Knocking on Heaven's Door: A Left-Atrial Ball-Like Thrombus in a Cardiomyopathic Cat with Cardiomyopathy, Atrial Fibrillation and Triplegia

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ABSTRACT

Congestive heart failure (CHF) and systemic arterial thromboembolism (ATE) are the most common clinical complications in cats with hypertrophic cardiomyopathy (HCM). We describe a 7-year-old, male castrated domestic short hair cat with a free floating ball thrombus (FFBT) in the left atrial cavity. The cat was diagnosed with HCM, atrial fibrillation, suspected myocardial infarction, ATE affecting three limbs, and a large, sonographically heterogenic, counterclockwise-rotating, left atrial FFBT. An intra-cardiac FFBT is a rare finding in cardiomyopathic cats with a pro-thrombotic state, some of which present with co-morbidities. This condition likely further increases the already high risk of thromboembolization. Systemic embolization can lead to multiple fragments lodging in one or several downstream coronary and systemic arteries, resulting in devastating complications, and likely worsening prognosis.

Keywords: Clot; Embolus; Emboli; Hypertrophic Cardiomyopathy; Aortic Thromboembolism; Feline.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM), the most common cardiac disease in cats, is characterized by primary hypertrophy of the left ventricular (LV) myocardium and impaired diastolic relaxation and/or compliance (1, 2). Systemic arterial thromboembolism (ATE) is a common clinical complication in feline HCM, reportedly developing in up to 48% of affected cats (2-4). Systemic ATE is believed to typically result from a thrombus forming within the left atrium. Risk factors for thrombus formation in cats are thought to include severe left atrial (LA) enlargement, persistent atrial fibrillation (AF), evidence of LA spontaneous echo-contrast (all of which increase the risk of blood stasis), and a history of previous ATE (5-8). In humans, a left-atrial free-floating "ball" thrombus (LA-FFBT) unattached to either the atrial wall or the mitral valve leaflets is a rare and devastating clinical manifestation of heart disease (9). To the best of the authors' knowledge, LA-FFBT has only been rarely mentioned in the veterinary clinical literature. (10-12) The present report describes a LA-FFBT in a cat with HCM presenting with paralysis of both hind limbs and of the left front limb, along with persistent AF and several findings suggestive of myocardial infarction.

CASE REPORT

A 7-year-old, male castrated domestic short hair cat presented with an acute onset of paresis, followed by flacid paralysis of the left front and both hind limbs. Upon presentation, the cat appeared anxious and painful. Spinal reflexes and a deep pain response were absent in these limbs, all of which were cold to the touch and had cyanotic foot-pads. Femoral pulses were bilaterally absent. Auscultation revealed an irregular

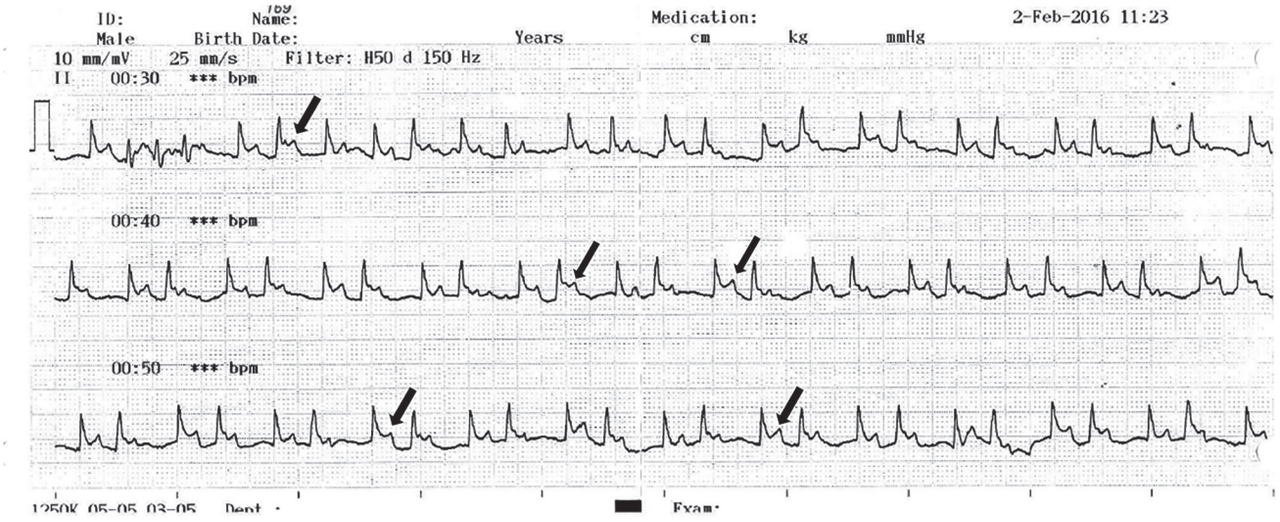

Figure 1: A 30 second long, continuous Lead-II rhythm strip (25 mm/sec, 10 mm/mV) from a cat with atrial fibrillation, multiple limb paralysis, and a left-atrial, free-floating ball-like thrombus. Note the irregularly irregular rhythm, lack of P-waves, and the transiently lower-than-expected ventricular response rate of 152/min. Also present is a left bundle branch block pattern, and a 0.25mV, ST-segment elevation (arrows).

tachyarrhythmia with a grade I/VI left parasternal systolic murmur, and tachypnea of 68 breaths per minute. Rectal temperature was 35.9°C.

Blood-work (Tables 1 & 2; Advia 120, Siemens Medical Solutions Diagnostics, Erfurt, Germany; Cobas-Integra 400 Plus, Roche, Mannheim, Germany; at 37° C) demonstrated mild thrombocytopenia, elevated muscle enzymes, azotemia, hyperamylasemia, hyperphosphatemia, hyperkalemia, hypocalcemia, and a low total CO_2. D-dimer (Cobas-Integra 400 plus, Roche, Mannheim, Germany, Tina-quant D-dimer Gen 2, Roche, Mannheim, Germany) was 1440 ηg/ml [reference interval (RI) <250 ηg/ml], antithrombin III (Chromogenic substrate, HemosIL 0020008910, Instrumentation Laboratory, Milano, Italy, Factor Xa reagent, HemosIL 0020008920, Instrumentation Laboratory, Milano, Italy) was 131% (RI 100-117%) and fibrinogen (HemosIL PT-fibrinogen 0008469810, Instrumentation Laboratory, Milano, Italy) was 323mg/dl (RI 150-300mg/dL).

A six-lead electrocardiogram, followed by a Lead-II rhythm strip (Nihon Kohden, Cardiofax GEM ECG-9029K, Japan) revealed persistent AF with a changing ventricular response rate of 150-240/min, a left bundle branch block, and an ST-segment elevation, potentially consistent with myocardial infarction (Figure 1). A complete echocardiogram (Vivid 3, General Electric, Tirat Carmel, Israel) demonstrated regional HCM with severe LA enlargement (the end diastolic LA/Aorta -ratio at the right parasternal short axis view of the heart base was 2.07/0.76=2.74) and no evidence of systolic LV outflow tract obstruction. The interventricular septum was severely hypokinetic and LV fractional shortening was 38.6%, compatible with myocardial failure. A 1.5 x 1cm LA-FFBT of heterogeneic echogenicity, was demonstrated at several imaging planes (Figure 2A, B, C, D). Serum cardiac troponin T (cTnT) (Troponin T hs STAT, Cobas, Roche, Mannheim, Germany) was elevated at 0.114 ηg/ml (RI <0.011 ηg).

Due to the combined findings of multiple limb paralysis, hypothermia, regional left ventricular hypokinesis with a suspected myocardial infarction and the presence of multiple concurrent risk factors for recurrent thrombus formation and thromboembolism, the most important of which were AF and especially the highly mobile, heterogenic LA-FFBT, a grave prognosis was given, based on which the owner elected euthanasia, but declined necropsy.

DISCUSSION

Feline systemic ATE is often a devastating condition, mostly associated with underlying cardiac diseases. It is clinically manifested by an acute onset of limb paresis or paralysis, weak or absent arterial pulses, pain, pale or cyanotic footpads, and cold extremities (7). It most commonly affects both hind limbs, although a single hind limb, or one (typically the right)

Table 1: Complete blood count results.

Analyte (units)	Value	Reference interval
Packed cell volume (%)	32.0	24-45
Total plasma protein (g/dL)	8.2*	5.5-7.5
Red blood cells (x10^6/μL)	9.9	6.0-10.1
Hemoglobin (g/dL)	10.6	8.1-14.2
Hematocrit (%)	29.5	27.7-46.8
Platelets (x10^3/μL)	159**	160-625
White blood cell (x10^3/μL)	19.4	6.3-19.6
Band neutrophils (%)	3.0	0-3
Neutrophils segmented (%)	64.0	35-75
Lymphocytes (%)	20.0	20-55
Monocytes (%)	6.0*	0-4
Eosinophils (%)	7.0*	0-4
Basophils (%)	0	Rare
Band neutrophils (x10^3/μL)	0.6	Rare
Neutrophils (x10^3/μL)	12.4	3-13.5
Lymphocytes (x10^3/μL)	3.8	2-7.7
Monocytes (x10^3/μL)	1.2*	0-1
Eosinophils (x10^3/μL)	1.4	0.3-1.7
Basophils (x10^3/μL)	0	0-0.1

*A value above the reference range.
** A value below the reference range.

Table 2. Biochemistry results.

Analyte (units)	Value	Reference interval
Alanine transaminase (ALT) (UL)	333.0*	27-101
Albumin (g/dL)	3.8	2.2-4.6
Alkaline phosphatase (ALP) (U/L)	77.2*	14-71
Amylase (U/L)	3,426.5*	279-1254
Aspartate transaminase (AST) (U/L)	1735.1*	12-58
Total bilirubin (mg/dL)	0.05	0.00-0.20
Total calcium (mg/dL)	7.9**	9-11
Chloride (mmol/L)	114.9	108-118
Cholesterol (mg/dL)	174.5	90-260
Total CO2 (mmol/L)	13.2**	15-21
Creatinine (mg/dl)	3.8*	1.1-2.2
Creatine kinase (CK)(U/L)	116,093.0*	73-260
Gamma glutamyl transferase (GGT) (U/L)	3.2	0.0-4.0
Glucose (mg/dL)	222.9*	63-118
Phosphorus (mg/dL)	14.6*	3.2-6.3
Potassium (mmol/L)	8.3*	3.6-4.9
Total protein (g/dL)	8.1	6.60-8.40
Sodium (mmol/L)	151.8	145-154
Triglycerides (mg/dL)	76.8	8-80
Urea (mg/dL)	135.7*	39-71

* A value above the reference range.
** A value below the reference range.

front limb, might be affected (18). It is considered uncommon for a cat presenting with ATE to experience paresis or paralysis of more than two limbs (13). The cat described here developed a highly atypical "triple-paresis", which included the left rather than the right-front limb (14).

A LA-FFBT is a rare clinical manifestation of chronic, left-sided heart disease in humans, and to the best of the authors' knowledge has only been rarely mentioned in the veterinary literature (10-12, 15).

For ATE to develop, thrombus formation must take place in the LA body or appendage, or, rarely, the LV. Myoendocardial lesions of atrial walls, a reported risk factor for thrombus formation, are considered rare in feline cardiomyopathy (14). Left atrial enlargement, on the other hand, is commonly demonstrated in severe, chronic feline cardiomyopathy and is attributed to a decrease in LV compliance. It contributes to blood stasis, decreases the clearance of clotting factors, and increases the probability of platelet aggregation. These, as well as the naturally hyper-coagulable state of diseased cats (16-18) increase the risk of thrombus formation. Although persistent AF is rare in cats due to their typically small atrial size, once it develops it increases the risk of blood stasis and thrombus formation, even further (19).

Once a thrombus develops, it can fully adhere to the atrial wall, or remain loosely attached to it through a peduncle, or migrate through the LV into a downstream artery of which the anatomical location depends on the size of the embolus. In humans this is usually the result of an enlarged LA associated with a stenotic mitral valve or following mitral valve replacement, and chronic AF (20-29).

The clinical presentation of human patients with a LA-FFBT can include syncope (23, 25), respiratory manifestations of pulmonary edema (26, 27), stroke (21, 27, 28), or sudden death from a ball-valve effect (20, 21). Repeated collisions with atrial walls and the mitral valve apparatus may cause fragmentation and consequent embolization of fragments to the coronary-bed and systemic-circulation (28, 30). Cerebrovascular accidents (21, 27, 28), or embolization to a limb artery (22, 29), or, rarely, to a renal or a mesentery artery may ensue. Many of these reported secondary complications might have explained several of the findings documented in the presently reported cat, including limb ischemia, hypothermia, and suspected myocardial infarction.

Echocardiographic characterization of the intra-

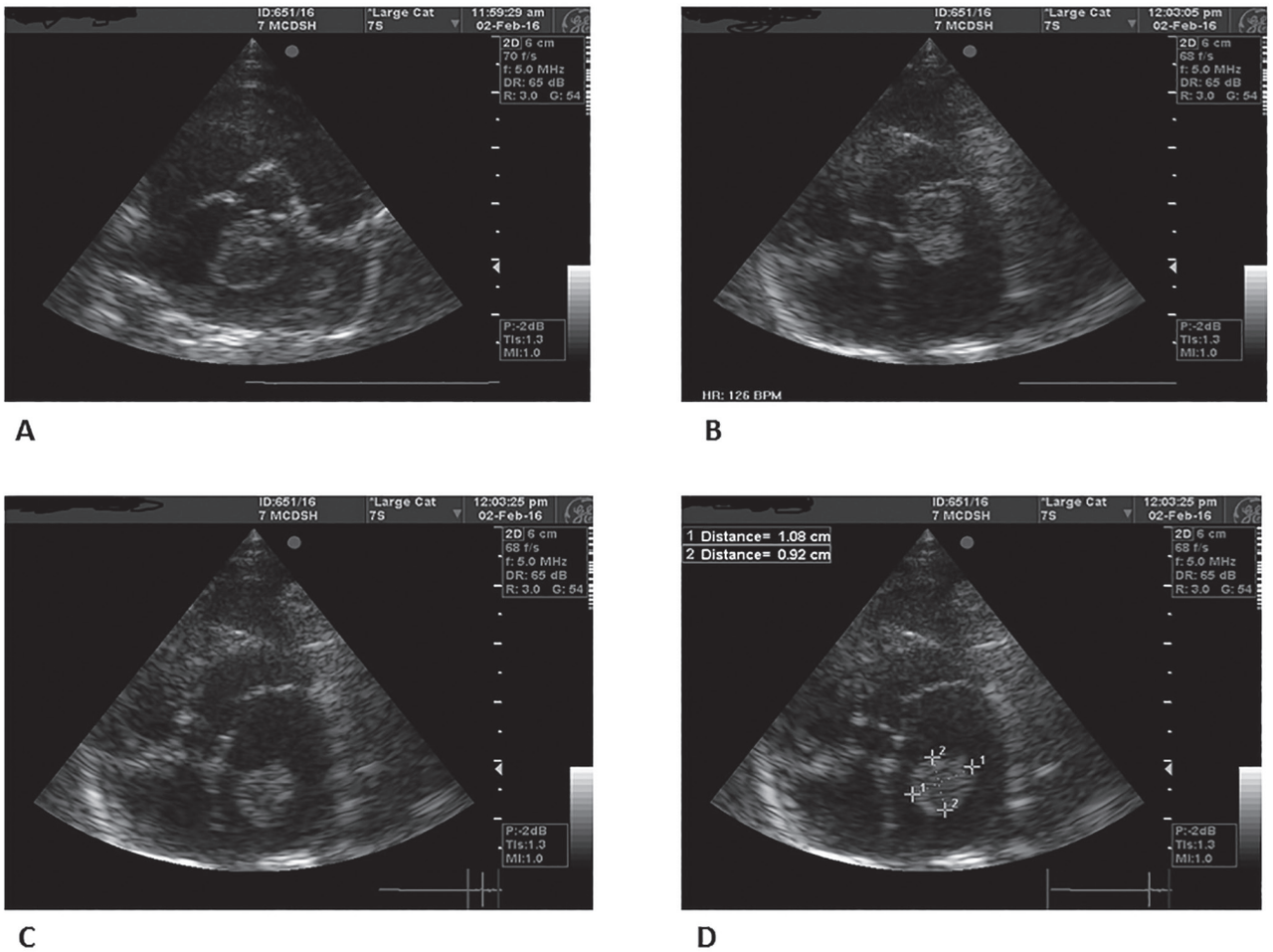

Figure 2: A free-floating, sonographically heterogeneic thrombus whirling in the left atrial cavity of a cat with atrial fibrillation and multiple limb paralysis. A. The intra-atrial thrombus next to the aortic root, as seen from the right parasternal, short axis view of the heart base during ventricular systole. B. A modified apical five-chamber view of the heart demonstrating the sonographically heterogeneic (and possibly cavitated) thrombus when located next to the mitral valve annulus. C. An apical five-chamber view demonstrating the thombus at the mid-left-atrial level. D. The same apical five-chamber view as in C, demonstrating the thombus dimensions as measured when temporarily located at the mid-left-atrial level.

atrial mass can theoretically help stratify the embolic risk. Thrombus size and sonographic heterogeneity may further contribute to this risk stratification (31). Specifically, mobile-ball type thrombi embolize more frequently than fixed, adhered, or pedunculated masses (31-33).

In humans, the location of a thrombus within the LA and the profile or dynamics of the sometimes related murmur may be altered depending on the patient's posture (23, 26, 34). Changes in body position can also adversely affect the erratic kinetics of the mass within the LA and readily promote cardiac arrest due to acute LV inflow occlusion (26, 33-35). If this is witnessed immediately, a prompt body position change might also change the clot location and abruptly, at least transiently relieve the inflow occlusion, thus increasing the likelihood of return of systemic circulation. A definitive treatment suggested for human patients is an urgent surgical intervention (9, 29). There are a few reports of either successful resolution or catastrophic embolization following detachment of an intra-cardiac thrombus using anticoagulants, along with systemic and intra-atrial thrombolytics, depending on whether the treated thrombus is an adhered or a pedunculated mass (24, 35, 36).

The diagnosis of ATE in the present case was based on the clinical presentation, an elevated serum D-dimer concentration, severe hyperkalemia, and massive elevation of activity of muscle enzymes.

Elevated serum muscle enzymes have been explained by compromised arterial perfusion leading to skeletal muscle

ischemia/necrosis, while hyperglycemia could reflect stress and pain (7, 14). Azotemia, hyperphosphatemia, hyperkalemia and hyperamylasemia could result from acute kidney injury (AKI) due to a retrograde build-up of an embolus lodged at the aortic trifurcation, or an antegrade newly embolized thrombus lodging directly into renal arteries, or from the low cardiac output secondary to myocardial failure combined with an elevated afterload following the aortic trifurcation occlusion, or from rhabdomyolysis (7, 14). Hyperamylasemia might also result from acute pancreatitis , ishemia or infartction of the pancreas, due to systemic embolism, or a low cardiac output. Hypocalcemia, too, could be the result of AKI or pancreatitis, and a low total CO_2 could result from reperfusion-related metabolic acidosis, AKI, or a low cardiac output.

It is tempting to speculate that a small thrombus initially adhered to the atrial septum, atrial free wall, or, less likely, to the atrial appendage wall. It might then have grown progressively to form a projecting pedunculated mass that remained adhered to the atrial wall. As the thrombus size gradually increased to dimensions that exceed the mitral valve annular diameter, the peduncle might have stretched, thinning enough to eventually detach. Thereafter, the thrombus might have moved about to freely swirl in the LA cavity, occasionally being swept towards the mitral valve leaflets without being able to pass through in its entirety, due to its relatively large dimensions.

Electrocardiographic and echocardiographic findings and the elevated serum cTnT in this patient are suggestive of myocardial infarction, likely due to microembolization of a clot fragment. This complication is rarely reported in the human literature (28, 30). In the only other case report of a cat with HCM demonstrating a LA-FFBT (12), there was no indication of peripheral embolization, nor was there any evidence suggestive of myocardial infarction. This cat died suddenly at home, 36 days after initial presentation.

In summary, a LA-FFBT is a rare, but ominous finding in cardiomyopathic cats with co-existing risk factors, and likely further increases the risk of thromboembolization. It can embolize and lead to multiple fragments lodging in one or several downstream coronary and systemic arteries. The rarity of this condition in cats makes the ability to gather information from a controlled case series, highly challenging, and would likely require the joint efforts involved in a prospective, multi-center, longitudinal study.

REFERENCES

1. Rush, J. E., Freeman, L. M., Fenollosa, N. K. and Brown, D. J.: Population and survival characteristics of cats with hypertrophic cardiomyopathy: 260 cases (1990-1999). JAVMA. 220: 202-207, 2002.
2. MacDonald, K.: Myocardial Disease: Faline. In: Textbook of veterinary internal medicine. Diseases of the dog and cat. 7th ed. Eds S. J. Ettinger and E. C. Feldman. W. B. Saunders, Philadelphia. pp. 1328-1341, 2010.
3. Tilley, L. P.: Cardiomyopathy and thromboembolism in the cat. Vet. Med., Small Anim. Clinic. 70: 313-316,1975.
4. Tilley, L. P., Liu, S. K., Gilbertson, S. R., Wagner, B. M. and Lord, P. F.: Primary myocardial disease in the cat. A model for human cardiomyopathy. Am. J. Pathol. 86: 493-522, 1977.
5. Laste, N. J. and Harpster, N. K.: A retrospective study of 100 cases of feline distal aortic thromboembolism: 1977-1993. JAAHA. 31: 492-500, 1994.
6. Rastegar, R., Harnick, D. J., Weidemann, P., Fuster, V., Coller , B., Badimon, J.J., Chesebro , J. and Goldman, M.E.: Spontaneous echo contrast videodensity is flow-related and is dependent on the relative concentrations of fibrinogen and red blood cells. J. Am. College Card. 41: 603-610, 2003.
7. Smith, S. A., Tobias, A. H., Jacob, K. A., Fine, D.M. and Grumbles, P.L.: Arterial Thromboembolism in Cats: Acute Crisis in 127 Cases (1992-2001) and Long-Term Management with Low-Dose Aspirin in 24 Cases. J. Vet. Int. Med. 17: 73-83, 2003.
8. Schober, K. E. and Maerz, I.: Assessment of left atrial appendage flow velocity and its relation to spontaneous echocardiographic contrast in 89 cats with myocardial disease. J. Vet. Int. Med. 20: 120-130, 2006.
9. Blanche, C., Chaux, A., Kass, R. M., Helfenstein, J. and Sugarman, G.: Free-floating ball thrombus in the left atrium after mitral valve replacement: successful surgical management. Ann. Thorac. Surg. 39: 566-568, 1985.
10. Buchanan, J. W., Baker, G. J. and Hill, J. D.: Aortic embolism in cats: prevalence, surgical treatment and electrocardiography. Vet. Rec.79: 496-505, 1966.
11. Baty, C.J., Malarkey, B. C. J., Atkins, D. E., DeFrancesco, C. E., Sidley, J. and Keene, B.W.: Natural history of hypertrophic cardiomyopathy and aortic thromboembolism in a family of domestic shorthair cats. J. Vet. Int. Med. 15, 595-599, 2001.
12. Takemura, N., Nakagawa, K. and Hirose, H.: Left atrial free-floating ball thrombus in a cat with hypertrophic cardiomyopathy. Adv. Anim. Card. 36: 36-40, 2003.
13. Bowles, D. B., Coleman, M. G. and Harvey, C. J.: Cardiogenic arterial thromboembolism causing non-ambulatory tetraparesis in a cat. J. Feline Med. Surg. 12: 144-150, 2010.
14. Kittleson, M. D.: Hypertrophic cardiomyopathy, in: Small Animal Cardiovascular Medicine. 1st ed. Eds. M. D. Kittleson and R. D. Kienle. Elsevier, St Louis. pp. 347-362, 1998.
15. Buchanan, J.: Selective Angiography and angiocardiography in dogs with acquired cardiovascular disease. Vet. Rad. 6: 5-20, 1965.
16. Tschopp, T. B.: Aggregation of cat platelets in vitro. Thromb. Diath. Haemorrh. 23: 601-620, 1970.
17. Helenski, C. A. and Ross, J. N.: Platelet aggregation in feline cardiomyopathy. J. Vet. Int. Med.1: 24-28, 1987.

18. Kittleson, M. D.: Thromboembolic disease, in: Small Animal Cardiovascular Medicine. 1st ed. Eds. M. D. Kittleson and R. D. Kienle. Elsevier, St Louis. pp. 540-551, 1998.
19. Côté, E., Harpster, N. K., Laste, N. J., MacDonald, K.A., Kittleson. M.D., Bond, B.R., Barrett, K.A., Ettinger, S.A. and Atkins. C.E.: Atrial fibrillation in cats: 50 cases (1979-2002). JAVMA. 225: 256-260, 2004.
20. Lie, J. T. and Entman, M. L.: "Hole-in-one" sudden death: mitral stenosis and left atrial ball thrombus. Am. Heart J. 91: 798-804, 1976.
21. Furukawa, K., Katsume, H., Matsukubo, H. and Inoue, D.: Echocardiographic findings of floating thrombus in left atrium. Br. Heart J. 44: 599-601, 1980.
22. Sunagawa, K., Orita, Y., Tanaka, S., Kikuchi, Y., Nakamura, M. and Hirata, T.: Left atrial ball thrombus diagnosed by two-dimensional echocardiography. Am. Heart J. 100: 89-94, 1980.
23. Chen, C. C., Hsiung, M. C. and Chiang, B. N.: Variable diastolic rumbling murmur caused by floating left atrial thrombus. Br. Heart J.50: 190-192, 1983.
24. Szkopiec, R. L., Torstveit, J. R., Prakash, N. S., Desser, K.B. and Benchimol, A.: Non-invasive diagnosis of a free-floating left atrial thrombus with emphasis on two-dimensional echocardiographic features. Angiology. 34: 102-110, 1983.
25. Gottdiener, J. S., Temeck, B. K., Patterson, R. H. and Fletcher, R.D.: Transient ("hole-in-one") occlusion of the mitral valve orifice by a free-floating left atrial ball thrombus: Identification by two-dimensional echocardiography. Am. J. Cardiol. 53: 1730, 1984
26. Warda, M., Garcia, J., Pechacek, L. W., Massumkhani, A. and Hall, R.J.: Auscultatory and echocardiographic features of mobile left atrial thrombus. J. Am. Coll. Card. 5: 379-382, 1985.
27. Balbarini, A., Pugliese, P. and Mariani, M.: Echocardiographic and surgical findings of a ball-like thrombus floating freely in the left atrium. J. Cardiovasc. Surg. 28: 135-138, 1986.
28. Wrisley, D., Giambartolomei, A., Levy, I., Brownlee, W., Lee, I. and Erickson, J.: Left atrial ball thrombus: Apparent detachment following initiation of anticoagulant therapy. Am. Heart J. 116: 1351-1352, 1988.
29. Wrisley, D., Lee, I., Parker, F., Brownlee, W. and Ismail, M.: Recurrent systemic embolization from left atrial ball thrombus: the case of early surgical intervention. NY State J. Med., 9: 74-75, 1990.
30. Kim, M. S., Park, J. H., Kang, S. K., Na, M.H., Lee, J.W., Choi, S.W., Jenog, J.O. and Seong, I.W.: Acute ST-segment elevation myocardial infarction due to a huge floating thrombus mimicking a myxoma in the left atrium. J. Am. Soc. Echocardiog. 22: 1085-e1, 2009.
31. Wrisley, D., Giambartolomei, A., Lee, I. and Brownlee, W.: Left atrial ball thrombus: review of clinical and echocardiographic manifestations with suggestions for management. Am. Heart J. 121: 1784-1790, 1991.
32. Stöllberger, C., Chnupa, P., Kronik, G., Brainin, M., Finsterer, J., Schneider, B. and Slany, J.: Transesophageal echocardiography to assess embolic risk in patients with atrial fibrillation. ELAT Study Group. Embolism in Left Atrial Thrombi. Annals Int. Med. 128: 630-638, 1998.
33. Abernathy III, J. H., Locke, A. B. and Shernan, S. K.: Dynamic left ventricular inflow obstruction associated with a left atrial myxoma. Anesth Analg. 103: 1406-1407, 2006.
34. Miyamoto, S., Hadama, T., Mori, Y., Shingemitsu, O., Sako, H., Soeda, T., Yoshinatsu, T. and Ucida, Y.: The effect of body position on a free-floating ball thrombus as observed by transesophageal echocardiography. Clin. Cardiol. 18: 1995, 535-538.
35. Maron, B. A., Goldhaber, S. Z., Sturzu, A. C., Rhee, D.K., Ali, B.S., Shah, P.B. and Kirshenbaum, J.M.: Catheter-directed thrombolysis for giant right atrial thrombus. Circulation: Cardiovasc. Imag. 3: 126-127, 2010.
36. Nagamoto, Y., Shiomi, T., Matsuura, T., Okahara, A., Takegami, A., Mine, D., Shirahama, T., Koga, W., Yoshida, K., Sadamatsu, K. and Hayashida, K.: Resolution of a left ventricular thrombus by the thrombolytic action of dabigatran. Heart and Vessels. 29: 560-562, 2014.