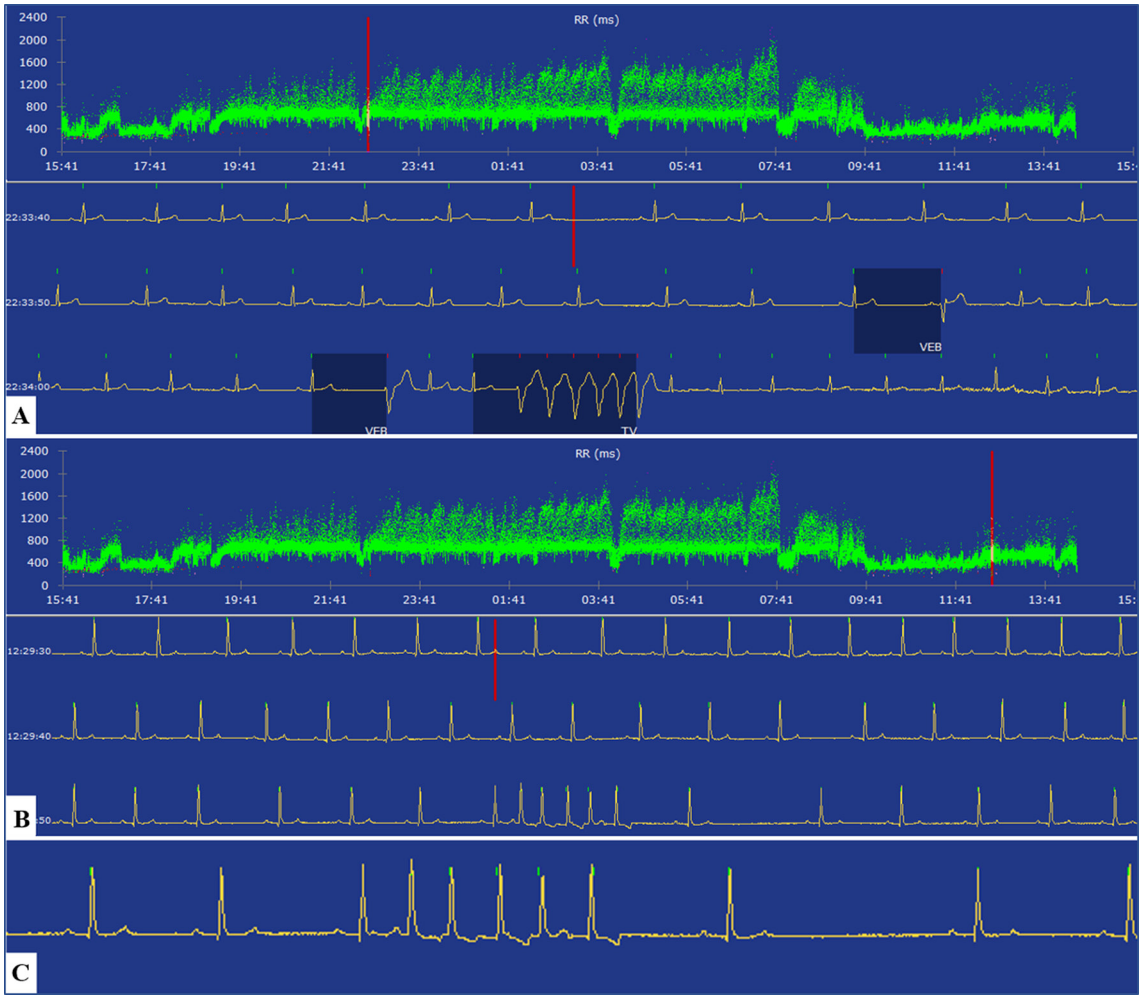

Fig. 3. Holter monitoring obtained in Case 2. **A**. The selected portion of electrocardiogram shows a run of non-sustained ventricular tachycardia (maximal heart rate 251 beats/min). Paper speed: 44.3 mm/sec. Amplitude: 5 mm/1 mV. Channel: X axis. **B**. Another selected portion of electrocardiogram of the same patients shows a run of non-sustained atrial tachycardia (maximal heart rate 288 beats/min). Paper speed: 44.3 mm/sec. Amplitude: 5 mm/1 mV. Channel: X axis. **C**. Close-up of a selected portion of electrocardiographic tracing aimed at providing further visual details on atrial tachycardia. Paper speed: 44.3 mm/sec. Amplitude: 5 mm/1 mV. Channels: Z axis.

ischaemic origin [3, 27]. Both infectious and non-infectious diseases can cause myocarditis, with the former appearing more relevant in dogs [6, 10, 14, 17, 23, 24, 27].

Among infectious diseases, toxoplasmosis represents an oft-cited cause of myocarditis. Nevertheless, pre-mortem descriptions of canine TM are scant [14], and published investigations are largely limited to necropsy reports [7, 8, 30]. The true incidence of TM in the general canine population is unknown, mainly because definitive diagnosis requires histological confirmation and, therefore, is obtainable at post-mortem examination or with endomyocardial biopsy [6–8, 14, 19, 27, 30]. However, the latter is used infrequently in this species, due mainly to its invasiveness and clinically relevant intraprocedural risks (e.g., cardiac tamponade due ventricular wall perforation and aggravation/induction of arrhythmias) [11, 14, 27]. Consequently, the pre-mortem diagnosis of canine TM is often presumptive and is based on anamnestic and clinical information combined with findings from non-invasive diagnostic tests, such as laboratory exams, echocardiography and electrocardiography [6, 14, 27]. Unfortunately, both toxoplasmosis and myocarditis are polymorphic diseases characterised by great variability in clinical presentation; therefore, no consistently recognisable clinical syndrome exists [2, 6, 14, 27]. With specific regard to toxoplasmosis, the clinical picture in dogs may range from neurological signs (e.g., seizures, cranial nerve deficits, tremors, ataxia, and paresis or paralysis often due to encephalomyelitis) to myositis with muscle wasting and stiffness, ocular compromise (e.g., necrotizing conjunctivitis, anterior uveitis, endophthalmitis, and chorioretinitis) or cutaneous manifestations (e.g., erythematous epidermal nodules, pyogranulomatous or necrotizing dermatitis, and panniculitis) [2, 6]. In contrast, in dogs, cardiac compromise represents an exceptionally rare complication of this parasitic disease, especially if not associated with involvement of other organs [6, 14].

Given the above, a holistic approach considering all the available findings from initial evaluation and rechecks is necessary to provide convincing evidence of TM and guide treatment. In our dogs, cumulative data suggested that *T. gondii* had likely triggered myocarditis since (1) no other obvious causes of disease were identified despite the extensive diagnostic workup aimed

at researching cardiac as well as extracardiac disorders able to induce arrhythmias, systolic dysfunction and cTnI elevation; (2) etiological diagnosis (i.e., all dogs had IgM titres ≥1:64 [6]) and concomitantly increased cTnI indicated ongoing infection associated with simultaneous MI [15, 24]; (3) the decline of *T. gondii* serology titres coincided with normalisation of cTnI as well as with clinical, echocardiographic and electrocardiographic improvement; and (4) the aforesaid results were achieved only after specific antiprotozoal therapy administration. A similar, rational diagnostic approach has been already described for clinical diagnosis in human [16, 18] and feline TM [29].

Concerning TM pathogenesis, as *T. gondii* does not produces toxins, myocardial compromise results from tachyzoite replication within cardiomyocytes or, if tachyzoite replication is attenuated by an appropriate immune response, from cardiac cyst formation/rupture [6, 9, 16, 18]. Histologically, this results in myocardial inflammation and necrosis as well as myocardial and interstitial fibrosis [16, 18]. The clinical course of TM is variable, ranging from subclinical changes (e.g., mild LV morphological/functional abnormalities) to life-threatening complications (e.g., arrhythmias, heart failure) [14, 16, 18, 29]. Such variability may depend on the host species, its immune response, the degree of virulence of the *T. gondii* strain and extension of cardiomyocyte infection/injury [6, 16, 18]. In this report, arrhythmias represented the predominant disease manifestation. Intriguingly, this clinical picture has not previously been reported in canine TM but represents a known scenario in human medicine [16, 18].

This case series has some limitations, first of all the lack of histopathology to conclusively confirm TM. The lack of pathology was due to our choice of not performing an endomyocardial biopsy (as, in our opinion, the risk/benefit assessment was in favour of risks) as well as to the improvement of patients, who survived to the disease state thanks to the prompt diagnosis and proper therapy (thus precluding post-mortem evaluation). Although the outcome of these cases was favourable and supported our diagnostic and therapeutic choices, the lack of histopathology could lead to speculate that the *T. gondii* infection was incidental and did not represent the primary cause of MI in these cases. However, this speculation presupposes that some comorbidities had arisen previously/concomitantly that had triggered cardiac injury. Nevertheless, in light of the extensive diagnostic work-up, we considered this theory unlikely. Indeed, apart from toxoplasmosis, only a stage B1 MMVD was found (2/3 cases), which is unlikely to cause the increased cTnI or the clinical and electrocardiographic abnormalities reported herein. Second, as our dogs were not tested for all the reported infective causes of myocarditis (although a remarkable number of infectious diseases were tested, to rule out the most diffuse in our country [20]), it cannot be completely excluded that possible, concomitant pathogens may have also contributed to MI. However, it should be considered that simultaneous detection of *T. gondii* along with other cardiotropic pathogens during myocarditis represents an exceptionally rare condition in dogs [8].

In conclusion, despite the aforesaid limitations, this report supports a role for *T. gondii* as causative agent of canine MI, particularly in dogs with complex arrhythmias. Clinicians should be aware of the electrocardiographic and echocardiographic features as well as clinical significance of cardiac involvement in *T. gondii*-positive dogs and consider this parasitic disease in the list of triggers of MI in this specie.

CONFLICT OF INTEREST. None of the authors has a conflict of interest to declare.

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