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Leishmania spp. ile Doğal Enfekte Köpeklerin Artrosentezinde Ksilazin'in Elektrokardiyografik Etkisi

Electrocardiographic Effects of Xylazine in Arthrocentesis of Dogs Naturally Infected with *Leishmania* spp.

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ÖZ

Amaç: Bu çalışmanın, amacı *Leishmania* spp. ile doğal enfekte köpeklerde, genu eklemlerinin aseptik artrosentezi için preanestezik ajan olarak ksilazin ile sedasyon uygulanan köpeklerdeki elektrokardiyografik değişiklikleri araştırmaktı. **Gereç-Yöntem:** On üç enfekte yetişkin melez köpeğe (8 erkek, 5 dişi) premedikasyon olarak 1,5 mg/kg Xylazine HCl intramusküler olarak uygulandı. On iki derivasyonlu bilgisayarlı elektrokardiyografik muayeneler premedikasyondan önce ve indüksiyondan 30 dakika sonra yapıldı. Poliartritli köpeklerin artikulasiyo genu eklemlerinde amastigot tespiti için sinoviyal sıvı (SF) yaymaları mikroskop altında değerlendirildi. Kanin visseral leishmaniasis (CVL) tanısı *Leishmania* test kitleri (IDEXX SNAP® Leishmania Test) ve immünofloresan antikor testine (IFAT) dayanılarak konuldu. **Bulgular:** Mikroskopik olarak 11 köpeğin (%84,61) genu eklemlerinin SF'sinde amastigotlar tespit edildi. Ksilazin uygulamasından önce ve ilk uygulamada iki olguda ya hafif sinüs taşikardi ya da atriyal prematüre kompleks görüldü. Ksilazin uygulamasından 30 dakika sonra bradikardi (6/13), hafif sinüs taşikardi (2/13), atriyal prematüre kompleks (APC; 2/13), ventriküler prematüre kompleks (VPC; 2/13) ve birinci derece AV blok (1/13) görüldü. **Sonuç:** Ksilazin ile premedikasyon bradikardi, hafif sinüs taşikardi, APC/VPC veya birinci derece AV blok gibi istenmeyen yan etkilere neden olur ve bu da CVL'li köpeklerde ksilazin kullanımının dikkatle yapılması gerektiğini düşündürmektedir. Özellikle herhangi bir sedatif uygulamadan önce kardiyolojik muayene yapılmalıdır. Ayrıca, doğal enfekte köpeklerde *Leishmania* spp. enfeksiyonunun parazitolojik teşhisi için SF analizinin avantajlı olabileceği sonucuna varılmaktadır.

ABSTRACT

Objective: Aim of this study was to investigate the changes in electrocardiographic (ECG) parameters in naturally *Leishmania* infected dogs sedated with xylazine as a preanesthetic agent for aseptic arthrocentesis of the stifle joints. **Material and Methods:** Thirteen diseased adult mix dogs (8 male, 5 female) were administered 1.5 mg/kg Xylazine HCl intramuscularly as premedication. Twelve-lead computerized ECG examinations were made before premedication and at 30 min after induction. The synovial fluid (SF) smears were evaluated under microscopy for amastigotes detection in stifle joints of dogs with polyarthritis. A diagnosis of canine visceral leishmaniasis was made basing it on *Leishmania* test kits (IDEXX SNAP® Leishmania Test) and the immunofluorescence antibody test (IFAT). **Results:** The amastigotes were detected microscopically in the SF of stifle joints of 11 dogs (84.61%). Before xylazine administration and on initial administration, either mild sinus tachycardia or atrial premature complex (APC) was detected in two cases. Following 30 minutes of xylazine administration, bradycardia (6/13), mild sinus tachycardia (2/13), APC (2/13), ventricular premature complex (VPC; 2/13) and first degree AV block (1/13) were noticed. **Conclusion:** Premedication with xylazine induced undesirable side effects involving bradycardia, mild sinus tachycardia, APC/VPC or first degree AV block, which might suggest that the usage of xylazine in dog with CVL, must be done with cautions. Especially, prior to any sedative administration, cardiologic examination must be performed. It might also be concluded that SF analysis for the parasitological diagnosis of *Leishmania* spp. infection in naturally infected dogs might be advantageous.

INTRODUCTION

Canine joint diseases may be encountered in dogs of all age and breeds and evaluated by the cause as infectious and non-infectious. Inflammatory arthritis may result from Canine Visceral Leishmaniasis (CVL),[1-3] considered one of the most important protozoal diseases[4] and a common infection in the Mediterranean area.[5]

During CVL, arthritis may exist in two ways: first in existence of the parasite in the joint with granulomatous inflammatory response and second a type III hypersensitivity respond, with deposition of immune complexes within the joint.[3]

Arthrocentesis, synovial fluid aspiration from the joints via needle, is generally conducted under deep sedation or general anaesthesia. Frequently it is used for both diagnostic evaluation (synovial fluid analysis, microbiologic cultures, cytological evaluation, and injection of contrast material) and/or therapeutic applications (joint lavage to removal of fibrin and exudate, decompression of swelling, and drug injections).[6] Alpha-2 adrenoreceptor agonists (α_2-agonists) are attractive options in arthrocentesis because of their characteristics, making their usage popular as premedication for general anaesthesia. Their other pharmacological effects include analgesia, sedation, and anxiolysis.[7-9]

Xylazine has long been used in dogs for sedation and anaesthetic procedures.[9,10] Indeed, α_2-agonists, through stimulation of central and peripheral adrenoreceptors, significantly affect cardiovascular function, which becomes most significant in sick, unstable, or cardiovascular compromised patients.[7-9] From a point of view the cardiovascular effects of xylazine is quite important because CVL might affect cardiovascular system, in which the usage of xylazine remains unclear. Besides CVL might also affect cardiovascular system, foremostly causing myocarditis,[11-13] which might have influence or limit on the usage of drugs, such as xylazine, making alterations on the cardiologic parameters. The main negative cardiovascular effects of all α_2-agonists include bradycardia, and arrhythmias (1st and 2nd degree atrioventricular heart block), a dramatic reduction in cardiac output by up to 50% and an increase in systemic vascular resistance (SVR). [9,10]

Xylazine as a traditional agent and was the first α_2-adrenergic agonist to be used as a sedative and analgesic in veterinary practice.[14] Considering the arrhythmogenic and cardio-depressant effects of α_2-agonists, clinicians should be careful on the use of xylazine.[15-19]

Electrocardiography (ECG) is a valuable tool for interpretation of the possible arrhythmogenic effects of drugs on the cardiovascular system. It may provide valuable data regarding alterations in the electrophysiological function with being easy and cheaper method compared to other (none) invasive methods.[20] No previous work has been published on the effects of the xylazine on the ECG parameters in dogs with CVL subjected to arthrocentesis. These measurements are of value in ECG, suggesting possible safety usage of this compound. Therefore, the objectives of the present study were 1) to evaluate ECG parameters in naturally Leishmania-infected dogs under the sedation with xylazine for aseptic arthrocentesis of the stifle joints, and to evaluate diagnostic utility of microscopically SF analysis for leishmaniasis in dogs with polyarthritis.

MATERIAL and METHODS

Since the procedures used in the present study were classified as “routine clinical applications for diagnosis and treatment”, there was no need to get permission of local ethics committee, according to the Regulation on the Working Procedures and principles of Animal Experiments Ethics Committee published in the Official Gazette of Türkiye (15.02.2014/28914). Thirteen symptomatic dogs, 8 females and 5 males, were involved in this study. The dogs were referred to the University of Adnan Menderes, Faculty of Veterinary, Departments of Internal Medicine and Surgery due to CVL. The dogs presented polyarthritis, stiffness on hind legs, exfoliative dermatitis, onychogryphosis, lymphadenopathy, and/or loss of weight were screened for the presence of CVL due to CVL-related clinical signs.[21-23] In these dogs, CVL was diagnosed by a SNAP test, and then confirmed by IFAT, as described below. On the other hand to comparatively evaluate the efficacy of Xylazine HCl, control group was designed with Leishmania negative dogs which were presented for arthrocentesis. These dogs were sedated with the same protocol described for Leishmania positive dogs. The dogs were diagnosed with immune-mediated (non-infectious) nonerosive polyarthritis (IMPA).[24,25]

At initial administration, a tentative diagnosis of CVL was made by rapid diagnostic test kits (IDEXX SNAP® Leishmania Test) and by IFAT technique, with the cut-off titer of 1:40 as confirmatory.[26] The dogs underwent to sedation with Xylazine HCl (1.5 mg/kg IV) prior to arthrocentesis.

Afterwards, the samples of SF were obtained from both stifle joints of each animal by aseptic arthrosynthesis as described by Clements.[6] The feasible amount of SF, summing up 26 arthrocentesis, were collected[27] via a fine needle (25x7mm), and a 5 ml syringe containing ethylenediamine tetraacetic acid (EDTA) to prevent clot formation. ECG signals of each animal were obtained by 12-channels and 10 - lead computerized ECG device (BTL®-08 MT Plus), simultaneously. ECG was performed by bi-polar extremity derivations with augmented leads, and derivation II was used to evaluate ECG parameters including heart rate and rhythms, durations and amplitudes of ECG waves and segments.

Afterwards, smears were prepared on glass slides without centrifugation, following arthrocentesis and then were stained using Wright-Giemsa. At least 5 glass slides were prepared from the SF obtained from each stifle joint. The stained smears were examined

under a microscope (1000X) and classified as positive or negative for the presence of *Leishmania* spp.

RESULTS

Leishmania snap test kits revealed that all 13 cases were positive. Besides, IFAT showed that all cases had seropositive with titters ranging from 1:40 to 1:640. The SF specimens were examined under microscopy and amastigotes were noticed in the SF of both stifle joints of 11 dogs (84.61%). Before xylazine administration and on initial administration, mild sinus tachycardia and APC were observed in 1 dog amongst cases. Following 30 minutes of xylazine administration, bradycardia (6/13), mild sinus tachycardia (2/13), APC (2/13), VPC (2/13), and first-degree of AV block (1/13) were noticed (Table 1).

Table 1. Electrocardiographic changes during arthrocentesis procedure in dogs with CVL. Control group involved Leishmania negative dogs with IMPA submitted for arthrocentesis and sedated according to the protocol described.

	Before and After Xylazine Administration			
	Diseased dogs		Control dogs	
ECG abnormality	Before	After	Before	After
Mild sinus tachycardia	1/13	2/13	-	-
Bradycardia	-	6/13	-	4/7
Atrial premature complex	1/13	2/13	-	-
Ventricular premature complex	-	2/13	-	-
First degree AV block	-	1/13	-	1/7

DISCUSSION

The present study showed the ECG changes in naturally infected Leishmaniasis in dogs, before and after intramuscular xylazine injections, underwent arthrocentesis. In a previous experimental study evaluating cardiovascular and respiratory effects of romifidine and/or xylazine in ketamine anaesthesia in dogs,[28] ECG showed arrhythmias. In that study, the vast majority of cardiovascular alterations induced by xylazine or romifidine involved bradycardia. Second-degree atrioventricular (AV) heart block was also noticed in some of the dogs, whereas there was no evidence of first-degree and third-degree AV heart block.[28] In the present study, in good accordance with the literature information,[15-20] bradycardia most seen arrhythmia in 8 out of 13 dogs. Cardiac and respiratory depression caused by xylazine has long been recognized in the literature,[17-19,28] whereas their details are lacking in animals subjected to arthrocentesis, an important procedure in the diagnosis of polyarthritis in dogs. In parallel line with the purpose of this study, before the arthrocentesis which was performed to collect SF samples for the diagnosis of CVL, xylazine was administered to all cases. As aforementioned above, xylazine administration lead to the changes in cardiac electrophysiology, such as bradycardia, mild sinus tachycardia, APC/VPC or first-degree AV-block in dogs involved in the present study. The results were comparable to those of xylazine administration in other animal species.[29-32]

Xylazine caused bradycardia and AV-block in goats injected intravenous xylazine HCl at a dose of 0.1 mg/kg.[29] This should be interpreted cautiously because of animals episodes of missed[30,31], and irregular heart-beats along with bradycardia after xylazine administration.[32] In ponies, intravenous administration of xylazine caused sinoatrial (SA) blocks and transient AV-blocks within the 1st minute of its injection.[33] Similarly ECG alterations were observed in the dogs involved in the present study. Besides, in control group, 4 out of 7 *Leishmania* negative dogs presented and sedated for arthrocentesis suffered from bradycardia. Although only a limited portion of control cases were enrolled, due to ethical concerns, it may be comparatively and safely suggested that xylazine side effects were more often detected in dogs with Leishmaniasis, in contrast to dogs with IMPA.

Serological examinations, mostly Enzyme-Linked Immunosorbent Assays (ELISAs) and IFATs are strongly suggested by the World Organization for Animal Health[34] for the diagnosis of CVL. Contrarily, serological studies may cause false-positive results (i.e. cross reactions with other etiological agents).[27] Besides, serological tests are more expensive than the other techniques of parasitological diagnosis.[35] Parasitological analyses provide 100% specificity, and are reasonably priced with variable sensitivity.[36] Samples of skin lesions, lymph node, spleen and bone marrow might be used for parasitological diagnosis of CVL in naturally infected dogs, whereas the use of SF for this propose has been rarely reported.[36,37] Arthritis might be a sequel of CVL, due to the presence of the *Leishmania* spp. or immune complex deposition in the joint.[27] Relatively very few studies have already stated the identification of amastigotes on canine SF.[22,27,38] In the present study, SF analysis for the parasitological diagnosis of *Leishmania* spp. infection in naturally infected dogs revealed that 11 specimen out of 13 were detected to have amastigotes, suggesting the advantage of this technique in clinical settings.

CONCLUSION

Premedication with xylazine induced undesirable side effects involving bradycardia, mild sinus tachycardia, APC/VPC or first-degree AV block which might

suggest that the usage of xylazine in dog with CVL must be done with cautions. Especially prior to any sedative administration, cardiologic examination should be performed. Thus, based on these findings, it may be recommended to administer anti-arrhythmic drugs such as atropine to prevent xylazine-induced arrhythmias before xylazine administration.

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Olgu sunumu
Case report

Hipertrofik Kardiyomiyopatiye Bağlı Arteriyel Tromboembolizmi Olan Üç Kedide Pıhtılaşma Durumunun Tromboelastografik Değerlendirilmesi

Thromboelastrographic Evaluation of Coagulation Status in Three Cats with Arterial Thromboembolism due to Hypertrophic Cardiomyopathy

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Cats,
Coagulation,
Hypertrophic cardiyomyopathy

ÖZ

Arteriyel tromboembolizm (ATE) ile komplike olan veya olmayan hipertrofik kardiyomiyopatili (HCM) kedilerde tromboelastografi (TEG) kullanılarak pıhtılaşma ve fibrinolitik durumun nasıl değiştiğine dair bilgi eksikliği vardır. Bu nedenle burada HCM'ye bağlı ATE'li üç kedide koagülasyon durumu TEG ile değerlendirildi. Pıhtılaşma, protrombin zamanı (PT), aktive parsiyel tromboplastin zamanı (aPTT), d-dimer ve TEG parametreleri ile değerlendirildi. Bu klinik rapor, PT ve aPTT'nin hiper pıhtılaşmayı ve devam eden tromboz sürecini belirtmek için yeterli olmayabileceğini göstermiştir. TEG kullanılarak hiperkoagülabilitenin kedilerde tromboz tanısında bir kriter olarak kullanılabileceği düşünülmüştür.

ABSTRACT

There is lack of information on how coagulation and fibrinolytic status using thromboelastography (TEG) are altered in cats with hypertrophic cardiomyopathy (HCM) complicated with or without arterial thromboembolism (ATE). Thus, herein, coagulation status was evaluated with TEG in three cats with ATE due to HCM. Coagulation was evaluated by prothrombin time (PT), activated partial thromboplastin time (aPTT), d-dimer, and TEG parameters. This clinical report has showed that PT and aPTT may not be sufficient to indicate hypercoagulation and ongoing process of thrombosis. Hypercoagulability using TEG was thought to be able to use as a criterion for the diagnosis of thrombosis in cats.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) causes the thickening of heart muscle resulting in poor left ventricular relaxation and filling ability. HCM is the most common cardiac disease in cats, leading to arterial thromboembolism (ATE) with a high mortality rate.[1,2] The most common factors predisposing to the ATE are endothelial dysfunction, blood stasis, and a hypercoagulable state (Virchow's triad) in cats with HCM.[3]

Thromboelastography (TEG) measures the global viscoelastic properties of whole blood clot formation and gives detail on hypocoagulable and hypercoagulable states.[4-6] TEG parameters show platelet (PLT) functions and their interactions with each coagulation process such as clot time, clot kinetics, clot strength, clot elasticity, and fibrinolysis,[5-7] thereby providing advantages to the prothrombin time (PT), activated partial thromboplastin time (aPTT), and d-dimer.[7] There is no knowledge about TEG evaluation in cats with HCM and/or ATE. Also, the potential of TEG to describe hypercoagulation has not been reported in those cases yet. Thus, in this clinical study, coagulation status was evaluated by TEG, in conjunctive with the results of routine clinical and laboratory analysis in three cats with ATE due to symptomatic HCM.

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CASE HISTORY

Three cats with different breeds, ages, and body weights were included (Table 1). These cats were presented to the small animal clinic with the main symptoms of sudden onset painful paralysis in one (Case 1) or both hind limbs (Case 2 and 3). The transthoracic echocardiography was performed to evaluate cardiac geometry and function (CarisPlus®, Florence, Italy) (Table 2).[7] Blood samples were collected for hematological and biochemical analysis (VetScan®, Abaxis, USA). Serum levels of cardiac troponin (cTnI), pro-brain natriuretic peptide (ProBNP), and an inflammatory marker serum amyloid A (SAA) were measured using specific kits (VCheck® V200, Bionote, USA). Coagulation status was evaluated by PT and aPTT (VsPro, Abaxis, USA) and d-dimer levels (VCheck® V200, Bionote, USA) (Table 3), and kaolin-activated TEG (TEG®5000, MA, USA) (Table 4), as described in our[5,7] and other previous studies.[6] Computed tomographic angiography was performed to evaluate the blood flows of the arteries (Somatome Scope®, Siemens, Germany).[8]

Table 1. Signalment, selected parameters of physical examination and hemato-biochemical analysis in three cats with arterial thromboembolism (ATE) due to hypertrophic cardiomyopathy (HCM).

Parameters	Case 1	Case 2	Case 3	References*
Breed	Scottish fold	Mix	Mix	NA
Age – years	1	7	16	NA
Sex	Male	Male	Male	NA
Body weight Kg	3.5	5.2	4.3	NA
Temperature ^{0}C	38.6	39.1	38.7	38.1 – 39.2
Heart rate bpm	240	230	246	<220
Respiratory rate rpm	64	80	140	<40
WBC x10^3/uL	29.9	26.1	17.5	5.5 – 19.5
Hct %	32.9	22.8	31.0	30-45
PLT count x10^3/uL	106	68	246	300-800
ALT IU/L	112	563	187	22 – 84
ALP IU/L	84	68	142	9 - 53
BUN mg/dL	112.7	45.4	52.0	17.6-32.8
Cr mg/dL	2.8	0.8	1.8	0.8 – 1.8
cTnI ng/mL	3.8	3.5	1.3	0.00 – 0.16
Pro-BNP pmol/L	>1500	>1500	1496	<50
fSAA ug/ml	4.2	3.8	3.0	<5.0

*www.msdvetmanuel.com WBC: White blood cell count, Hct: Hematocrit, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, BUN: Blood urea nitrogen, Cr: Creatinine, Pro-BNP: Pro-brain natriuretic peptide, fSAA: Feline serum amyloid ANA: Not applicable

Table 2. Some echocardiographic parameters obtained from three cats with arterial thromboembolism (ATE) due to hypertrophic cardiomyopathy (HCM).

Parameters	Case 1	Case 2	Case 3	References*
IVSd mm	6.2	6.5	6.2	4.6 ± 0.6*
LVIDd mm	18.9	10.7	15.7	15.9 ± 2.3*
LVPWd mm	6.0	11.0	9.6	4.3 ± 0.7*
IVSs mm	8.1	7.3	7.7	7.4 ± 1.3*
LVIDs mm	9.9	6.0	11.0	8.1 ± 1.8*
LVPWs mm	6.7	12.1	9.7	7.5 ± 1.1*
FS %	47.6	43.9	29.7	49 ± 7*
LA/Ao	2.9	1.8	2.9	0.9 ± 0.1*
AoVmax m/s	0.8	2.8	1.0	1.1 ± 0.2*
Mitral E/A	1.7	1.9	1.9	1.5 ± 0.3*
LA vol ml A2Ch	11.9	9.7	8.9	1.8 – 2.1**
LAA Vmax m/s	0.18	0.17	0.21	0.24-1.0***

IVSD: Interventricular septum diastole; LVIDd: Left ventricular internal diameter diastole; IVSs: Interventricular septum systole; LVIDs: Left ventricular internal diameter systole; LVPWd: Left ventricular post wall diastole; LVPWs: Left ventricular post wall systole; FS: Fractional shortening; LA/Ao: Left atrium/ aorta ratio; AoVmax: Aort maximal velocity; Mitral E/A: Mitral early ventricular filling (E) and late atrial contraction (A); LA vol A2Ch: Left atrial volume at apical 4-chamber view; LAA Vmax: Left atrial appendage maximal flow velocity. References were collected from *Boon JA (Veterinary Echocardiography, 2nd ed., Wiley-Blackwell, USA, 2010), **Rauch et al. (BMC Vet. Res. 16: 263, 2020), and ***Schober and Maez (J Vet Intern Med, 20:120-30, 2006).

Table 3. Prothrombin time (PT), activated partial thromboplastin time (aPTT), and d-dimer in three cats with arterial thromboembolism due to hypertrophic cardiomyopathy.

Parameters	Coagulation cascade	Case 1	Case 2	Case 3	References*
PT sec	Extrinsic system	18.5	15.9	16.7	15-21
aPTT sec	Intrinsic system	100.7	110.5	97.0	94-125
D-dimer ug/mL	Fibrinolytic system	0.1	0.1	0.2	<0.3

*according to suggested reference values by manufactures; PT and aPTT (VsPro, Abaxis, USA) and d-dimer (VCheck V200, Bionote, USA).

Table 4. Thromboelastographic analysis in three cats with arterial thromboembolism due to hypertrophic cardiomyopathy.

Parameters	Case 1	Case 2	Case 3	References
Clot time				
– **R time min**	0.7	1.2	1.8	1.4 – 9.5[#]
– **SP min**	ND	1.0	1.6	2.4 – 15.8[*]
Clot kinetics				
– **K time min**	0.8	0.8	0.8	1.2 – 3.9[#]
– **α-angle degree**	83.9	80.7	81.6	45.5 – 73.5[#]
Clot strength				
– **MA mm**	76.3	76.8	80.3	46.8 – 66.1[#]
– **PMA**	1.0	0.0	0.0	RI
– **TMA min**	ND	15.4	13.0	13.4 – 39.4[Ψ]
– **G Dyn/sc**	16.1	16.6	20.4	7.1 ± 2.4
– **E Dyn/sc**	ND	331.2	407.1	92 – 217
– **TPI sec**	ND	198.8	244.3	5-90[β]
Clot stability				
– **A30 mm**	69.5	76.8	76.3	36.3 +/- 17.9
– **A60 mm**	68.2	73.6	71.1	30.3 +/- 17.0
Clot lysis				
– **EPL %**	0.1	0.0	2.0	0 – 15[β]
– **Ly30 %**	0.1	0.0	2.0	2.4 – 15.8[*]
– **Ly60 %**	1.2	1.1	5.0	1.1 – 13.1[#]
– **CLT min**	ND	60.6	60.6	RI
Overall assessment				
– **CI**	7.2	6.7	6.7	-4.6 – 2.5[*]

References were collected from [#] Marschner et al. (2010); [*] Engelen et al. (2017); [Ψ] Çöl et al. (2013); and [β] Liu et al. (2016).
ND: Not determined; RI: Reference intervals could not be found for related parameters.

RESULTS and DISCUSSION

Our observations such as acute onset of paralysis, weak (Case 1) or undetectable pulses (Case 2 and 3) of the femoral artery in the affected legs, and pale (Case 1) or cyanotic paw pads (Case 2 and 3) were typical signs for representing ATE compatible with the previous studies.[2,3] HCM was suspected on the clinical and radiological findings, and was confirmed by interventricular septum and left ventricular (LV) wall thickness, and different severity of left atrial (LA) dilation (Table 2), as reported earlier.[1,2] HCM was sub-classified as an obstructive form (HOCM) due to a high velocity of aortal flow in Case 2. Micro-clot and thrombus formation were characterized by the spontaneous echo contrast in dilated LA using M-mode echocardiography. The micro (Case 1 and 2) and large clots (Case 3) may move from the LA to the aortic trifurcation, right iliac artery (Case 1), and the caudal part of the abdominal aorta (Case 2 and 3; Figure 1). Increased cardiomyocyte necrosis and LV wall stress (represented by increased cTnI and pro-BNP levels) with pleural and pulmonary edema, were suggestive for congestive heart failure in cats studied[3] (Table 1).

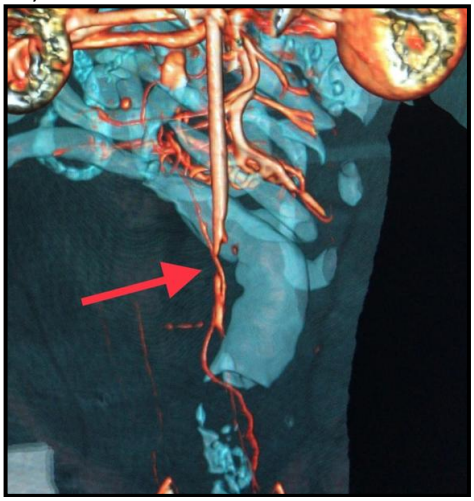

Figure 1. Computed Tomography (CT) Angiography shows the blockade of blood flow (red arrow) at the level of abdominal aorta in a cat (Case 2).

As seen in Table 3, our results were compatible with the previous studies reporting that PT and aPTT might be better for identifying hypocoagulability rather than hypercoagulability[2], and that plasma d-dimer were within the reference ranges in cats with HCM.[2] TEG provides a comprehensive overview of the clotting process, from initial thrombin generation to fibrinolysis.[4] Observed decreases in the reaction (R), split (SP), and kinetic times (K), and an increase in α-angle (Table 4) revealed the shortened duration required for initial fibrin formation, meaning the increased tendency of blood to coagulate (hypercoagulability).[9] Among TEG parameters, maximum amplitude (MA) and G values are widely used to evaluate clot strength. An increase in MA means that the patient's blood is in a hypercoagulable state and is prone to thrombosis.[10] In this study, while MA increased, time to MA (TMA) was detected at a low normal level, showing that the ultimate strength of the fibrin clot might be increased in cats with ATE due to HCM. G value is the single most important value of the entire assay because of representing the overall function or effectiveness of the clot.[10] In addition to higher G value, clot elasticity parameters (E and thrombodynamic potential index-TPI) were found higher than their references, indicating the presence of a thrombotic state in cats with ATE, as suggested.[9]

Clot stability and fibrinolysis were evaluated by TEG amplitude (A), lysis (Ly), and estimated percent lysis (EPL).[6,7] Herein, observed changes in these parameters may be associated with an increase in clot stability (represented by increased A values), decreased fibrinolysis (represented by low Ly values), and increased resistance to lysis (represented by prolonged clot lysis time) in the cats studied.[11] TEG CI value is a unique parameter providing an overall global assessment of the clotting process, from fibrin formation to clot lysis, in real-time.[10] The usefulness of the CI value for identifying hypercoagulability and predicting thromboembolic events was published in patients with prostate cancer[12] and gynecological oncology patients.[13] In this study, the observed increase in CI value was compatible with the changes in other TEG parameters representing hypercoagulability in three cats (Figure 2).

This is a pilot study, and thus, included the limited number of cases with ATE. Coagulation status is evaluated by a comprehensive coagulation panel. Some parameters such as plasma thrombin-antithrombin complex (TAT), fibrinogen level, clotting factors, and natural anticoagulant levels in this panel were not analyzed in our cases. These cats were discharged 5 days (Case 1), 10 days (Case 2), and 7 days (Case 3) after the admission, with a minimal restriction of walking in the affected legs, with a standard treatment protocol for ATE and HCM.[14]

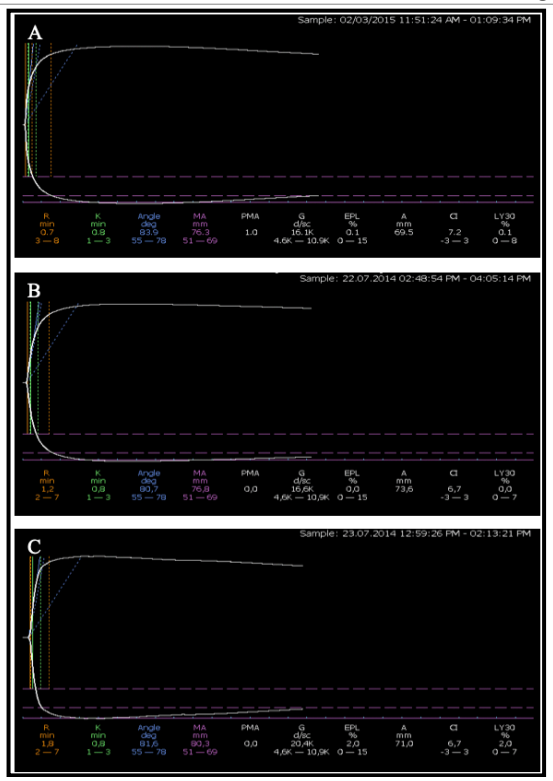

Figure 2. Thromboelastography tracings in Case 1 (A), 2 (B) and 3 (C).

Another limitation may be that coagulation status could not be reassessed before the cats were discharged from the hospital.

This case series showed that PT and aPTT may not be enough to indicate hypercoagulation and the ongoing process of thrombosis. Hypercoagulability using TEG may be used as a criterion for the diagnosis of thrombosis. Faster initiation of blood clotting, increased clot strength, and stability, and low clot lysis rate should be kept in mind to develop new diagnostic, and potential prophylactic and therapeutic strategies in HCM cats with ATE.

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Olgu sunumu
Case report

Hipertrofik Kardiyomiyopatiye Bağlı Akut Aortik Tromboembolisi Olan Bir Kedide Doku Plazminojen Aktivatörü Tedavisinin Tromboelastografi ile Değerlendirilmesi

Thromboelastography Evaluation of Tissue Plasminogen Activator Therapy in a Cat with Acute Aortic Thromboembolism due to Hypertrophic Cardiomyopathy

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Anahtar kelimler:
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Tromboelastografi,
Doku plazminojen aktivatörü,
Kedi

Key words:
Acute aortic thromboembolism,
Thromboelastography,
Tissue plasminogen activator,
Cat

ÖZ

Akut arteriyel tromboembolizm (ATE), trombusun aortun trifürkasyonuna yerleştiği, hemen tedavi edilmezse ölüme veya organlarda ciddi hasara yol açan çok ağrılı ve ölümcül ciddiyetli bir durumdur. ATE tedavisinde ilk seçenek olarak doku plazminojen aktivatörü (tPA) gibi trombolitik ajanlar tercih edilmektedir; ancak insan ve hayvanlarda spontan kanama gibi olası yan etkileri nedeniyle dikkatli kullanılmaları gerekir. Bu nedenle pıhtılaşma durumunun izlenmesi, çözünen intravasküler pıhtıların yönetimi ve tedavisinde önemli bir rol oynar. Pıhtı oluşumu, gücü ve lizis dinamiklerini ölçen ve pıhtı tutarlılığı hakkında bilgi sağlayan tromboelastografi (TEG), pıhtılaşma durumunu ve trombolitik tedaviye yanıtı değerlendirmede yararlı bir araç olarak kabul edilmiştir. Kedilerde intravenöz tPA ile uygulanan trombolitik tedavinin tromboelastografik takibini gösteren bir çalışma bulunmamaktadır. Bu nedenle burada hipertrofik kardiyomiyopatiye (HCM) bağlı ATE'li bir kedide tPA kullanılarak başarılı bir tromboliz rapor edilmiş ve ilk kez TEG ile trobolitik tedavi izlenmiştir.

ABSTRACT

Acute arterial thromboembolism (ATE) is an extremely painful and fatal serious condition in which the thrombus lodges in the trifurcation of the aorta, resulting in death or severe damage to organs if not treated immediately. Thrombolytic agents such as tissue plasminogen activator (tPA) are preferred as a first choice of the treatment for ATE; however, they should be used carefully because of their possible side effects such as spontaneous bleeding in human and animals. Therefore, monitoring coagulation status plays an important role in the management and treatment of dissolving intravascular clots. Thromboelastography (TEG) that measures the dynamics of clot formation, strength, and lysis, and provides information of clot consistency has been accepted as a useful tool for assessing coagulation status and response to thrombolytic therapy. There is no study showing the thromboelastographic monitoring of the thrombolytic therapy with intravenous tPA in cats. Therefore, we reported here thrombolysis by using tPA successfully in a cat with ATE due to hypertrophic cardiomyopathy (HCM) and for the first time monitoring the lytic treatment by TEG.

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INTRODUCTION

Aortic thromboembolism (ATE) is a condition in which a large blood clot (thrombus) has traveled and lodged itself in a location that cuts off the blood supply to parts of the body such as legs, kidneys, and brain.[1] Possible reasons for ATE include heart diseases, kidney diseases (renal failure and nephrotic syndrome), endocrine diseases (hypothyroidism and hyperadrenocorticism), neoplasia and pancreatitis.[2] ATE is one of the most common complications of hypertrophic cardiomyopathy (HCM) in humans[3,4] and cats.[5]

In the case of HCM, enlarged left atrium (LA) that promotes smoke-like stagnant or turbulent blood flow activating the coagulation pathway and promote clot formation. The cats suffering from ATE (FATE) are presented in general with an acute and distressing presentation with hyperventilation and severe pain, and are suddenly unable to use their hind legs appropriately. Physical examination shows absence of pulse in the affected legs and cold paws with cyanotic (blue-tinged) pads and nail beds confirming loss of blood supply along the extremity.[7]

Several studies suggest the use of thrombolytic as a gold standard therapy for ATE since surgical removal of the clot have risks (anesthesia, spontaneous reperfusion, and sepsis, etc.) in patients with heart disease.[1,5-7] However, there are limited clinical experience with thrombolytic agents such as streptokinase and recombinant tissue plasminogen activators (tPA) in dogs[8] and cats.[9-11] It was reported that tPA achieved better lysis rate than streptokinase in humans[13]. Drugs of tPA (alteplase, reteplase and tenecteplase) are one of the key components of the dissolution of blood clots. Primary function of tPA includes catalyzing the conversion of plasminogen to plasmin, the primary enzyme involved in the dissolution of blood clots.[9] The common points of the studies performed about thrombolytics are that close monitorization of coagulation during tPA therapy due to bleeding tendency and its intravenous administration as early as possible following diagnosis of ATE have been needed.[9]

Thromboelastography (TEG) is a viscoelastic hemostatic assay evaluating primary, secondary and tertiary hemostasis in whole blood. A major advantage of TEG compared to traditional methods evaluating hemostasis such as platelet count and global clotting times (prothrombin time – PT and activated partial thromboplastin time - aPTT) is the ability to assess clot formation from its initiation to fibrinolysis. TEG is also able to assess the interactions between platelets and clotting proteins, as well as other blood cells, a feature of coagulation that cannot be assessed by other currently clinically available methods.[9,14,16-19] To the best of the authors' knowledge, there is no information yet on the use of TEG in monitoring coagulation status in cats receiving tPA therapy. In this report, therefore, the effect of tPA treatment was evaluated using TEG in a cat with ATE due to HCM, before and 24 hrs after administration.

Case Description

A 3-year-old intact female domestic shorthair cat was presented to the animal hospital with a history of acute onset of dyspnea / tachypnea (84 respiration per minute [rpm]), hypothermia (36.5 °C), lameness and severe pain in hind legs. First clinical examination was performed at 6 hrs after initial of the symptoms and revealed the severe pain and loss of sensation in the hind legs, bruising on the extremity pads and ischemic purple color at the nail base. The cat was placed to oxygen cage after administering of furosemide (2 mg/kg, IV, bolus, and then two times at the same dose with 2 hrs. intervals; Lasix 20 mg/2 ml, Sanofi, İstanbul) and buthorphanol (0.25 mg/kg, SC; Butomidor 10 mg/ml, Interhas, Turkey) for the treatment of respiratory distress (possibly due to pulmonary edema) and pain stabilization, respectively.

Just before furosemide administration, blood samples were collected to evaluate complete blood cell count (CBC; HM5, Abaxis, USA), serum biochemistry profile (VetScan VS2, Abaxis, USA) and coagulation status (TEG 5000, Haemoscope Hemostasis Analyser, USA). Results revealed a hemoconcentration and increases in serum total protein, albumin, alanine aminotransferase, and blood glucose levels. Serum NT-ProBNP level of 75 pmol/L (Vcheck, Bionote, USA) was compatible with the suspicious of a heart disease (Table 1). The immunochromatographic tests for FeCoV, FIV and FeLV were negative, as well.

Right after the patient stabilization (meaning that respiration rate was reduced from 84 rpm to 52 rpm with resolving in dyspnea), radiological examination was performed. Latero-lateral (A) and ventro-dorsal (B) x-ray of the thorax revealed pulmonary edema (just like in the first physical examination), mild pulmonary artery enlargement and elongation of the heart (cardiomegaly) with noticeable aerophagia due to dyspnea (Figure 1). Electrocardiographic (ECG) examination revealed sinus arrhythmia, QS complexes (absence of R waves and presence of deep S waves in lead II and III), right axis deviation, and a wide complex ventricular extra systole (VES), with a heart rate of 136 bpm (CareWell 1103L, China) (Figure 2).

Echocardiographic examination was performed as suggested.[20] Briefly, interventricular septum (IVSd) and left ventricular free wall thickness at diastole (LVFWd) and left atrial to aortic root diameter ratio (LA/Ao) were measured at right parasternal short axis view (RPSAx) of the LV at the papillary muscles and aortic levels, respectively (Caris Plus, Color Doppler, Esoate, Italy). Aortic flow was assessed by color Doppler at left apical 5 chamber view. Results showed asymmetrically thickened IVS (6.5 mm; reference ≤ 6 mm) and LVFW (7.1 mm; reference ≤ 6 mm), and increased LA/Ao (2.8, reference < 1.5), indicating a moderate asymmetric concentric LV hypertrophy and marked dilation of the LA, respectively. Severe spontaneous smoke echocardiographic contrast (SEC) in the enlarged LA was observed, as well.

In addition to these findings, that LV outflow tract diameter (LVOT: 7.0 mm) and Ao maximal pressure gradient (Ao-maxPG: 6.7 mmHg) were found within reference ranges showed the presence of non-obstructive HCM.[21] Doppler ultrasonography revealed the absence of pulse and flow in the femoral arteries bilaterally. The findings were clinically indicative of ATE due to HCM.[22]

Table 1. Hematologic and serum biochemistry panel of the patient presented with feline references.

Hemogram	Patient	Reference	Serum Biochemistry	Patient	Reference
WBC (K/µL)	6.16	5-12	ALB (G/dL)	4.9	2.2-4.4
Nötrofil (K/µL)	4.01	2.50-12.50	ALP (U/L)	42	10-90
Lenfosit (K/µL)	2.09	0.4-6.8	ALT (U/L)	733	20-100
Monosit (K/µL)	0.04	0.15-1.70	AMY (U/L)	1191	300-1100
Eozinofil(K/µL)	0.01	0.1-0.79	TBIL (mg/dL)	0.3	0.1-0.6
Bazofil (K/µL)	0.00	0.00-0.10	BUN (mg/dL)	29	10-30
RBC (M/µL)	12.50	5.5-8.5	Ca (mg/dL)	10.3	8.0-11.8
HCT (%)	60.9	30-45	Phos (mg/dL)	3.7	3.4-8.5
HGB (G/dL)	18.9	9-15	Crea (mg/dL)	2.2	0.3-2.1
MCV (fL)	49	41-58	Glu (mg/dL)	284	70-150
MCH (pg)	15.2	12-20	Na^+ (mmol/L)	153	142-164
MCHC (G/dL)	31.1	29-37.5	K^+ (mmol/L)	4.2	3.7-5.8
RDW (%)	19.2	17.3-22	TP (G/dL)	9.7	5.4-8.2
PLT (K/ µL)	269	200-500	GLOB (G/dL)	4.8	1.5-5.7
MPV (fL)	14.4		NT-ProBNP	75	<100 pmol/L
PDW (%)	37.3				
PCT (%)	0.39				

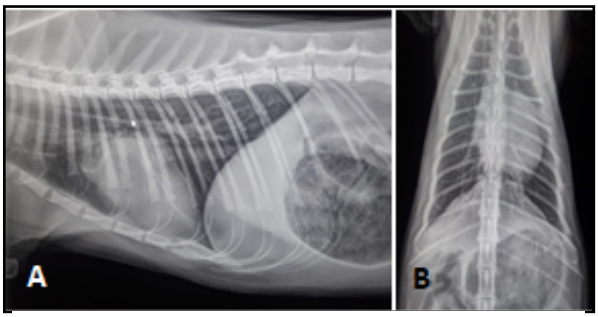

Figure 1: Laterolateral (A) and ventrodorsal (B) x-ray of the thorax revealed broncho-alveolar pattern and elongation of the heart with noticeable aerophagia due to dyspnea.

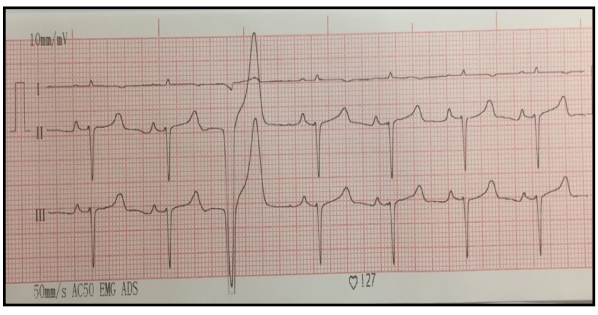

Figure 2: Electrocardiographic examination of the cat revealed sinus arrhythmia, QS pattern, and a wide complex ventricular extra systole (50 mm/sec., 10 mm/1 mV).

A magnetic resonance angiography (MRA) was performed to confirm the presence of ATE, as reported in a previous study.[23] MRA images showed that the contrast medium (Iohexol, 10 ml, iv.; Omnipaque, Opakim, Türkiye) did not progress caudally at the level of femoral arteries (data not shown).[23] Based on the results of clinical and laboratory examinations, another risk factor for the development of ATE was not found.

Coagulation status was evaluated by TEG (TEG 5000, Haemoscope Hemostasis Analyser, USA), using anticoagulated blood samples (Vacuette®, sodium citrate 3.2% Greiner Bio-One, Germany). TEG analyses were performed before (baseline) and 6 and 24 hrs after the treatment, within 30 minutes following the blood collection[24]. TEG analysis included reaction time (R time) and kinetic time (K time) of clot kinetic, alpha angle (α-angle) of clot strengthening, maximum amplitude (MA) of platelet function, and lysis rate (LY30, the percentage of lysis 30 min after MA) of clot stability.[16]

For thrombolytic treatment, tPA was preferred because of achieving better lysis rate as compared with other well-known agents such streptokinase.[9,10] Central venous catheter (CVC) was placed and then tPA therapy was started as suggested in a previous study.[25] Briefly, alteplase (Actilyse®, Boehringer Ingelheim, Germany), a recombinant tPA, was administered at 1 mg/kg IV via cephalic veins over 1 hr with the first 10% of the infusion administered as an IV bolus over 10 min.[9] Right after the drug administration, the cat was evaluated by physical examination and abdominal and thoracic ultrasonography for any evidence of external or cavitary hemorrhage, respectively.

TEG analysis showed that R time, MA and LY30 values were found to be normal, but K time and α-angle were out of the reference ranges at admission (Table 2 and Figure 3A). R time increased dramatically from 6.2 min of pre-treatment value to 112.7 min at 6 hrs after tPA treatment (Figure 3B), with value returning to normal at post-treatment 24 hrs. K time, α-angle, MA and LY30 could not be measurable at 6 hrs following the tPA administration, and then while K and LY30 values were normalized, α-angle and MA values increased at 24 hrs compared to those of their initial values (Figure 3c). In this period, clinically a significant decrease in pain perception, along with the patient's starting to step on his hind legs, and an increased perception of deep pain were observed in the neurological examination. Bruised extremity pads and ischemic nail bases returned almost to their healthy colors and respiration rate returned below 30 rpm.

The cat was discharged home with a medical protocol of thromboprophylaxis; clopidogrel (18.75 mg, PO, SID; Plavix 75 mg tb., Sanofi, Türkiye) and aspirin (5 mg/kg, PO, once every 72 hr, Coraspin 100 mg tb., Bayer Türk Kimya, Türkiye), and cardiomyopathy (HCM); furosemide (1 mg/kg, PO, BID, Lasix 40 mg tb., Sanofi, Turkey) and benazepril (0.25 mg/kg, PO, SID, Cibacen 5 mg tb., MEDA, Türkiye)[21]. An echocardiographic follow up was applied seven days later to re-evaluate the health status. At the time of writing, the cat was still living with drugs with reducing dosage of furosemide (1 mg/kg, once a day) and close contact with the owner was established to control the drug regimen and patient wellness. Also, the periodical controls including ECG, thoracic x-ray, CBC and renal panel (serum BUN and Cr) as well as serum electrolytes such as Na and K were carried out to observe possible side effects of medicals in every 3 months during the patient monitorization. The cat received thromboprophylaxis but did not need thrombolytic treatment after the first admission.

Table 2. Thrombolestographic evaluation of the cat.

Time / TEG parameters	R minutes	K minutes	α angle degrees	MA mm	LY30 %
Pre-treatment	6.2	11.4	21.8	58.3	0.0
6 hrs after the treatment	112.7	-		--	-
24 hrs after the treatment	7.2	3.8	41.4	77.6	0.0
References*	2.4-9.5	1.2-3.9	45.5-73.5	46.8-66.1	0.0-9.0

R: reaction time; K: clotting time; α angle: alpha angle; MA: maximum amplitude; LY30: clot lysis 30 min after MA is reached.

* Marschner C.B., Bjørnvad C.R., Kristensen A.T., Wiinberg B.: Thromboelastography results on citrated whole blood from clinically healthy cats depend on modes of activation. Acta Vet Scand. 2010, 52(1):38.

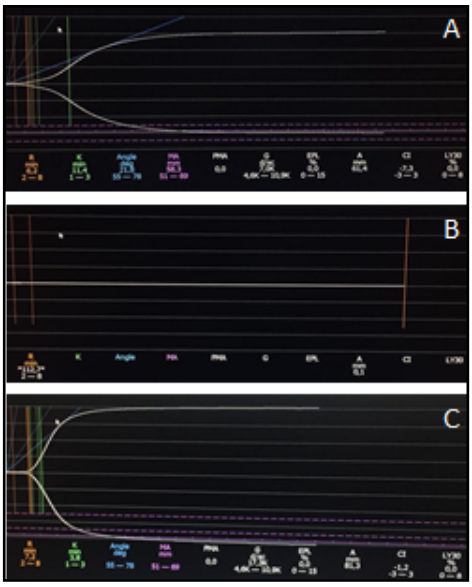

Figure 3: Thrombolestographic evaluation of the cat before (A), 6 hrs (B) and 24 hrs after (C) the tPA treatment.

DISCUSSION

This case report represents the therapeutic effectiveness of administration of intravenous tPA for thrombolysis, and how the coagulation status could be monitored using TEG in a cat with ATE due to HCM in practice. Considering the operative and anesthetic risks of thrombectomy, we have shared this case report stating that using tPA in the elimination of thrombus at the dose described here can lead to success with a much cheaper and risk-free method, and for the first time, TEG may be a useful and practical tool in monitoring the safe management of the thrombolysis in the first 24 hrs. of the treatment.

ATE, a very painful and fatal serious condition, affects approximately 25-30 percent of cats with heart disease such as HCM.[26] In this case, HCM as a causative factor for ATE was diagnosed based on the clinical, radiographic, and echocardiographic examinations, and the presence of ATE was confirmed using the MRI as reported previously.[22,23] Based on the imaging techniques and the comprehensive clinical and laboratory examinations, there were no other underlying disease for the development of ATE was found.

In cats with HCM, SEC and/or thrombus formation occurred especially in enlarged LA are associated with the blood stasis leading to increase in platelet activity (hypercoagulation) and endothelial damage.[1,5-7] Formatted thromboses may remain mobile or adhered to a wall of the LA, become enlarged and block the exit to the LV, or may break apart as an emboly and pass from the Ao to femoral arteries.[1,5-7] Arterial occlusion and impaired collateral circulation may explain the presence of the bruising on the

extremity pads and ischemic purple color at the nail base in the presented cat.

If the thrombus can be surgically removed or medically resolved within a short time, survival time may be longer and life quality may be increased.[27] However, the surgical treatment (embolectomy) is not recommended because of the high risk of death during and potential re-embolization after the procedure.[6] In human medicine, after an acute ischemic stroke, intervention with intravenous tPA for up to 6 hrs can provide complete cure.[3,4,28,29] Thus, thrombolytic therapy is suggested as a standard practice for acute thromboembolism in humans, as well as dogs and cats.[9-11,25] On the other hand, there are limited clinical experience with thrombolytic agents such as streptokinase and tPA in dogs[8] and cats.[9-11] In this case, we decided to use the tPA to resolve the thrombus and improve the tissue perfusion since the timing of starting thrombolytic therapy seemed appropriate, and it achieves better lysis rate than streptokinase.[12]

tPA, a 69 kD glycoprotein and an enzyme of serine protease family, shows thrombolytic activity by catalyzing the conversion of plasminogen to plasmin, the primary enzyme involved in the dissolution of blood clots.[30] Thus, while thrombolytics are used, close monitorization of coagulation is needed due to spontaneous bleeding tendency.[6] In this cat, TEG, a whole blood coagulation analyzer, was used to evaluate coagulation status because it is accepted as a sensitive and useful method to evaluate coagulation abnormalities such as hypercoagulopathy, hypocoagulapathy and disseminated intravascular coagulation in dogs[14,19,31] cats[15,17,18,24], and humans.[32] Additionally, that TEG is used to characterize the whole clotting cascade from initiation of clot formation to fibrinolysis provides it a great advantage as compared with the traditional coagulation tests such as PT and aPTT.[31]

In veterinary medicine, TEG analysis has been used to evaluate coagulation status in health and disease in dogs and cats. Yilmaz et al.[19] evaluated the hemostatic function by TEG in dogs with dilated cardiomyopathy (DCM) in which majority of the dogs showed a hypercoagulation rather than hypocoagulation state. In another study, Bae et al.[32] used TEG to therapeutically monitor the use of rivaroxaban (anticoagulant) in dogs, and the usefulness of TEG in determining the individual dose regimen and monitoring the treatment was noted. TEG analysis was performed in healthy[15,34,35] or diseased cats such as obesity[36], acute trauma[37], hyperthyroidism[38], infection[39], liver disease[18], and was used to monitor feline anticoagulant therapy.[34] In a study conducted in healthy cats, significant changes in the TEG parameters after an anticoagulant (factor Xa inhibitor) administration was found compatible with hypocoagulable state.[40] However, there is no study yet showing the thromboelastographic monitoring of the thrombolytic therapy with intravenous tPA in cats with heart disease.

In this cat, TEG values before the treatment showed an abnormal clot kinetic and strengthening based on the prolonged R time and decreased α-angle compared to the references reported for healthy cats[15], although we expected to see a hypercoagulation state. Six hours after the tPA administration, prolonged coagulation time was revealed by a straight line, and TEG analysis was thus truncated at 112 min., which was most probably due to thrombolytic activity of tPA relating with catalyzing the conversion of plasminogen to plasmin. Following the tPA treatment, at 24 hrs, all TEG parameters measured in this cat were within reference ranges, indicating that coagulation cascade was returned to normal coagulation status from hypocoagulation due to thrombolytic.

Although intravenous alteplase (tPA) is cleared primarily by the liver with an initial half-life of fewer than 5 min. and a terminal half-life of 72 min.[41], in our case thrombolytic activity/hypocoagulation state in response to tPA was stable till 6 hrs. This may be due to species differences, and/or long-lasting elimination of tPA clearance in cats. In addition to the normalization of TEG parameters, cat improved clinically and started to step on his hind limbs. In this period, bruised extremity pads and ischemic nail bases returned almost to their healthy colors and respiration rate returned into the reference range at rest. The cat was discharged home with a medical protocol of thromboprophylaxis (clopidogrel and aspirin) and cardiomyopathy (furosemide and benazepril). Cats receiving tPA therapy could be monitored on the possible tPA-related side effects such as reperfusion injury and acute kidney injury.[25,42] We couldn't observe any side effects and/or replaces of ATE during 3 months, based on the comprehensive diagnostic approaches.

As a result, the case report presents the advantages of clinical therapeutic monitoring of tPA treatment with TEG include the following: (i) prevention of possible over-dose drug administration; (ii) gives chance to safely monitor the thrombolytic process created during the treatment; (iii) assesses the effectivity of anticoagulant drug regimen immediately during the monitorization of tPA treatment in cats with ATE. Clinicians should be kept in mind that coagulation should be closely monitored in both HCM and thrombolytic treatments in cats with ATE, and TEG may be considered as a useful and practical tool to evaluate coagulation status and to monitor tPA treatments in cat practice.

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Editöre mektup
Letter to the Editor

Bir Köpekte Hatalı Kısırlaştırma Sonucu Oluşmuş Jinekolojik ve İntraabdominal Patolojiler

Gynecological and Intra-abdominal Pathologies Caused by Malpracticed Neutering in a Dog

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ÖZ

Bu olgu ile hatalı kısırlaştırmaya bağlı oluşmuş jinekolojik ve intraabdominal patolojilerin meslektaşlarımızla paylaşılması amaçlandı. Yaklaşık 2 yaşlı, melez ırk bir köpek farklı kliniklerde farklı zamanlarda yapılan kısırlaştırma operasyonu sonucu dikişlerin açılması şikayeti ile getirildi. Muayenede abdomendeki operasyon hattı enfekteydi ve omentum evantre olmuştu. Hematolojik ve serobiyokimyasal değerlerden sadece total lökosit ve alkalen fosfataz değerlerinin yükseldiği gözlendi. Genel anestezi altında acil operasyona alınan hastada abdominal boşlukta adezyonlar, omentumda parsiyal nekroz alanları, mezovaryumda emilmeyen dikiş materyali ile ligatüre edilmiş alanlarda apse, uterusun ligatüre edildiği korpus kısmında yaygın yangı ve enfeksiyon alanı ve güdük pyometrası tespit edildi. Tüm yangısal, enfektif ve nekrotik dokular uzaklaştırılarak kuralına uygun kısırlaştırma işlemi kontrol edilerek tamamlandı. Dokular makroskopik ve histopatolojik olarak incelendi ve uterus ve yağ dokusunda gözlenen değişikliklerin dikiş materyali nedeniyle gelişen yangısal reaksiyon, kanama ve nekroz olduğu değerlendirildi. Sonuç olarak, klinik pratikte yapılan hatalı uygulamaların önüne geçilmesi için pratisyen veteriner hekimlerin mesleki yeterliliklerini bilerek cerrahi girişimlerde bulunması ve edinemediği bilgiler ile de jinekolojik uygulamaları gerçekleştirmemeleri gerekir. Bu anlamda mesleğimizde yetkinliklerin düzenlenmesinin faydalı olabileceği önerilmiştir.

ABSTRACT

With this case, it was aimed to share the gynecological and intra-abdominal pathologies caused by malpracticed neutering with our colleagues. A 2-year-old, mixed breed dog was brought in with the complaint of suture line breakage following neutering operations performed at different times in different clinics. On examination, the abdominal operation line was infected and the omentum was evantrated. It was observed that only total leukocyte and alkaline phosphatase values increased among hematological and serobiochemical values. Adhesions in the abdominal cavity, partial necrosis areas in the omentum, abscess in the areas ligated with non-absorbable suture material in the mesovarium, widespread inflammation and infection area in the corpus where the uterus was ligated, and stump pyometra were detected in the dog which underwent an emergency operation under general anesthesia. All inflammatory, infective and necrotic tissues were removed and neutering was completed in accordance with the rule. The tissues were examined macroscopically and histopathologically, and the changes observed in the uterus and adipose tissue were evaluated as inflammatory reaction, bleeding and necrosis due to the suture material. As a result, in order to prevent malpractices in clinical practice, veterinarians should perform surgical interventions knowing their professional qualifications and should not perform gynecological practice without an adequate knowledge and experience. It has also been suggested that the regulation of competencies in our profession may be beneficial.

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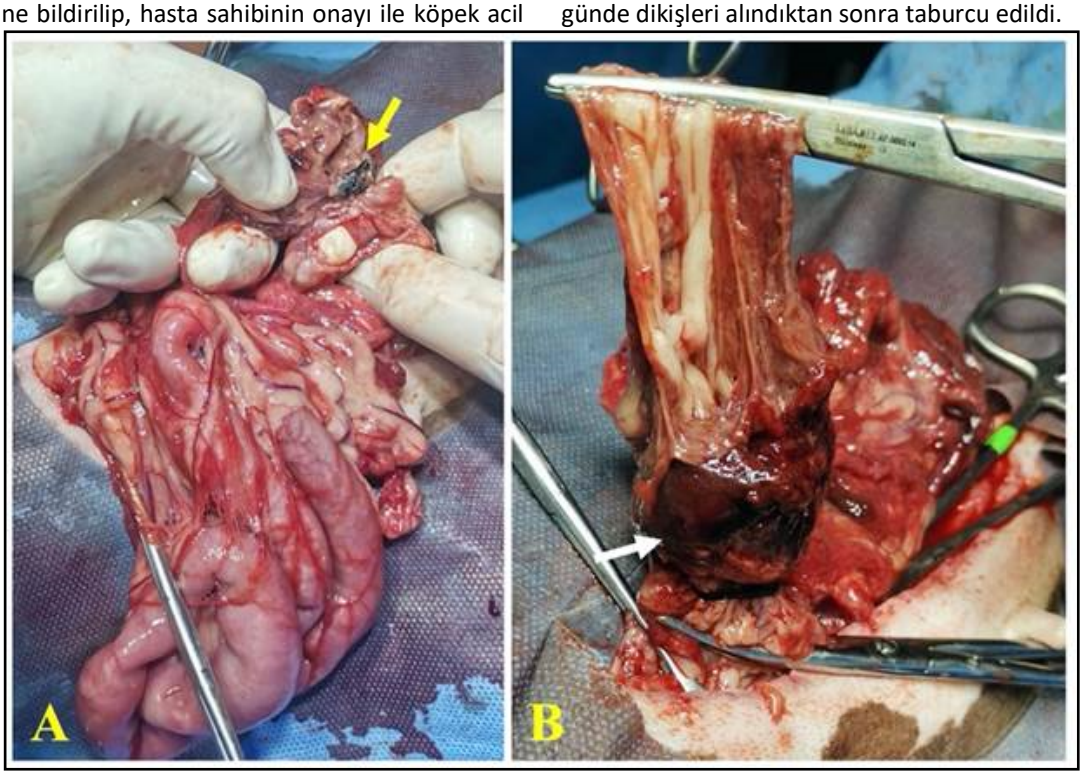
Ovariohisterektomi (OHE) istenmeyen gebelikleri önlemek veya sonlandırmak, östrus sikluslarının hormonal faaliyetlerine bağlı hayvanlardaki davranışsal problemleri ortadan kaldırmak, genital organ patolojilerini vücuttan uzaklaştırmak, reprodüktif organ problemleriyle (pyometra, endometriyal hiperplazi, uterus, serviks ve ovarium tümörleri vs.) karşılaşma olasılığını önlemek ve yaşa bağlı meme tümörü riskini azaltmak amacıyla uygulanır.[1,2] Tüm operasyonlarda olduğu gibi, küçük hayvanlarda yapılan OHE'nin anestezi, hemoraji, postoperatif enfeksiyon ve yara iyileşmesi bozukluğu gibi operasyon sırası ve sonrasında karşılaşılabilecek komplikasyonları bulunur.[1,2]

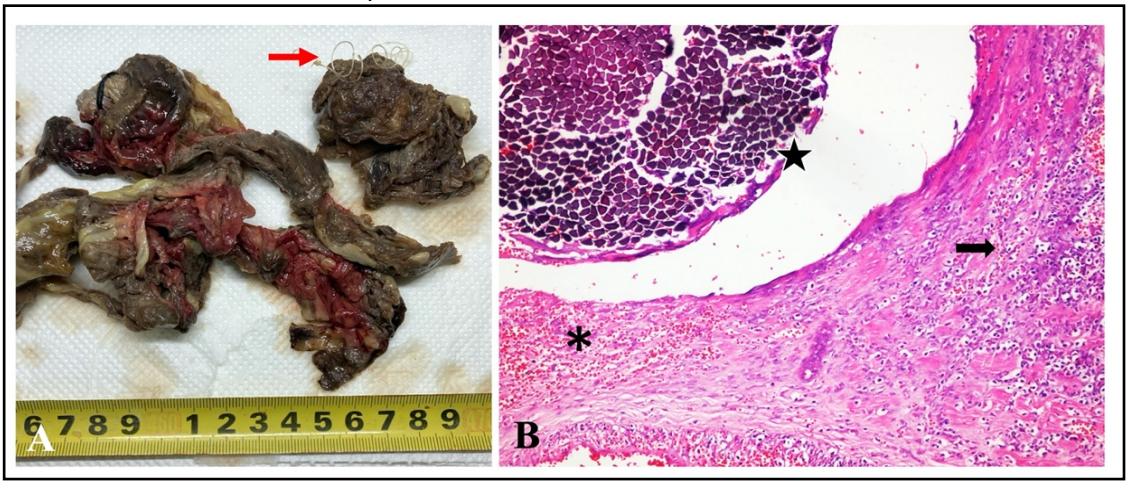
OHE'nin postoperatif komplikasyon riski %20,6[3] ve intraoperatif ve postoperatif komplikasyon oranları ise %6,3 ve %14,1 olarak bildirilir.[2] OHE sonrası %3,3 oranında major (intraabdominal adezyon) ve %9,5 oranında da minor komplikasyon (parankimal serozal problem) şekillenir.[4] Genellikle, ovaryum pediküllerinden, ligamentten ya da uterustan kaynaklanan hemoraji, ovaryan remnant sendrom, stump pyometra, yangı ve granuloma oluşumu, emilmeyen dikiş materyali kullanımına bağlı fistül oluşumu, üreterin bağlanması, vücut ağırlığında artış ve üriner inkontinens gibi patolojiler OHE'ye spesifik olarak gözlenmektedir.[3,5]

Yaklaşık 2 yaşlı, 21,5 kg ağırlığında melez ırk kısırlaştırılmış bir köpek, farklı zamanlarda ve farklı kliniklerde yapılan ayrı operasyonlar sonrası deri dikişlerinin açılması şikâyeti ile kliniklerimize getirildi. Köpeğin 3 ay önce OHE geçirdiği ve ovaryumların alınmaması nedeniyle de 3 gün öncesinde operasyonun tekrarlandığı bildirildi. Rutin klinik muayenede köpeğin bilateral mandibular lenf yumrularının büyümüş ve beden ısısının artmış olduğu belirlendi. Abdomendeki operasyon hattı enfekteydi ve omentum evantre olmuştu. Hematolojik olarak köpeğin total lökosit değeri (26,74 10^9/L) yüksekti ve kanın serobiyokimyasal analizinde de sadece karaciğer enzimi olan Alkalen Fosfataz'ın (178 U/l) yükseldiği görüldü. Muayene bulguları hasta sahibine bildirilip, hasta sahibinin onayı ile köpek acil operasyona alındı. Premedikasyon ve indüksiyon amacıyla ksilazin HCl (1 mg/kg, im), ketamin HCl (10 mg/kg, im) uygulandı. Venöz giriş 22 no anjiocat ile sağlanarak %0,9'luk NaCl solüsyonu pre, intra ve postoperatif olarak infüze edildi. Genel anestezi ve idamesi %2'lik izofloran ile sağlandı. Operasyon masasına dorsal pozisyonda yatırılan köpeğin ventral abdominal duvarı cerrahi olarak hazırlandıktan sonra daha önce median hatta bulunan ensizyon hattı genişletilerek abdominal boşluğa ulaşıldı. Abdominal eksplorasyonda intraabdominal adezyonlar, omentumda parsiyal nekroz alanları, mezovaryumda emilmeyen dikiş materyali ile ligatüre edilmiş alanlarda apse, uterusun ligatüre edildiği korpus kısmında yaygın yangı ve enfeksiyon alanı gözlendi ve ayrıca güdük pyometrası tespit edildi (Şekil 1A-B). Tüm yangısal, enfektif ve nekrotik kısımlar uzaklaştırıldıktan sonra serviks'in cranial'inden uterus ligatüre edilerek önceki operasyonlar sırasında abdomen içerisinde bırakılan parça vücuttan uzaklaştırıldı. Ovariektomi bölgesi de kontrol edildi kalan ovaryum olduğu düşünülen doku da uzaklaştırıldı. Abdominal boşluk rifamisin içeren %0,9'luk NaCl ile yıkandıktan sonra abdominal ensizyon hattı kuralına uygun olarak kapatıldı. Postoperatif olarak %0,9'luk NaCl infüzyonu, sefuroksim (20 mg/kg, iv.) ve tolfenamik asit (4 mg/kg, sc.) uygulandı ve köpek postoperatif 15. günde dikişleri alındıktan sonra taburcu edildi.



Şekil 1. A. Mezovaryum üzerinde karşılaşılan emilmeyen dikiş materyali ile uygulanmış ligatür (sarı ok).
B. Abdominal boşluk içerisinde gözlenen nekrotik uterus (beyaz ok).

Operatif olarak abdominal boşluktan uzaklaştırılan dokular alındı ve makroskopik incelemesinde uterus ve ovaryum olduğu düşünülen yapıların etraftaki yağ dokusu ile birlikte koyu renkte ve kalın bir dikiş materyali ile (katgüt) dikildiği, dikiş materyalinin emilmediği ve etrafında açık renkli alanların olduğu (dejenerasyon, nekroz) gözlendi (Şekil 2A). Tüm dokular %10'luk formalin solüsyonuna alındı. Dokuların histopatolojik inceleme için yapılan hazırlıklarından sonra hazırlanan preparatlar hematoksilen-eozin ile boyandı. Preparatlar ışık mikroskobu altında değerlendirildi. Mikroskopik olarak incelenen kesitlerde ovaryum dokusuna rastlanmadı, uterusta dikiş materyali etrafında bu yabancı cisme karşı gelişen az sayıda lenfositler ile birlikte çoğunluğunu nötrofillerin oluşturduğu bir reaksiyon dikkati çekti. Bu hücrelerin etrafında serbest halde eritrositler ve yaygın nekroz alanları gözlendi. Uterustaki damarların çoğunda trombus mevcuttu. Bazı damarların etrafında kanama alanlarına rastlandı. Yağ dokusu incelendiğinde yaygın kanama alanları dikkati çekti. (Şekil 2B). Uterus ve yağ dokusunda gözlenen değişikliklerin dikiş materyali nedeniyle gelişen yangısal reaksiyon, kanama ve nekroz olduğu değerlendirildi.



Şekil 2. A. Abdominal boşluktan uzaklaştırılan genital organ yapıları ile nekrotik ve enfektif yağ dokusu. Emilmeyen dikiş materyali (kırmızı ok) **B.** Uterus mukozasında yabancı cisme karşı gelişen şiddetli yangı hücresi infiltrasyonları (ok), kanama alanları (asteriks), nekroz ve uygulanmış dikiş materyali (yıldız).

Sonuç olarak, farklı zamanlarda farklı iki klinikte kısırlaştırma girişiminde bulunulan bu olgu ile; küçük hayvanlarda kısırlaştırma operasyonları, pratisyen veteriner hekimlerin yapmaya yetkin oldukları rutin jinekolojik uygulamalardır. Klinik pratikte yapılan hatalı uygulamaların önüne geçilmesi için pratisyen veteriner hekimlerin mesleki yeterliliklerini bilerek cerrahi girişimlerde bulunması ve edinemediği bilgiler ile de jinekolojik uygulamaları gerçekleştirmemeleri gerekir. Bununla birlikte hayvan refahı, hayvan sahiplerinin mağduriyetlerinin önlenmesi, mesleki saygınlığımızın korunması ve geliştirilmesi bakımından; veteriner hekimliğinde de beceri, tecrübe veya özel donanım gerektiren yetkinliklerin ruhsatlandırma, akreditasyon, meslek içi eğitim sertifikaları, ek yüksek lisans, doktora, PhD, uzmanlık, diplomatlık gibi mesleki yetkilendirme ve kariyer aşamaları ile ilişkilendirilmesinin düşünülmesi, planlanması ve hayata geçirilmesi kanaatimizce uygun olacaktır.

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Editöre mektup
Letter to the Editor

Bir Kedide Paratiroid Adenokarsinomu

Parathyroid Adenocarsinoma in a Cat

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ÖZ

Paratiroid adenokarsinomu kedilerde nadir görülen ve hiperparatiroidizm ile seyreden bir hastalıktır. Scottish Fold ırkı 1,5 yaşında bir kedi solunum yetmezliği sebebiyle sevk edildi. Boyun bölgesinde trakea ve larinkse bası yapan bir şişkinlik farkedildi. Ancak ani solunum arresti sonucu kedide exitus letalis şekillendi. Hasta sahibinin istemi üzerine yapılan postmortem muayeneler ve histopatolojik incelemeler sonucu kitleye paratiroid adenokarsinom tanısı konuldu. Boyun bölgesindeki kitleler larinks ve trakea'ya basınç yaparak solunum arresti oluşturabilir. Bu nedenle solunum problemi olan hastalarda klinik muayenelerin detaylı yapılması gerekir.

ABSTRACT

Parathyroid adenocarcinoma is a rare disease characterized by hyperparathyroidism in cats. A one and half year old Scottisch Fold cat was referred for further assessment of respiratory failure. A mass compressing the trachea and larynx was detected in the neck region. Exitus lethalis occurred in the cat as a result of sudden respiratory arrest. The mass was diagnosed parathyroid adenocarcinoma as a result of post-mortem and histopathologic examinations performed upon the request of the owner. Masses in the neck region may cause respiratory arrest by pressure on the larynx and trachea. Therefore, clinical examinations should be performed in detail especially in patients with respiratory problems.

Sayın Editör,

Kedi ve köpeklerde servikal bölge patolojilerine sıklıkla rastlanılır. Bu bölgede önemli anatomik yapılar bulunur ve bu nedenle servikal bölgedeki patolojilerin tanı ve tedavi süreci zordur.[1] Şişkinlikle seyreden tiroid ve paratiroid bezi neoplazileri, apse, lenfadenopati, sialadenopati gibi çeşitli hastalıklar bu bölgede görülür. Paratiroid bezleri, 5. ve 8. trakea halkalarının lateralinde, tiroid bezleriyle iç içe geçmiş ancak yapısal olarak bağımsız dört küçük elipsoid disk şeklinde bulunur.[2] Kedi ve köpeklerdeki endokrin tümörlerden olan paratiroid bezi karsinomu ile nadiren karşılaşılır ve bu durum primer hiperparatiroidizme (PHPT) neden olur.[3] Paratiroid bezinden aşırı parathormon salgılanması sonucu hiperkalsemiye neden olur.[4] Literatürde tanımlanmış çok az sayıda PHPT'li kedi mevcuttur. Çoğunlukla serum kalsiyum düzeyindeki artışa bağlı olarak tanı konur.[3] Genellikle klinik olarak anoreksi, letarji ve konstipasyon görülür. Paratiroid bezi büyümüş ise klinik muayene ile kolayca tanınabilir.[4] PHPT'nin tanısında ultrasonografi ve sintigrafiden de yararlanılır. Kesin tanı için serum parathormon düzeyinin ölçülmesi önemlidir ancak kedilere özgü parathormon testi bulunmaması tanıyı güçleştirmektedir.[5]

Scottish Fold ırkı, 1,5 yaşlı bir kedi, boyun bölgesinde şişkinlik ve solunum problemi şikayetiyle hastanemize getirildi. Anamnezde kedinin bir veteriner kliniğinde oksijen tedavisi aldığı ve boyun bölgesinde fark edilen şişkinlik nedeniyle kliniğimize sevk edildiği bildirildi. Klinik olarak boynun sol tarafında trakeayı sağa doğru iten palpasyonda katı esnek kıvamlı bir kitle fark edildi. Ancak kedide inspiratorik dispne mevcuttu ve mukoz membran rengi siyanotikti.

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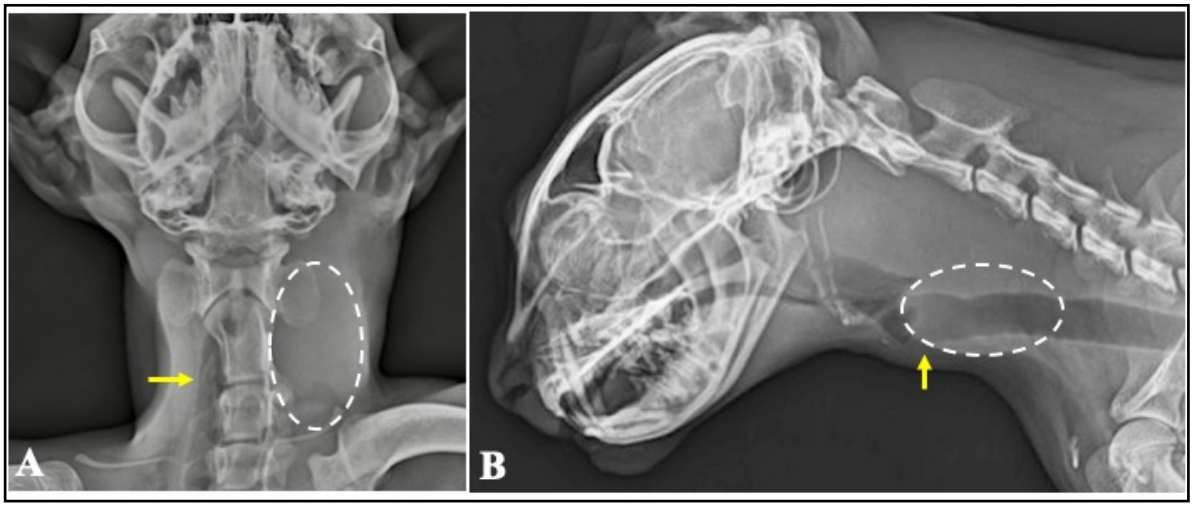
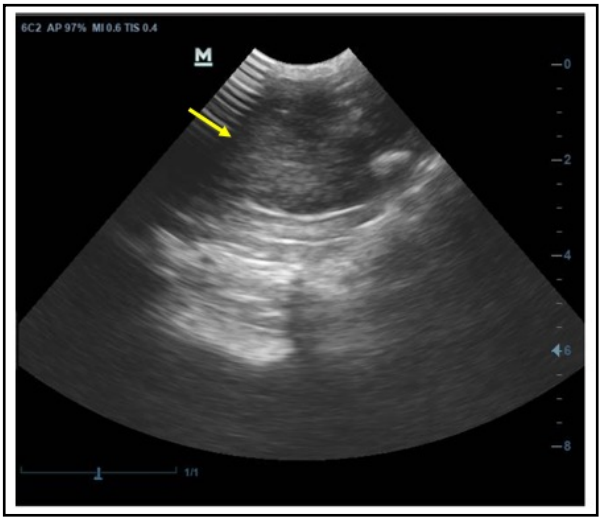
Maske ile oksijenize edilirken kedinin solunum arrestine girmesi ile endotrakeal entübasyon yapıldı ancak yapılan resüsitasyona cevap alınamayarak kedide exitus letalis şekillendi. Hematolojik ve serobiyokimyasal analizler için kan numunesi alımı gerçekleştirilemedi. Hasta sahibinin istemi üzerine postmortem radyolojik muayenede; ventrodorsal radyografide kitlenin trakea'yı sağa doğru deviye ettiği belirlendi. Boynun lateral radyografisinde de larinks ve trakea'nın dorsalinde lokal opasite artışı görüldü (Şekil 1 A-B).



Şekil 1. Olgunun radyografileri. A: Ventrodorsal radyografide sağa deviye olmuş trakea (ok) ve kitlenin (elips) görünümü. Lateral radyografide larinks ve trakeanın (ok) dorsaline yerleşmiş kitle (elips).

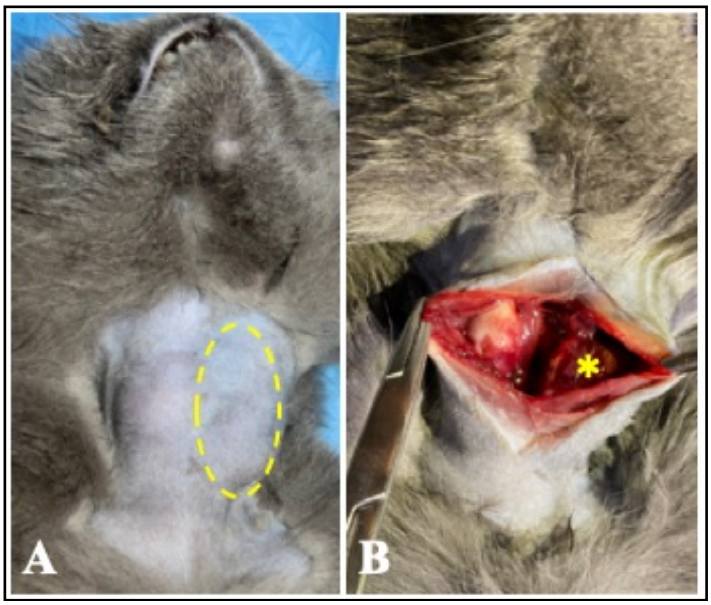


Şekil 2. Ultrasonografik değerlendirmede; kitlenin (ok) merkezinin hiperekoik görünümde olduğu ve yer yer anekoik odaklar içerdiği görülmektedir.

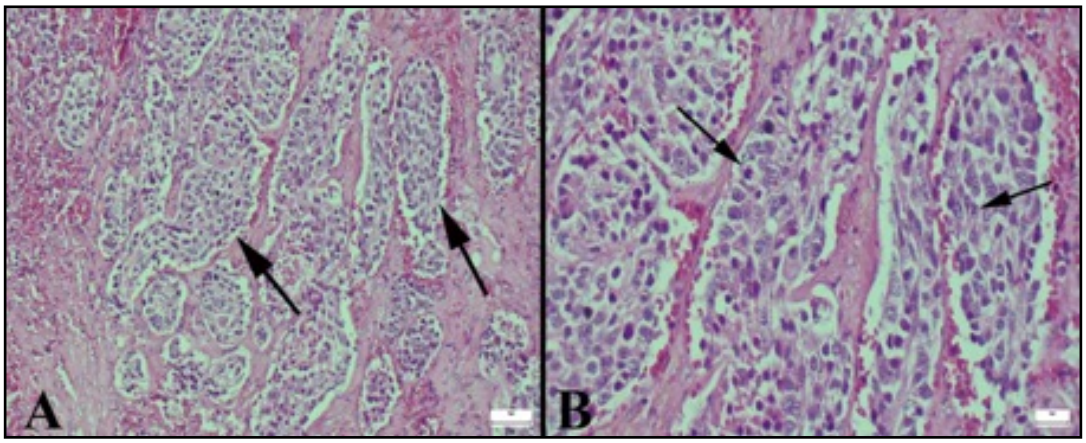
Ultrasonografik muayenede, larinks'in lateral sınırından başlayan ve trakea'ya doğru seyreden merkezi hiperekoik ve yer yer anekoik odaklar içeren, yaklaşık 2 cm uzunluğunda heterojen bir kitle saptandı (Şekil 2).

Hasta sahibinin istemi üzerine yapılan nekropsi ve histopatolojik incelemelerde, yaklaşık 2 cm longitudinal uzunlukta düzgün konturlara sahip bir kitle ve bu kitlenin peritrakeal olarak yerleştiği görüldü (Şekil 3). Kitleden alınan örnekler %10 tamponlu formaldehit içinde tespit edildi. Takiben yapılan parafin bloklardan döner mikrotomlar (Leica RM2155, Leica Microsystems, Wetzlar, Almanya) ile 5µm kalınlığında kesitler alındı. Deparafinizasyon, azalan miktarlarda kademeli etanol ile rehidrasyon, hematoksilen-eozin (H&E) ile boyama, ksilen ile temizleme ve kesitlerin kapatılması adımları ile histopatolojik inceleme için preparatlar hazırlandı. Işık mikroskop altında yapılan incelemede, kitlenin lobüllerde ve kitlede gruplanmış olan orta ile büyük hücrelerden oluştuğu görüldü. Bu durum kitleye psöudonodüler bir görünüm vermekteydi. Sitonükleer atipilere işaret eden çok sayıda düzensiz, nükleollü çekirdek

ve yüksek mitotik aktivite dikkati çekti (Şekil 4A-B). Bu bulgulara göre, kitle için paratiroid adenokarsinomu tanısı koyuldu.



Şekil 3. Olgunun postmortem ve nekropsi görüntüsü. A: Postmortem görüntüde kitlenin lokal yerleşimi (elips). B: nekropsi esnasında kitlenin görünümü (asteriks).



Şekil 4. Tümöral kitlenin histopatolojik görünümü. **A:** Kitlenin psödonodüler görünümü (oklar), H&E, Bar= 50µm. **B:** Yüksek mitotik aktiviteye (oklar) sahip tümöral kitlede atipik ve pleomorfik hücrelerin daha yüksek büyütülmesi, H&E, Bar= 50µm.

Sonuç olarak boyun bölgesinde oluşan peritrakeal veya perilaringeal kitleler solunum yollarında yaptıkları kompresyon ile solunum arresti oluşturabilir. Bu nedenle solunum problemi olan hastalarda ilk acil yaklaşım olan hava yolu kontrolü yapılmalı ve hava yolu açıklığı önleyebilecek bu olgudaki gibi patolojilerin (paratiroid adenokarsinomu) atlanmaması için klinik muayenelerin detaylı yapılması gerekir.

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