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Multiple organ dysfunction syndrome in a dog with *Klebsiella pneumoniae* septicemia

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Abstract

Multiple organ dysfunction syndrome is defined as the presence of altered organ function in an acutely ill patient such that homeostasis could not be maintained without intervention. It is reported that mortality rate in humans with 4 organ systems failing reaches nearly 100%, while there are few publications documenting this syndrome in dogs. To the author's knowledge, this is the first report that describes the clinical manifestations and the favourable outcome to intensive medical care in a dog with *Klebsiella pneumoniae* septicemia and multiple organ dysfunction with 6 organ systems failing. Derangement of cardiovascular, respiratory, gastrointestinal, pancreatic, renal and coagulation system developed. This dog manifested reversible myocardial depression that is a common complication of sepsis in people but it is rarely reported in dogs.

Introduction

Sepsis is defined as a systemic inflammatory response to infection, and septic shock is a progression of this inflammatory process, which leads to cardiovascular dysfunction (Bone et al., 1992; Costello et al., 2003). Gram-negative enteric bacteria, followed by gram-positive cocci and obligate anaerobes, are the most commonly described causes of sepsis (Brady and Otto, 2001). *Klebsiella pneumoniae* is a facultatively anaerobic gram-negative bacterium. It is a minor intestinal commensal and an opportunistic pathogen. In dogs, *K. pneumoniae* has been implicated in pneumonia, enteritis, endocarditis, urinary tract infections, and bacteremia while it is rarely reported as a cause of septicemia (Dow et al., 1989; Roberts et al., 2000). It was isolated from organs of dead puppies infected by milk of the bitches with mastitis and from two septicemic adult dogs on necropsy (Roberts et al., 2000; Schafer-Somi et al., 2003). Sepsis and endotoxic shock still remain associated with high mortality rate. Failure to initiate therapy immediately or ineffective therapeutic intervention can result in multiple organ dysfunction syndrome (MODS) (Day, 2000). The organ systems to be compromised generally include the respiratory, cardiovascular, gastrointestinal, renal, hepatic, coagulation and nervous system. Occasionally, the musculoskeletal or adrenal systems may also be affected. In humans, it has been established that there is a worse prognosis with increasing numbers of failing organs. While the reported mortality rate in patients with 1 organ system failing is 20%, mortality typically reaches nearly 100% with 4 organ systems failing (Johnson et al., 2004). In veterinary literature, there are few publications documenting MODS in dogs (Welzl et al., 2001; Johnson et al., 2004; Mathe et al., 2006). This report describes an uncommon case of MODS with 6 organ systems failing in a dog with *K. pneumoniae* septicemia. Besides, this report documents reversible sepsis-induced myocardial depression (SIMD) that is a widely recognized complication in septic patients but is rarely reported in dogs (Dickinson et al., 2007).

History and diagnostic procedure

A 2-year-old neutered mixed breed male dog weighing 10 kg was referred for sudden severe weakness and lethargy. The owner reported that the dog had been depressed and lacking in appetite for the previous 2 days. The dog was unable to stand, there was hyperthermia (40°C) and dehydration was estimated at 6%. Bradycardia (65 beats/min), tachypnea (50 breaths/min), weak pulse, pale mucous membranes and prolonged capillary refill time (3 seconds) were noted. Systolic blood pressure, measured by Doppler, was 60 mmHg. Pulse oximetry revealed saturation of hemoglobin at 88%. Blood samples were taken for laboratory evaluations. There was leucocytosis (82,6 x10³/f.Û.; I,r, 5,2-13,9 x10³/fl) with neutrophilia (mature neutrophils, 66,9 x10³/fl; r.r. 3,9-8,0 x10³/fl), left shift (bands neutrophils, 7,4 x10³/fl; I,I, 0,0-0,3 x10³/fl) and monocytosis (4,9 x10³/fl; r.r. 0,2-1,1 x10³/fl). Marked toxic changes in neutrophils were observed. Increase in alkaline phosphatase (353 U/l; r.r. 20-156 U/l), and high total proteins (10 g/dl; I,r, 5,4-7,5 g/dl) were present. Serum protein electrophoresis showed albumin 1,9 g/dl (r.r. 2,9-3,5 g/dl), ul-globulin 1,52 g/dl (r,r, 0,3 -0,6 g/dl), U 2globulin 3,19 g/dl (r.r. 0,7-1,1 g/dl), ~I-globulin 1,74 g/dl (r,r, 0,6 -1,2 g/dl), ~2-globulin 0,84 g/dl (r.I. 0,6-0,9 g/dl), and y-globulin 0,78 g/dl (r.r. 0,4-0,8 g/dl). Serum glucose concentration was 63 mg/dl (r.r. 60-115 mg/dl). Other haematological and biochemical parameters (transaminases, y-glutamyltransferase, total bilirubin, cholesterol, creatinine, urea, electrolytes) and urinalysis were unremarkable. On the basis of these findings, the working diagnosis was septic shock.

Treatment

The dog was admitted to the intensive care unit and treated with bolus of colloids (20 ml/kg ev, Voluven, Fresenius Kabi, Italy) to expand intravascular volume. Then colloids (8 ml/h) were combined with lactated Ringer's solution (20 ml/h ev, Bieffe Medical, Italy) and an oxygen supplementation was supplied by endonasal tube. Despite fluid resuscitation, systolic blood pressure was <80 mmHg, than a dobutamine constant-rate infusion (CRI) was initiated at 2.5 flg/Kg/min (Bioindustria, Italy) and a dopamine CRI started simultaneously at 3 flg/Kg/min (Revivan, AstraZeneca, Italy) to support myocardial contractility and visceral perfusion, respectively (Brady and Otto, 2001). A urinary catheter was positioned for monitoring urine output and a 5% dextrose solution was added to fluid therapy for 24 hours to increase extracellular fluid glucose concentration to approximately 100 mg/dl (Bistner et al., 2000; Macintire et al., 2005). The dog received buprenorphine (10 flg/Kg q8h ev, Temgesic, Scherig-Plough, UK) for anxiolysis and analgesia and ranitidine (2 mg/kg q12h ev, Hexal, Italy) to minimize risk of gastrointestinal ulceration. Antibiotic therapy was initiated with amoxicillin-clavulanic acid (20 mg/kg q 12h ev, Teva Pharma, Italy) and marbofloxacin (2 mg/kg q24h ev, Marbocyl, V  toquinol, France). As a result, this treatment maintained mean blood pressure at 100 mmHg, mean heart rate at 90 bpm and urine output >2 ml/kg/h. Electrocardiography and pulse oximetry monitored continuously, while temperature and blood pressure were checked every 4 hours, and urine output, packed cell volume, total proteins, glycemia and electrolytes were monitored every 6 hours. Complete blood count, albumin, creatinine, urea, hepatic enzymes, prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen were checked every day. The fluid rate was recalculated based on the monitoring results. Thoracic and abdominal radiography, abdominal ultrasonography did not detect any abnormalities. Echocardiographic findings showed hypokinetic left ventricle with a decrease in fractional shortening (FS=13%; r.r. 30-45%), low ejection fraction (EF=28%; r.r. 60-80%) and an endsystolic volume index (ESVI) which had increased to 44 mL/m² (r.I. <30 mL/m²). Three blood samples taken over a 24-hr period were inoculated into blood culture bottles (Isolator 1.5, Oxoid, Milan, Italy) and cultures were processed for isolation of aerobic and anaerobic bacteria. Urine culture was performed in Columbia Agar with 5% sheep blood and Trislide E (Oxoid, Milan, Italy) and no bacterial growth was observed. On day 3, the dog developed acute respiratory distress and gastrointestinal dysfunction. Mucous membranes were cyanotic and pulse oximetry fell to 82%. Gastrointestinal manifestations included vomiting and haemorrhagic diarrhoea. Furosemide (2 mg/kg q8h ev, Dimazon, Intervet, Italy) for pulmonary edema, sucralfat (40 mg/Kg q8h os, Teva Pharma, Italy) against possible gastrointestinal ulcerations, metronidazol (8 mg/kg q8h ev, Deflamon, Societ   Prodotti Antibiotici, Italy) to oppose anaerobic organisms and a metoclopramide CRI (1mg/kg/day, Intervet, Italy) as an antiemetic were administered. Fluid therapy was decreased from 670 ml/day, that is the maintenance water requirement, to 30-40 ml/kg/day as recommended in patients at risk of developing pulmonary edema (Bonagura et al., 2000). On day 5, acute renal failure (ARF) with oliguria, diabetes mellitus and disseminated intravascular coagulation (DIC) developed. Biochemical abnormalities included increased creatinine (2.7 mg/dl; r.r. 0.5-1.5 mg/dl) and urea (193 mg/dl; r.r. 21-60 mg/dl), high cholesterol (488 mg/dl; r.r. 135-270 mg/dl) and hyperglycemia (593 mg/dl; r.r. 65-118 mg/dl). Hypoalbuminaemia (2.1 g/dl) and increased ALP (318 D/l) were persistent. Urinalysis revealed low urine specific gravity (1010; r.r. 1015-1045) and glycosuria. Coagulation abnormalities included abnormal aPTT (26.7 seconds; r.r. 12-15 seconds), increased fibrinogen degradation products (>20 mg/dl; r.r. <5 mg/dl) and low plasma fibrinogen concentration (57 mg/dl; r.r. 150-450 mg/dl). Thrombocytopenia (79 x10³ /fl; r.r. 143-400 x10³/fl) and normocytic, normochromic, non regenerative anemia (3.9 x10⁶/fl; r.r. 5.7 -8.8 x10⁶/fl; reticulocytes, 40.7 x10⁹/l; r.r. 8.8-129.3x10⁹/l) were present. Leucocytosis (61.3 x10³/fl) with neutrophilia (52.3 x10³/fl) and monocytosis (6.1 x10³/fl) persisted. Abdominal ultrasonography revealed an enlarged hypoechoic pancreas compatible with pancreatitis and functional small bowel ileus. No peritonitis signs were noted. A sterile indwelling jugular venous catheter was inserted and lactated Ringer's solution at 40-60 ml/h combined with colloids (8 ml/h) was carried out. The dog received calcic heparin (100 D/kg q6h sc, Calciparina, Italfarmaco, Italy) for DIC and a regular insulin loading dose of 0.2 D/kg im followed by 0.1 D/kg im every 1 to 2 hours (Actrapid, Novo Nordisk, Denmark). Once the blood glucose concentration reached nearly 250 mg/dl, regular insulin was given every 4 to 6 hours (0.1 to 0.3 D/kg sc). With this treatment glycemia was maintained between 150 and 300 mg/dl, urine output at least 2 ml/kg/h and central venous pressure at 2-5 cmH₂O. Parenteral nutrition (PN) was initiated to provide nutritional support. The dog received by jugular catheter a nutrient admixture made up of 18% dextrose (72 Kcal/day; S.A.L.E S.p.A., Italy), 20% amino acids (80 Kcal/day; Freamine 8.5%, Bieffe Medital, Italy) and 62% lipids (248 Kcal/day; Intralipid 20%, Fresenius Kabi, Italy) supplemented with potassium chloride (20 mEq/l, Monico, Italy) to meet a resting energy requirement of 400 Kcal/day. Solution osmolality was about 800 mOsmol/L. The percentage of protein calories and non protein calories as well as the dextrose to lipid ratio were established based on current recommendations for PN (Remillard, 2000; Seim and Bartges, 2003; Michel and Eirmann, 2009). Glycemia, electrolytes, urea, liver enzymes and triglycerides were closely monitored.

On day 10, hypotension, pulmonary edema, vomitus and diarrhoea, and hyperglycemia were kept under control by support therapy. Urine production was 1.5 ml/kg/hour; creatinine and urea concentration was 1.5 mg/dl and 55 mg/dl, respectively. Heart rate was 85 beats/min. There were no clinical signs of DIC, although coagulation abnormalities were still present. Thrombocytopenia and leukocytosis were persistent, while anemia became regenerative (4.44 x10⁶/fl;

reticulocytes, $277.5 \times 10^9/l$). Blood culture result confirmed septicemia. A *K. pneumoniae* strain susceptible to colistin, doxycycline, trimethoprim/ sulphonamide, amikacina and netilmicine was identified from 2 blood cultures. Antibiotic therapy with doxycycline (10 mg/kg q24h os, Vibravet, Pfizer, Italy) was initiated. After one week of doxycycline administration, the dog was eating on its own. Mean blood pressure of 120 mmHg, mean heart rate of 90 bpm and pulse oximetry about 95% were maintained without drug support. First of all, respiratory and cardiovascular failure, then gastrointestinal manifestations and diabetes mellitus re-solved. On echocardiographic examination, all evidence of the previous myocardial dysfunction resolved. Fraction shortening was 30% and ejection fraction was 59%. ESVI decreased at 26 mL/m². A tricuspid valve vegetation compatible with infectious endocarditis (IE) and a mild regurgitation were visualized. Haematological, biochemical and coagulation parameters returned within the normal range apart from a mild leucocytosis ($19.2 \times 10^3/fll$) with neutrophilia ($14.8 \times 10^3/fll$), compatible with IE. The dog was discharged and treated with doxycycline for two months. At the end of therapy, the tricuspid valve vegetation and the regurgitation were not visualized. Haematological, biochemical and coagulation parameters were within the reference range. The dog was clinically normal with no recurrence of infection.

Discussion

Sepsis and septic shock should be suspected in any animal with hypotension, tachycardia, hypovolemia, fever or hypothermia, high or low white blood count, and signs of multiple organ involvement (Haskins, 1992). In our case, this dog on admission presented relative bradycardia that is an inappropriately low heart rate for the hemodynamic status of the patient. This is an unusual finding since in dogs reports of sepsis describe an initial hyperdynamic phase followed by a hypodynamic phase both characterized by tachycardia. Bradycardia is reported in cats with severe sepsis and in septic children (Tobias et al, 1991; Brady et al, 2000). The mechanism of this inappropriate bradycardia is unclear but it has been postulated to be secondary to increased vagal tone or cytokine-associated myocardial depression (Oral et al, 1997; Costello et al, 2004). In this case, it may be further hypothesized that on admission the dog was in the decompensatory stage of shock, whereby a low heart rate may accompany severe hypotension, impairment of cardiac contractility, pale or cyanotic mucous membranes, slow or no capillary refill time, weak or absent pulses. Multiple organ failure and cardiopulmonary arrest may develop and lead to death without aggressive resuscitation and organ support (Day, 2000). In this dog, another uncommon finding is the severe neutrophilic leukocytosis. In dogs, extreme leukocytosis is usually reported in association with 10-calized purulent diseases, Hepatozoon and Babesia infection, haemolytic anemia, paraneoplastic syndromes and granulocytic leukemia (Gaunt, 2000). However, it is reported that in sepsis the degree of leukocytosis can occasionally be extreme with white blood cell counts of more than $50 \times 10^9/l$ (Lucroy and Madewell, 2001; Aird, 2003). Several mechanisms contribute to extreme neutrophilia, including demargination of intravascular neutrophils, decreased vascular emigration, increased release from the bone marrow and increase production of neutrophils (Gaunt, 2000). Although, the increase of white blood cell count is important component of host response to infection, excessive increase in the number of neutrophils may be deleterious to the patient because extreme neutrophilia can increase blood viscosity and excessive release of reactive oxygen species from neutrophils may also contribute to the pathophysiology of severe sepsis. In fact, a high mortality rate has been associated with extreme neutrophilic leukocytosis (Lucroy and Madewell, 2001; Aird, 2003). This dog had exhibited no health problems before the outbreak of septicemia and the areas of high est suspicion for harboring the infectious focus such as the urinary and reproductive tract, respiratory system, abdominal cavity, teeth and heart valves were explored but the source of the *K. pneumoniae* infection remained unknown. Identification of the nidus of infection can be difficult and 30% of humans who die from bacteremia have no known site of infection. Prompt collection of blood culture is recommended (Brady and Otto, 2001). In this case, the recovery of *K. pneumoniae* from blood culture was taken as evidence of true bacteremia because it is a potentially pathogenic bacterium, not a normal skin commensal and the same strain was isolated from two blood samples obtained from different venipuncture sites (Dow et al., 1989; Dow and Jones, 1989). The intensive medical care enabled the support of organ function but it did not succeed in preventing the development of severe MODS, To date, there is a lack of documentation describing this syndrome in dogs (Welzl et al., 2001; Johnson et al., 2004; Mathe et al., 2006). In our case, the dog initially presented cardiovascular dysfunction, It showed myocardial depression and hypotension. In humans, SIMD is a complication recognized by transthoracic echocardiography in 40-50% of septic patients (Dickinson et al., 2007). Research suggests that it develops secondary to the effects of cytokines, circulating myocardial depressant factors, nitric oxide, tissue hypoxia and reperfusion injury (Costello et al., 2003). Echocardiographic findings include ventricular dilatation, reduced SF and EF, and increased ESVI. Treatment aims at supporting the patient and recovery tends to parallel recovery from sepsis. In veterinary medicine, although the evaluation of contractile function in primary cardiomyopathy is well-characterized, acute myocardial depression has been poorly reported in dogs with naturally occurring sepsis (Dickinson et al., 2007). In this report, the echocardiographic findings of the dog indicating SIMD included low SF, low EF and increased ESVI, all of which resolved with correction of sepsis. Ventricular dilatation was not noted. On day 3, the dog developed acute respiratory distress and gastrointestinal dysfunction. Lungs and the gastrointestinal tract are common sites of injury in MODS. According to authors, this dog developed a non cardiogenic edema caused by increased vascular permeability. In fact, during sepsis the complex interactions between endotoxin and inflammatory mediators cause vascular damage and fluid leakage from blood vessels that can lead to pulmonary edema and impaired gas exchange (Haskins, 1992; Fein and Calalang-Colucci, 2000). This dog improved with furosemide, buprenorphine and oxygen. Fluid therapy was

decreased. However, diuresis and fluid restriction remain an area of controversy in the management of edema by increased microvascular permeability. In general, diuretics may be less beneficial for edema which develops secondary to increased vascular permeability disorders and it is recommended to minimize fluid administration, without affecting tissue perfusion (Parent et al., 1996; Nelson and Sellon, 2005). Gastrointestinal damage may be related to tissue hypoxia, diminished organ perfusion, and deterioration of the mucous barrier. The result is malnutrition whose major consequences are altered intermediary drug metabolism and decreased immunocompetence. More-over, increased protein requirements are present during sepsis (Ziegler et al., 1994). In our case, PN was maintained until the dog was eating on its own since enter al feeding was not tolerated. On day 5, ARF, diabetes mellitus and mc developed. Currently, there is limited information on ARF as a component of MODS in dogs, while it is common in humans (Johnson et al., 2004). According to literature (Grauer and Lane, 1995; Johnson et al., 2004), this dog showed an early stage ARF which was detected thanks to the close monitoring of the patient when the increase of creatinine and urea was still mild. The primary mechanism appears to be acute tubular necrosis that may derive from cellular ischemia and hypoxia. Ischemic injury also causes damage to the glomerulus and to renal vasculature with decreased glomerular filtration, and compromised renal blood flow (Johnson et al., 2004). Diabetes mellitus developed probably as a result of acute pancreatitis. In our case, bacterial invasion of the pancreas during bacteremia or pancreatic ischemia secondarily to hypotension and hypovolemic shock could cause significant injury. This dog also showed laboratory findings compatible with a subclinical form of DIC. The DIC encompasses various haemostatic dysfunctions from an acute and fulminating process to a chronic form. Although the DIC is often considered a bleeding disorder, it is conceptually a prothrombotic process in which haemorrhage is a late event. Currently various studies support a shift of the diagnostic cutpoint for DIC closer to initiation of the disease, when haemostatic dysfunction is less severe (Bateman et al., 1999; Hopper and Bateman, 2005). This dog did not manifest any bleeding disorder and the presence of microvascular thrombosis might have contributed to organ failure. Sepsis is associated with the development of a procoagulant state but in veterinary medicine there is limited ability in recognizing this state (De Laforcade et al., 2003) . The dog also developed IE of the tricuspid valve. In fact, transient or persistent bacteremia is considered a predisposing factor for a cardiac infection (Miller et al, 2004). In conclusion, this case confirms the fact that *K. pneumoniae* can be considered a cause of septicemia in dog and underlines the importance of blood cultures in critically ill patients that develop signs of sepsis unexplainable by a preexisting infection. This report shows that relative bradycardia, extreme leukocytosis and reverseble myocardial dysfunction are conditions that should be considered in dogs with sepsis and that, despite the numerous organ systems failing, early recognition and aggressive supportive therapy is an effective means to improve outcome when MODS develops.

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