

Case Report

Hydroxychloroquine-induced lipidosis of the kidney mimicking Fabry disease: a case report

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Abstract: A 51-year-old female patient with Sjogren's syndrome had a renal insufficiency after 2 months' history of hydroxychloroquine therapy (300 mg/d, cumulative dose of about 18 g). The renal biopsy suggested Fabry disease. The gene analysis and plasma α -galactosidase A activity were in the normal range. After quitting the therapy of hydroxychloroquine, the renal function returned to its normal state in the next 3 months' follow-up.

Keywords: Fabry disease, hydroxychloroquine, renal function

Introduction

Fabry disease is a hereditary disease caused by the lack or little synthesis of α -galactosidase A, which is characterized at early stage by the acroparesthesia. Gradually skin, cardiovascular, kidney, neural, eye, ear, skeletal system is involved in this disease. Some medicines such as chloroquine [1] and amiodarone [2] could induce typical pathological changes mimicking Fabry disease. Here we report a case showing as Sjogren's syndrome with renal dysfunction after intaking hydroxychloroquine, and the renal pathology was Fabry disease.

Materials and methods

A 51-year-old female patient was admitted in our hospital for 3 years' history of intermittent neck and lumbosacral pain on 06/07/2014. 3 years ago, the patient suffered neck and lumbosacral pain, but no attention was paid. 2 months ago, the pain and swelling of bilateral hip joints deteriorated, accompanying xerostomia and keratoconjunctivitis. She went to the local hospital, the laboratory results showed ANA (-), Anti-SSA (+), Anti-SSB (+). Labial gland pathology showed mixed gland interstitial chronic inflammation coupled with focal gland atrophy and benign lymphoepithelial lesions. She was diagnosed as Sjogren's syndrome in

the local hospital. She was given prednisone 30 mg/d, hydroxychloroquine 300 mg/d, and methotrexate 15 mg/week for 2 months. She came to our department for further diagnosis this time. The laboratory results were as follows. Blood routine test was WBC $6.8 \times 10^9/L$, RBC $3.87 \times 10^{12}/L$, Hb 108 g/L, PLT $318 \times 10^9/L$ and renal function test showed Cr 128 $\mu\text{mol}/L$, BUN 6.03 mmol/L, UA 362 $\mu\text{mol}/L$. Liver function, serum lipids, electrolytic analysis were in the normal range. 24 hours urine protein was 0.07 g. Autoimmune antibodies showed ANA 1:320, Anti-SSA (+), Anti-SSB (+), Anti-Ro52 (+), Anti-dsDNA (-), Anti-GSM (-), ANCA (-). Schemers test showed that left eye was 5 mm/5 min, right eye was 6 mm/5 min. The patient's α -galactosidase A was within the normal range. Mutation analysis was performed, but it did not identify a mutation in the patient's α -galactosidase A gene analysis.

Pathology findings

Light microscopy

12 glomeruli could be seen, and 7 of which showed ischemic arteriosclerosis or atrophy. The remaining glomeruli showed hypertrophy and regional thickening of GBM. Granular and vacuolar degeneration and protein cast can be seen in tubular epithelial cells. Interstitial fibro-

Hydroxychloroquine-induced kidney injury

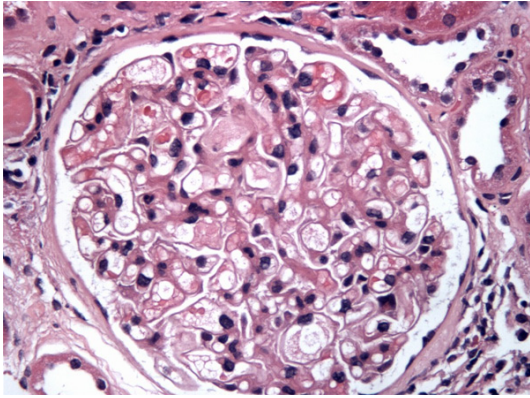


Figure 1. Ischemic arteriosclerosis or atrophy of some glomeruli, and Interstitial fibrosis and infiltration by multiple inflammatory cells in the light microscope. (400 × HE).

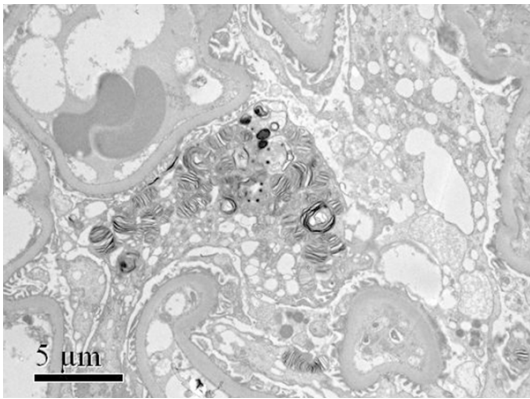


Figure 2. Osmiophilic lamellated bodies were seen in some podocytes by Electron microscope.

sis and infiltration by multiple inflammatory cells also can be seen. Vacuolization of the tubular system or podocytes could not be seen in the renal tissue (**Figure 1**).

Electron microscopy

Osmiophilic lamellated bodies were seen in some podocytes. No obvious abnormality in interstitial tissues, suspected as Fabry disease (**Figure 2**).

Results

She was diagnosed as Sjogren's syndrome and hydroxychloroquine-induced kidney disease finally. Hydroxychloroquine was stopped and prednisone of 30 mg/d was continued. Afterwards, she went to our hospital for review, serum creatinine returned to normal level grad-

ually; however she suffered lumbosacral and bilateral knees pain occasionally.

Discussion

Fabry disease is an X-linked hereditary disease, which occurs mostly in male patients. Gene mutation is located in Xq22.1 [3]. Morbidity rate is 1/110000~1/10000 in foreign articles. The morbidity rate of Fabry disease in dialysis patients of ESRD is 0.12% [4]. The diagnosis of Fabry disease relies on clinical manifestation, a-galactosidase A activity assay and gene sequence analysis. If kidney is involved, then renal pathology shows as follows. In Light microscope, vacuolar degeneration occurs can be seen in podocytes, epithelium, distal tubular cells. And the electron microscope, medullary sheath inclusion body (zebra-like bodies) are formed [5].

As to this patient, the patient lacked of classical Fabry disease symptoms such as acroparesthesia, decreased or absent of sweating, cutaneous angiokeratoma, vision damage or hearing damage. And there is no foam cell in light microscope (**Figure 1**). Although there is osmiophilic lamellated bodies in podocyte by electro microscope (**Figure 2**), the mutation site cannot be found in the gene testing and the a-galactosidase A activity was in the normal level. Furthermore, the patient's renal function improved after stopping hydroxychloroquine therapy (300 mg/d for 2 months, cumulative dose of approximately 18 g). Clinical, morphological, and biochemical findings were consistent with hydroxychloroquine-induced kidney disease.

In 2003, J. Muller-Hocker et al. [6] reported a 46-year-old female patient with Sjogren's syndrome and progressive renal disease under chloroquine treatment which accounted to 51 g totally. Later on in 2005 and 2006, Dinan Albay et al. [1] and Erika R. Bracamonte et al. [7] reported a patient of similar symptoms respectively as before, but they did not prescribe the exact doses of chloroquine or hydroxychloroquine. They were finally diagnosed as chloroquine or hydroxychloroquine induced kidney disease by testing plasma a-galactosidase A activity and (or) mutational analysis and excluded other diseases. Those 3 patients' kidney function returned to normal level in the follow-up.

Hydroxychloroquine-induced kidney injury

Hydroxychloroquine induces target organ damages, mainly attributed to the long period accumulation of the substance. In the literature, the latent phase of chloroquine-induced heart damage ranges from several months to 20 years [8]. However there is no related data about the latent time and accumulating dose of hydroxychloroquine resulting in renal dysfunction.

Hydroxychloroquine is an amphophilic substance. The main hydroxychloroquine toxicity is lysosomal damage. The mechanism is as follows. Hydroxychloroquine penetrate into the lysosome membrane and accumulate in it. Thus it changes the PH in lysosomes, resulting in the change of enzyme activity: phospholipase, α -galactosidase A, cathepsin, acid hydrolase [6, 9]. The lack or decreased activity of these enzymes induced the onset of lysosome accumulation disease, especially with the inhibition of α -galactosidase A, which induces the abnormal metabolism of glycosphingolipid. Hydroxychloroquine is mainly catabolized by kidney and liver. Especially Gb3 deposits in kidney and heart and zebra bodies could be validated in the renal tissue. This would be mistakenly diagnosed as Fabry disease. Besides decreasing lysosome enzymes activity, it is reported that hydroxychloroquine can decrease glomerular filtration rate and Ccr [10].

Here we report a case of renal dysfunction caused by Hydroxychloroquine, which mimicking Fabry disease. It is seldom reported before. Currently, hydroxychloroquine is widely used. To those who have a long history of hydroxychloroquine intaking and acute renal injury, renal biopsy is an effective way to find the reason of acute kidney injury. And if typical zebra bodies can be found, we should differentiate it with Fabry disease. Early diagnosis and stopping hydroxychloroquine treatment is a beneficial way to the recovery of renal function.

Disclosure of conflict of interest

None.

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