Nephrol Dial Transplant (2007) 1 of 4
doi:10.1093/ndt/gfm462

NDT
Nephrology Dialysis Transplantation

Teaching Point
(Section Editor: A. Meyrier)

A wild zebra chase

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Keywords: Anderson–Fabry disease; chloroquine; diagnosis; hydroxychloroquine; iatrogenic phospholipidosis; lysosomal storage disorder; renal biopsy

Introduction

Rare diseases provide the physician with an exciting opportunity to escape from what may be perceived as boring routine. This endeavour, however, may hold dangers, particularly if the physician has never before encountered the disease in real life. All too easily, an open-mind approach is abandoned. From then on, new data will be used in a relentless quest to support a pre-formed diagnosis [1]. To illustrate this common and dangerous mechanism of error, we present the case of a 70-year-old patient with systemic lupus erythematosus with renal impairment and proteinuria, in whom renal biopsy seemed to provide us with a rare and interesting diagnosis.

Case

A 70-year-old woman with systemic lupus erythematosus (SLE) presented in January 2005 with new-onset proteinuria and impaired renal function. The SLE had been diagnosed in 1996 with involvement of skin and joints. Treatment with steroids and azathioprine had induced remission, but azathioprine had to be discontinued, due to hepatotoxicity. Since 1997, remission had been maintained with steroids, methotrexate and hydroxychloroquine. Since then, she had been free of skin symptoms, arthralgias, chest pain, shortness of breath and fever. Laboratory studies, however, now revealed a serum creatinine of 113 μmol/l with heavy proteinuria on dipstick examination. The patient also had a history of hypertension, although she admitted to not measuring her blood pressure regularly; occasional readings had been between 140/80 and 160/90 mmHg while the patient was on no antihypertensive therapy. Ultrasound studies performed some years earlier had revealed a shrunken left kidney of unknown cause. Finally, there was a remote history of deep vein thrombosis many years previously. Current medication included prednisolone (4 mg daily), methotrexate (15 mg weekly) and hydroxychloroquine. The remainder of the medical history was entirely unremarkable. The patient was a retired pharmacist with two healthy children. Both her father and sister suffered from poorly defined rheumatic disease. On examination, the patient was in good health. Blood pressure was 160/95 mmHg, pulse rate was 76/min and temperature was 97.7°F (36.5°C). There was a non-radiating II/VI systolic murmur at the left sternal border but the apex beat was not displaced and the jugular venous pressure was normal. The chest was clear. There were no signs of arthritis or connective tissue disease and the remainder of the physical examination was unremarkable. Laboratory studies showed a creatinine-clearance of 64 ml/min with 2 g/day proteinuria. Anti-nuclear antibodies were 1 : 80 (normal 1 : 40), while C3 and C4 complement levels were normal. Antibodies against double-stranded DNA and extractable nuclear antigens were absent and Coombs testing for anti-erythrocyte antibodies was negative. Urine microscopy showed hyaline casts and some dysmorphic erythrocytes. Ultrasound revealed a shrunken 6.3 cm kidney on the left and a 12 cm kidney with well-maintained parenchyma on the right; renal artery stenosis was excluded by colour duplex studies. An electrocardiogram showed incomplete right bundle branch block and chest X-ray was normal.

Renal biopsy was discussed, as were the risks of this procedure in a functional solitary kidney. In our

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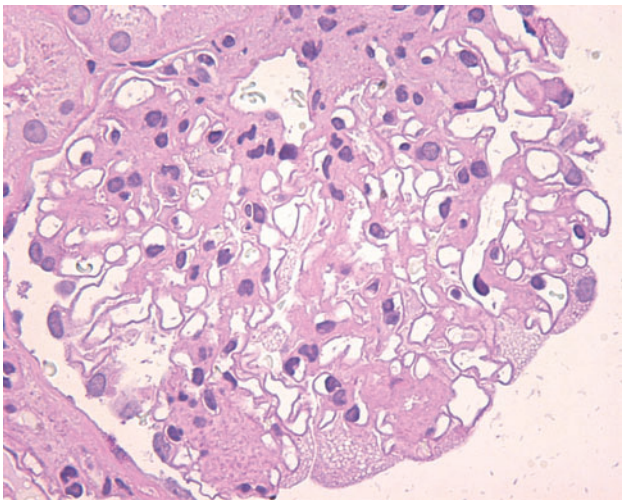

Fig. 1. Foamy inclusions within podocytes and tubular epithelial cells (renal biopsy, haematoxylin/eosin stain, 400× magnification).

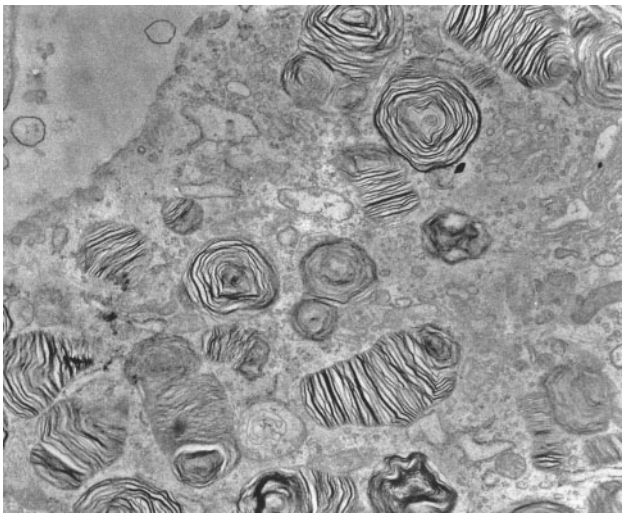

Fig. 2. Laminated intra-cytoplasmic inclusions ('zebra bodies') and myelin figures within podocytes (renal biopsy, transmission electron microscopy, 8000× magnification).

opinion, the likelihood of glomerulonephritis outweighed the risks of biopsy. The situation was discussed with the patient, consent was obtained and biopsy of the right kidney was performed without complications. Renal biopsy demonstrated arterio-nephrosclerosis and arteriolar hyalinosis consistent with hypertensive nephropathy but there were no signs of lupus nephritis. The most striking features, however, were foamy inclusions within podocytes and tubular epithelial cells (Figure 1). Electron microscopy confirmed osmiophilic intracellular deposits (Figure 2). These inclusions were identified as myelin bodies ('zebra bodies'), indicating a lysosomal storage disorder. A diagnosis of Anderson–Fabry disease was made, implications of the biopsy results were discussed, and a search for other manifestations was begun. The family history revealed no possible cases of the disease and we learned that the patient's two healthy daughters were eager to have children. An ophthalmologist observed corneal deposits consistent with Anderson–Fabry disease and echocardiography demonstrated aortic sclerosis but no cardiomyopathy. A meticulous clinical examination failed to reveal angiokeratomas. At this point, we noted the paucity of clinical manifestations and assumed a mild phenotype in a female heterozygote. We discussed the situation with the patient and her family who all wished a definitive diagnosis, more so since they had read about the disease on the Internet. We submitted a serum sample to a referral centre for Anderson–Fabry disease and an assay of serum alpha galactosidase (*GLA*) activity was performed, which came back as normal; hence we proceeded to genetic testing, which failed to reveal any *GLA* mutation. We discussed the case in great detail with the referral centre and learned that chloroquine causes iatrogenic phospholipidosis with renal deposits and corneal abnormalities, both of which are impossible to distinguish from Anderson–Fabry disease. A diagnosis of iatrogenic phospholipidosis (drug-induced lysosomal storage disorder) was made, hydroxychloroquine was stopped and the dose of methotrexate was reduced to 10 mg/week. When last seen in March 2006 the patient was doing well, with no signs or symptoms of SLE. Blood pressure control was good with ramipril and metoprolol. Proteinuria ranged between 1.8 and 5 g/day, while the creatinine clearance remained stable.

Discussion

Anderson–Fabry disease is a lysosomal storage disorder of glycosphingolipid catabolism caused by deficiency of α-galactosidase (*GLA*). The disease is named after Johannes Fabry and William Anderson, who both described the disease in the 19th century [2] although others may have contributed as well. The *GLA* gene is located on the X chromosome, resulting in X-linked inheritance with a pan-ethnic incidence of 1 : 40 000. Most mutations are believed to affect the hydrophobic core of the protein, thus Anderson–Fabry disease is primarily a disease of protein-folding. Heterozygous women can also be affected, due to skewed inactivation of the X chromosome but severe disease is uncommon [3]. Clinical manifestations include cardiomyopathy, angiokeratomas, hypohydrosis, debilitating neuropathic pain and premature atherosclerosis [4]. The latter is caused by distorted lysosomal storage in endothelial cells. 'Whorled' corneal opacities are another salient feature of the disease. Renal involvement includes proteinuria, renal impairment and end-stage renal failure. A typical patient will be a middle-aged male with episodes of painful and severe neuropathy, renal impairment and premature vascular disease [5]. Many patients may not undergo renal biopsy prior to dialysis, to the effect that dialysis is begun with a diagnosis of end-stage renal failure of unknown origin. There is reason to suspect unrecognized cases among the dialysis population.

The diagnosis of Anderson–Fabry disease is suggested by demonstration of low α-galactosidase activity in serum or histological findings and confirmed by mutation analysis. Novel diagnostic approaches have been described, such as electron microscopy [6] or mass spectometry [7] of the urinary sediment. The use of these sophisticated techniques may be contemplated if a diagnosis of Anderson–Fabry is already suspected. Treatment with recombinant α-galactosidase is now available although recent evidence suggests that long-term effects may not be as good as previously hoped [8].

Anderson–Fabry disease is rare and few physicians are familiar with the disease. Even less known is the fact that a strikingly similar pattern of deposits has been described as a sequel to chloroquine treatment [9,10]. Cornea and kidney are usually affected. Rheumatologists and nephrologists should be particularly sensitive to this issue. Chloroquine is a weak base and crosses the lysosomal membrane, leading to inhibition of various enzymes. As a matter of fact, endothelial cell exposure to chloroquine serves as a model of Anderson–Fabry disease [11]. A recent case of biopsy-confirmed Anderson–Fabry-type cardiomyopathy associated with chloroquine [12] underscores the potential severity of the disorder. Based on their similar structure, it is reasonable to assume that hydroxychloroquine may also cause iatrogenic phospholipidosis as suggested by a recent report [13]. The differential diagnosis includes iatrogenic phospholipidosis due to other drugs, such as amiodarone, as well as a variety of exceedingly rare lysosomal storage disorders as described in great detail elsewhere [13].

Our case illustrates a common error in diagnostic reasoning, namely the over-enthusiastic chase for an obscure disease. The term 'wild goose chase' derives from 16th century horse racing in England and figuratively describes an erratic course taken by one person and followed by another. Shakespeare used the phrase in this sense in 'Romeo and Juliet' [14] but the origins of the term were soon forgotten and it was later used to denote a hopeless quest. In our case, 'zebra' bodies led us on a hopeless quest for Anderson–Fabry disease, a rather unlikely disease in a 70-year-old female lupus patient. Rare diseases have been dubbed 'zebras' by medical jargonists and an often-quoted saying reminds us not to expect a zebra when we hear hoofbeats. Here, the gender of the patient, the negative family history, normal α-galactosidase, and paucity of clinical manifestations should have cautioned us earlier. In comparison to our tentative and obscure diagnosis, side effects of drugs are much more common across all specialties of medicine. In our case, an in-depth discussion with a referral centre should have occurred prior to a host of useless and unnecessary tests. Finally, the impact of the disease on patients and relatives has been described, [15] and we must be chided for causing unnecessary anxiety in this regard.

Teaching points

(i) Anderson–Fabry disease is a rare, X-linked lysosomal disorder of glycosphingolipid catabolism caused by deficiency of α-galactosidase (*GLA*). Salient clinical manifestations include painful neuropathy, proteinuria with renal failure, and premature atherosclerosis.

(ii) The finding of lysosomal inclusions on renal biopsy proves a lysosomal storage disorder, not Anderson–Fabry disease. The differential diagnosis includes other rare storage disorders as well as iatrogenic phospholipidosis; the latter may be caused by a variety of drugs, such as amiodarone, chloroquine and hydroxychloroquine.

(iii) Enthusiasm for rare and complex diseases is not *per se* harmful, but an over-enthusiastic search for obscure diseases should be discouraged, particularly if the physician has never before encountered the disease in real life. An in-depth discussion with a referral centre should occur early on.

(iv) Great care must be taken if a diagnosis such as Anderson–Fabry's disease is contemplated, because the prospect of an inherited and debilitating disease may have profound implications on patient and relatives.

Conflict of interest statement. None declared.

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Received for publication: 31.5.07
Accepted in revised form: 14.6.07