ISSN: 1220-3173; E-ISSN: 2457-7618

UNDERLYING CONDITIONS IN A SHAR-PEI DOG WITH KIDNEY DISEASE - CASE STUDY

AFECŢIUNI ASOCIATE CU BOALA RENALĂ A SHAR-PEIULUI - STUDIU DE CAZ

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ABSTRACT | REZUMAT

Renal disease in a Shar-Pei dog is a condition that should make one consider Shar-Pei Fever, but diseases such as nephrotic syndrome, renal amyloidosis, glomerulonephritis, diabetic ketoacidosis, also Lyme disease (in endemic areas) should also be on the list of differential diagnoses, due to their lack of specific clinical findings. The aim of this paper is to bring into attention the underlying conditions of the Shar-Pei breed's renal disease in order to provide a more relevant prognosis. With the presentation of this clinical case, we try to broaden the range of differential diagnoses in kidney disorders and to help the clinician to establish the specific therapeutic protocol in each case. A seven years old female Shar-Pei was presented with clinical signs of intermittent weakness, acute generalized oedema, decreased appetite, weight loss, and lethargy. It was diagnosed with an acute renal injury one day before the presentation. Physical examination revealed normothermia, tachycardia and tachypnea, arterial hypertension, moderate dehydration, mild ulceration of the oral cavity, and pale mucous membranes. Also, significant oedema of the head and limbs was observed. Further diagnostic investigations revealed hyperglobulinaemia, hypoalbuminaemia, mild hypoglycaemia, as well as elevated serum activities of lipase, amylase, creatinine, blood urea nitrogen, calcium, and phosphorus. Blood gases and electrolytes were significantly modified. Urinalysis revealed proteinuria. Without a morphopathologic diagnosis, supportive and symptomatic treatment was initiated.

Keywords: Shar-Pei fever, amyloidosis, glomerulonephritis, nephrotic syndrome

Boala renală a Shar-Peiului este o manifestare clinică care ar trebui întotdeauna asociată cu febra Shar-Peiului, fiind necesară includerea mai multor boli pe lista diagnosticului diferențial, cum ar fi: sindromul nefrotic, amiloidoza renală, glomerulonefrita, cetoacidoza diabetică, boala Lyme (în zonele endemice) datorită similitudinii constatărilor clinice și paraclinice. Scopul acestei lucrări este de evidenția condițiile preexistente asociate cu boala renală în cazul Shar-Peiului pentru a oferi un prognostic vital mai relevant. Odată cu prezentarea acestui caz clinic, ne dorim să extindem gama diagnosticelor diferențiale în tulburările renale și să ajutăm clinicianul să stabilească protocolul terapeutic specific pentru fiecare afecțiune în parte. O femelă Shar-Pei de șapte ani a fost prezentată cu semne clinice de slăbiciune intermitentă, edeme generalizate, inapetență, scădere în greutate și letargie. Acesta a fost diagnosticată cu insuficiență renală acută cu o zi înainte și a primit recomandare de hemodializă. Examinarea fizică a evidențiat normotermie, tahicardie și tahipnee, hipertensiune arterială, grad moderat de deshidratare, ulcerație ușoară a cavității orale și mucoase palide. De asemenea, a fost observat edem pregnant la nivelul membrelor și capului. Investigațiile suplimentare au evidențiat hiperglobulinemie, hipoalbuminemie, hipoglicemie ușoară, valori crescute ale lipazei, amilazei, creatininei, ureei, calciului și fosforului, precum și modificări semnificative ale ionogramei, iar analizele de urină au evidențiat proteinurie. În absența unui diagnostic histopatologic de certitudine, a fost inițiat un tratament de susținere și simptomatic.

Cuvinte cheie: febră Shar-Pei, amilodoză, glomerulonefrită, sindrom nefrotic

A 7-year-old, neutered Shar-Pei female was presented to the Clinic of the Faculty of Veterinary Medicine Bucharest for acute general swelling, lameness, decreased appetite, progressive weight loss, lethargy, for last two weeks. The dog was born and raised in Bucharest, Romania and it lived with another clinically healthy neutered Shar-Pei male. One day before the presentation, the dog had been evaluated in a private clinic and it was diagnosed with acute renal injury.

During the physical examination, the rectal temperature was 38.7 °C, pulse rate was 167 bpm, respiratory rate was 52 rpm and systolic blood pressure

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was 190 mm Hg. The dog was estimated to be 8% dehydrated based on moderate loss of skin turgor, dry mucous membranes, weak rapid pulses, enophthalmia. There were mild ulcerations of the oral cavity. Thoracic and pelvic limbs were swollen with pitting oedema and also the face and the neck were significantly oedematous. No subcutaneous nodules or other kinds of abnormalities were noted.

ELISA SNAP 4Dx and Urine Protein Creatinine ratio (IDEXX Laboratories, Westbank, Maine, USA) had been performed at the private veterinary clinic and the result was negative for *Borrelia burgdorferi, Ehrlichia canis, Anaplasma phagocytophilum*, and *Dirofilaria immitis* antigen. Urine Protein/Creatinine (UP/C) ratio was 0.8. According to the recommendations from the 2004 ACVIM Forum Consensus Statement (Small Animal): Assessment and Management of Proteinuria in Dogs and Cats, a severe azotemic dog with UP/C ≥ 0.5 and inactive urine sediment is considered to be significantly proteinuric (6).

INVESTIGATIONS IN THE FIRST DAY

All the bloodwork was carried out at the laboratory of the clinic of the Faculty of Veterinary Medicine.

Complete blood count performed at presentation revealed mild non-regenerative anemia (hematocrit 26.7%, reference range (RR) 37-55% and hemoglobin 9.5 g/dL, RR: 12-18g/dL, red blood cells 3.65M/µL, RR: 5.5-8.5M/µL, mild thrombocytosis (PLT 577K/µL, RR: 175-500), eosinopenia (Eos 0.05 K/µL, RI: 0.10-1.49).

Findings on the chemistry panel were: significantly increased kidney parameters: Creatinine 28.2 mg/dL, RR: 0.5-1.8 mg/dL, Blood Urea Nitrogen (BUN) 199 mg/dL, RR: 7-27 mg/dL and pancreatic enzymes: Amylase: 1972 U/L, RR: 500-1500 U/L, Lipase 4684 U/L, RR: 200-1800 U/L, moderate hypoalbuminemia (Albumin 2.0 g/dL, RR, 74–143 g/dL), hyperglobulinemia (Globulins 4.9 g/dL, RR: 2.5-4.5 g/dL), hypercalcemia (Calcium 24.5 mg/dL, RR: 9-12 mg/dL), hyperphosphatemia (Phos 23 mg/dL, RI: 2.5-6.8). The hepatobiliary parameters: Alanine Aminotransferase (ALT), Gamma-Glutamyl Transferase (GGT), Total Bilirubin (T BIL), Alkaline Phosphatase (ALKP) were in normal ranges. Chemistry results for the analyzer run were multiplied by the dilution factor for a dilution of 1 in 3 total.

Venous blood gases and electrolytes performed at the same time revealed normochloraemic metabolic acidosis: pH 7.23, RR: 7.31-7.42, HCO3 12 mmol/L, RR: 20-29, PCO2 31 mmHg, RR: 32-49, AnGap 35 mmol/L, tCO2 12.9 mmol/L, RR: 21-31, Na 153 mmol/L, RR: 144-160, K 5.4 mmol/L, RR: 3.5-5.8, Cl 112 mmol/L, RR: 109-122.

Test	Results	Reference Interval		LOW NORMAL HIGH
LaserCyte (January 25, 2019 9:59 AM)				
RBC	3.65 M/µL	5.50 - 8.50	LOW	
HCT	26.7 %	37.0 - 55.0	LOW	
HGB	9.5 g/dL	12.0 - 18.0	LOW	
MCV	73.2 fL	60.0 - 77.0		
MCH	26.1 pg	18.5 - 30.0		
MCHC	35.7 g/dL	30.0 - 37.5		
RDW	19.0 %	14.7 - 17.9	HIGH	
%RETIC	0.4 %			
RETIC	13.2 K/µL	10.0 - 110.0		
WBC	12.25 K/µL	5.50 - 16.90		
%NEU	76.9 %			
%LYM	10.2 %			
%MONO	11.7 %			
%EOS	0.4 %			
%BASO	0.8 %			
NEU	9.43 K/µL	2.00 - 12.00		
LYM	1.25 K/µL	0.50 - 4.90		
MONO	1.43 K/µL	0.30 - 2.00		
EOS	0.05 K/µL	0.10 - 1.49	LOW	
BASO	0.10 K/µL	0.00 - 0.10		
PLT	577 K/µL	175 - 500	HIGH	
MPV	10.1 fL			
PDW	23.9 %			
PCT	0.58 %			

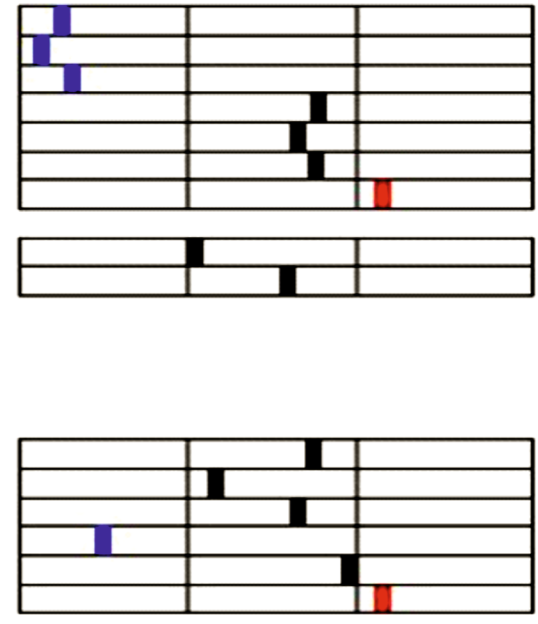

Fig. 1. Complete blood count, Shar-Pei breed, neutered female, 7-year-old

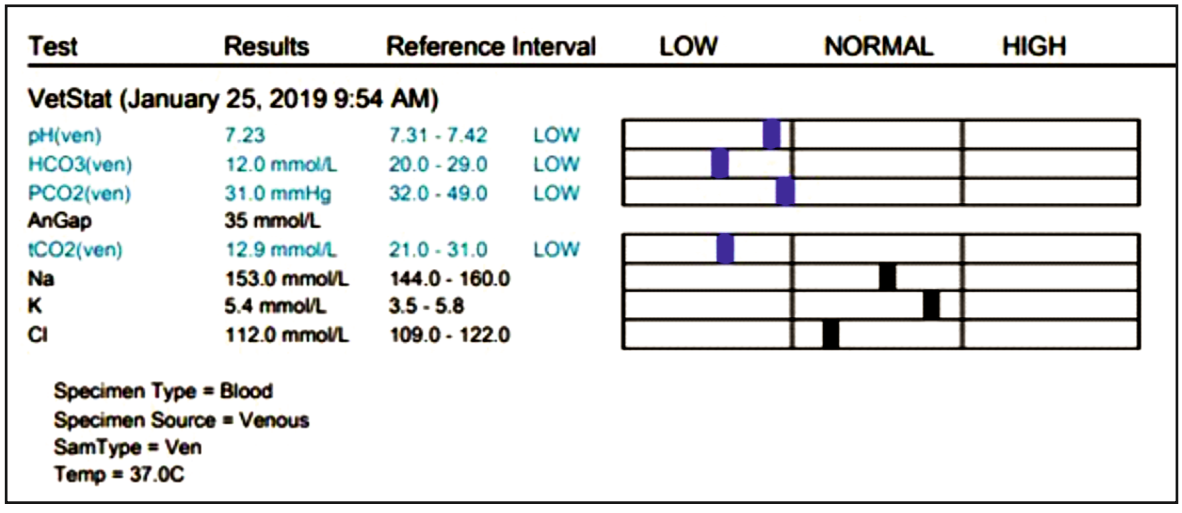

Fig. 2. Venous blood gases and electrolytes, Shar-Pei breed, neutered female, 7-years-old

A direct blood smear was also performed and revealed the presence of microfilaria.

Ultrasound examination revealed normal shaped kidneys of normal size according to the animal's weight and size and with little distinction between cortical and medullary tissue; the hyperechoic cortex suggesting renal parenchymal disease.

DIFFERENTIAL DIAGNOSIS

Differential diagnoses, in this case, were numerous, and the clinical signs were not diagnostic for any specific disease. The mild normochromic, normocytic and non-regenerative anaemia can be due to acute haemorrhage or haemolysis and it can also be associated with inflammatory disease (not in this case), bone marrow disorders, maturation abnormalities, or erythropoietin deficiency due to renal disease.

Severe hypertension with acute impairment of one or more organ systems (especially central nervous system, cardiovascular, renal) may determine irreversible ischemic kidneys, which causes renal vasoconstriction, increased aldosterone secretion and salt retention, which elevate blood pressure even further (12).

Hypoalbuminemia may occur with decreased production of albumin secondary to liver disease or inflammation, but in this case, it is probably the consequence of a glomerulonephropathy which leads to protein loss via the kidneys (proteinuria). Also, serum concentrations of albumin were significantly lower in hypocobalaminemic Shar-Pei (median: 2.5 g/dl) than in normocobalaminemic Shar-Pei (median: 2.9 g/dl; $P < 0.0001$) (4, 11).

THERAPEUTIC APPROACH

In the first day of hospitalization, treatment included correcting the fluid and electrolyte imbalance using: crystalloids (polyionic solution) and levo amino acids completed with sodium bicarbonate (bicarbonate deficiency (meq) = body weight (kg) x 0.3 x (desired bicarbonate – patient bicarbonate) (13). Also, beta erythropoietin was taken into account to stimulate erythropoiesis (100 UI/kg each other day, three days per week), which was associated with cyanocobalamin (50 µg/kg IM once per week), iron supplements, vitamin C and folic acid (14).

The next day, blood work reevaluation showed an insignificant decrease in creatinine (26.7 mg/dL), BUN 197 mg/dL, phosphorus 18.1 mg/dL and calcium 24.2 mg/dL. Blood gas analysis revealed a slight improvement of the metabolic acidosis: pH 7.26, HCO3 15.6 mmol/L, PCO2 38 mmHg, AnGap 33 mmol/L, tCO2 16.8 mmol/L. Electrolytes were insignificantly modified: Na 157 mmol/L, K 5.5 mmol/L, Cl 114 mmol/L.

Patient clinic status was almost the same, except for the urine output, which became normal (2 ml/kg per day). Systolic arterial pressure was 20 mmHg. Treatment was completed with Prednisolone (1 mg/kg BID), Spironolactone (2 mg/kg BID) and Amlodipine (0.25 mg/kg daily).

After 24 hours the patient status was reevaluated: general oedema was still significant, systolic arterial pressure was 133/77 mm Hg, no clinical improvement of the animal status was noted.

Acid-base balance was restored, but significant elevated values of Creatine (25.9 mg/dL), Blood Urea Nitrogen (196 mg/dL), Calcium (23.7 mg/dL) and Phosphorus (17.3 mg/dL) were observed. Mild hypernatremia was still detected: 167 mmol/L. The therapeutic protocol remained the same.

The persistently elevated levels of the kidney parameters (Creatinine > 25 mg/dL, Blood Urea Nitrogen > 190 mg/dL) even after 48 hours of continuous rate infusion and the ultrasonographic renal structure suggested significant renal damage.

Table 1

Evolution of renal parameters during hospitalization, Shar-Pei breed, neutered female, 7-year-old

Parameter	Initial moment	After 24 hours	After 48 hours
Creatinine	28.2 mg/dL	26.7 mg/dL	25.9 mg/dL
Blood Urea Nitrogen	199 mg/dL	197 mg/dL	196 mg/dL
Phosphorus	23.0 mg/dL	18.1 mg/dL	17.3 mg/dL
Calcium	24.5 mg/dL	24.2 mg/dL	23.7 mg/dL

Due to increased vascular fragility, the peripheral veins were not an option any longer. We recommended central venous catheterisation, but anaesthesia was considered to be a high risk for the patient. The risk-benefit assessment for the patient was concluded with the suggestion of euthanasia, considering that in this situation haemodialysis would be more risky than helpful.

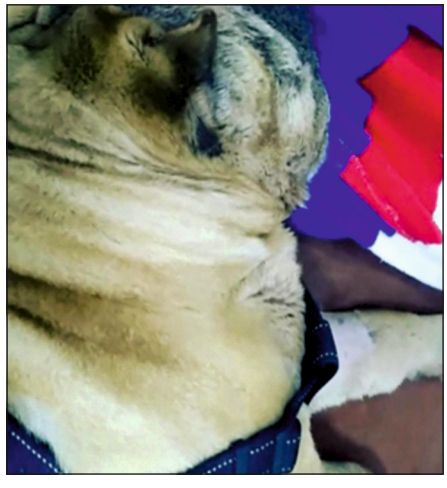

Fig. 3. Severe oedema, Shar-Pei breed, neutered female, 7-year-old

OUTCOME AND FOLLOW-UP

The owners chose at-home euthanasia to be performed by their previous veterinarian. On the next day, they announced the death of the animal. Unfortunately, they declined necropsy of the animal and subsequent morphopathologic examination of kidneys.

DISCUSSION

According to the results of the investigations performed both previously and immediately after the arrival in our clinic, the origin of the lesion was considered to be renal. Based on patient signalmen [familial predisposition, clinical renal disease and ultrasonographic renal parenchymal involvement (5)], the case was diagnosed as familial renal amyloidosis. The amyloidosis reported in Shar-Pei is believed to be a reactive one because the primary protein involved, amyloid A, is associated with inflammatory disease. Amyloid A protein is formed by the polymerization of the amino acid terminal portion of serum amyloid A protein. It was established that affected Shar-Pei have increased values of the serum interleukin-6 (a cytokine involved in the serum amyloid A protein synthesis and initiates the acute phase response of the inflammation), characterized by hepatic production of acute-phase proteins, fever, and neutrophil mobilization (10). If in the liver will be present the amyloidosis then high levels of alkaline phosphatase (>102 IU/L), alanine transaminase (>100 IU/L), aspartate transaminase (>100 IU/L), and total bilirubin (>0.4 mg/dl) may be present, findings which were not present in this case.

The nephropathies that arise with the involvement of glomeruli in the processes that initiate renal injury are defined as the primary glomerulopathies, and the glomerular changes occur after renal tubular or whole nephron damage are defined as the secondary glomerulopathies (8). The two major categories of glomerulopathies in dogs are renal amyloidosis and glomerulonephritis. A definitive diagnosis is realised by using a renal biopsy. This allows differentiation between amyloidosis and glomerulonephritis. A variety of morphologic patterns may be seen with glomerular pathology (e.g., membranous, and membranoproliferative), and the differentiation is of prognostic or therapeutic importance (1).

Nephrotic syndrome occurs as a result of glomerular disease and is characterised by proteinuria, hypoalbuminaemia, hyperlipidaemia, and oedema (2).

In the case presented above, hypoalbuminemia may have contributed to general oedema. However, as the development of oedema is dependent not only on the oncotic pressure of albumin but also on vascular endothelial integrity and hydrostatic pressure (7), it might explain general oedema. Many Shar-Peis have a history of recurrent fever and swelling of the tibio-tarsal joints (commonly called Shar-Pei fever or Shar-Pei swollen hock syndrome) before renal amyloidosis develops, even if in this case the owner said that this is the first time when the dog was ill. Proteinuria with renal amyloidosis can be massive and may lead to the development of the nephrotic syndrome. This syndrome in Chinese Shar-Pei is believed to be an autosomal recessive inherited trait (10).

Conditions that are known to be associated with naturally occurring glomerulonephritis in the dog include pyometra, neoplasia, systemic lupus erythematosus, dirofilariasis, Lyme disease, canine adenovirus I infection, pancreatitis, and diabetes mellitus (8, 15). In the case presented above, only microfilaria discovered accidentally could be considered an underlying cause of glomerulonephritis.

Due to the complex clinical findings, supportive therapy should be provided as indicated to maintain hydration and to resolve the metabolic acidosis. According to the International Renal Interest Society, immunosuppressive treatment of dogs with proteinuric kidney diseases even if in the absence of a histopathologic diagnosis is recommended (3, 8, 9). Also, additional antihypertensive agents may be needed if hypertension (systolic blood pressure >160 mm Hg) persists after initiation of angiotensin-converting enzyme inhibitor therapy: Amlodipine: 0.1 mg/kg PO twice daily. The dose can be titrated upward weekly (to 0.2-0.4 mg/kg PO twice daily) if indicated; blood pressure should be monitored weekly until normotensive, and then once every three to six months.

CONCLUSIONS

Dramatic renal disease in a Shar-Pei dog should include more than Acute/Cronic Kidney Disease in its differential diagnosis, so one should consider all relevant clinical findings: familial Shar-Pei amyloidosis as a result of Shar-Pei Fever: the history of recurrent fever and swelling of the tibiotarsal joints, massive proteinuria, general signs of renal injury; glomerulonephritis: proteinuria, polyuria/polydipsia, hematuria, oedema; nephrotic syndrome: simultaneous proteinuria, hypoalbuminaemia, hyperlipidaemia and oedema. The Shar-Pei's renal disease may be associated with underlying conditions such as glomerulonephritis, amyloidosis, nephrotic syndrome in order to offer a correct and fair prognosis, although a certain diagnosis of each of these conditions is difficult due to similarities in the laboratory and clinical signs and absence of histopathological diagnosis. It is necessary to use basic examination methods for each case of renal disease that should include: abdominal ultrasonography, cardiologic evaluation, blood pressure measurement, blood and urine testing and also, complex polymerase chain reaction (PCR) analyses. Ideally, the investigations should be concluded with a renal biopsy, histopathological and immunologic examination to obtain the final diagnosis, which is still difficult to obtain because of patient status, risks, costs, and owners' reluctance.

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