Pheochromocytoma in a horse with polymorphic ventricular tachycardia

Feochromocytoma bij een paard met polymorfe ventriculaire tachycardie

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ABSTRACT

A twenty-four-year-old mare, which had been examined seven years earlier for mitral valve regurgitation and mild left sided cardiomegaly, was presented with tachycardia, profuse sweating and muscle fasciculations. Blood examination revealed an increased packed cell volume, metabolic acidosis, hypocalcemia, hyperglycemia and increased cardiac troponin I concentration. ECG revealed ventricular premature beats and monomorphic ventricular tachycardia followed by polymorphic ventricular tachycardia with R-on-T phenomenon. The horse was treated immediately with hypertonic solution followed by isotonic solution and calcium, but the general condition deteriorated within forty-five minutes after arrival. The horse was euthanized due to poor prognosis. On necropsy, a pheochromocytoma of the left adrenal gland was found. Although this horse had undergone a cardiovascular examination seven and one year prior to the onset of the clinical signs, no indications for a neoplastic process or symptoms of a pheochromocytoma were found at that time. Early diagnosis of pheochromocytoma is based on catecholamine mediated cardiovascular effects, blood examination, blood pressure measurement, rectal palpation and rectal ultrasound of the adrenal gland. Based on a retrospective analysis of echocardiographic images and measurements, no predisposing factors were found. In this article, the importance of including pheochromocytoma as a differential diagnosis is highlighted, especially in older horses with acute polymorphic ventricular tachycardia, sweating, muscle tremors and signs of acute abdominal pain.

SAMENVATTING

Een vierentwintig jaar oude merrie die zeven jaar geleden onderzocht werd voor een mitralisklepregurgitatie en milde, linkszijdige cardiomegalie, werd aangeboden voor tachycardie, uitgesproken zweten en spiertremor. Het bloedonderzoek toonde een verhoogde hematocriet, metabole acidose, hypocalcemie, hyperglycemie en een verhoogde cardiaal troponine I-concentratie aan. Elektrocardiografie toonde talrijke ventriculaire premature contracties en monomorfe ventriculaire tachycardie die gevolgd werd door polymorfe ventriculaire tachycardie met R-op-T fenomeen. Ondanks onmiddellijke behandeling met hypertoon en calciuminfuus verslechterde de klinische situatie progressief binnen de vijfenveertig minuten na aankomst. Omwille van de gereserveerde prognose werd het paard geëuthanaseerd. Pathologisch onderzoek toonde een bijniermergtumor (feochromocytoom) van de linkerbijnier aan. Alhoewel dit paard reeds zeven en één jaar vóór het begin van de klinische tekenen van feochromocytoom onderzocht werd, konden op die momenten geen indicaties voor een neoplastisch proces of klinische tekenen van een feochromocytoom worden waargenomen. Een vroege diagnose van bijniermergtumoren kan gebaseerd zijn op catecholamine gemedieerde cardiovasculaire effecten, bloedonderzoek, bloeddrukmeting, rectaal onderzoek en rectale echografie van de bijnier. Aan de hand van een retrospectieve analyse van echocardiografische beelden en metingen konden in het voorliggende geval geen predisponerende factoren gevonden worden. In dit artikel wordt het belang van het overwegen van een feochromocytoom in de differentiaaldiagnose benadrukt, voornamelijk bij oudere paarden met polymorfe ventriculaire tachycardie, zweten, spiertremoren en acute kolieksymptomen.

INTRODUCTION

Tumors of chromaffin and non-chromaffin paraganglia are relatively rare in all species (Calsyn et al., 2010), but pheochromocytoma is the most frequently occurring medullary adrenal neoplasm in domestic animals and the most common adrenal tumor in older horses (Appelby, 1976; Johnson et al., 1995; Luethy et al., 2016; Wilson et al., 1986). The prevalence of pheochromocytomas is higher than the prevalence of cortical tumors (Appleby, 1976). Prolonged stimulation of the adrenal gland might lead to neoplastic change with a continuous gradient from hyperplasia to adenoma (Appleby, 1976; De Cock and MacLachlan, 1999). In humans, pheochromocytoma may have a familial occurrence and can occur together with other endocrine neoplasms, i. e. multiple endocrine neoplasia (MEN-) (De Cock and MacLachlan, 1999; Germann et al., 2006; Luethy et al., 2016; Pugsley and Spratt, 1984; Tischler et al., 2004). Usually, equine pheochromocytomas are unilateral, non-functional and have a low incidence of malignancy. There is no breed or gender predisposition, but older horses (> twelve years) are at higher risk for developing the neoplasia (Germann et al., 2006; Johnson et al., 1995; Luethy et al., 2016; Toribio, 2010; Yovich et al., 1984).

Functional, catecholamine-producing pheochromocytomas occur in horses, and they mainly secrete epinephrine, but also norepinephrine secreting pheochromocytomas have been identified (Johnson et al., 1995; Toribio, 2010). In cattle and dogs, they predominantly produce norepinephrine, while in humans, both hormones are often produced (Edmondson et al., 2015; Johnson et al., 1995; Luethy et al., 2016). The sudden inappropriate release of catecholamines in the blood may lead to lethargy, polydipsia, polyuria, weight loss with a variable appetite, tachypnea, hyperthermia, pyrexia, abdominal distention, ileus, abdominal pain, recurrent colic, diarrhea, edema, excessive sweating, excitability, mydriasis, restlessness, anxiety, muscle fasciculations, ataxia, hypertension, abortion, concentric cardiac hypertrophy, tachycardia, supraventricular and ventricular arrhythmia or sudden death (Anderson and Aitken, 1977; Buckingham, 1970; De Simone G, 2004; Dybdal and McFarlane, 2009; Froscher and Power, 1982; Gelberg at al., 1979; Germann et al., 2006; Johnson et al, 1995; Kline et al., 1961; Snow, 1979; Luethy et al., 2016; Toribio, 2010; Yovich and Ducharme, 1983; Yovich et al., 1984). Dopamine is a precursor of epinephrine and norepinephrine. Tumors, which are deficient in beta hydroxylase, the enzyme that converts dopamine into norepinephrine, predominantly secrete dopamine (Dubois, 2005). Dopamine secreting pheochromocytomas are less common and occur occasionally with an asymptomatic, non-classical presentation with vague, non-specific signs and a normal blood pressure (Calsyn et al., 2010; Dubois, 2005; Johnson et al., 1995).

The sudden onset of the severe, non-specific clinical signs makes it difficult to make the diagnosis before necropsy (Luethy et al., 2016). Ante mortem diagnosis can sometimes be made by the combination of the clinical signs, including especially profuse sweating with tachycardia in absence of colic, enteritis or septicemia, coccygeal blood pressure measurement, abdominocentesis, determination of circulating serum catecholamines and their urinary metabolites, rectal examination or transrectal ultrasonography (Durie et al., 2010; Johnson et al, 1995; Luethy et al., 2016; Wilson et al., 1986). In this case report, a twenty-four-year-old horse with acute polymorphic ventricular tachycardia due to a functional pheochromocytoma is described.

CASE HISTORY

A seventeen-year-old warmblood mare was initially presented at the Department of Large Animal Internal Medicine (Faculty of Veterinary Medicine, Ghent University) for the evaluation of an asymptomatic, left-sided, mid-end systolic, crescendo murmur over the mitral valve region with a grade 3/6. A limited ultrasound examination, which included only two dimensional (2D) images and Doppler evaluation of the mitral valve, was performed for a murmur that was detected immediately before induction of anesthesia for elective surgery on a hoof abscess. The horse had a regular heart rhythm at a frequency of 36 beats per minute. Ultrasonography revealed moderate mitral valve regurgitation (MR) with a slightly dilated left atrium (LA) (Table 1). The LA/Ao end-systolic diameter ratio was increased to 1.32 (reference value: < 1.25) (Van der Vekens et al., 2016).

Six years later, the twenty-three-year-old horse showed sudden ventral edema. On auscultation, a regular heart rhythm and a normal heart rate of 44 beats per minute were present. A holosystolic, crescendo murmur grade 4/6 was present over the mitral valve region. On the right side, a holosystolic plateau type murmur grade 2/6 was detected. Electrocardiographic (ECG) recording showed a normal sinus rhythm. The general clinical examination was normal, except for ventral edema. A general blood examination performed at home revealed no abnormalities. Ultrasound of the thorax and abdomen was normal. Echocardiography revealed a slightly thickened mitral valve with severe regurgitation and a mild aortic and tricuspid regurgitation in combination with a slightly thickened aortic valve. On M-mode of the left ventricle, a mild hyperkinetic movement of the interventricular septum was observed. A 2D echocardiographic examination revealed an increased mean and relative wall thickness and left ventricular area in diastole. The interventricular septum thickness in dia-

Table 1. Cardiac measurements obtained in 2008 and 2013 (reference values are based on [1] Sabev, 2014; [2] Ven et al., 2016; [3] Trachsel et al., 2013; [4] Patteson et al., 1995).

Measurement	2DE 2008	2D Ultra-sound 2013	Reference	Measurement	M-Mode 2013	Reference
			Mean ± SD			Mean ± SD
R-LVFWd4C (cm)	1.8	1.8	3.1 ±0.6[1]	R-LVFWd$_{ch}$ (cm)	2.0	2.4±0.2[1]
R-LVFWs4C (cm)	3.0	3.2	4.0±0.4[4^]	R-LVFWs$_{ch}$ (cm)	3.6	3.7±0.6[1]
R-LVDd4C (cm)	11.4	11.7	11.9±0.6[4^]	R-LVIDd$_{ch}$ (cm)	12.6	9.8 – 12.6[2]
R-LVDs4C (cm)	8.3	8.2	7.5±0.7[4^]	R-LVIDs$_{ch}$ (cm)	8.2	4.7 – 8.1[2]
R-LVAd4C (cm^2)	180.5	**187.6**	105.9 – 184.7[2]		/	/
R-LVAs4C (cm^2)	65.8	77.5	43.1 – 92.7[2]		/	/
MWT (cm)	1.8	2.5	no data °	MWT (cm)	2.2	2.8 ± 0.3[3]
RWT	0.32	0.43	no data°	RWT	0.35	0.5±0.1[3]
R-IVSd4C (cm)	1.9	3.2	3.4 ±0.2[1]	R-IVSd$_{ch}$ (cm)	2.4	2.9 ±0.2[1]
R-IVSs4C (cm)	3.2	2.8	4.1±0.3[4^]	R-IVSs$_{ch}$ (cm)	3.5	3.8±0.3[1]
R-LAD$_{SAX}$ (cm)	**9.70**	**10.00**	7.54 – 9.62[2]		/	/
R-AoD$_{SAX}$ (cm)	7.30	7.60	6.22 – 8.46[2]		/	/
R-LA/AoD$_{SAX}$	**1.32**	**1.32**	1.05 – 1.29[2]		/	/

R-LVFWd4C: end-diastolic left ventricular free wall thickness from the four-chamber view; R-LVFWs4C: end-systolic left ventricular free wall thickness from the four-chamber view; R-LVDd4C: end-diastolic left ventricular internal diameter from the four-chamber view; R-LVDs4C: end-systolic left ventricular internal diameter from the four-chamber view; R-LVAd4C: end-diastolic left ventricular area from the four-chamber view; R-LVAs4C: end-systolic left ventricular area from the four-chamber view; MWT: mean wall thickness; RWT: relative wall thickness; R-IVSd4C: end-diastolic interventricular septum thickness at chordal level from the four-chamber view; R-IVSs4C: end-systolic interventricular septum thickness at chordal level from the four-chamber view; R-LAD$_{SAX}$: end-systolic left atrial short-axis diameter; R-AoD$_{SAX}$. end-systolic aortic short-axis diameter; R-LVFWd$_{ch}$: end-diastolic left ventricular free wall thickness at chordal level; R-LVFWs$_{ch}$: end-systolic left ventricular free wall thickness at chordal level; R-LVIDd$_{ch}$: end-diastolic left ventricular internal diameter at chordal level; R-LVIDs$_{ch}$: end-systolic left ventricular internal diameter at chordal level; R-IVSd$_{ch}$: end-diastolic interventricular septum thickness at chordal level; R-IVSs$_{ch}$. end-systolic interventricular septum thickness at chordal level
° no data in Warmblood horses
^ data in Thoroughbred horses

stole had increased, but did not reach values above the reference value. An increase in left atrial and aortic diameter occurred without a significant change in La/Ao ratio. The echocardiographic measurements of 2008 and 2013 are compared in Table 1. Based upon the ultrasonographic findings, the ventral edema was not related to the cardiac problem. No additional tests were performed in the diagnosis of the ventral edema. After a prednisolone therapy given at home, the edema disappeared.

Clinical examination

At the age of twenty-four, the horse was presented because of excessive sweating, muscle fasciculation and signs of colic. Previously, no signs of restlessness, sweating or excitation were seen. Rectal palpation performed at home by the referring veterinarian had not revealed any abnormalities. The horse had been treated before referral to the clinic with 30 cc of N-butylscopolaminiumbromide with metamizolum IV (Buscopan compositum®, Boehringer Ingelheim, Belgium) and 10 cc of dexamethasone IV (Rapidexon®, Ecuphar, Belgium).

Upon arrival at the clinic, the horse had hyperemic mucous membranes and a normal rectal temperature of 37.4 °C. The horse weighed 457 kg and had a body condition score of 5/9. The mare was sweating and showed severe muscle trembling. On auscultation, there were reduced gut sounds and pronounced vesicular breathing. Cardiac auscultation revealed a tachyarrhythmia at 100 beats per minute with a holosystolic murmur grade 4/6 over the mitral valve area and loud heart sounds. The pulse quality was good. No ventral edema was present. Blood examination revealed a metabolic acidosis, hypocalcemia, hyperglycemia and an increased packed cell volume (Table 2). Serum cardiac troponin I was directly send to the lab and determined by the acridinium ester-based ADVIA centaur troponin I-ultra assay. The value was markedly increased (Table 2).

Apart from tachycardia, echocardiography showed a good contractile function and was not suggestive of primary cardiac failure. A resting ECG (Televet

Table 2. Analysis of a venous blood sample of the horse with a pheochromocytoma.

Sample	Value	Reference values
pH	7.24	7.40 ± 0.50
Base Exces	**- 6 mEq/L**	0 ± 5 mEq/L
Packed cell volume	**62 %**	40 ± 5 %
Ionized Calcium	**1.17 mmol/L**	1.40 – 1.60 mmol/L
Sodium	140 mmol/L	135 - 150 mmol/L
Potassium	3.0 mmol/L	3.0 – 4.0 mmol/L
Chloride	82 mmol/L	95 - 105 mmol/L
Glucose	**368 mg/dL**	80 - 120 mg/dL
Cardiac Troponin I	**17.40 ng/mL**	< 0.03 ng/mL

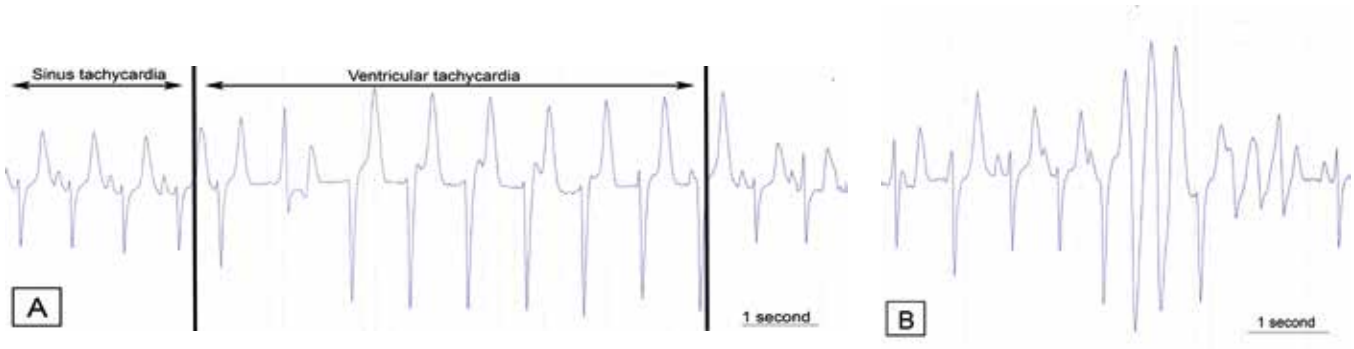

Figure 1. A. Sinus tachycardia followed by ventricular tachycardia with different QRS morphologies B. Run of polymorphic ventricular tachycardia and R- on-T phenomenon.

100®, Engel Engineering Service GmbH, Offenbach, Germany) showed sinus tachycardia, with episodes of ventricular premature depolarizations (VPD) and polymorphic ventricular tachycardia (VT) (Figure 1A). During the placement of a catheter in the jugular vein, a short run of polymorphic ventricular tachycardia with R-on-T morphology was seen (Figure1B). No blood pressure measurements were performed.

Thoracic ultrasonography revealed no abnormalities. Abdominal ultrasound showed a few mildly dilated, contractile small intestines. There was no increase in free abdominal fluid. The stomach had a normal size of three intercostal spaces without any gas-fluid line. On rectal palpation, no abnormalities were palpated in the region of the left kidney, the nephrosplenic ligament and the spleen. There was dry feces present in the rectum and the cecum was slightly distended with gas.

Sampling of the abdominal fluid showed clear yellowish transudate with a white blood cell count of 1000 cells/µL (refence value: < 5000 cells/µL), a total protein of 2 g/dL (reference value: < 2.5 g/dL) and a lactate of 20 mmol/L (refence value: < 4.1 mmol/L).

Four ml/kg of hypertonic saline (7.2% NaCl®, Braun, Belgium), 0.5 mg/kg of calciumborogluconate (Calcii Borogluconas®, Eurovet, Belgium) and bicarbonate supplementation, followed by 11 ml/kg of lactated Ringer's solution (Dirinco®, Haemopharm Biofluids, Italy) were administered. Within 45 minutes after arrival in the clinic, the general condition of the horse deteriorated and the owner decided to let the horse be euthanized.

Post-mortem findings

Macroscopic examination

A full necropsy was performed within 24 hours after death by a recognized European specialist pathology. A hemorrhagic mass (5 x 3 cm) was found at the craniomedial aspect of the left kidney. The neoplastic adrenal gland was not enlarged (reference length: 7-8 cm, width: 2.4-4.5 cm, thickness: 0.6-1.6 cm) (Durie et al., 2010). Multiple petechiae were found on the pleura, spleen, mesentery and coronary vessels. Additionally, multiple subendocardial white plaques were found in the myocardium. The left atrium appeared slightly dilated. Macroscopic examination of the different cardiac valves did not reveal clear abnormalities. The liver was diffusely congested, moderately firm and irregular, and had an accentuated zonal pattern.

Microscopic examination

Samples taken during necropsy were fixed in 4%-buffered formalin and embedded in paraffin. Sections of 4 µm were made and subsequently stained with hematoxylin-eosin (HE) for routine histological evaluation. The adrenal medulla consisted of packets of columnar to cubic cells with a high amount of eosinophilic to brownish, granular cytoplasm and an eccentrically located hyperchromatic nucleus. Anisokaryosis and anisocytosis were moderate. The packets were separated by delicate strands of highly vascularized fibrovascular stroma. There was less than one mitotic figure per high power field. The histological presentation was indicative of a pheochromocytoma (Figures 2A and 2B). No immunohistochemistry was performed due to the typical eosinophilic intracytoplasmic granular aspect. An indication about the normal architecture of an adrenal medulla is given in Figure 2C. In the heart, there was mild, multifocal hypertrophy of the cardiomyocytes as judged by the pathologist. The nuclei were surrounded by a yellow-brownish pigment (lipofuscin). Subendocardially, multiple fibrotic zones with centrally accumulated mineralization indicative of chronic and/or acute cardiac dilation were present (Robinson and Robinson, 2016). The liver showed diffuse capsular fibrosis and the presence of coalescing subcapsular vascular spaces (teleangiectasia), which can be interpreted as incidental findings. The Kuppfer cells, as well as some hepatocytes, contained a moderate amount of hemosiderin, which is indicative of an increased red blood cell turn-over. Multifocal single cell necrosis was present. The portal areas were infiltrated by small amounts of lymphocytes, plasma cells and hemosiderin-laden macrophages, which suggested a non-specific, reactive hepatitis. Additionally, lymphoplasmacytic infiltration of the colonic lamina propria was found.

DISCUSSION

Pheochromocytomas are the most frequently occurring adrenal medullary tumors in older horses, but they are a relatively rare finding with a prevalence of 0.95 % (Luethy et al., 2016). Yet, the ante-mortem diagnosis of pheochromocytomas in equine medicine is difficult and the definitive diagnosis is often made on necropsy (Luethy et al., 2016), despite the existence of data on catecholamine concentrations in normal and affected horses (Fouché et al., 2016; Yovich et al., 1984). The clinical signs of a pheochromocytoma are correlated with the functionality of the tumor cells and occur continuously or paroxysmally (Calsyn et al., 2010; Johnson et al, 1995; Yovich et al., 1984). The clinical signs in the horse of the present case were noticed for the first time when it was presented at the age of twenty-four. Retroperitoneal hemorrhage or hemoperitoneum may result from severe bleeding and rupture of the tumor due to a weak vascular integrity in combination with a rapid growth and an increased intracapsular pressure (Herbach et al., 2010; Johnson et al., 1995; Yovich and Ducharme, 1983). In the present case, no signs of abdominal bleeding were seen by abdominal ultrasonography and abdominocentesis. Moreover, on rectal palpation, no mass was palpated in the region of the left kidney, which actually could have been missed due to the cranial position of the adrenal gland in the abdominal cavity. No rupture of the neoplasm was seen macroscopically on post-mortem examination. These facts suggests that the horse suffered from a functional, non-ruptured neoplasm of the left adrenal gland. In most cases, the medullary tumor compresses the adjacent hemorrhagic cortex (Luethy et al., 2016; Pugsley and Spratt, 1984). As in the present case, histology of the adrenal gland tumor reveals cellular trabeculae, packets or nests, which are separated by large vascular spaces and fibrous stroma. Round to oval nuclei are located in the apical part of the cells distant to the vascular channel or are located centrally. The cytoplasm is eosinophilic and filled up by just one type of eosinophilic secretory granules (Buckingham, 1970; Froscher and Power, 1982; Gelberg et al., 1979; Germann et al.,2006; Herbach et al., 2010; Johnson et al., 1995; Luethy et al., 2016; Pugsley and Spratt, 1984; Wilson et al.,1986).

Biochemically, dopamine has α- and β-adrenergic and dopaminergic receptor activity with a predominance of α-adrenergic effects (Marsh, 2010). The effects of epinephrine (α- and β- adrenergic effects) and norepinephrine (only α-adrenergic effect) may lead to an increased rate of alpha-mediated hepatic glycogenolysis and beta-mediated muscle glycogenolysis resulting in hyperglycemia (Luethy et al., 2016; Snow, 1979). Acute stress situations in horses are likely to cause initially a rise in blood glucose levels. Furthermore, circulatory compromises, splanchnic vasoconstriction, ischemia and β2-mediated muscle glycogenolysis may increase the blood lactate values,

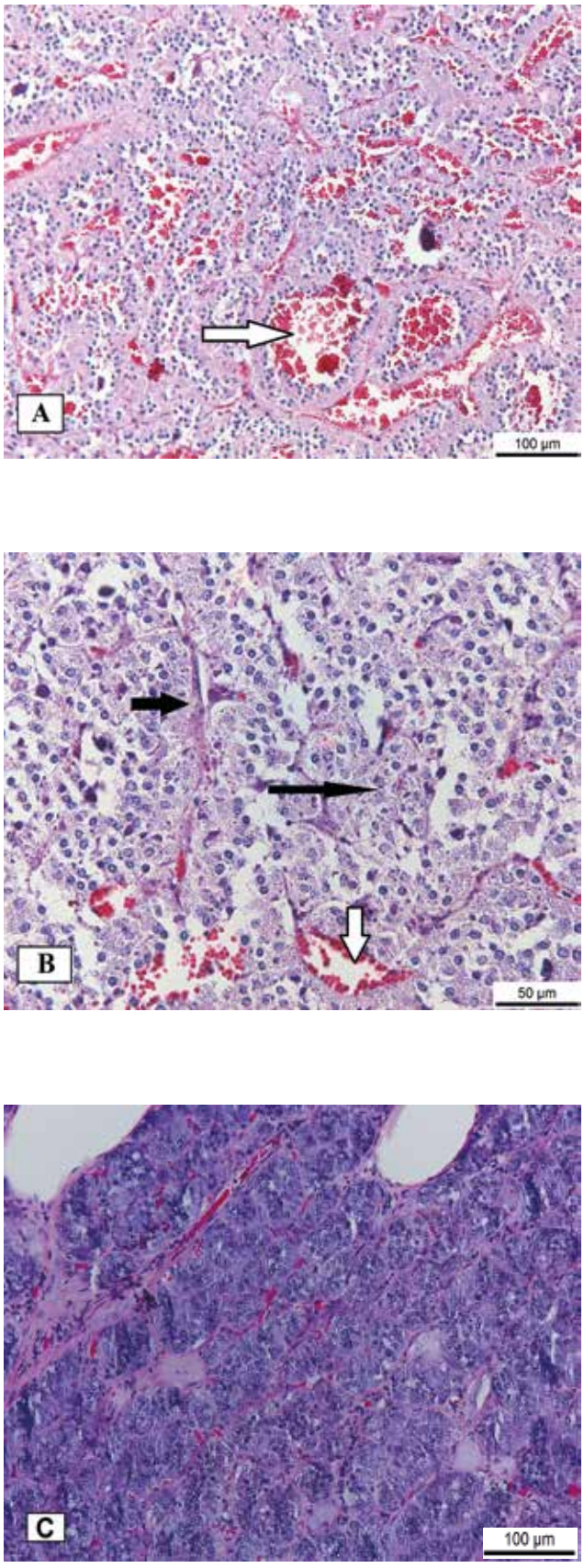

Figure 2. A. H&E stain. Histological presentation of the left adrenal pheochromocytoma, showing trabeculae and packets of moderately sized, polygonal cells (→), separated by highly vascularized (⇨) stroma (➡). B. H&E stain. Close-up of tumor cells. C. H&E stain. Normal adrenal medulla with less eosinophilic cytoplasm and less vascular spaces.

resulting in metabolic acidosis (Germann et al., 2006; Luethy et al., 2016; Snow, 1979). In the present case, no blood lactate measurement was performed, but lactate values of the abdominal fluid were increased to 20 mmol/l. As increased blood lactate values are a reflection of generalized hyperlactatemia, the increased level of lactate in the abdominal fluid of the patient of the present case is also a potent reflection of this hyperlactatemia. Maximal splenic contraction raises the packed cell volume and results in a higher number of circulating erythrocytes (Snow, 1979). The intestinal sequestration of fluids and splanchnic vasoconstriction may lead to hypovolemia and hemoconcentration. In the present case, no reason for severe systemic dehydration was found on clinical and pathological examimation. Hence, splenic contraction was in this case the most plausible cause of a rise in circulating erythrocytes. Positive chronotropic effects of the catecholamines on β2-receptors may be an explanation for the increased heart rate (Luethy et al. 2016; Anderson and Aitken, 1977; Snow, 1979). Alternatively, tachycardia may also be induced by severe pain, dehydration, endotoxemic or hemorrhagic shock or cardiovascular disease. Excessive sweating and pronounced muscle tremors in the patient of the present case might also be explained by β2-adrenergic stimulation (Germann et al., 2006; Luethy et al., 2016; Toribio, 2010; Yovich and Ducharme, 1983), but hypocalcemia and physiological stress or pain might also be the reason for these clinical findings. Electrolyte changes have been reported in horses with functional pheochromocytomas and may result in hypocalcemia, hypo- or hyperkalemia, hypochloremia, hyponatremia or hyperphosphatemia (Toribio, 2010). These electrolyte changes may be the result of severe electrolyte losses due to sweating or severe muscle fasciculation and stress. Abdominal pain may destabilize patient (Froscher and Power, 1982), and makes the differentiation with an acute colic extremely difficult. The sympaticomimetic effects on the postganglionic nerves of the gastrointestinal system may cause functional ileus with possible secondary gaseous distention and impaction of the large intestine (Yovich and Ducharme, 1983). Low-grade lymphocytic enteritis has already been described in association with pheochromocytoma (Gelberg at al., 1979; Johnson et al, 1995; Yovich et al., 1984).

Catecholamine mediated overstimulation increases cardiac contractility and heart rate, with an increase in myocardial oxygen demand. Functional hypoxia induced by vasoconstriction in the coronary macro- and microcirculations results in an uncoupling of the oxidative phosphorylation and induces electrolyte imbalances (Liaudet et al., 2014). An increase in cytosolic and mitochondrial calcium triggers mitochondrial oxidative stress and permeability, resulting in apoptotic and necrotic cell death and progressive focal myocardial fibrosis (Liaudet et al., 2014). The presence of subendocardial mineralization may occur in association with an acute onset of heart disease (Robinson and Robinson, 2016). Although dehydration and valvular regurgitation might induce a mild cardiac troponin increase, the extremely high value found in the horse of the present case (17.4 ng/ml) was probably due to direct catecholamine-induced myocardial damage (Van der Vekens et. al, 2015a; Van der Vekens et. al, 2015b).

The cardiac arrhythmia seen in this horse might be explained by catecholamine release, which causes myocardial hypoxia and myocardial damage on the one hand and hypertension related to concentric hypertrophy and cardiomyopathy on the other hand. These effects of catecholamines may be an explanation for a hypertrophic left ventricle in horses with pheochromocytoma (Kline, 1961; Johnson et al, 1995; Parry, 1984; Toribio, 2010; Yovich and Ducharme, 1983; Yovich et al., 1984). While chronic hypertensive effects may lead to concentric cardiac hypertrophy, mitral and aortic valve regurgitation may finally result in eccentric cardiac hypertrophy. In the present case, during the last presentation, a full cardiac examination could not be performed due to the instable condition of the horse. Therefore, the exact contribution and type of hypertrophy due to the combined effect of mitral valve regurgitation and pheochromocytoma could not be assessed. Due to the acute onset of the clinical signs, catecholamines were thought to be unlikely to result in concentric hypertrophy, but they were the most likely cause of ventricular tachycardia. In addition, the ventricles had a normal appearance on necropsy.

Hypertension is a common finding in horses with functional pheochromocytoma. Direct blood pressure monitoring or indirect blood pressure monitoring from the coccygeal artery is useful for the early diag-nosis of a functional pheochromocytoma (Johnson et al., 1995; Parry, 1984) and is more important than serum sampling for catecholamines. Unfortunately, blood pressure monitoring in this horse with functional pheochromocytoma was not performed due to instability and the rapid aggravation of the clinical signs. Normal norepinephrine levels in horses and ponies range between 120 – 300 pg/mL and 140 – 450 pg/mL, respectively. Due to excitation, these values quickly rise to 400 – 1200 pg/mL (Yovich et al., 1984). Epinephrine and norepinephrine are rapidly inactivated and excreted as glucuronides (metanephrines or urine vanillylmandelic acid) (Calsyn et al., 2010; Fouché et al., 2016; Johnson et al, 1995; Wilson et al., 1986), so the plasma concentrations of catecholamines are not stable. Good sampling and rapid determination are essential for obtaining representative values. Blood should be collected on EDTA tubes that contain bisulfate, an antioxidant, to prevent the degradation of norepinephrine (Hardee et al., 1982; Parry, 1984). Metabolite screening is extremely

insensitive for diagnosing a dopamine secreting pheochromocytoma. Therefore, in human patients' serum and urine, dopamine levels are measured for screening (Dubois and Daryl, 2005). The determination of catecholamines is not a standard analytic procedure and finding an adequate laboratory may be difficult. In addition, dopamine plasma concentrations vary widely among individuals (Marsh, 2010). Blood catecholamines and their urinary metabolites are a good diagnostic parameter for ante-mortem diagnosis of epinephrine of norepinephrine secreting tumors with a high sensitivity and a high specificity (Calsyn et al., 2010), but due to the rapid onset and the fast evolution of the clinical signs, plasma epinephrine and urinary metabolites were not analyzed in the patient of the present case, as the results would not have been known on time for contributing in making a definite diagnosis.

Any retroperitoneal mass palpable in the dorsal abdomen near the abdominal aorta may be indicative of a pheochromocytoma. Depending on horse and tumor size, the right kidney and right adrenal gland cannot always be reached by rectal palpation. Unfortunately, the normal right adrenal gland cannot be visualized by rectal ultrasonography in most horses. The deep abdominal location of the adrenal glands in adult horses makes it hard to use transabdominal ultrasonography for diagnostic imaging (Durie et al., 2010). By a rectal approach, the left adrenal gland potentially can be rectally palpated and visualized by ultrasound. As in the present case, the tumor is often missed (Buckingham, 1970; Froscher, 1982; Johnson, et al., 1995; Yovich, 1983), due to the cranial position or an inappropriate inspection or palpation of this abdominal region, especially in an instable patient. If a presumptive diagnosis of an abdominal mass is made by rectal examination, rectal ultrasound can be used to examine the morphology of the mass (Durie et al., 2010; Johnson et al., 1995). A normal equine adrenal gland has a length of 7-8 cm, a mean thickness of 0.6-1.6 cm and a width of 2.4-4.5 cm (Durie et al., 2010).

Curative treatment of horses with functional pheochromocytomas is difficult. Symptomatic treatment of the metabolic acidosis and electrolyte disturbances should be done by infusion therapy (Johnson et al., 1995; Yovich and Ducharme, 1983). Resection by laparotomy is possible but difficult due to the anatomi-cal position of the adrenal gland (Toribio, 2010). On the other side, general anesthesia enables to monitor the patient better. Standing laparoscopic adrenalectomy in horses seems to be a possible surgical technique in case of a stable patient (Fouché et al., 2016; Vanschandevijl et al., 2008). Mechanical manipulation of the tumor during surgery might result in tachycardia and hypertension (Germann et al., 2006). Therefore, cardiovascular monitoring by ECG and blood pressure measurement during the intervention are essential and the combination of early interruption of tumor vessels, which are directly draining into the inferior vena cava and a careful dissection are recommended (Pillinger et al., 2002; Toribio, 2010). Laparoscopic transperitoneal adrenalectomy is the method of choice for resection of a benign adrenal tumor and has become the golden standard with an excellent prognosis in human medicine (Johnson et al., 1995; Pillinger et al., 2002). Complete surgical removal is usually curative in human medicine (Parry, 1984). Preoperatively, α-adrenergic antagonists, such as phentolamine, phenoxybenzamine hydrochloride (0.2 – 0.5 mg/kg q12h orally) (Fouché et al., 2016) or prazosin hydrochloride can be used as hypotensive agents (Fouché et al., 2016; Toribio, 2010). Acepromazine maleate as dopamine receptor antagonist can also be used for its hypotensive characteristics. Propranolol (0.78 mg/kg orally) can block β-receptors, which reduces tachycardia, sweat response and the effects of glycogenolysis and lipolysis (Toribio, 2010; Fouché et al., 2016). Administration of β-blockers without prior administration of α-adrenergic blockers is contraindicated due to a risk of unopposed α-adrenergic receptor stimulation causing a hypertensive reaction (Fouché et al., 2016). Dopamine (D2) receptors are expressed in human pheochromocytomas and have inhibitory effects on norepinephrine secretion. Pergolide, a dopamine agonist, is supposed to have remissive effects on clinical signs (Fouché et al., 2016). Alpha-adrenergic blockage is contraindicated for the treatment of dopamine-secreting tumors because of the hypotensive effects and cardiovascular collapse. This illustrates the need to analyze which catecholamine is secreted by the tumor before starting medical therapy. Metyrosine, which inhibits the enzyme tyrosine hydroxylase, can be used in humans for conservative treatment by blocking the dopamine synthesis (Dubois and Daryl, 2005). Successful treatment of horses with functional pheochromocytomas has not been reported yet, and for the above mentioned medication, effective dosages in horses are poorly documented or based on a single case report.

CONCLUSION

The prognosis of a functional equine pheochromocytoma remains poor due to the difficulty of early diagnosis and the rapid onset of clinical signs. Although the cardiovascular system of the horse had been examined seven and one year prior to the onset of the clinical signs of pheochromocytoma, no indications for the neoplastic process or symptoms of a pheochromocytoma were found at that time. Based on general examination and the achieved cardiac parameters, no signs of catecholamine induced hypertensive effects on the equine myocardium could be found. Even if careful inspection of the left caudo-dorsal abdominal region would have been performed, the diagnosis

could have been missed because of normal adrenal size and the absence of hemorrhage. Tachycardia, polycythemia, muscle trembling, profuse sweating and acute colic were the most important signs in this case. Prompt cardiac examination including echocardiography, ECG recording and cardiac troponin assessment are valuable in order to include pheochromocytoma in the differential diagnosis of colic signs.

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