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Congenital hepatic fibrosis and polycystic kidney disease not linked to C >A mutation in exon 29 of *PKD1* in a Persian cat

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Abstract

Case summary We describe the case of a 1-year-old male Persian cat diagnosed with congenital hepatic fibrosis (CHF) associated with renal polycystic disease and, for the first time, we have shown that there was no C >A mutation in exon 29 of *PKD1* (polycystic kidney disease 1). The cat presented with a history of chronic weight loss, anorexia, vomiting, depression and lethargy, with profuse salivation and ascites on clinical examination. A mild elevation in liver-associated plasma enzymes suggested a hepatic disease. Owing to the cat's deteriorating condition, it was euthanized. During necropsy, the liver was found to be enlarged, firm and reddish, and the kidney had multiple small cortical cysts. Immunohistochemistry revealed that bile duct cells and epithelial cells of renal cysts showed positive immunoreactivity to keratin 19. Collagen fibers surrounding bile ducts within portal areas demonstrated reactivity to type IV collagen antibody, confirming the congenital nature of the process. A diagnosis of ductal plate malformation consistent with CHF associated with polycystic kidney in a young Persian cat was made. Interestingly, genetic testing revealed a wild-type sequence at position 3284 in exon 29 of *PKD1*.

Relevance and novel information The absence of the classic genetic mutation associated with the particular clinical presentation supports the hypothesis of a distinct etiopathogenesis among fibropolycystic diseases in domestic cats. Moreover, congenital hepatic fibrosis is a rare but important differential diagnosis for young Persian cats and their crosses with clinical signs of chronic end-stage liver disease.

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Introduction

Congenital hepatic fibrosis (CHF) represents one of many fibrocystic hepatic diseases derived from biliary dysgenesis secondary to ductal plate malformation.[1] The condition is described in humans and some animal species,[2] characterized by the persistence of embryonic bile ducts, abnormal branching of the intrahepatic portal veins and progressive fibrosis of the portal tracts.[3]

In humans, CHF is often associated with other cyst-forming syndromes, such as autosomal recessive polycystic kidney disease (ARPKD), autosomal dominant polycystic kidney disease (ADPKD) (rarely), Meckel–Gruber syndrome, Jeune syndrome and with many other genetic abnormalities.[2] In veterinary medicine, CHF has been described in dogs, Swiss Freiberger foals, bovine fetuses and calves, and in an African green monkeys.[2,4–7]

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Feline ADPKD affects mainly Persian cats and crossbreeds, presenting with variable expression.[8] Although only a single mutation in *PKD1* has been identified in feline ADPKD, the phenotypic spectrum is diverse, with most cats demonstrating renal rather than biliary malformations, with isolated cysts in the liver with or without involvement of the pancreas.[9–11] However, not all cats with polycystic kidneys have a mutated *PKD1*.[12] Hepatic fibrosis has been reported in 22–48% of cats with feline polycystic kidney disease (PKD); however, clinical signs associated with liver failure have rarely been reported,[9,13–15] and the congenital nature of this process has not been established. Moreover, these cases of hepatic fibrosis in cats with PKD were described before the discovery of the C >A transversion in exon 29 of feline *PKD1*, so genetic testing had not been performed.

Here we describe the clinical, morphological and genetic features of CHF associated with PKD in a Persian cat, in order to advise on a possible alternative genetic mutation for this specific clinical presentation.

Case description

A 1-year-old male Persian cat weighing 3.1 kg was admitted to a veterinary teaching hospital (Faculty of Veterinary Medicine, Methodist University of São Paulo, SP, Brazil), with a 4 week history of chronic weight loss, anorexia, vomiting and lethargy. Other symptoms included depression, episodes of stupor and ptyalism. On clinical examination the cat was lethargic, with reduced spinal reflexes and ascites. Clinical parameters were within normal reference intervals (RIs). Ascites fluid was classified as a modified transudate characterized by an albumin:globulin ratio of 0.89 (RI >1.0) and mild cellularity (1.500 cell/µl) composed of neutrophils and small lymphocytes. Hematology revealed a low packed cell volume (23%; RI 25–45%). Serum biochemistry findings included mild increases in alanine aminotransferase (108 U/l; RI 30–70 U/l), alkaline phosphatase (198 U/l; RI 20–70 U/l), γ-glutamyl transferase (7 U/l; RI 1–5 U/l) and aspartate aminotransferase (67 U/l; RI 1–40 U/l). Albumin was low (1.4 g/dl; RI 2.1–3.3 mg/dl). Bilirubin, urea, creatinine and glucose levels were within the normal RIs. A commercial immunoassay for feline leukemia virus antigen detection and feline immunodeficiency virus antibody (IDEXX Laboratories) detection was negative. The clinical symptoms and biochemical profile suggested a liver disease. Owing to financial reasons and the cat's clinical status, the owner opted for euthanasia.

At necropsy, there was an increased amount of slightly turbid abdominal fluid and fibrin clots throughout the hepatic serosa. The liver was enlarged, firm and red, with multifocal pale, white-to-tan circular areas measuring 0.5–1.0 cm in diameter restricted to the liver capsule. No biliary obstruction was evident. Kidneys exhibited multiple small cortical cysts around 1–2 mm in diameter. Other organs were normal. Tissue samples were obtained, formalin-fixed, paraffin-embedded, sectioned and stained with hematoxylin and eosin for microscopic examination.

Microscopically, the liver was divided by portal-to-portal bridging bands of dense fibrous tissue, with numerous, small, irregular bile duct profiles that were often mildly to moderately ectatic. These ducts were lined by oval-to-cuboidal epithelial cells with finely stippled chromatin and a variably prominent nucleolus (Figure 1). A few small, non-portal-associated bile ducts with spindle cells were dispersed throughout the liver section. Multiple and swollen hepatocytes containing one or more clear cytoplasmic vacuoles were observed. Small amount of lymphocytes, plasma cells and macrophages infiltrated fibrous bands and portal areas. Masson's trichrome stain revealed dense collagenous tissue in the periportal area (Figure 2).

The kidneys showed multiple, sometimes multiloculated cysts that were 0.5–2.0 mm in diameter in the renal cortex, lined by cuboidal or squamous epithelium. Some cysts contained abundant mild eosinophilic material (protein) and multiple detached epithelial cells (Figure 3). There was mild interstitial lymphoplasmacytic inflammation and fibrosis.

For immunohistochemical analysis, liver and kidney histological sections were deparaffinized, rehydrated and submitted to antigen retrieval in citrate buffer solution (10 mM, pH 6.0) in a pressure cooker for 3.5 mins. After blockade of endogenous peroxidase with 6% H_2O_2 solution (Merck) for 30 mins, the slides were incubated in a humidified chamber overnight at 4°C with the following primary antibodies: keratin 19 (K19) (Novocastra; Leica Microsystems) for liver and kidney, and type IV collagen (Dako North America) for liver. The slides were then incubated with a goat anti-mouse horseradish peroxidase polymer from a commercial kit (Zymed Laboratories) for 30 mins. The reaction was visualized with 3'3 diaminobenzidine chromogen and counterstained with Harris hematoxylin. Kidney tissues were used as a positive control for K19 and type IV collagen expression.

Bile duct cells and epithelial cells lining kidney cystic structures showed positive granular cytoplasmic immunoreactivity to K19 (Figure 4). Collagen fibers surrounding bile ducts within portal areas demonstrated prominent reactivity to type IV collagen antibody (Figure 5).

For PCR, restriction fragment length polymorphism (RFLP) analysis and sequencing, genomic DNA was isolated from formalin-fixed, paraffin-embedded

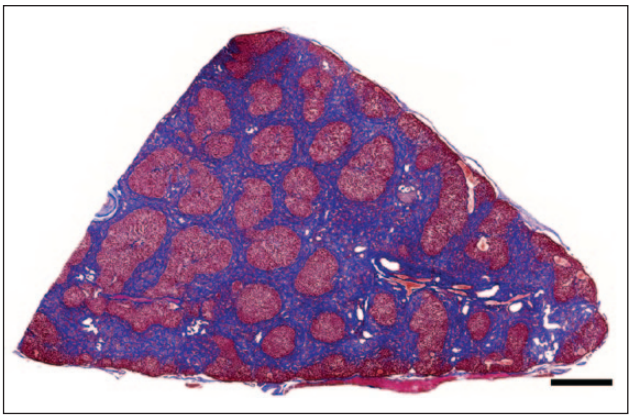

Figure 1 Photomicrograph of feline liver with congenital hepatic fibrosis. Islands of hepatocytes are separated by irregular bands of fibrous tissue (portal–portal bridging fibrosis). Masson's trichrome stain. Scale bar = 1 cm

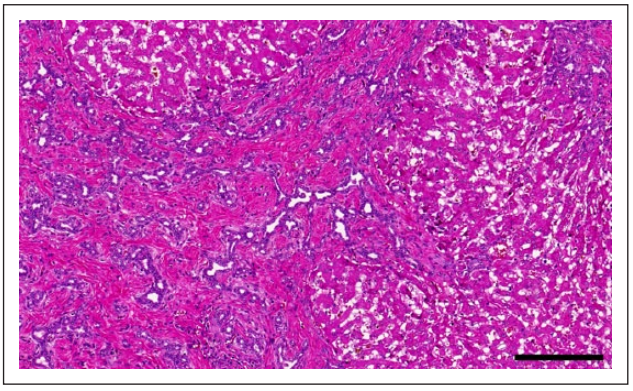

Figure 2 Photomicrograph of feline liver with congenital hepatic fibrosis. Portal–portal bridging fibrosis with abnormally structured, irregular intrahepatic bile ducts is observed. Hematoxylin and eosin. Scale bar = 200 µm

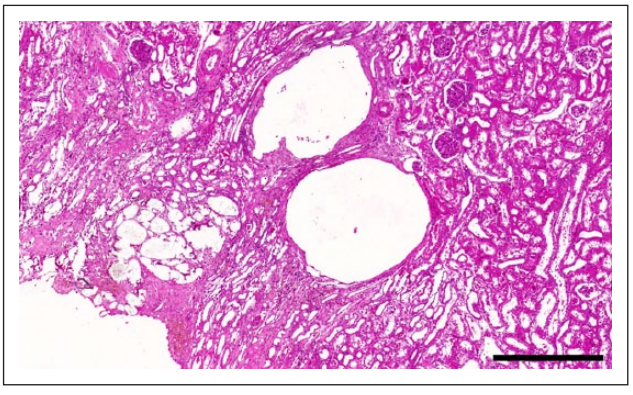

Figure 3 Photomicrograph of feline kidney. Rounded cysts are present in the kidney with compression of the surrounding tissue. Hematoxylin and eosin. Scale bar = 500 µm

5 µm-thick tissue sections and immediately placed into 1.5 ml sterile DNA/RNA-free plastic microtubes with

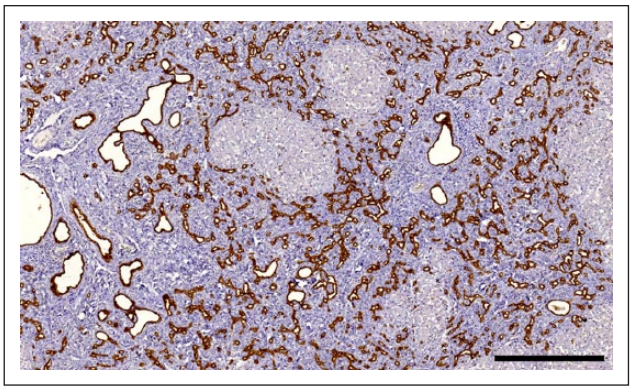

Figure 4 Photomicrograph of feline liver with congenital hepatic fibrosis. Bile duct epithelium is diffusely and strongly immunoreactive to K19. Scale bar = 500 µm

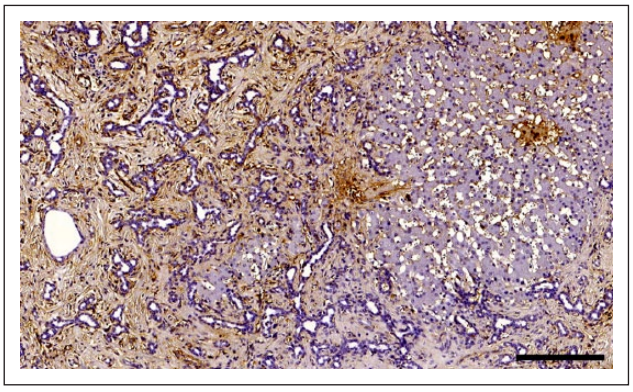

Figure 5 Photomicrograph of feline liver with congenital hepatic fibrosis. Collagen immediately surrounding the bile ductules is most strongly immunoreactive to collagen IV. Scale bar = 200 µm

1 ml of xylol to remove paraffin and 100% ethanol. Subsequently, a genomic DNA mini kit was used accordingly to manufacturer's instructions (QIAamp DNA FFPE Tissue Kit; QIAgen). PCR was performed to amplify exon 29 of *PKD1*, as previously described.[10,16] For the PCR-RFLP analysis, approximately 5 µl amplification product was digested with 10 U *MLY1* (New England Biolabs) in a 10 µl reaction that contained 1× NE Buffer 4 at 37°C for 3 h followed by inactivation of the enzyme at 65°C for 10 mins. The complete digestion reaction was analyzed in 2% agarose gel. For DNA sequencing, residual amplification primers and deoxynucleotide triphosphates were removed from the PCR product using a QIAquick PCR Purification Kit (Qiagen). Amplicons were then subjected to nucleotide sequence determination and analyzed on an ABI Prism 377 Sequencer (Applied Biosystems). In both techniques, the result was negative for the C >A transversion in exon 29 of *PKD1* in this cat (Figure 6).

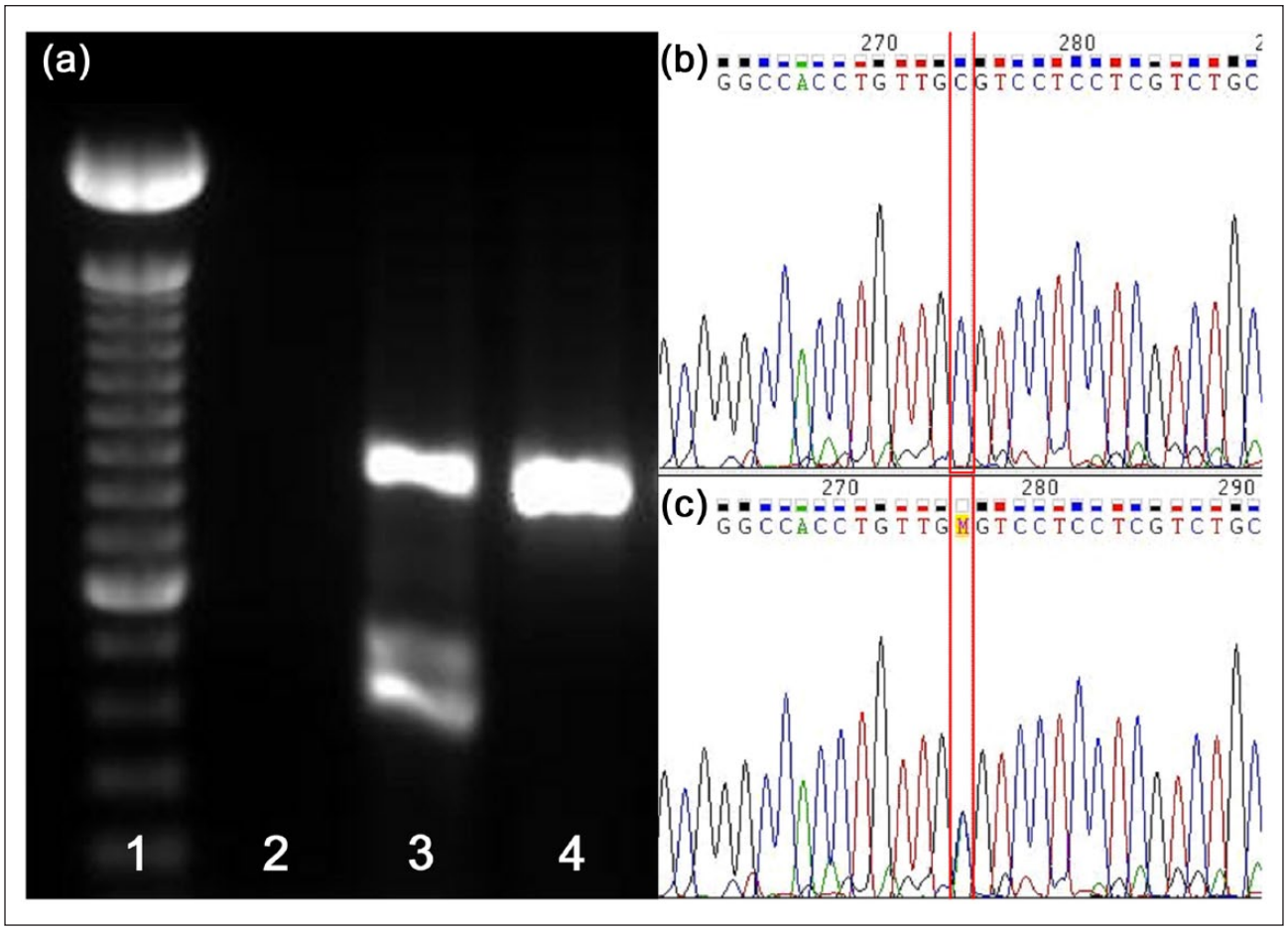

Figure 6 (a) PCR fragment length polymorphism typing for feline polycystic kidney disease (PKD) mutation. Persian cat with congenital hepatic fibrosis and PKD without C >A mutation of exon 29 of *PKD1* in lane 4. Lane 1 = ladder; lane 2 = blank; lane 3 = positive control. (b) Nucleotide sequences of the wild-type in exon 29 of feline *PKD1* in a Persian cat with congenital hepatic fibrosis. (c) Nucleotide sequences of the C >A transversion at position 3284 in exon 29 of *PKD1* in a Persian cat with PKD (positive control)

Discussion

CHF features a ductal plate malformation of interlobular bile ducts associated with fibrosis,[17–19] and in humans often coexists with Caroli's disease, von Meyenburg complexes (intrahepatic bile duct hamartomas), ARPKD and ADPKD.[2,20,21] The present case had portal–portal bridging fibrosis, with marked increase in small or irregular bile duct profiles, minimal to absent inflammation, and lack of nodular regeneration or other histologic evidence of chronic hepatitis. These histologic criteria allow the diagnosis of a ductal plate malformation closely resembling CHF.

Primitive bi-potential progenitor cells in the liver express keratins 8, 18 and 19. During gestation, progenitor cells that are committed to form hepatocytes lose K19 expression, whereas those destined to form bile ducts retain it and gain K7 expression. Previous studies on ductal plate malformations in humans have documented the expression of keratins 7, 8 and 19 in ductal plate cells.[18] In the present case, a diffuse positive K19 immunoexpression was observed in all ductular structures, identifying them as bile ducts or progenitor cells rather than mature hepatocytes. Regarding the immunoreactivity for type IV collagen, several studies have attempted to establish the pathophysiological mechanism behind the abnormal and excessive fibrotic response associated with CHF. Degradation of the basement membrane and extracellular matrix (ECM) constituents, and the remodeling of the ECM are important processes of embryonic development. Type IV collagen, which is present in the mesenchymal tissue surrounding the ductal plate cells, may help in the migration of these cells, as well as in their differentiation and maturation into intrahepatic bile ducts. Additionally, type IV collagen is present in mesenchyme surrounding ductal plates early in gestation. In this context, persistent type IV collagen immunoreactivity in the present report case supports the diagnosis of a ductal plate malformation.[2,18]

Some humans with CHF have concurrent renal cystic disease, similar to this case,[20,21] and this clinical presentation has been mainly associated with ARPKD. ARPKD is a severe form of human PKD that primarily

presents itself in infancy and childhood, being characterized by enlarged kidneys and dilated cystic bile ducts, extensive hepatic fibrosis and hepatic failure. Mutations at a single locus, *PKHD1* (polycystic kidney and hepatic disease 1), are responsible for all typical forms of ARPKD.[22]

Although rare, CHF with ADPKD occurs in humans.[23,24] ADPKD is the most common inherited renal cystic disease, occurring worldwide and across all ethnicities. Two main genes have been identified (*PKD1* [chromosome region 16p13.3; ≈85% cases] and *PKD2* [chromosome region 4q21; ≈15% cases]). However, several genetic mechanisms may contribute to the phenotypic expression of the disease. Clinically relevant aspects include both renal (impaired urinary concentrating capacity, renal failure, hypertension and pain) and extrarenal manifestations where involvement of the liver is the most common, owing to slow and variable expansion of the cysts.[25]

In cats, ADPKD is a well-described disease, especially in Persian cats.[26,27] Congenital cysts originate from both the proximal and distal tubules, and can be found in both renal cortex and medulla. The disease is progressive, and both the size and number of cysts can increase over time and may result in chronic renal failure later in life.[9] Also, it is fairly well described that ADPKD in most cats is associated with congenital biliary cystic lesions, as multiple large cysts.[9,13,14,28,29] However, the renal form is the more common variant in cats and is most commonly associated with clinical disease.[26] Hepatic fibrosis is reported in 22–48% of cats with PKD, with an age range of 1–14 years.[9,13,14] Clinical signs of liver failure, such as emaciation, diarrhea and coma, secondary to severe CHF have been reported only four times before in cats with PKD.[9,13–15] In none of these cases was the genetic test for C >A transversion in exon 29 of feline *PKD1* performed.

In the present case, the cat exhibited chronic weight loss, anorexia, vomiting, lethargy and altered mental status, consistent with hepatic failure and hepatic secondary encephalopathy. Hepatic enzymes were slightly elevated, but in CHF, the liver function tests may be normal with no regenerative hyperplasia present – in contrast to end-stage disease or cirrhosis.[20,30–32] Portal hypertension was considered the most probable cause of the abdominal effusion. This clinical presentation is uncommon in young cats, with the cat described herein only 12 months of age.

Owing to the low ratio of globulin to albumin in the ascitic fluid, feline infectious peritonitis was clinically suspected. However, no gross and histological evidence was observed to support this assumption. Because of the paucity of portal vein profiles, congenital portosystemic shunt or portal vein hypoplasia might be considered in the differential diagnosis but were unlikely given the presumed portal hypertension in this case.[14] Prominent biliary proliferation in these cases of CHF might prompt the consideration of chronic extrahepatic biliary obstruction. CHF can be distinguished from chronic extrahepatic biliary obstruction by the typical lack of inflammation or evidence of cholestasis, but in some cases, the history and clinical and imaging data will need to be evaluated carefully.[4]

Feline ADPKD can be diagnosed by ultrasound screening, which is recommended when cats are older than 10 months, in order to avoid a false-negative result, associated with the *PKD1* genetic test or with kidney biopsy, which may show lesions suggestive of ADPKD at an earlier stage.[23,33]

The pathogenesis of ADPKD in cats is unknown; however, in humans, abnormalities in gene expression, cell polarity, fluid secretion, apoptosis and ECM are hypothesized.[34,35] In cats, only a C >A transversion in exon 29 of *PKD1* was described as the genetic cause of ADPKD.[10,16] Although several studies showed that about 5% of animals observed with ultrasound or histopathological changes consistent with PKD are negative for this point mutation,[11,36] none of them directly describes the relationship between renal cysts, CHF and the absence of C >A transversion. Because information on littermates was not available in the current case, a hereditary basis could not be investigated. Therefore, this is the first case to show, through sequencing, CHF in a cat with PKD not linked to C >A transversion in exon 29 of feline *PKD1*.

It is likely that, as in humans, CHF and PKD should be assigned to a specific gene and its mutation in juvenile Persian and Persian families of cats. Although we did not find the C >A transversion in *PKD1* in this case, it is possible that other regions of this gene or even other genes, such as *PKHD1* (characteristic of the human ARPKD form), which have not yet been described in cats, are involved in the pathogenesis of this particular phenotype. Linkage, candidate gene or genome-wide analyses should be considered in further genetic investigations.

Conclusions

The absence of the classic genetic mutation associated with the particular clinical presentation supports the hypothesis of a distinct etiopathogenesis among fibropolycystic diseases in domestic cats. Moreover, CHF is a rare but important differential diagnosis for young Persian cats and their crosses with clinical signs of chronic end-stage liver disease.

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