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Case Report
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Zebra Bodies on Renal Biopsy: Fabry Disease or Not Fabry? A Tale of Two Cases

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Abstract

Background: *Zebra bodies are intracellular lamellar inclusions detected by electron microscopy (EM) on renal biopsy, classically found in Fabry disease. This EM finding prompts genetic testing for α-galactosidase A enzyme deficiency to diagnose Fabry disease, and thus consider enzyme replacement therapy. Zebra bodies have also been associated with certain medications, including statins and hydroxychloroquine. We present two contrasting cases, both presented within a year of each other with zebra bodies found in renal biopsy.*

Case Presentations

Case 1: *An 83-year-old lady with type II diabetes mellitus and hypertension was presumed to have diabetic or hypertensive nephropathy, however in ruling out alternative causes, was found to have asymptomatic myeloma. Renal biopsy to detect renal amyloidosis or myeloma kidney instead found zebra bodies on EM. Genetic testing confirmed Fabry disease. She was managed conservatively.*

Case 2: *This contrasts with an 80-year-old woman with rapid decline in her renal function following coronary angiography. Renal biopsy showed hypertensive nephropathy on light microscopy, and zebra bodies on EM. She tested negative for Fabry disease. She was taking sertraline, and had previously been on atorvastatin, but this had been stopped four years prior to the biopsy.*

Conclusion: *Drug-induced renal phospholipidosis is an important differential diagnosis to be considered in cases with zebra bodies that are negative for Fabry disease. It is unclear for how long a patient needs to be taking a culprit medication to develop these changes, and whether they may persist many years later. From our findings, it is clear that more research is needed to identify alternative causes of zebra bodies to guide earlier diagnosis and treatment, which would improve outcomes.*

Keywords: Chronic kidney disease, Electron microscopy, Fabry disease, Phospholipidosis

1. Background

Zebra or myelin bodies are intracellular osmiophilic membrane structures seen in electron microscopy [1]. They are representative of the accumulation of lysosomal inclusion bodies, which is classically seen in Fabry disease. Zebra bodies have also been associated with phospholipidosis as a result of some medications, including hydroxychloroquine, chloroquine, amiodarone and statins [2].

Fabry disease is an X-linked lysosomal storage disorder in which there is a deficiency of the α-Galactosidase A enzyme, leading to the accumulation of the enzyme's substrates, globotriaosylceramide (GL-3). This accumulation leads to cellular damage and ischaemia due to small vessel disease. The result is the typical symptoms of Fabry disease, acroparaesthesias, angiokeratomas and corneal opacities. When the kidneys are affected, there is progressive renal dysfunction with proteinuria and non-visible haematuria. Diagnosis is made by detecting low leukocyte α-Galactosidase A enzyme levels or from abnormal GLA gene detection. In this paper we present two cases to contrast.

2. Case Presentations

2.1 Case 1

An 83 year-old lady was referred routinely to the renal clinic with chronic kidney disease stage 3b (CKD3b) and fluid overload. She had a past medical history of type two diabetes mellitus, hypertension, atrial fibrillation and ischaemic heart disease. She had a background of diabetic retinopathy. Therefore, the most likely causes of her CKD were diabetic and hypertensive nephropathy. A screen for alternative causes was sent, which demonstrated a raised p-ANCA incidentally, but with negative anti-MPO and anti-PR3 antibodies. There were also elevated serum kappa light chains

at 403mg/L (3–19 mg/L) and serum lambda light chains at 52mg/L (6–26 mg/L), corresponding to an elevated kappa: lambda ratio of 7.75 (0.26–1.65). There was paraprotein detected in her blood at 7.6g/L.

She was referred to the haematology team to investigate this abnormal paraprotein. Bone marrow biopsy diagnosed asymptomatic myeloma. It was to be managed conservatively in a watch-and-wait approach. In light of this haematological diagnosis, a renal biopsy was organised to rule out renal myeloma and amyloidosis as the cause of CKD. Light microscopy showed no evidence of amyloid deposition or myeloma kidney but had changes consistent with diabetic and hypertensive nephropathy. Subsequently, electron microscopy was performed that showed osmiophilic lamellated inclusions bodies, or zebra bodies (Figure 1).

Fabry Disease diagnosis was made by genetic testing which was positive with heterozygosity for c.1087C>T (p.Arg363Cys). GLA sequencing included the coding region, splice sites and the intronic region harbouring c.639+919G>A. She had no other systemic features of Fabry disease, including having a normal echocardiogram, so plasma lysoGb3 levels were not tested. As this lady had clear alternative causes for having renal disease, enzymatic replacement therapy was not deemed necessary in her case. The focus of her treatment remained the control of her hypertension and diabetes.

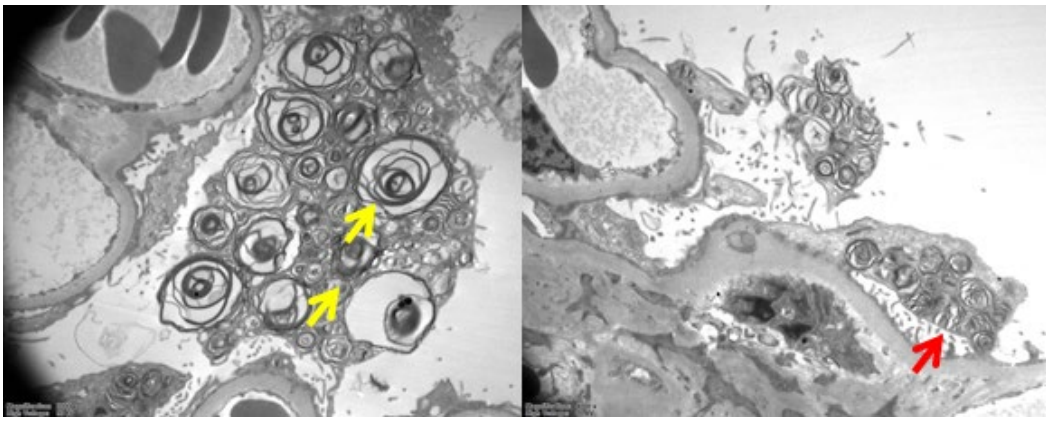

Figure 1: Two electron microscopy images, with arrows pointing to zebra bodies, in patient diagnosed with Fabry disease (Case 1).

2.2 Case 2

An 80 year-old lady was admitted to the hospital with AKI stage 3 and pulmonary oedema following the insertion of a permanent pacemaker one week previously. She had proteinuria and non-visible haematuria on urinalysis. A renal screen was negative for secondary causes, including normal ANA, ANCA, and ultrasound results. Her renal function did not improve with intravenous fluid or cessation of nephrotoxic medications, so she was transferred to the renal unit for a renal biopsy.

On light microscopy, the biopsy showed changes consistent with hypertensive nephropathy. Similar to the previous case, electron microscopy incidentally identified zebra bodies (Figure 2). Genetic testing in this case proved negative for pathological variant GLA genes. Plasma α-galactosidase A levels were 21.9nmol/hr/ml (4 – 21.9nmol/hr/ml). She was managed as hypertensive nephropathy with modification of risk factors and control of proteinuria.

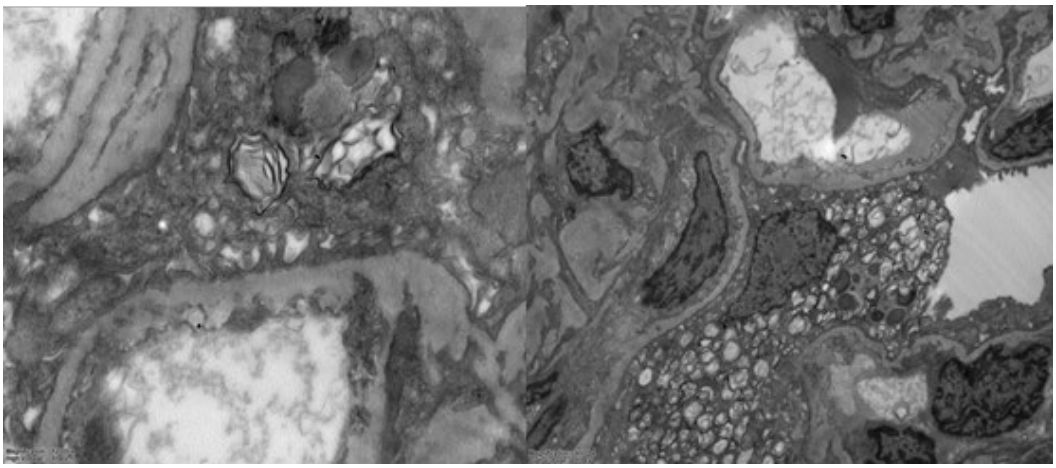

Figure 2: Two electron microscopy images, with arrows pointing to zebra bodies, in patient with suspected drug-induced phospholipidosis (Case 2).

3. Discussion and Conclusion

These two cases are similar in that electron microscopy has incidentally found zebra bodies on renal biopsy. In the first case, this led to the diagnosis of Fabry's disease; in the second genetic testing was negative. These cases raise two important questions for nephrologists: what is the significance of finding zebra bodies on renal biopsy, and can we use this finding to guide specific effective treatments?

The first patient was ultimately diagnosed with Fabry disease. This finding was unexpected, as the working diagnosis had been renal myeloma or amyloidosis. The concurrent findings of diabetic and hypertensive nephropathy on biopsy were more significant than the diagnosis of Fabry disease, so the focus of care was on risk factor management than specific enzyme replacement therapy. Specific treatment for Fabry disease has been shown to be of benefit in improving life expenctancy [3], however this appears to be of greatest benefit when patients initiate treatment much earlier in the course of their disease [4]. Ultimately this patient died of other causes soon within a year of diagnosis.

In contrast, there is no clear reason for the finding of zebra bodies in the second case. At the time, her medications included: sertraline–which she had been taking for many years; ezetimibe–which had been started a few months before presentation; and she had taken atorvastatin in the past – which she had been taking for many years but had stopped four years before diagnosis. Of these, atorvastatin and sertraline are recognised as causing phospholipidosis [2,5].

In animal models, the introduction of amiodarone and hydroxychloroquine led to increased phospholipidosis in multiple organs. Experimental Chloroquine Myopathy: Morphological and Biochemical Studies, highlighting the phenomenon [6]. In another model, this phospholipidosis did not lead to a change in a-GAL levels [7]. This shows that Fabry disease and drug-induced phospholipidosis (DIP) are distinct conditions with similar underlying processes. Clearly, the use of enzyme replacement therapy, as in Fabry disease, has no role to play in DIP.

There is very little evidence regarding the time course of DIP following the introduction of a culpable medication. Phospholipids have been identified in mouse circulation between 24 and 72 hours of intravenous medication injection, while evidence of DIP from some medications may only show after three months [8]. DIP is reversible to some extent, although the affected organ damage often persists [9]. This tells us that we do not know how long it takes for the features of phospholipidosis to develop and how long or to what extent these changes recover after stopping the medication.

In both cases described, no specific treatment was given to either patient due to the finding of renal phospholipidosis. In the case of the second patient, her renal function remained stable for several years after diagnosis. Both patients were managed by reducing their risk factors for the progression of renal disease, such as blood pressure and diabetes control. This raises the question of the importance of phospholipidosis in any case. If these patients had had their biopsies earlier into the course of their kidney disease, and at a time in their lives when they were less frail, alternative treatment options could have been considered, such as stopping relevant medications.

These two cases highlight that not enough is yet known about the process of phospholipidosis in renal disease. The correlation is recognised between medications and this finding, but as yet, the underlying causative mechanism is unclear. Equally, the importance of this is not obvious; our patients may or may not have benefited from targeted treatment following diagnosis. Our cases demonstrate the need to investigate this phenomenon further because if identified in younger patients sooner, it may suggest alternative treatments might improve the prognosis of their kidney disease.

Declarations

Ethics Approval and Consent to Participate

Non-application.

Consent for Publication

Written consent has been gained from the relatives of both patients.

Availability of Data and Materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing Interests

The authors declare that they have no competing interests.

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Non-applicable.

Authors' Contributions

James Larkworthy and Farid Ghalli both contributed to manuscript preparation. All authors read and approved the final manuscript.

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References

1. Colpart, P., & Félix, S. (2017). Fabry Nephropathy. *Archives of pathology & laboratory medicine, 141*(8), 1127–1131.
2. Bracamonte, E. R., Kowalewska, J., Starr, J., Gitomer, J., & Alpers, C. E. (2006). Iatrogenic phospholipidosis mimicking Fabry disease. *American journal of kidney diseases : the official journal of the National Kidney Foundation, 48*(5), 844–850.
3. Umer, M., & Kalra, D. K. (2023). Treatment of Fabry Disease: Established and Emerging Therapies. *Pharmaceuticals (Basel, Switzerland), 16*(2), 320.
4. Hopkin, R. J., Cabrera, G. H., Jefferies, J. L., Yang, M., Ponce, E., Brand, E., Feldt-Rasmussen, U., Germain, D. P., Guffon, N., Jovanovic, A., Kantola, I., Karaa, A., Martins, A. M., Tøndel, C., Wilcox, W. R., Yoo, H. W., Burlina, A. P., &

Mauer, M. (2023). Clinical outcomes among young patients with Fabry disease who initiated agalsidase beta treatment before 30 years of age: An analysis from the Fabry Registry. *Molecular genetics and metabolism, 138*(2), 106967.
5. Reasor, M. J., Hastings, K. L., & Ulrich, R. G. (2006). Drug-induced phospholipidosis: issues and future directions. *Expert opinion on drug safety, 5*(4), 567–583.
6. Kumamoto, T., Araki, S., Watanabe, S., Ikebe, N., & Fukuhara, N. (1989). Experimental chloroquine myopathy: morphological and biochemical studies. *European neurology, 29*(4), 202–207.
7. Tsukimura, T., Shiga, T., Saito, K., Ogawa, Y., Sakuraba, H., & Togawa, T. (2021). Does administration of hydroxychloroquine/amiodarone accelerate accumulation of globotriaosylceramide and globotriaosylsphingosine in Fabry mice?. *Molecular genetics and metabolism reports, 28*, 100773.
8. Chatman, L. A., Morton, D., Johnson, T. O., & Anway, S. D. (2009). A strategy for risk management of drug-induced phospholipidosis. *Toxicologic pathology, 37*(7), 997–1005.
9. Bernstein, P.R., Ciaccio, P., Morelli, J. (2011). Drug-Induced Phospholipidosis. In: Annual Reports in Medicinal Chemistry. Academic Press, 46, 419-430.