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Exceptional Case

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Myeloid bodies caused by *COQ2* mutation: a case of concurrent COQ2 nephropathy and IgA nephropathy

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ABSTRACT

Immunoglobulin A (IgA) nephropathy, in the presence of myeloid bodies, has been reported in Fabry disease (FD). In this case, we excluded the diagnosis of FD by demonstrating the absence of mutation in the α-galactosidase A(*GLA*)gene. Our patient also denied any history of use of cationic amphiphilic drugs. Interestingly, we identified a novel missense mutation for Coenzyme Q2(COQ2) , which is known to cause *COQ2* mutation-associated nephropathy. We also found heteromorphic mitochondria and good treatment response in our patient following coenzyme Q10 supplementation. In light of our findings, our patient was diagnosed with COQ2 nephropathy and IgA nephropathy. To our knowledge, this is the first case report of COQ2 nephropathy with pathologic manifestations of myeloid bodies in podocytes.

Keywords: COQ2, COQ2 nephropathy, genetic kidney disease, IgA nephropathy, myeloid bodies

BACKGROUND

Myeloid bodies are commonly found in Fabry disease (FD), which is a lysosomal storage disease due to α-galactosidase A (*GLA*) gene mutation [1]. Recently, studies reported that cationic amphiphilic drugs (CADs) also induce the formation of myeloid bodies. CADs diffuse into lysosomes where they are protonated and become trapped, inhibiting the degradation of sphingolipids and eventually inducing pathogenic phospholipid-like changes.

COQ2 mediates the second step in the final reaction sequence of coenzyme Q10 (CoQ10) biosynthesis, which is condensation of the polyisoprenoid side chain with prenylation of para-hydroxybenzoate, generating the first membrane-bound Q intermediate [2]. *COQ2* mutations can disrupt CoQ10 synthesis leading to CoQ10 deficiency. CoQ10 deficiency is an autosomal recessive disorder with a myriad of phenotypes, including encephalomyopathy with ataxia and seizures, multisystem infantile type with encephalopathy, cardiomyopathy and renal dysfunction, a predominantly cerebellar type with ataxia and cerebellar atrophy, Leigh syndrome and an isolated myopathic type.

In this case report, we present a patient with a novel mutation c.973A>G in NM_015697.6 predicting COQ2 p.T325A substitution. To the best of our knowledge, this is the first case report of COQ2

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nephropathy with pathologic manifestations of increased myeloid bodies and vacuolar degeneration in podocytes.

CASE REPORT

A 47-year-old woman was admitted to hospital in July 2019 with a 2-year history of foamy urine. She presented with moderate albuminuria, but no gross hematuria, no skin purpura, no fingertip sensation abnormality and no pain. She denied a past medical history of systemic lupus erythematosus and malaria. Her place of residence was not known to be affected by epidemics such as malaria. On examination, her blood pressure was 116/70 mmHg; her chest was clear on auscultation and she was in sinus rhythm, with no audible pathological murmurs. She had no eyelid or pedal edema.

Urinalysis showed proteinuria (0.84 g/24 h). Biochemistry analysis showed serum albumin level of 37.8 g/L and serum creatinine level of 59 μmol/L. Serology showed absence of antinuclear, anti-double-stranded DNA, anti-neutrophil cytoplasmic, anti-glomerular basement membrane and Anti-Phospholipase A2 Receptor (anti-PLA2R) antibodies; hepatitis B virus and tumor markers were also negative. No abnormalities were found on abdominal ultrasound scanning and echocardiography. The patient worked in an electronic manufacturing factory and had been using hair dye once or twice a year for 20 years; hair dyes are known to be rich in lead, mercury, cadmium and other heavy metals. However, on assessment, blood and urine concentrations of heavy metals were found to be normal (Supplementary data, Table S1).

A renal biopsy was performed, revealing a total of 19 glomeruli in the specimens. Light microscopy demonstrated the presence of glomerular mesangial cells and slightly increased matrix proliferation, with no evidence of endothelial cell proliferation. Diffuse glomerular podocyte swelling was observed, as well as abundant vacuoles, giving the cytoplasm a honeycomb-like appearance (Figure 1A and B). Immunofluorescence showed prominent immunoglobulin A (IgA) and C3 deposits in the mesangium with a granular pattern (Figure 1C). Electron microscopy (EM) demonstrated electron-dense mesangial deposition (Figure 1D). Surprisingly, EM also revealed the presence of zebra bodies in all podocytes (Figure 1E and Supplementary data, Figure S1). Interestingly, granular substances distributed in podocytes were observed on toluidine blue staining (Figure 1F).

Further, we performed next-generation sequencing (NGS) to assess for genes implicated in glomerular diseases that have been reported so far (Supplementary data, Table S2). We found that the *GLA* gene did not show any suspicious variation or copy number variation (CNV) abnormality (Supplementary data, Figure S2). The activity of α-galactosidase A was 99.71 nmol/h/mg (reference $\geq$37 nmol/h/mg). The level of lyso-Gb3 was found to be 0.83 ng/mL (reference $<$1.11 ng/mL) using tandem mass spectrometry. However, the patient denied any history of use of suspicious drugs known to induce the formation of myeloid bodies (Supplementary data, Table S3).

Interestingly, the NGS results identified a novel mutation c.973A>G in NM_015697.6 predicting COQ2 p.T325A substitution (Supplementary data, Figure S3A). This novel mutation was predicted to be pathogenic using the Rare Exome Variant Ensemble Learner (REVEL) software. In addition, searches using the National Center for Biotechnology Information databases revealed the amino acid at this locus to be highly conserved in many species (Supplementary data, Figure S3B). In 2007, Diomedi-Camassei *et al.* reported the case of four patients with CoQ10 deficiency who presented with nephrotic syndrome (NS) as a result of *COQ2* mutation, which the authors termed as COQ2 nephropathy—renal biopsy specimens from all four patients showed the presence of heterologous mitochondria [3]. Strikingly, in our patient, we found many heteromorphic mitochondria in the renal tubules (Supplementary data, Figure S4). Since COQ2 is an important enzyme in CoQ10 synthesis, we determined our patient's plasma level of CoQ10, which was 2.0 μmol/L (0.46–1.85 μmol/L).

After 5 months of prednisone treatment, we found a gradual increase in proteinuria level in our patient. Therefore, our patient was treated with CoQ10 supplementation at 15 mg/kg/day, which led to a gradual decrease in 24-h proteinuria level after 2 months of treatment (Supplementary data, Figure S5).

DISCUSSION

IgA nephropathy combined with the presence of myeloid bodies has been reported in FD. However, in our case presented here, we have excluded the presence of FD through genetic testing, as well as by demonstrating normal α-galactosidase A activity. Also, we ruled out use of CADs and heavy metal poisoning, which have been shown to induce the formation of myeloid bodies like in FD. It is known that any substance or gene mutation interfering with lysosomal function and degradation of sphingolipids or phospholipids can induce the formation of myeloid bodies like in FD. Further, a study found that mitochondrial respiratory chain deficiency could inhibit lysosomal hydrolysis through AMP-activated protein kinase (AMPK) signaling, thus disrupting the normal function of lysosomes [4]. Therefore, we speculate that *COQ2* mutation could contribute to CoQ10 synthesis disorder and mitochondrial dysfunction, thereby disrupting lysosomal degradation and eventually leading to increased formation of myeloid bodies (Supplementary data, Figure S6). Our hypothesis is strongly supported by the good treatment response of our patient with CoQ10 supplementation.

COQ2 is essential to the synthesis of CoQ10 [2]. In 2005, Salviati *et al.*[5] reported a case of CoQ10 deficiency in children with nervous and renal system dysfunction. Cases of kidney diseases caused by *COQ2* mutations have also been reported since but are still very rare. In 2007, Diomedi-Camassei *et al.* reported the case of four patients with CoQ10 deficiency who presented with NS as a result of *COQ2* mutation, which they termed as COQ2 nephropathy [3]. In our case, our patient had a *COQ2* mutation (c.973A>G), with a clinical phenotype of moderate proteinuria. *COQ2* mutations have been previously reported to cause NS in children [6]. A'Another study reported the case of a 5-day-old patient with oliguria which rapidly progressed to end-stage renal disease [3]. It has been suggested that *COQ2* mutations could induce glomerular disease that varies in severity and may be related to the age of onset.

Treatment for COQ2 nephropathy consists of high-dose CoQ10 substitution, albeit with variability in treatment response. A study reported three patients presenting with NS related to *COQ2* variants, two of whom were successfully treated; however, one patient did not show clinical improvement after CoQ10 supplementation [6]. In our case, the patient was given high-dose CoQ10 supplementation and showed good treatment response, which further supports our diagnosis.

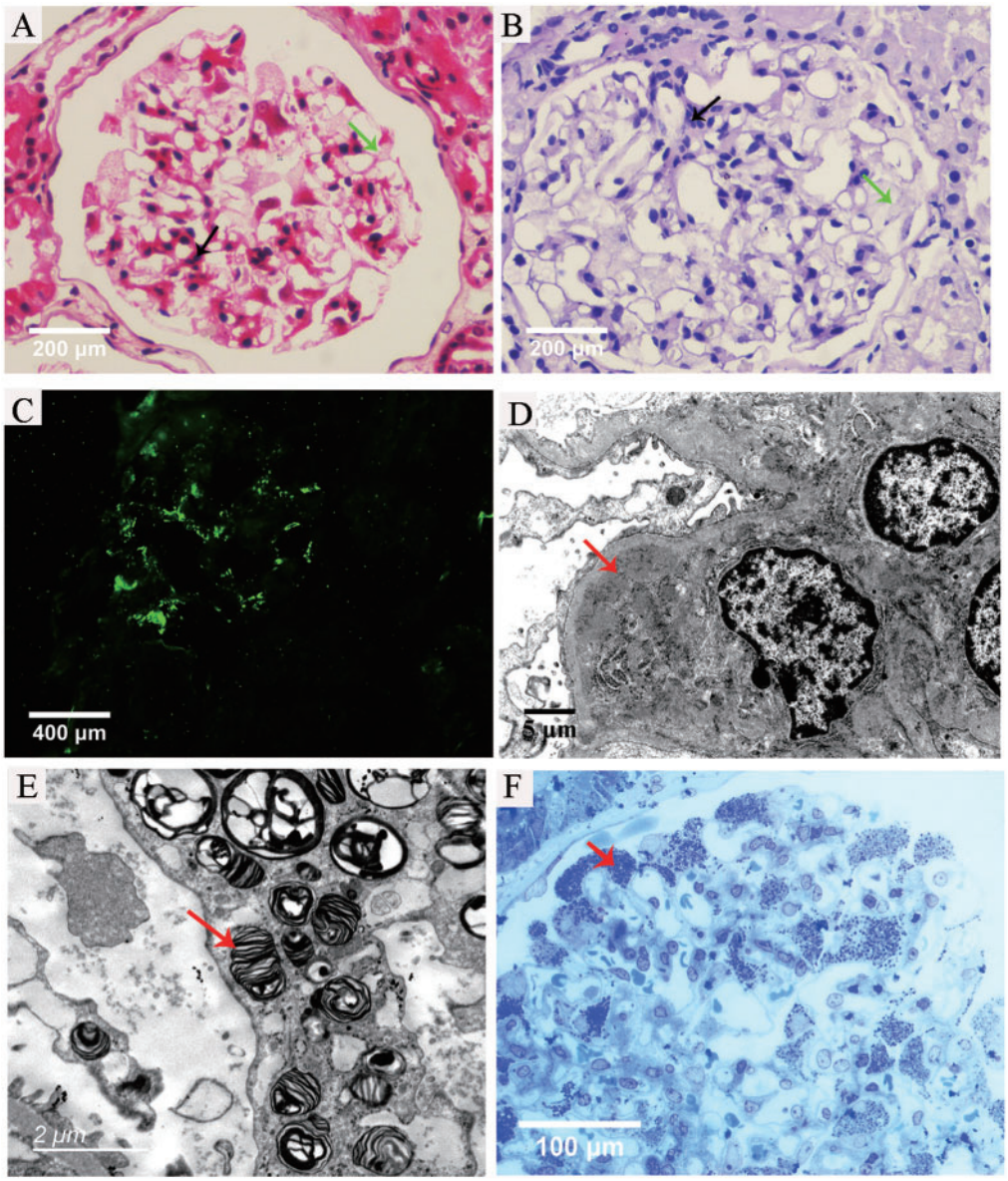

FIGURE 1: The pathological results of renal biopsy. (**A** and **B**) Light microscopy demonstrating mesangial hypercellularity and increased mesangial matrix, indicated by black arrows in (**A**) (hematoxylin and eosin staining) and (**B**) (periodic acid–Schiff staining). Also observed are diffuse swollen podocytes and vacuoles in the cytoplasm with a honeycomb-like appearance (green arrows in **A** and **B**). (**C**) Immunofluorescence showing IgA deposited in the mesangium with a granular pattern. (**D**) EM of a glomerulus showing electron-dense deposits in the mesangium (red arrow). (**E**) EM displaying many myeloid bodies located in podocytes (indicated by red arrow). (**F**) Toluidine blue staining revealing granular substances distributed in podocytes (red arrow).

Interestingly, we found that the level of CoQ10 in our patient was normal (2.0 μmol/L). Some reports demonstrated that patients with *COQ2* mutation had normal leukocyte CoQ10 levels and after treatment with CoQ10, the level of CoQ10 increased to above normal levels, with good therapeutic effects [6]. Our case findings are consistent with previous reports. However, due to tissue specificity, it is unfortunate that the activity of CoQ10 and mitochondrial respiratory chain complexes could not be assessed. Nevertheless, our case provides three key results as strong evidence supporting the diagnosis. First, our patient had a *COQ2* mutation, which was predicted to be pathogenic. Second, many heteromorphic mitochondria were found in renal tubules. Although heteromorphic mitochondria were not directly observed in podocytes, we believe this could be due to a lower abundance of mitochondria in podocytes and the limited availability of EM specimens. Third, and most importantly, our patient's proteinuria level was reduced following oral CoQ10 treatment. Therefore, we propose the diagnosis of COQ2 nephropathy with IgA nephropathy (HASS I, M1E0S0T0C0).

Taken together, our case illustrates the fact that myeloid bodies can be caused by many factors, including *COQ2* mutation. Accordingly, the treatment strategy would differ, depending on the etiology.

PATIENT CONSENT

The study was approved by the Ethical Committee of Zhongda Hospital, Southeast University School of Medicine. The patient gave informed consent for this publication.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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CONFLICT OF INTEREST STATEMENT

All authors declared no competing interests. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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