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Renal Amyloidosis Associated With Kartagener Syndrome in a Dog

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A 4-year-old cocker spaniel, male, of 12 kg body weight was presented because of the onset of polyuria or polydipsia. From the first months of its life, the dog had exhibited constant serous to mucopurulent nasal discharge, productive cough, sneezing, reverse sneezing, otitis, and recurrent episodes of fever. The respiratory signs had been treated several times with antibiotics, without ever achieving a complete resolution. Clinical examination revealed normal rectal temperature (38.3°C), increased respiratory rate (40 breaths/min), a copious mucous nasal discharge and right deviation of the heart apex beat (*ictus cordis*). Increased respiratory sounds with moist rales and crackles were found on chest auscultation. An increase in serum creatinine, urea and phosphorus, hypoalbuminemia and proteinuria were found. Lateral and ventrodorsal radiographs of the thorax and of the abdomen showed the transposition of the heart, with the cardiac apex pointing toward the right (dextrocardia), bronchointerstitial lung pattern, areas of consolidation, lesions consistent with bronchiectasis caves and a mirror-image of abdominal organs, confirming the diagnosis of complete situs inversus (CSI). Respiratory signs, combined with CSI, suggested the diagnosis of Kartagener syndrome (KS). Abdominal ultrasound showed an increase in the echogenicity of the renal parenchyma, a loss of definition of the corticomedullary line, slight bilateral pyelectasis, and decreased cortical perfusion. The dog died 2 months later because of a further worsening of the clinical condition. Necroscopy demonstrated the existence of CSI, rhinosinusitis, bronchitis, and bronchiectasis, so confirming the diagnosis of KS, and renal amyloidosis. This is the first case reported in veterinary medicine of the presence of renal amyloidosis together with KS in a dog.

Introduction

Complete situs inversus (CSI) is a rare malformation characterized by the transposition of thoracic and abdominal organs. It has been reported in humans,[1,2] rats[3], dogs,[4-6] horses,[7] cattle, pigs, and once in a cat.[8] The precise cause of CSI is unknown, but some genes that express asymmetry in embryonic development were described in vertebrates.[9] The dysfunction of the monocilia of the embryonic node might lead to the randomization of the left-right body asymmetry and transportation of the thoracic and abdominal organ.[10] CSI has been reported in 1 of 8000-10,000 humans (.01%-.02%). No epidemiologic studies have been done in the canine species; however, it has been rarely described either alone or as a part of Kartegener syndrome (KS).[11]

KS is an uncommon genetic disease inherited as an autosomal recessive trait, consisting in a triad of rhinosinusitis, bronchiectasis, and CSI. Clinical findings, especially rhinosinusitis and bronchiectasis, are related to a primary ciliary dysfunction of the upper and lower airways. For this reason, the term primary ciliary dyskinesia (PCD) has been applied to the disease.[12] The breeds of dogs most commonly reported with PCD and KS are Golden retrievers,[4] Old English sheepdogs,[10] Staffordshire bull terriers,[13] Dalmatians,[11] Chow chows,[14] Rottweilers,[12] English cocker spaniels,[15] Newfoundlands,[16] Dachshunds,[17] Doberman pinschers, English Springer spaniels, English pointers, Bichon frises, Chinese shar peis, English setters, Chihuahuas, Border collies, Miniature poodles, and crossbreeds.[17] Ciliated cells can also be found in other organ systems than the respiratory one, such as genital tract, brain, and middle ear. All these organs can be affected in patients with PCD, due to ciliary dysfunction and impaired mucociliary clearance. The respiratory signs are usually the most obvious both in humans and in dogs. Recurrent or persistent respiratory infections due to the abnormal mucociliary clearance lead to bronchopneumonia, airway blockage, atelectasis, and eventually determine brochiectasis. Spermatozoa flagellum is a modified cilium; therefore, spermatozoa could be immotile or dysmotile, causing male sterility.[14] Cardiac malformations, associated with PCD have also been described in humans[1] and only once in a dog.[4]

Diagnosis of KS is basically clinical and necroscopic, following the simultaneous detection in the patient of rhinosinusitis, bronchiectasis, and CSI.[17,18] Diagnosis of PCD is achieved through the investigation of ciliary function and the demonstration of ultrastructural defects in the cilia by electron microscopy. Various types of ultrastructural abnormalities have been found in the cilia of patients with KS, but the most common defects identified in patients with PCD are dynein arms deficiency, spoke defects, absence of central microtubular pairs with possible transposition, and random orientation of cilia. Moreover, almost complete absence of dynein arms is the most reliable ultrastructural defect for a definitive diagnosis of PCD because the other abnormalities reported could also be found as acquired lesions in chronic respiratory diseases.[19] The absence of dynein arms results in an eggbeater-like rotation, with only the distal half of the axoneme bending at half the beat frequency.[20] However, variability of electron microscopic findings is common, and even cases of PCD with functional defects but without any detectable ultrastructural abnormality have been described.[4] The diagnostic value depends on the type of ultrastructural defect detected and on the frequency of occurrence; up to 2% of abnormal cilia can be found in normal patients, while up to 20% of cilia may present abnormalities in patients with respiratory diseases.[12] It has been suggested that various genetic defects may be responsible for each specific case.

Amyloidosis is a syndrome due to a heterogeneous group of diseases, characterized by extracellular deposition of insoluble,

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fibrillary proteins with a specific β-pleated sheet conformation, generally termed amyloid. Amyloid deposits can be localized, organ-limited, or generalized and can affect any tissue or organ type. In dogs and cats, a familiar amyloidosis has been described in Chinese shar peis and Abyssinian cats. However, the most common type found in animals is the reactive or secondary amyloidosis. In reactive amyloidosis, deposits are composed of the protein amyloid A, an amino-terminal fragment of serum amyloid A (SAA), an acute phase protein, produced during inflammation. Reactive amyloidosis is frequently idiopathic, but may be associated with chronic inflammation, infection, or neoplasia. In dogs, the kidney is the most frequent and often the sole site of amyloid deposition.[21] Bronchiectasis has been reported as a cause of secondary amyloidosis and nephrotic syndrome.[2] However, few reports exist of CSI and bronchiectasis due to KS associated with renal amyloidosis in 2 human patients.[22,23] To the authors' knowledge, no evidence of this association exists in veterinary medicine.

The present report describes a case of a dog presented with CSI, rhinosinusitis, and bronchiectasis, due to KS, and concomitant renal failure due to renal amyloidosis.

Case Description

A 4-year-old entire male Cocker spaniel, regularly vaccinated, of 12 kg body weight was presented because of the onset, in the previous 2 months, of polyuria or polydpsia, capricious appetite, and weight loss. From the first months of its life, the dog had exhibited bilateral constant nasal discharge, productive cough, sneezing, reverse sneezing, otitis and recurrent episodes of fever and weakness. Nasal discharge was serous during the period of relative health, but it became mucopurulent during times of illness. The respiratory signs had often been treated with antibiotics and steroidal or nonsteroidal anti-inflammatory drugs with an improvement in the clinical condition, without ever achieving a complete resolution. The clinical examination revealed weakness, poor body condition, normal rectal temperature (38.3°C), pale mucous membranes with normal capillary refill time (< 2 second), slightly enlarged submandibular and peripharyngeal lymph nodes bilaterally, increased respiratory rate (40 breaths/min), a copious bilateral mucous nasal discharge (Fig 1) and right deviation of the heart apex beat (*ictus cordis*). Productive cough was easily elicited on tracheal palpation. On chest auscultation, increased respiratory sounds with moist rales and crackles were found. Normal heart rate, without arrhythmias and heart murmurs, was detected on heart auscultation. Complete blood count revealed slightly macrocytic hypochromic anemia. Proteinuria, found at urinalysis (Table 1), and serum biochemical profile findings (Table 2), with an increase in serum creatinine, urea and phosphorus, hypoalbuminemia and hypercholesterolemia, were suggestive of a nephropathy. To exclude the common causes of chronic renal failure in an endemic area, serological tests for infectious diseases (ehrlichiosis, rickettsiosis, piroplasmosis, and leishmaniasis) were performed, with negative results.

Fig. 1. Image of mucous nasal discharge observed in the dog at first clinical examination.

Table 1
Urinalysis Results

Parameters	Laboratory reference range	Results
Color	/	Straw yellow
Odor	/	Sui generis
Aspect	/	Clear
Osmolarity (mOsm/kg)	600-2400	393
Specific gravity	1006-1056	1010
pH	5.0-8.5	6.0
Glucose (mg/dL)	.0-.0	.0
Ketones (mg/dL)	.0-.0	.0
Bilirubin (mg/dL)	.0-.5	.0
Hemoglobin (mg/dL)	Negative	Positive
Protein (mg/dL)	.0-100	250
WBC/hpf	.0-3.0	.0
RBC/hpf	.0-3.0	.0
Cylinders/hpf	Absent-rare	Absent
Crystals/hpf	Absent-rare	Absent
Bacteria/hpf	Absent	Absent
Epithelial cells/hpf	Absent-rare	Absent

Lateral and ventrodorsal radiographs of the thorax and of the abdomen were taken. Radiographs of the thorax showed the transposition of the heart, with the cardiac apex pointing toward the right (dextrocardia) and cardiac enlargement (vertebral heart score of 11.5; range: 8.7-10.6), a generalized bronchointerstitial lung pattern, areas of consolidation, consistent with bronchopneumonia, and lesions consistent with bronchiectasis caves (Fig 2). Ventrodorsal radiograph of the abdomen, like the subsequent ultrasound, revealed the same mirror-image of abdominal organs, confirming the diagnosis of CSI (Fig 3). Respiratory signs, combined with the CSI, strongly suggested a diagnosis of KS. Moreover, abdominal ultrasound showed a noticeable increase in the echogenicity of the renal parenchyma, with a loss of definition of the corticomedullary line, slight bilateral pyelectasis, and decreased cortical perfusion (Fig 4), as highlighted by color Doppler.

Echocardiography was performed, revealing a partial rotation of the heart with an inverted position of the pulmonary and aorta arteries, and a left ventricular enlargement with ventricular overload and septum-parietal hypokinesia.

The dog died 2 months later, while he was hospitalized, because of a further worsening of the clinical condition due to the renal failure.

Necroscopy confirmed the diagnosis of CSI, rhinosinusitis, bronchitis, and bronchiectasis, so providing a definitive diagnosis of KS. Tracheal histopathology showed hyperplasia, dysplasia, and moderate chronic multifocal tracheitis. Sections of the lungs displayed bronchopneumonia and generalized chronic interstitial pneumonia.

Kidney histopathology provided the diagnosis of amyloidosis, as confirmed by the histochemical staining with Congo Red.

Discussion

To the authors knowledge, few reports on KS exist in the Cocker spaniel.[15]

Table 2
Complete Blood Count (CBC) and Serum Biochemical Profile

Parameters	Laboratory reference range	Results	Parameters	Laboratory reference range	Results
RBC ($\times 10^{12}$/L)	5.65-8.87	3.21	Total cholesterol (mg/dL)	120-300	547
PCV (%)	37.3-61.7	24.3	Triglycerides (mg/dL)	30-85	35
Hemoglobin (g/dL)	13.1-20.5	7.4	Amylase (UI/L)	350-900	2824
MCV (fL)	61.6-73.5	75.7	Lipase (UI/L)	120-630	552
MCHC (g/dL)	32-37.9	30.5	Urea (mg/dL)	18-43	150
MCH (pg)	21.2-25.9	23.1	Creatinine (mg/dL)	.70-1.30	4.32
WBC ($\times 10^9$/L)	5.05-6.76	12.2	Glucose (mg/dL)	75-115	88
Neutrophils ($\times 10^9$/L)	148-484	7.13	Calcium (mg/dL)	9.6-11.7	6.9
Linfocytes ($\times 10^9$/L)	1.05-5.10	2.86	Corrected calcium (mg/dL)	9.6-11.7	8.9
Monocytes ($\times 10^9$/L)	0.16-1.12	2.04	Phosphorus (mg/dL)	2.5-5.3	14.5
Eosinophils ($\times 10^9$/L)	0.06-1.23	.00	Magnesium (mg/dL)	.64-.97	1.24
Basophils ($\times 10^9$/L)	.00-.10	.00	Sodium (mEq/L)	140-150	148
Platelets ($\times 10^9$/L)	148-484	370	Potassium (mEq/L)	3.9-4.8	5.9
CPK (UI/L)	40-150	65	Chloride (mEq/L)	107-115	123
AST (UI/L)	15-40	19	Corrected chloride (mEq/L)	107-115	121.3
ALT (UI/L)	15-65	25	HCO_3^- (mmol/L)	15.8-22.3	6.2
ALP (UI/L)	20-120	48	Anion gap	14.5-24.0	24.8
GGT (UI/L)	2.0-8.0	4.8	Calculated serum osmolarity (mOsm)	270-292	305
Cholinesterase (UI/L)	3350-6550	5242	Total iron (μg/dL)	81-220	100
Total bilirubin (mg/dL)	0.15-.28	0.23	UIBC (μg/dL)	150-300	145
Total proteins (g/dL)	5.7-7.4	4.3	TIBC (μg/dL)	270-460	245
Albumin (g/dL)	2.6-3.8	1.5	O_2 saturation (%)	25-52	40.8
Total globulins (g/dL)	2.6-4.0	2.8	C-reactive protein (mg/dL)	.0-.15	.17

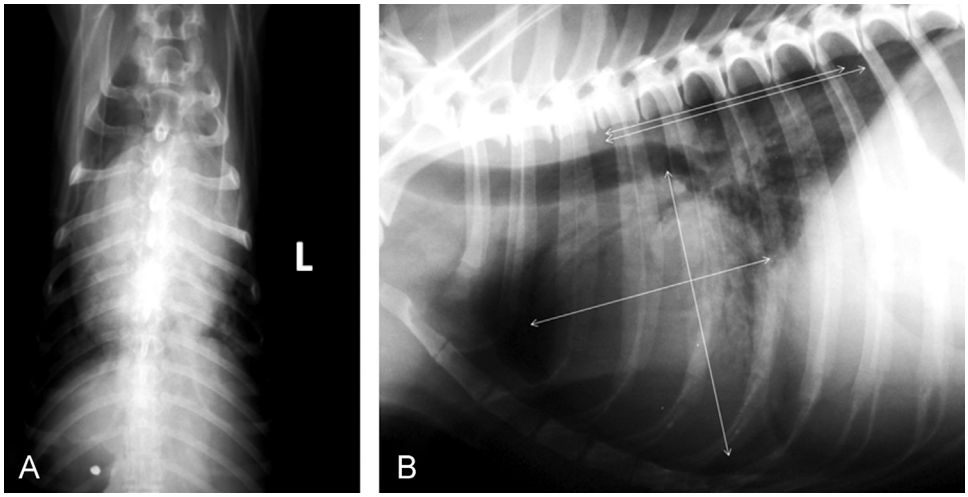

Fig. 2. Ventrodorsal (A) and lateral (B) radiographic views of the thorax; preserved cardiac silhouette (VHS = 11.5); generalized bronchointerstitial lung pattern and areas of consolidation, with lesions consistent with bronchiectasis caves (B). Note transposition of the heart, with the cardiac apex pointing towards the right (dextrocardia) in ventrodorsal view (A). VHS, vertebral heart score.

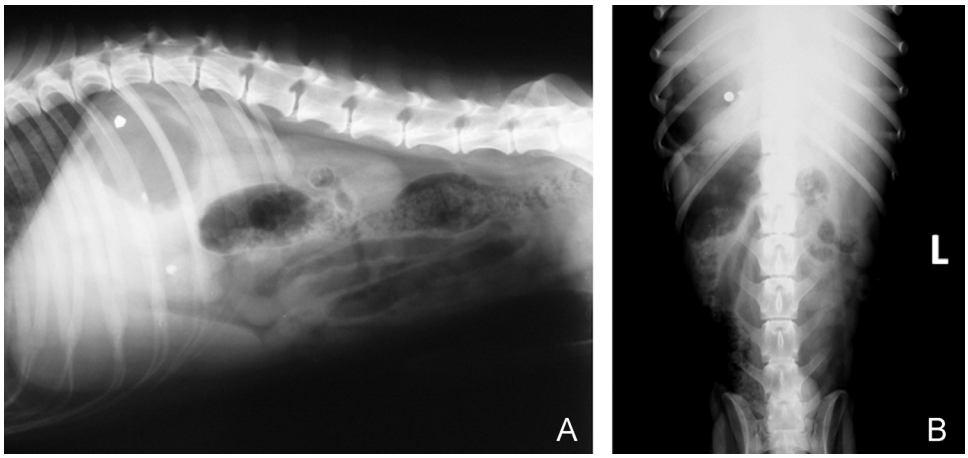

Fig. 3. Lateral (A) and ventrodorsal (B) radiographic views of the abdomen: mirror-image of abdominal organs.

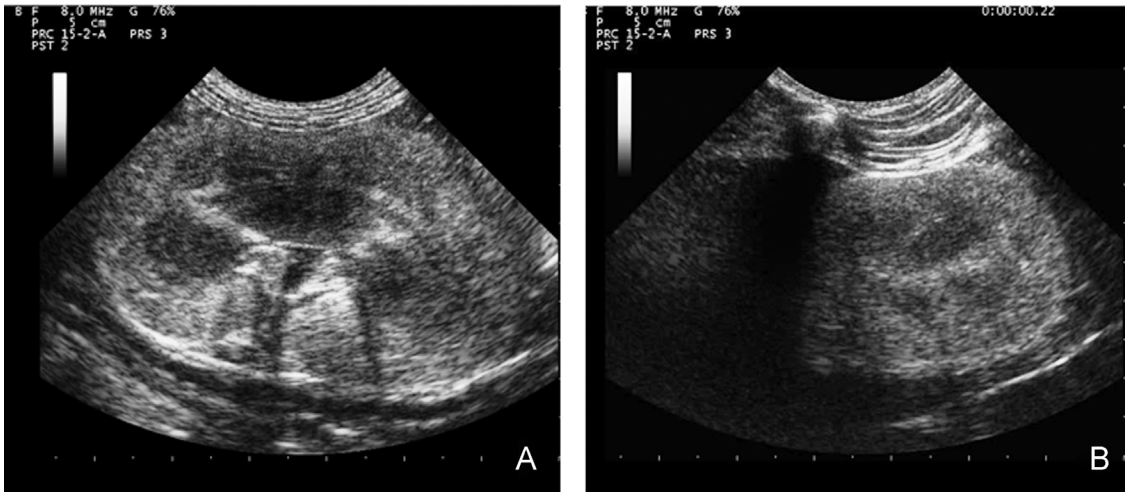

Fig. 4. Abdominal ultrasound images of the renal parenchyma (right and left kidneys): noticeable increase in the echogenicity of the renal parenchyma, with a loss of definition of the corticomedullary line, slight bilateral pyelectasis.

Although the precise cause of CSI is unknown, some genes—such as Lefty-1-2 Lefty, Nodal, and Pitx2, which express asymmetry in embryonic development—seem to be involved in determining the left-right axis.[9] CSI can be found together with PCD and other abnormalities in patients with KS, but it was also found in dogs without any clinical evidence of ciliary immobility.[11] Moreover, in KS, PCD seems to be the main cause which determines CSI and all the other possible abnormalities.[17]

Diagnosis of KS is basically clinical and necroscopic, following the simultaneous detection in the patient of rhinosinusitis, bronchiectasis, and CSI.[17] Diagnosis of PCD is achieved through the investigation of ciliary function, for example, by mucociliary scintigraphy and the demonstration of ultrastructural defects in the cilia by electron microscopy. Various types of ultrastructural abnormalities have been found in the cilia of patients with KS, but the most common and specific defect is the lack of the dynein arms. However, many reports of PCD due to functional defects, without cilia ultrastructural abnormalities, exist both in humans and in animals.

In our case, mucociliary scintigraphy and electron microscopy of the nasal and tracheal epithelium biopsies for the definitive diagnosis of PCD were proposed but not performed because the owner refused. However, the dog's history, respiratory signs, the evidence of CSI and histopathology findings led us to the diagnosis of KS and to strongly suspect PCD. In fact, the constant respiratory signs and the necroscopic findings of rhinosinusitis, bronchitis, and bronchiectasis were compatible abnormalities that have always been described in patients with PCD. Affected puppies may be mistaken by breeders and veterinary surgeons for “fading puppies” or cases of pneumonia due to inhalation of maternal fluids or cases of neonatal respiratory virus infection. In this case report, the recurrent respiratory signs that were refractory to several antibiotic treatments, is suggestive of PCD rather than other infectious diseases. Moreover, complete blood count performed after the first presentation of the dog, showed no abnormalities in the leukocytes values, despite the dog having manifested respiratory signs and nasal discharge for a long time, thus making an infectious etiology unlikely.

In this dog, clinical signs and laboratory findings of a chronic renal failure were concurrent with rhinosinusitis, bronchopneumonia, and CSI as confirmed by necroscopy and histopathology.

Primary renal amyloidosis is extremely rare in the dog, whereas the secondary or reactive type is more common. Chronic inflammation or neoplasia are the most common causes associated with the disease. In fact, SAA increases considerably with prolonged inflammatory stimuli, leading to its tissue deposition. In our case, chronic inflammation due to rhinosinusitis and bronchopneumonia, probably led to the SAA deposit in the kidneys.

Although we were not able to confirm the diagnosis of PCD through electronic microscopy, the history, as well as our clinical, radiological, and necroscopic findings led us to confirm the diagnosis of KS. In human medicine, few cases of renal amyloidosis together with KS have been described.[22,23] The present report shows similar findings in veterinary medicine.

Ethical Statement

Protocols of animal husbandry and experimentation were reviewed in accordance with the standards recommended by the *Guide for the Care and Use of Laboratory Animals* and Directive 2010/63/EU for animal experiments.

Authorship

All authors have materially participated in the article preparation and have approved the final article. In particular:

The idea for the paper was conceived by B. Celona and E. Giudice.

Data acquisition was performed by B. Celona and C. Bruno

Data analysis and interpretation were performed by S. Di Pietro and C. Bruno.

The study was designed by CCrinò and S. Di Pietro.

The paper was written by C. Crinò and E. Giudice.

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