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SPONTANEOUSLY ARISING DISEASE

Renal Interstitial Lipid Accumulation in Cats with Chronic Kidney Disease

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Summary

Chronic kidney disease (CKD) is a common progressive condition described in dogs and cats, involving several non-specific morphological and histological lesions. Recently, renal interstitial lipid accumulation was reported in cats with CKD; however, to date, little is known about this condition and its pathogenesis. The aim of this study was to investigate the occurrence and to characterize renal interstitial lipid deposits in dogs and cats. A total of 49 animals (27 cats and 22 dogs) with CKD were included in the study. Interstitial lipid accumulation was found exclusively in cats, affecting both males and females. In 55.6% of the cases, the extent of the lesion was not equally distributed in right and left kidneys. The lesion was always found in the cortical region, associated with an inflammatory reaction. Lipid macrovacuoles were also observed in the tubular epithelium, as well as in areas of tubulorrhexis. The amount of lipid deposited was variable, being more extensive in older animals. Data from this study suggest that interstitial lipid accumulation may be related to tubular lipidosis (typical of feline kidneys) associated with epithelial degeneration and lysis, and to tubular basement membrane fragmentation. Extended studies on this condition are necessary, as it appears to be involved in the progression of CKD and may, therefore, have repercussion in the clinical management of the disease and in the development of new approaches to delay its advance.

Keywords: cat; chronic kidney disease; interstitial lipid accumulation; tubular lipidosis

Introduction

Chronic kidney disease (CKD) is common in both dogs and cats and the prevalence of the disorder increases markedly with age (Khan and Khan, 2015; Brown *et al.*, 2016). CKD is a multifactorial progressive disease leading to irreversible structural and/or functional renal lesions with gastrointestinal, haematological, cardiovascular and metabolic complications (DiBartola *et al.*, 1987; Polzin, 2011; Bartges, 2012; Khan and Khan, 2015). The disease encompasses a broad spectrum of non-specific renal morphological and histological changes including mononuclear interstitial inflammation, tubular degeneration and atrophy, interstitial fibrosis, Bowman's capsule thickening and glomerulosclerosis (Chakrabarti *et al.*, 2013; McLeland *et al.*, 2015).

Recently, in a survey of 46 cats with CKD, McLeland *et al.* (2015) observed renal interstitial lipid deposits in nearly 85% of the animals which, according to the guidelines developed by the International Renal Interest Society (IRIS) (Elliott and Watson, 2014), were of CKD stages II to IV. Schmiedt *et al.* (2016) also described this feature as a late change following induced renal ischaemia in adult male cats. In a recent review, Brown *et al.* (2016) described interstitial lipid deposition as a pathological finding in cats with CKD and hypothesized about its possible pathogenesis. However, little is known about this rarely reported pathological feature and its aetiopathogenesis remains undetermined.

The aim of this study was to investigate the occurrence of renal interstitial lipid deposits in dogs and

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cats with clinicopathological signs characteristic of CKD and to characterize this condition, intending to clarify its pathogenesis.

Materials and Methods

A total of 49 animals (27 cats and 22 dogs), submitted for necropsy examination at the owner's request, at the Instituto de Ciências Biomédicas de Abel Salazar, Universidade do Porto, between 2012 and 2015, were included in this study. All of the animals had exhibited clinical signs and/or morphological renal changes suggestive of CKD. Additionally, 10 cats and 10 dogs of both sexes and different age groups, which died of causes not related to renal disease, were included in the study in order to compare the pattern of renal lipid deposition with that observed in CKD. Kidneys were cut in sagittal section in order to permit gross and histological observation of the cortex, medulla and pelvis. Kidney samples, comprising all the three anatomical areas, were collected and fixed in 10% neutral buffered formalin. Tissues were processed routinely and embedded in paraffin wax. Sections (3 μm) were stained with haematoxylin and eosin (HE).

The extent of the interstitial lipid deposits was evaluated semiquantitatively and graded as: +, lipid deposits occupied <25% of the interstitium; ++, lipid deposits occupied 26–50% of the interstitium; +++, lipid deposits occupied >50% of the interstitium. Periodic acid–Schiff (PAS) staining was performed in order to evaluate the integrity of basement membranes. Immunohistochemistry (IHC) was performed using the avidin–biotin peroxidase complex method and a pancytokeratin monoclonal primary antibody (clone AE1/AE3, Invitrogen, Waltham, Massachusetts, USA) diluted at 1 in 300.

For lipid visualization, fresh kidney fragments were frozen and 5 μm sections were prepared using a cryostat. Sections were stained with oil red O for 30 min and counterstained with Mayer's haematoxylin. Additionally, 1 mm^3 fragments of fresh kidney were fixed in 2.5% glutaraldehyde in sodium cacodylate–hydrochloric acid buffer (0.1 M, pH 7.2) and then post-fixed with 1% osmium tetroxide. Tissue fragments were then processed for epoxy resin embedding and semithin sections (1 μm) were cut in an ultramicrotome. Sections were stained in a mixture of Azure II and methylene blue (1:1).

Results

Lipid deposition was not observed in the renal interstitium of any of the control dogs and cats that died of causes unrelated to renal disease, regardless of the sex or age of the animal. Histological examination of the kidneys from animals with CKD revealed lipid interstitial infiltration in 24 of the 27 cats (88.9%), but in none of the canine kidneys. Interstitial lipid deposits were found in males ($n = 11$, including two neutered cats) and females ($n = 13$, including two neutered cats). Cats affected by this condition ranged from 5 to 23 years old, with a mean age of 12.6 years. The age of three cats was not recorded; however, these animals were all adults.

Kidneys from animals with CKD and having interstitial lipid deposits did not appear grossly different from the kidneys of animals with CKD and no lipid deposits. All animals with CKD exhibited variable degrees of renal atrophy; affected kidneys were pale and firm and the renal contour was highly irregular, with raised areas alternating with depressed ones, giving the organ a 'scalloped' appearance.

Variably-sized lipid droplets were observed exclusively in the cortical region of the kidneys. Lipid droplets were found free within the cortical interstitium, always associated with an inflammatory reaction mainly composed of lymphocytes, plasma cells and some macrophages (Fig. 1). The lesion had a multifocal or segmental distribution; however, in the most severe cases, lipid infiltrates were found diffusely in the cortical interstitium. The extent of the lesions was evaluated semiquantitatively. In nine cases lipid droplets were observed in <25% of the cortical interstitium, in seven cases between 26% and 50% of the interstitial space and in the remaining eight cases, lipid vacuoles comprised >50% of the cortical interstitium.

Tubular degeneration and atrophy, mainly affecting the proximal convoluted tubule, was a

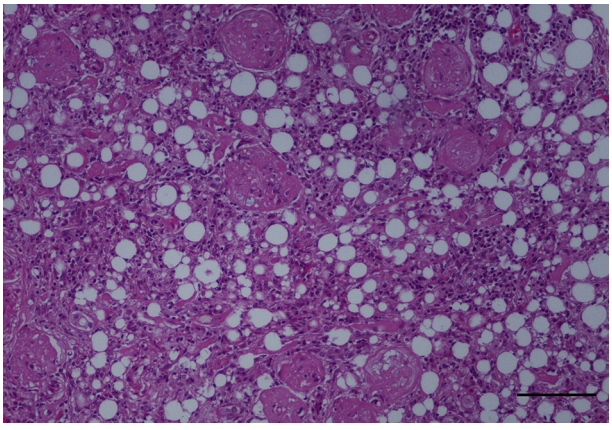

Fig. 1. Kidney, cat. Abundant lipid deposition in the cortical interstitium, with inflammatory infiltration. HE. Bar, 100 μm.