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Case and Review

Hydroxychloroquine-Induced Renal Phospholipidosis: Case Report and Review of Differential Diagnoses

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Abstract
Introduction: Renal phospholipidosis describes the accumulation of phospholipids in the lysosomes of kidney cells, in particular podocytes. Originally, this was described primarily in the context of the lysosomal storage disorder Fabry disease. It is now known that a variety of drugs can lead to the accumulation of lysosomal phospholipids. ***Case Presentation:*** We present the case of a 69-year-old female patient suffering chronic kidney disease and systemic lupus erythematosus who underwent a kidney biopsy because of a further increase in serum creatinine levels. There was no evidence of lupus nephritis, but electron microscopy showed zebra bodies as a morphological sign of phospholipidosis. This was most likely drug-induced after 25 years of continuous medication with hydroxychloroquine. A renal biopsy 2 years and 6 months earlier, when the renal function of the patient was distinctively better, showed no signs of renal phospholipidosis. Afterward, medication with hydroxychloroquine was discontinued, and renal function parameters remained stable in the 1-year course. ***Conclusion:*** This case raises the question of how severely impaired renal function affects the risk of hydroxychloroquine-induced renal phospholipidosis and underlines that hydroxychloroquine should be administered with caution in patients with kidney insufficiency. Moreover, we provide a review of the causes of renal phospholipidosis, which have been described in the literature and give an overview of possible differential diagnoses in cases with histologically proven phospholipidosis in renal biopsies.

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Introduction

Renal phospholipidosis is commonly linked to Fabry disease, which is a rare, X-linked recessive lysosomal storage disorder. A mutation in the GLA gene leads to a partial or complete defect of the lysosomal α-galactosidase A, which catalyzes the hydrolytic cleavage of galactose from sphingolipids [1]. The enzyme defect leads to intracellular deposition of the substrate of the enzyme, in this case, specifically globotriaosylceramide (Gb3). This causes cellular damage in multiple organ systems. The patients often suffer from small-fiber neuropathy, grouped angiokeratomas, hypo- or anhidrosis, as well as cardiac and cerebrovascular involvement [2]. In the kidney, the progressive deposition of Gb3 in podocytes, tubular epithelial cells, mesangial cells, glomerular, and vascular endothelial cells leads to proteinuria and a progressive decline in renal function, ultimately resulting in terminal renal failure [1]. Histopathological examination of renal tissue by light microscopy reveals vacuolization of the epithelium. In advanced stages, expansion of the mesangium, glomerulosclerosis, interstitial fibrosis, and tubular atrophy are noticed [1]. In electron microscopy, the deposits of glycosphingolipids appear as intralysosomal lamellar bodies, which are called zebra bodies due to their striped morphology [1].

Although zebra bodies are a characteristic electron microscopic finding in patients with Fabry disease, they are not pathognomonic for the disease. Zebra bodies can, for instance, also be related to the intake of cationic amphiphilic drugs (CADs). CADs have a hydrophobic ring structure and a hydrophilic side chain and can easily pass through plasma membranes. In acidotic cytoplasmic vesicles, such as lysosomes, CADs are protonated and then cannot pass the hydrophobic layer of the plasma membrane anymore [3]. The accumulation of CADs in lysosomes leads to impaired lipid catabolism via various mechanisms [3–5]. This leads to the accumulation of phospholipids and sphingolipids in increasingly dysfunctional intracytoplasmic lamellar bodies of lysosomal origin [3, 6]. Therefore, CADs, for instance, chloroquine and hydroxychloroquine, can lead to the formation of lamellar bodies in various tissues, including the heart, skeletal muscle, cornea, kidney, liver, and lung [6–8].

Herein, we report a case of an incidental finding of zebra bodies in kidney biopsy specimen in a patient with systemic lupus erythematosus (SLE) and advanced chronic kidney disease. The zebra bodies represented, most likely, drug-induced renal phospholipidosis due to long-term medication with hydroxychloroquine, since genetic evaluation ruled out Fabry disease. Interestingly, a kidney biopsy 2 years earlier, when the patient still had significantly better kidney function, did not show any zebra bodies. This raises the question if the declined renal excretion of hydroxychloroquine resulted in hydroxychloroquine accumulation and the formation of renal phospholipidosis. Furthermore, causes of renal phospholipidosis are presented tabularly to provide potential support in cases of unexpected detection of zebra bodies in renal biopsy specimens. The authors declare that they followed the CARE guidelines for case reports; a CARE checklist is attached as online supplementary Data 1 (for all online suppl. material, see https://doi.org/10.1159/000536448).

Case Presentation

A 69-year-old female patient with a previously diagnosed SLE was admitted to the hospital in July 2022 due to a slowly progressive increase in serum creatinine levels up to 3.3 mg/dL with an estimated glomerular filtration rate (eGFR) of 14 mL/min/1.73 m^2 according to the CKD-EPI equation (serum creatinine levels of 1.7 mg/dL 2 years and 6 months earlier and 2.9 mg/dL 1 year earlier) and an increasing proteinuria (2 g/g creatinine) with suspected renal disease activity of SLE (chronic kidney disease stage CKD5A3 according to

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2012 KDIGO classification). The diagnosis of SLE was established approximately 25 years ago when the patient initially presented with erythema, arthritis, and tendomyopathia and serologic evidence of anti-nuclear antibodies, anti-double-stranded DNA, anti-SSA(Ro), and anti-SSB(La) antibodies was obtained. A recent admission physical examination revealed skin and joint involvement with generalized tendomyopathy in an unaltered, stable degree in comparison to the last presentation. Serologically, there was no evidence of increased disease activity of SLE under continued immunosuppressive therapy with mycophenolate mofetil (500 mg/day) and prednisolone (5 mg/day). Furthermore, immunosuppressive therapy with hydroxychloroquine (200 mg/day) had been administered for approximately 25 years and has been reduced to an application once every 48 h in the previous month because of declined renal function. The cumulative dose of hydroxychloroquine was approximately 1,800 g. Annual ophthalmologic check-ups during treatment with hydroxychloroquine have so far been without pathological findings. Sonographically, the kidneys showed signs of advanced chronic parenchymal damage with a narrowed parenchymal margin.

In January 2020, at this time with a serum creatinine of 1.7 mg/dL (eGFR 31 mL/min/1.73 m^2), a renal biopsy was performed externally to clarify the genesis of the deterioration of renal function. Histopathological work-up showed chronic damage with mild nephrosclerosis and reactive focal segmental and global glomerulosclerosis (in 3 of 7 glomeruli), as well as focal tubular atrophy and interstitial fibrosis with a degree of 40%. Immunofluorescence staining revealed negativity for IgA and positivity for C1q, C3c, and IgM mesangial and for C1q, IgM, and IgG in scarred glomerular sections. Electron microscopy did not show basement membrane deposits but extensive podocyte foot process effacement without evidence for uncommon intracellular structures, for instance, lamellar bodies. Accordingly, no active renal involvement of SLE had been diagnosed.

With regard to the continued progressive renal function impairment and the limited significance of this renal biopsy, containing only 7 glomeruli, the indication of performing a new renal biopsy was set after careful consideration to clarify whether the patient developed an SLE activity in the kidney requiring subsequent intensification of immunosuppression. Sequential renal biopsy performed in July 2022 revealed moderate chronic parenchymal damage of the cortex with moderate nephrosclerosis, focal segmental and global glomerulosclerosis (in 5 of 11 glomeruli), and minor arteriolohyalinosis, as well as tubulointerstitial inflammation with focal acute tubular damage (Fig. 1a). In addition, mild vacuolization of the cytoplasm was noted (Fig. 1b). There was no evidence of lupus nephritis since immunofluorescence showed negativity for IgA and IgG and discrete, questionable-specific mesangial deposits of IgM, C1q, and C3c (online suppl. Fig. 1). Electron microscopy did not reveal any evidence of basement membrane deposits but podocyte foot process effacement and numerous lamellar bodies predominantly localized in podocytes (Fig. 1c), which were not described in the previous biopsy from 2020. Since zebra bodies may indicate the presence of Fabry disease, we performed further diagnostics in this regard. Clinically, there were no further indications of Fabry disease, especially neither grouped angiokeratomas, hypohidrosis, nor small fiber neuropathy, and the family history was unremarkable in this respect. Genetic evaluation of the GLA gene by Sanger sequencing was without pathological findings, excluding Fabry disease as the cause of the present renal insufficiency and the zebra bodies.

In summary, there was no evidence of Fabry disease regarding the medical history, physical examination, and molecular genetic analysis. Considering the drug history, the zebra bodies in podocytes are most probably signs of drug-induced renal phospholipidosis. Hereby, the histomorphological picture of Fabry disease is imitated, in which the zebra bodies are the typical sign of renal phospho- and sphingolipid deposition. With the exception of hydroxychloroquine, the patient was not taking any medication at the time of the second biopsy that is currently known to cause drug-induced phospholipidosis [9].

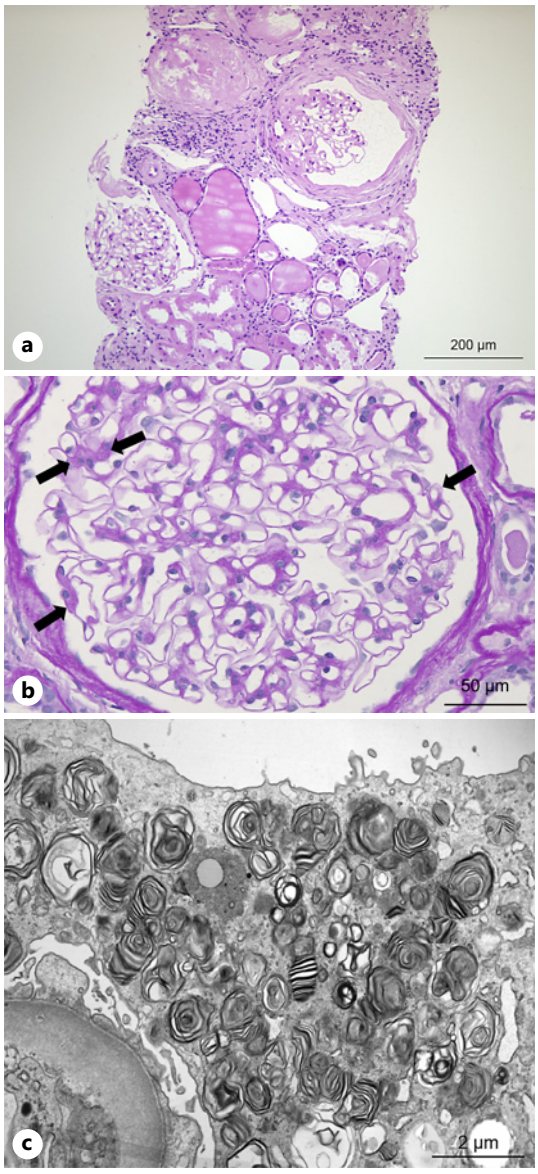

Fig. 1. a Hematoxylin-eosin stain of a renal tissue section. Moderate-grade parenchymal damage of the cortex with moderate nephrosclerosis and minor arteriolohyalinosis, as well as tubulointerstitial inflammation with focal acute tubule damage, are present. **b** Vacuolated cytoplasm (marked with arrows) is noticed in the podocytes in periodic acid-Schiff-stained sections. **c** Electron microscopy displays an exemplary podocyte with numerous lamellar bodies, the so-called zebra bodies.

With progressive renal function impairment with proteinuria and evidence of zebra bodies as an indicator of a relevant lysosomal storage disease in the podocytes, we discontinued the medication with hydroxychloroquine. During the 1-year course, renal function remained stable at a low level (serum creatinine 2.94 mg/dL, eGFR 16 mL/min/1.73 m^2 by CKD-EPI equation), and the proteinuria was unchanged so far. After discontinuation of hydroxychloroquine, there were no serological (anti-double-stranded DNA antibodies, complement consumption, platelets) or clinical signs of resurrected SLE disease activity.

Discussion

Hydroxychloroquine is a potent immunomodulator [4] and, according to the latest guidelines, should be administered in all patients with SLE and absent contraindications [10]. In association with hydroxychloroquine medication, cases of drug-induced

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phospholipidosis are known. Despite the frequent use of hydroxychloroquine, the overall prevalence of hydroxychloroquine-induced renal phospholipidosis is still unclear, as mainly isolated cases have been described in the literature [11–18]. In published case studies, zebra bodies were detected after a very heterogeneous duration of medication (0.3 months–9 years and 8 months) and concomitant heterogeneous cumulative dose (3 g–1,412 g) [11–19].

Some authors describe curvilinear bodies, representing twisted microtubular structures, as a possible histopathological distinguishing feature between Fabry disease and drug-induced renal phospholipidosis [7, 19]. However, these are absent in some cases, including ours. Current research focusses on the development of clinical biomarkers that provide a reliable distinction between congenital lysosomal storage diseases and drug-induced phospholipidosis [20, 21].

The clinical relevance of hydroxychloroquine-induced phospholipidosis is currently unclear as well. The accumulation of hydroxychloroquine in lysosomes with an increase in intralysosomal pH and a reduction in the activity of lysosomal enzymes disrupts processes of autophagy and heterophagy [4]. In principle, these effects are desired in the context of immunomodulatory therapy. In theory, this has to be distinguished from distinct cellular damage in the sense of hydroxychloroquine toxicity, which could contribute to a deterioration of kidney function. Although evidence of phospholipidosis as such is not directly equivalent to hydroxychloroquine toxicity, it is at least suggestive of drug accumulation in the cells of the affected tissue. Furthermore, the question arises whether phospholipidosis should also be assumed in other organs if zebra bodies are detected in the kidney. Costa et al. [19] (2013) were able to demonstrate asymptomatic discrete bilateral subepithelial corneal opacities and intralysosomal electron-dense deposits in a skin biopsy simultaneously with the occurrence of zebra bodies in the kidney. Different effects of a discontinuation of hydroxychloroquine treatment on kidney function are described in the literature: in a previously described case, no zebra bodies could be detected in a renal biopsy in the interval after cessation of hydroxychloroquine therapy [13]. However, cases are presented in which creatinine levels decline and/or proteinuria decreases after cessation [13, 18], as well as cases in which discontinuation of hydroxychloroquine had no relevant effect on renal function [16, 17, 19]. Based on this, Manabe and colleagues [12] (2021) draw attention to the fact that a discontinued immunomodulatory medication with hydroxychloroquine could pose the risk for an increase in SLE activity with subsequent decline in renal function. In summary, most authors recommend discontinuation of medication and regular monitoring of renal function parameters and proteinuria when zebra bodies occur during hydroxychloroquine medication, if justifiable in the context of the underlying rheumatic disease [11, 13, 14, 16–19].

In our case, renal phospholipidosis was not present in the first renal biopsy in 2020. It is debatable whether zebra bodies were undetectable in the first renal biopsy due to sampling error or whether certain conditions, as an increasing cumulative dose or a decrease in renal excretion in the setting of declined renal function, may have led to an increase in hydroxychloroquine tissue accumulation in the meantime with consecutive development of phospholipidosis. Regarding the fact that hydroxychloroquine had already been taken as medication for approximately 23 years at the time of the kidney biopsy in 2020, it seems rather unlikely that a patient-specific tipping point in the cumulative dose of hydroxychloroquine leading to markedly increased hydroxychloroquine accumulation has suddenly been reached in the following 2 years. When comparing kidney function over time, the difference in serum creatinine levels from 1.7 mg/dL in 2020 to 3.3 mg/dL in 2022 is striking. Lee and colleagues [22] (2017) showed that there was no significant association between renal function and the blood

Table 1. Causes of renal phospholipidosis

Causes of renal phospholipidosis	Reference
Pharmaceuticals	
Hydroxychloroquine	11–19
Chloroquine	7, 26, 27
Amiodarone	32
Gentamicin	28–31
Tobramycin	30
Amikacin	30
Putative	
Sertraline	33, 34
Carbamazepine	35
Ranolazine	36
Oxymorphone	37
Posaconazole	38
Viomycin	28
Contrast media	39
In rodents and human/mammalian kidney cell lines	
Chlorphentermine	40, 42
Iprindole	40
Imipramine	40, 41
Clomipramine	40
Netilmicin	43
Azithromycin	44
Toreforant	45
Dibucaine	46
Ketoconazole	47
Metals	
Silicon	48
Chromium	28
Genetic diseases	
Fabry disease	1
Niemann-Pick type C	49
COQ2 mutation-associated nephropathy	50
LMX1B-associated nephropathy	51, 52
Familial lecithin-cholesterol acyltransferase deficiency	53
Nutrition (in rodents)	
Excessive dietary lipid intake	54
Hypomagnesiemia plus excessive dietary lipid intake	55

concentration of hydroxychloroquine and N-desethylhydroxychloroquine, one of its major metabolites. In the mentioned study, 96.3% of the cases were assigned to CKD stages 1 and 2; no patient had a kidney insufficiency corresponding to CKD stage 5. Therefore, the informative value for high-grade kidney insufficiency is limited. Jallouli and colleagues [23] (2017) pointed out that in patients suffering from SLE and chronic kidney disease (serum creatinine clearance 23–58 mL/min according to the Cockcroft-Gault equation), the median blood concentration of hydroxychloroquine was significantly higher in comparison to patients with normal kidney function. Dialysis did not have a relevant effect on hydroxychloroquine blood concentration [23]. With regard to hydroxychloroquine toxicity, a study from Melles and colleagues [24] (2014) pointed out that kidney disease significantly increases the risk of retinal toxicity under

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hydroxychloroquine medication, one of the major adverse effects of hydroxychloroquine therapy. The FDA drug label states that a dose reduction may be necessary in patients with renal disease [25]. This case also hints towards an increased risk of hydroxychloroquine tissue accumulation in advanced renal insufficiency.

The occurrence of lamellar bodies in the renal biopsy of a patient can be – as it was in the herein presented case – an incidental finding. Lamellar bodies in renal cell types constitute the morphological correlate of renal phospholipidosis without representing a specific disease entity. Therefore, the question arises: which conditions can cause a renal phospholidosis? Table 1 summarizes the previously described causes of renal phospholipidosis. Several drugs, such as the immunomodulative drugs hydroxychloroquine [11–19] and chloroquine [7, 26, 27]; aminoglycoside antibiotics gentamicin [28–31], tobramycin [30], and amikacin [30]; as well as amiodarone [32], have already been shown to be able to evoke renal phospholipidosis. A heterogeneous group of other pharmaceuticals, namely sertraline [33, 34], carbamazepine [35], ranolazine [36], oxymorphone [37], posaconazole [38], viomycin [28], and contrast media [39], have been described as potential causes of renal phospholipidosis when lamellar bodies were found in renal biopsy specimen and no other known causes of phospholipidosis were identified. In addition, certain drugs have been found to induce renal phospholipidosis in rodents and human or mammalian renal cell lines, e.g., antidepressants such as iprindole, imipramine, and clomipramine [40, 41] and other pharmaceuticals [42–47].

Moreover, silicon [48] and chromium [28] have also been named as causes of renal phospholipidosis. In addition to Fabry disease, other genetic diseases can also disrupt the cellular lipid metabolism and cause renal phospholipidosis. These are Niemann-Pick type C [49], COQ2 mutation-associated nephropathy [50], LMX1B-associated nephropathy [51, 52], and familial lecithin-cholesterol acyltransferase deficiency [53]. In experimental conditions, excessive dietary lipid intake was shown to induce an acquired form of lipid storage disease with the presence of lamellar bodies in kidney cells [54, 55].

When lamellar bodies appear in renal biopsy specimen, in addition to screening for symptoms and a positive family history of Fabry disease and performing genetic testing for Fabry disease, a detailed history of the pharmaceutical therapies is essential. Furthermore, other genetic diseases should be taken into consideration.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of the details of her medical case and the accompanying images.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest directly relevant to the content of this article.

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Author Contributions

Menke A.F. collected data and wrote the manuscript. Pavenstädt H. and Jehn U. contributed to the concept and design of the case report and wrote the manuscript. Heitplatz B. and Van Marck V. performed the histopathological examination of the kidney biopsy specimen, provided the images of the hematoxylin-eosin staining and electron microscopy, and discussed and reviewed the article.

Data Availability Statement

The data used to support the findings of this case report are included within the article and the supplementary material. Further inquiries can be directed to the corresponding author.

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