

CASE REPORT

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Case report: lipid inclusion in glomerular endothelial and mesangial cells in a patient after contrast medium injection

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Abstract

Background: It is well-recognized that injection of iodinated radiographic contrast media (CM) sometimes causes acute renal injury via multiple mechanisms, such as vasoconstriction, toxicity on glomerular endothelium and tubular epithelium and so forth.

Case presentation: A 51-year-old man developed acute renal injury with proteinuria after CM administration. To our surprise, in his renal biopsy sample the myelin figure like structure was observed in glomerular endothelium and mesangial cells by transmission electron microscopy. However the patient didn't have any clinic clues of Fabry disease and other lysosomal storage disorders. Moreover in vitro cultured glomerular endothelial and mesangial cells we found CM triggers lipid aggregation along with the increased CD36 and decreased ABCA1 abundance. Thus this patient was administered statin to correct the aberrant lipid trafficking, 2 months later at his next visit we found his renal function partially recovered with reduced proteinuria.

Conclusions: Besides the well-known underlying mechanisms, CM may cause renal impairment by triggering the dysregulated transportation of lipid. Furthermore statin is suggested to be a very promising medicine to decrease side effects of CM.

Keywords: Case report, Contrast media, Lipidosis, Endothelial cells, Mesangial cells, CD36, ABCA1

Background

Contrast media (CM) administration may initiate acute renal injury and the underlying mechanisms including prolonged reduction of renal blood flow, endothelial dysfunction, dysregulation of tubular transport, etc. [1]. Prophylactic intravenous hydration to avoid ischemic insult and antioxidant therapy are believed to be the major preventive strategies for contrast-induced nephropathy (CIN). In this paper, we report a CIN case morphologically presented with lipid inclusion in glomerular resident cells, especially in endothelial and mesangial cells.

Case presentation

A 51-year-old man was referred to urology for adrenal mass and potentially related secondary

hypertension. Except for five years of uncontrolled hypertension with hypokalemia he has no other history of medication and diseases including renal disease, diabetes or other systemic disorders. His basal serum creatinine (sCr) was 1.9 mg/dl with microalbuminuria, but no hematuria and cylindruria were detected at admission. Apart from the increase blood pressure there was no significant physical abnormality was identified. And his renal disorder was deemed to be associated with benign nephrosclerosis caused by uncontrolled hypertension. To make a better evaluation for the adrenal mass before surgery he was subjected to enhanced adrenal CT scan with intravenous injection of iomeprol (a nonionic, monomeric iodinated contrast medium). Ahead of CM injection preventive therapies (intravenous hydration with reduced glutathione) were given to minimize the side effects of CM. The operation went extremely well and his blood pressure was well controlled after that; however his sCr was increased to 3.3 mg/dl with 2+ dysmorphic

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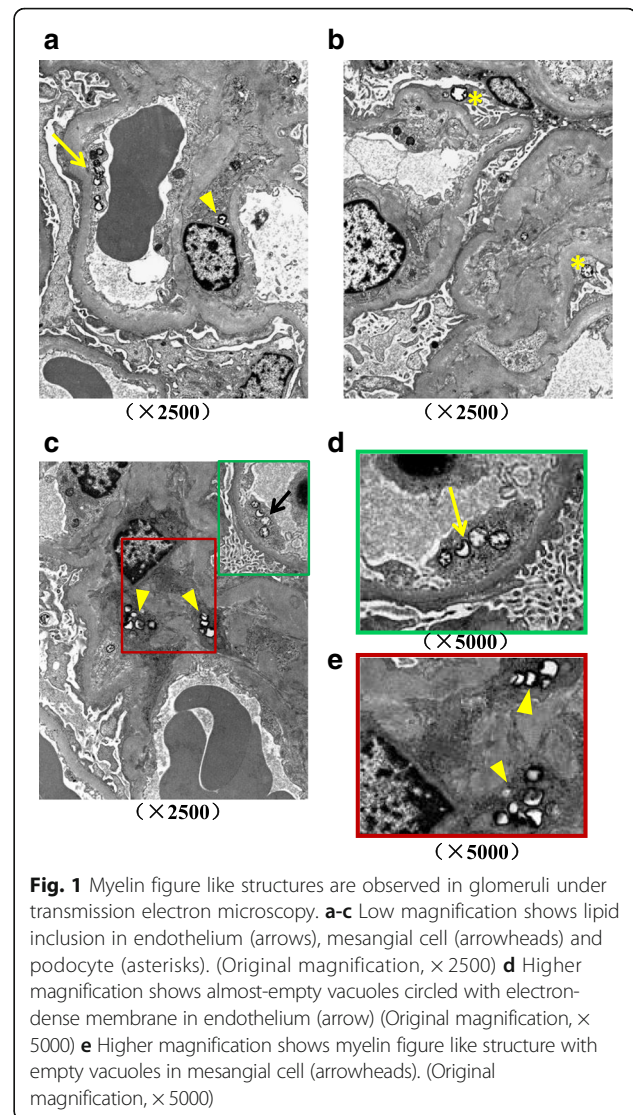


hematuria and 2+ proteinuria three days later after iomeprol injection. Therefore he remained hospitalized for the elevated sCr level; unfortunately the sCr failed to drop to his basal level despite three weeks comprehensive treatment (reduced glutathione plus prostaglandin E1 administration). And the hematuria and proteinuria still persisted.

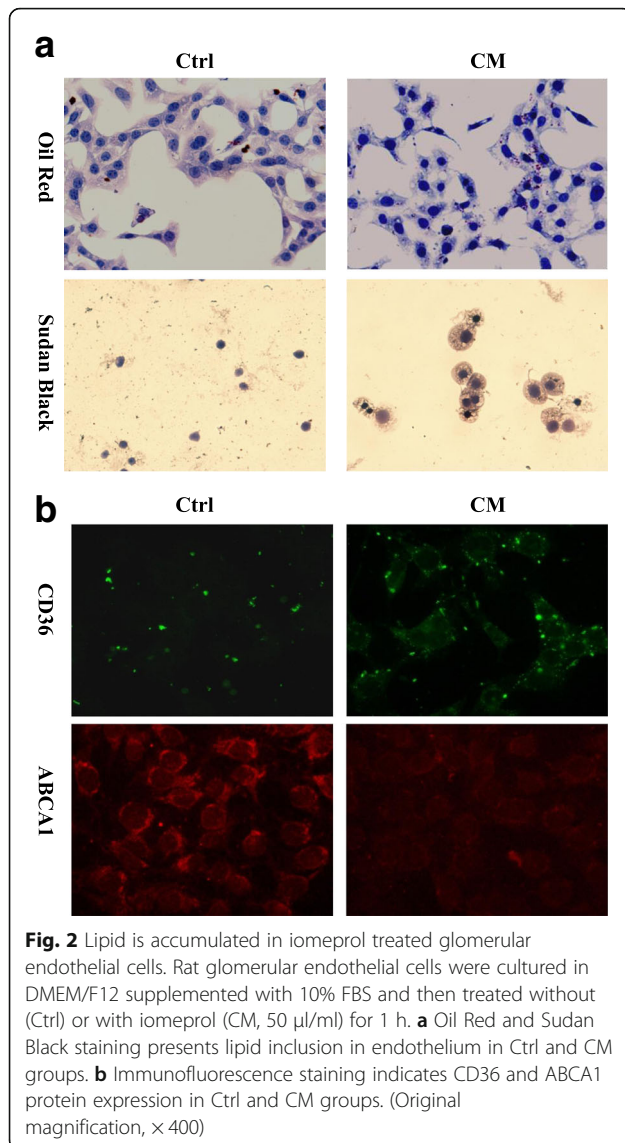
Then, he was transferred to nephrology. And he was diagnosed as acute kidney injury (AKI) superimposed on chronic kidney disease (CKD). A series of serologic and radiologic workup was ordered. Except for the elevated sCr other serologic results were unremarkable including serum potassium. Emission Computed Tomography indicated glomerular filtration rate was decreased. To get a better understanding of the nature of the renal injury the kidney biopsy was performed. On immunofluorescence microscopy no diagnostic staining of immunoglobulin and complement were detected in glomeruli, tubulointerstitium and vessels. Under light microscopy there was only mild to moderate ischemic alteration of glomeruli without proliferative lesions which is believed to be associated with the history of uncontrolled hypertension. Moreover focal mild acute tubular injury was identified presenting as the loss of brush border and isometric vacuolization of tubular epithelial cells. No coarse vacuole degeneration, the feature of hypokalemic nephrosis, was seen in tubular epithelium (data not shown). Interestingly, with the aid of transmission electron microscopy we found scattered distributed myelin figure like structure, presenting as almost-empty vacuoles circled with electron-dense membrane, in endothelium, mesangial cells and less frequently in podocyte (Fig. 1).

Combining the clinic features and pathologic findings we believed that in this case the CKD was due to moderate nephrosclerosis which could be explained by longstanding secondary hypertension. On the other hand the AKI may relate to mild acute tubular injury and scattered distributed myelin figure like structure was observed in glomerular cells.

What made us confused was the underlying etiology for the formation of myelin figure structure. As we known, zebra bodies and myelin-like figures are ordinarily seen in Fabry disease and various lysosomal storage disorders and usually infer lipid accumulation in cell bodies or subcellular organelles. However, our patient didn't have any other systemic symptoms or family history of that genetic diseases. More importantly, his renal impairment just aggravated after CM administration. Thus we were curious to study whether CM will lead to the lipidosis in glomerular endothelial and mesangial cells. To test that, we exposed the cultured glomerular endothelial and mesangial cells to the CM, iomeprol, to evaluate whether this treatment will cause the lipid accumulation as we observed in vivo (Additional file 1). In



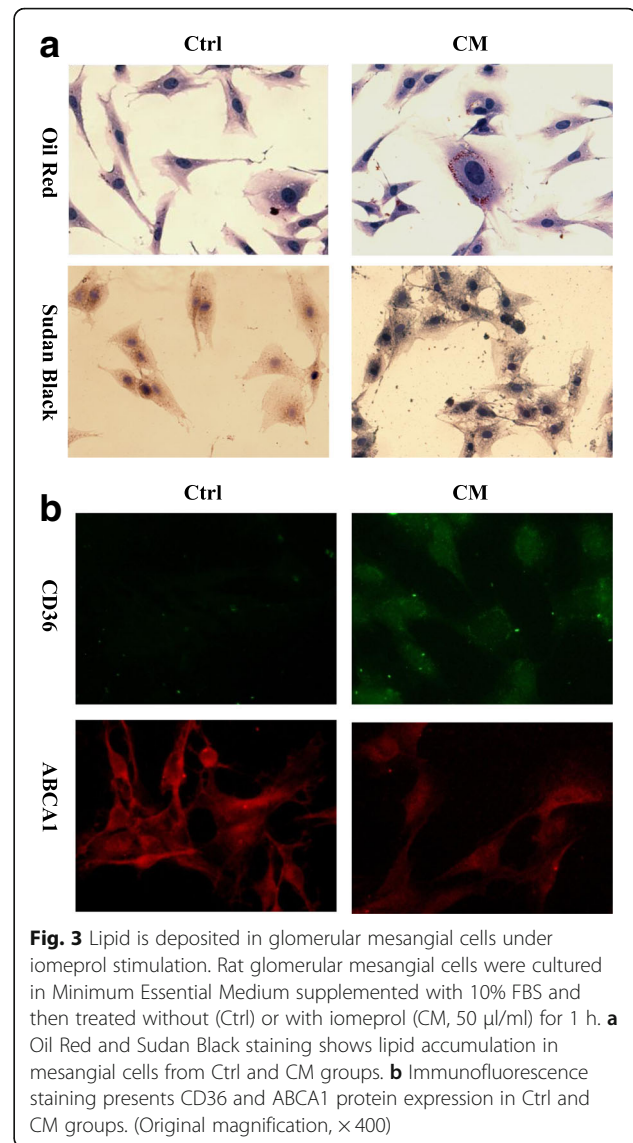
detail, cells were treated with iomeprol or cultured in regular medium for 1 h. After that they were stained with Oil Red O or Sudan Black to detect the deposition of neutral lipids and phospholipids. Interestingly, our data revealed that iomeprol exposure promotes the lipid accumulation in the cytoplasm of endothelial and mesangial cells obviously (Figs. 2a, 3a). Next we explored the underlying mechanisms of above abnormalities. It is well-established that CD36 is an essential transporter mediating lipid uptake, whereas ATP-binding cassette transporter A1 (ABCA1) accelerates the discharge of lipid from cytosol [2, 3]. Our immunofluorescence staining showed that with the treatment of iomeprol CD36 is upregulated accompanying with diminished ABCA1 intensity in both glomerular endothelial and mesangial cells (Figs. 2b, 3b) and which is the potential underlying mechanism accounting for the lipid aggregation during CM exposure.



Based on the morphologic alterations from biopsy sample and the experimental data from in vitro cultured cells, the patient was prescribed oral statins (fluvastatin, 20 mg, qn) and antioxidant (Atomolam, 0.4, tid). Two months later, his next visit, we found the hematuria was resolved, and the proteinuria decreased to 1+ with improved renal function (sCr was 2.4 mg/dl). (The whole timeline of this case is shown in Fig. 4).

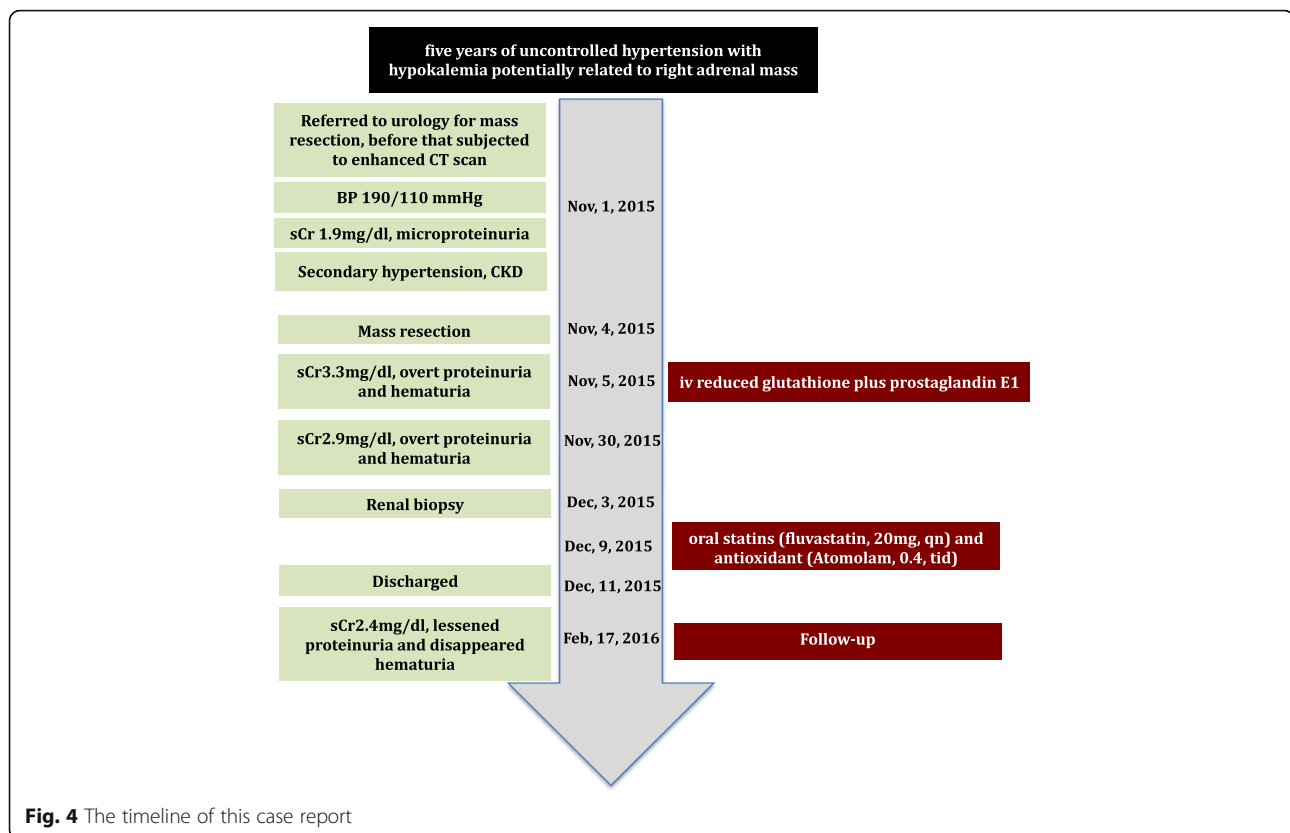
Discussion and Conclusions

Here we report the renal biopsy findings from an acute kidney injury case after CM injection. Conspicuously, scattered membrane-bound almost-empty vacuoles were observed in glomerular resident cells, primarily in endothelial and mesangial cells, under electron microscopy. However, this patient didn't have any typical clinical features of lysosomal storage



diseases or other hereditary disease frequently causing renal lipidosis. Also this patient didn't take any medicine affecting the activity of lysosomal enzymes, such as amiodarone and chloroquine, which has been reported to lead to lipid accumulation in kidney [4]. Concerning the deterioration of renal function and the presence of hematuria and proteinuria were occurred just after the CM administration, we speculated glomerular lipidosis may be related to the CM in this case.

CIN is generally described as an acute worsening of renal function with an absolute increase in sCr by ≥ 0.3 mg/dL from baseline or a relative increase in sCr levels by $\geq 50\%$ from baseline within 72 h [5]. Multiple mechanisms are involved in acute kidney injury during intravascular injection of CM. Of note, CM possesses a cytotoxic property on vascular and



glomerular endothelium, as well as tubular epithelium. A few contributing factors have been suggested for these toxicities, such as the elevated formation of reactive oxygen species and oxidative stress, reduced prostaglandins, nitric oxide and adenosine production, intracellular Ca^{2+} overload and so on [6, 7]. Besides its functional impairment, by scanning electron microscopy C. Gospos also observed the morphologic change of endothelium, such as, cell shrinkage, nuclear protrusion and formation of microvilli on the cell membrane [8]. Interestingly, here we observed lipid accumulation in glomerular resident cells, prominently in endothelial and mesangial cells after injection of CM. Furthermore, CM induces lipidosis in cultured glomerular endothelium and mesangial cell along with the increased CD36 and decreased ABCA1 expression. CD36, also named fatty acid translocase, is a plasma membrane transporter mediating long chain fatty acid uptake. While ABCA1, known as the cholesterol efflux regulatory protein, is a major regulator for the efflux of cellular cholesterol and phospholipid. Based on this, our findings suggest that CM induces aberrant CD36 and ABCA1 expression and which accounts for glomerular lipidosis.

Lipid overload triggers oxidation reaction, mitochondrial dysfunction, and other undesirable molecular processes

which eventually results in cell and tissue damage [9]. Statin therapy showed clinical benefit in terms of preventing CIN. In a meta-analysis Ukaigwe A [10] reported that patients with type 2 diabetes, chronic kidney disease, congestive heart failure who receiving > 140 ml of CM will benefit from statins therapy. Consistently, several other meta-analysis indicated that short-term, pre-procedural, potent statin (atorvastatin, rosuvastatin) therapy markedly minimized CIN risk, however the potential mechanism remains uncertain [11–13]. A few studies suggested that renoprotective effects of statin might be associated with reduction of apoptosis, oxidative stress and anti-inflammatory actions [14, 15]. Currently we provide evidence that CM induces glomerular lipid aggregation along with the aberrant CD36 and ABCA1 expression. Given the fact that statin could depress CD36 and stimulate ABCA1 expression [16, 17], early administration of statin might be an ideal measurement for CIN prevention by correcting the aberrant lipid trafficking. Although we do not get the direct evidence to prove CM attributes to myelin figure formation in vivo, our finding still advances the understanding of the mechanisms of CIN and renoprotective effects of statin. In the near future we will perform examinations to firmly confirm the link between CM and glomerular lipid accumulation.

Additional file

Additional file 1: Materials and Methods. (DOCX 13 kb)

Abbreviations

ABCA1: ATP-binding cassette transporter A1; AKI: Acute Kidney Injury; CIN: Contrast Induced Nephropathy; CKD: Chronic Kidney Disease; CM: Contrast Medium; sCr: Serum Creatinine

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Availability of data and materials

All data generated during this study are included in this published article and its supplementary information files.

Authors' contributions

HS, HZ and LY are responsible for the diagnostic and technical processes of the renal biopsy. HS, CY and QW participated in the organization and implementation of the in vitro studies. CZ contributed to patient management and contributed to manuscript. HS and CZ designed the study and edited and reviewed the manuscript. HS and CZ wrote the first and last drafts of the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Informed consent was obtained from each patient for renal biopsy and this study was in compliance with the Declaration of Helsinki and was approved by the local ethical committees. Otherwise, no additional ethical approval was required for this case report.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the editor of this journal.

Competing interests

The authors declare that they have no competing interests.

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