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Dimethyl Oxalate Exposure Induced Oxalate Nephropathy in Two Patients: An Uncommon Trigger for Acute Kidney Injury

Huang X[1,2,3], Ren X[1,2,3], Zhang R[1,2,3], Zhang C[1,2,3], Yuan H[4] and Zhou X[1,2,3]**

[1]Department of Nephrology, Shanxi Provincial People's Hospital, The Fifth Clinical Medical College of Shanxi Medical University, Fifth Hospital of Shanxi Medical University, China

[2]Department of Nephrology, The Fifth Clinical Medical College of Shanxi Medical University, Fifth Hospital of Shanxi Medical University, China

[3]Shanxi Provincial Key Laboratory of Kidney Disease, Shanxi Provincial People's Hospital, China

[4]Department of Nephrology, The First Hospital of Jilin University, Changchun, China

Abstract

Dimethyl oxalate, a prevalent petrochemical, plays a crucial role in organic synthesis application. However, intoxication from dimethyl oxalate, although rare, can potentially lead to acute kidney injury or even chronic kidney disease. The challenge lies in the insufficient knowledge its symptoms, diagnosis and treatment. This can cause dimethyl oxalate induced-oxalate nephropathy to yield severe consequence. In the present study, we detailed two cases of oxalate nephropathy induced by dimethyl oxalate exposure. Both patients having worked on repairing chemical equipment over extended hours, primarily exhibited symptoms of nausea and vomiting. Renal biopsy from the second patient demonstrated both moderate acute injury and mild chronic changes. Notably, the biopsy revealed multifocal tubular atrophy, eroded brush borders, and the presence of oxalate crystal deposits with the tubules, due to their birefringence under polarized light. Treatment for both individuals encompassed hemodialysis and a daily 30 mg dose of prednisone, resulting in improved renal function upon discharge. This investigation underscored the paramount importance of early detection and adept intervention to thwart the progression to acute kidney injury from oxalate nephropathy. Physicians must remain vigilant, recognizing that oxalate nephropathy, stemming from exposure to volatile dimethyl oxalate, is an exceedingly rare occurrence.

Keywords: Dimethyl Oxalate; Oxalate Nephropathy; Acute Kidney Injury

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Correspondence:
Hang Yuan, Department of Nephrology, The First Hospital of Jilin University, Changchun, China
Xiaoshuang Zhou, Department of Nephrology, Shanxi Provincial People's Hospital, The Fifth Clinical Medical College of Shanxi Medical University, Fifth Hospital of Shanxi Medical University, Taiyuan, China

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Introduction

Dimethyl oxalate, a commonly used petrochemical in organic synthesis, has applications in producing compounds such as ethanol, methyl glycolate, and ethylene glycol [1,2]. When exposed to higher temperatures, it readily decomposed into oxalic acid. Once into the body, this acid could bind with calcium, forming calcium oxalate crystals that deposit within the kidney [3]. Given that the kidneys are primarily responsible for excreting circulating oxalate [4], they are particularly susceptible to oxalate intoxication, leading to a condition termed oxalate nephropathy. Characterized by the deposition of oxalate crystals, this nephropathy can induce tubular injuries, interstitial fibrosis, tubular atrophy, and eventually give rise to both Acute Kidney Injury (AKI) and chronic kidney diseases [5,6]. The probable underlying mechanisms encompass oxalate-driven cytotoxicity within renal tubules and inflammation-mediated cell necrosis [7,8]. Etiologically, oxalate nephropathy can be delineated into primary and secondary forms, with the latter being more prevalent in clinical scenarios. However, dimethyl oxalate as a trigger for secondary nephropathy remains a scarcely documented phenomenon. Only a single case report existed, and it lacked a pathological examination [9]. In this study, we present two cases of previously healthy individuals who developed AKI following exposure to dimethyl oxalate, emphasizing the clinical presentations, diagnosis, management strategies, and prognosis.

Case Series

Case 1

A 32-year-old man, previously healthy, was admitted to the hospital with a 4-day history of

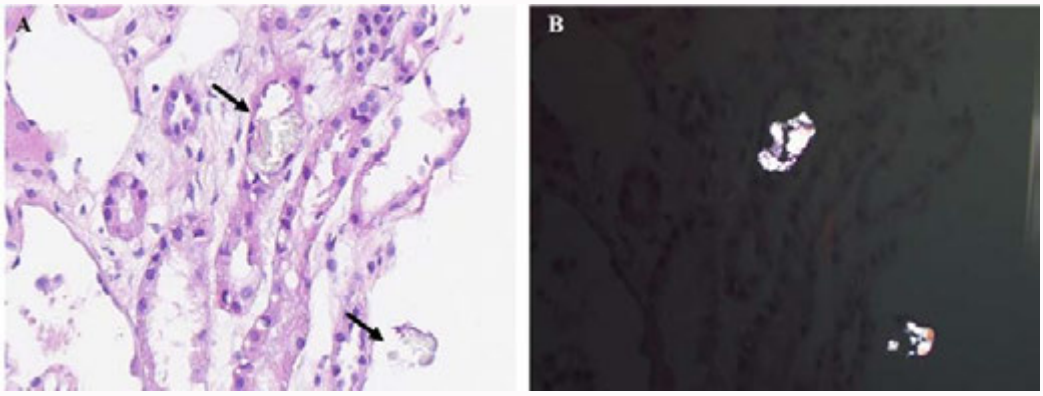

Figure 1: A =Oxalate nephropathy. The second patient kidney biopsy specimen show calcium oxalate crystals in tubules (arrowhead). The crystals are clear on light microscopy (hematoxylin and eosin stain; original magnification ×200). B =Oxalate nephropathy. The same calcium oxalate crystals present bright birefringence when viewed by the polarizing light microscope (hematoxylin and eosin stain; original magnification ×200).

nausea and vomiting, heartburn and myalgia. Before these symptoms appeared, he was routinely engaged in tasks like making repairs at a local chemical industry. At admission, his serum urea nitrogen level, creatinine level, serum total bilirubin level, serum unconjugated bilirubin level, and gamma-glutamyl transferase level were 16.23 (reference range, 2.3-7) mmol/L, 433.2 (reference range, 53-106) μmol/L, 35.42 (reference range, 2-20) μmol/L, 30.88 (reference range, 0-14) μmol/L, and 34.90 (reference range, 0-30) μmol/L, respectively. Urine analysis showed 3 to 5 White Blood Cells (WBCs) per field. Additionally, serological tests for anti-Glomerular Basement Membrane (anti-GBM) antibodies, Myeloperoxidase-Antineutrophil Cytoplasmic Antibodies (MPO-ANCA), and Proteinase 3 Antineutrophil Cytoplasmic Autoantibodies (PR3-ANCA) were all negative. Renal ultrasound showed kidneys of normal size and no indications of stones or obstructions. Prior to admission, the patient had no history of excessive dietary oxalate intake, digestive systems surgeries, or family history of primary oxalate nephropathy. Unfortunately, he declined to undergo renal biopsy. Given his past involvement with a potential dimethyl oxalate exposure, our primary suspicion for the cause of AKI shifted towards poisoning from this chemical, leading to oxalate crystal deposition in the kidneys. By the fourth day, hemodialysis was commenced, accompanied by a hemoperfusion session. Additionally, he was prescribed a daily dose of 30 mg prednisone as part of his treatment plan. As a result, his serum creatinine level steadily decreased, normalizing over a span of approximately three months.

Case 2

A 33-year-old man presented to our hospital with abdominal pain, nausea, and vomiting for 30 h. Over recent years, he had been involved in technical support roles, such as pipeline repair, at petrochemical factories. He had no history of dehydration, autoimmune disease, or surgical procedures. He denied any habits of smoking or drinking alcohol. On examination, his vital signs were stable with a pulse rate of 78 beats/min, respiratory rate of 20 breaths/min, blood pressure of 141/104 mmHg. He exhibited no signs of fever. Laboratory investigations showed the following results (reference interval provided parenthetically): Serum urea nitrogen level of 14.29 (reference range, 2.3-7) mmol/L; creatinine level of 714 (reference range, 53-106) μmol/L, alanine transaminase level of 234.90 (reference range, 0-40) IU/L, albumin level of 31.61 (reference range, 38-60) g/L, gamma-glutamyl transferase level of 425.32 (reference range, 0-30) μmol/L, C-reactive protein level of 23.62 (reference range, 0-8) mg/L, and 24-h proteinuria of 0.30 (reference range, 0-0.25) g/day. Midstream urinalysis indicated proteinuria, the presence of red blood cells, and 5 to 10 WBCs per high power field. However, the results from both autoimmune and infectious screens were unremarkable, with negative testing of anti-GBM, MPO-ANCA, and PR3-ANCA antibodies. A renal ultrasound showed no abnormalities, maintaining a typical cortico-medullary demarcation. The non-contrast chest computed tomography revealed minor fluid accumulation in both pleural cavities, with slight atelectasis in the left lung. Notably, there was no indication of neoplasm, infection, tuberculosis, or adenopathy. By the 10th day, to pinpoint the cause of AKI, a right-sided renal biopsy was conducted under ultrasound-guidance (Figure 1). The light microscopy findings included a mildly expanded mesangial matrix and thickening of focal capillary loops. The renal tubules displayed moderate acute injury signs, consistent with mild chronic damage. Polarizing light microscope revealed multifocal tubular atrophy, eroded brush borders, and the deposits of oxalate crystals within the tubules. Mild interstitial fibrosis was observed, along with focal infiltration of monocytes in the interstitium. The immunofluorescence staining results were negative. Electron microscopy included the mild fusion of focal epithelial cell foot processes. Given these findings, a diagnosis of oxalate nephropathy induced by dimethyl oxalate was confirmed. Upon hospital admission, the significantly elevated serum creatinine level prompted the initiation of hemodialysis and a prescription of prednisone at 30 mg daily. After several rounds of hemodialysis, the patient was discharged 15 days later. His renal function began to show improvement in the subsequent days, and he experienced a complete recovery six months later.

Discussion

In this study, we report two unique cases of secondary oxalate nephropathy due to dimethyl oxalate poisoning exposure in individuals without any prior relevant medical history. While there has been a prior mention of dimethyl oxalate's nephrotoxicity in the literature [9], no renal biopsy was performed to thoroughly investigate the condition in that study. In contrast, our report presents the first documented case of dimethyl oxalate-induced oxalate nephropathy, which is supported by renal biopsy findings, shedding light on the clinical manifestations, diagnosis, and management. Through this, our goal is to heighten awareness among physicians about the potential risks associated with dimethyl oxalate exposure in triggering

secondary oxalate nephropathy.

Dimethyl oxalate, widely used as a chemical raw material in the pharmaceutical industry [1], can lead to intoxication due to its toxic decomposition product. This toxicity manifests as oxalate nephropathy, characterized by the deposition of oxalate crystals within the kidneys. This condition can precipitate interstitial fibrosis, tubular atrophy, and subsequently, the onset of both AKI and chronic kidney disease [5,6]. A robust study conducted in Belgian between 2010 to 2018 retrospectively analyzed renal biopsies from 2,265 participants. Remarkably, around 1% of these participants were diagnosed with oxalate nephropathy [8]. In contrast, separate research in Manhasset between 2011 and 2018 reported oxalate deposits in 4.07% of the biopsy specimens [10]. Furthermore, a recent review estimated the prevalence of these deposits at 3.6% [11]. Although rare, it is important to consider oxalate nephropathy as a potential cause of unexplained renal insufficiency. This condition can be categorized into primary and secondary nephropathy, based on its etiology. Considering our patients, which form of oxalate nephropathy is more likely? The two patients had no related family history of primary oxalate. Given their occupation and oxalate crystals observed by renal biopsy, as they were both exposed to the volatile dimethyl oxalate for a long time before admitting to the hospital, dimethyl oxalate-induced secondary nephropathy was diagnosed.

Secondary oxalate nephropathy is a crucial factor of AKI, which is attributed to a variety of etiologies. It was demonstrated that high intake of oxalate precursors, increased enteric oxalate availability, decreased intestinal oxalate degradation, and increased colonic permeability to oxalate [6,12] are associated with secondary oxalate nephropathy. According to a series of studies [8,10,13] and a systematic review [14], researchers found that fat malabsorption resulted in reduced availability of intestinal calcium. This decrease in availability led to an increase presence of oxalate in the colon, which significantly contributed to the primary cause of secondary oxalate nephropathy. The potential mechanism involves the binding of free fatty acids to calcium as a result of malabsorption. This leads to the ionization and absorbability of oxalate [15]. Regarding patients investigated in this study, they were exposed to dimethyl oxalate, leading to increase of urine oxalate filtration through glomerulus and kidney function may be consequently impaired attributing to deposition of oxalate crystals in tubules and interstitium. The possible mechanisms include obstruction of tubules, apoptosis, and an inflammatory process by NALP3-mediated [16].

Studies found that the most common presentations were AKI and proteinuria, respectively [13,14]. The main symptoms of the two patients in this study were nausea, vomiting, and acute kidney injury. Notably, both patients in our study experienced liver dysfunction, and recovered slowly after treated with glutathione. Up to now, this is the first reported cases of dimethyl oxalate intoxication causing liver dysfunction, warranting caution for clinical physicians. We searched the relevant literatures and they were recovered slowly after treatment with glutathione. Therefore, further investigation is necessary to determine whether the liver dysfunction in the patients can be attributed to exposure to dimethyl oxalate. Once symptoms had manifested, a renal biopsy is the most important method for a definitive diagnosis. However, pathological examinations were not performed in one previous report. In our study, the kidney biopsy showed that the deposition of oxalate crystals was mainly found in tubules and/or the interstitium, and these were consistent with literature [14]. When oxalate nephropathy occurs, it is vital for physicians to use effective methods to prevent AKI and the associated pathways of renal dysfunction should be immediately blocked. Renal replacement therapy is one of the important treatments for AKI. The overall proportion of patients who needed to undergo renal replacement therapy was about 55% [13]. Hemodialysis is not only utilized as a treatment for AKI, but it also plays a critical role to keep away from oxalate crystals [17,18], while peritoneal dialysis is ineffective for permanently degrading of the oxalate [19]. Glucocorticoids were prescribed with renal tubulointerstitial injury [13], while according to Wang et al.'s research, steroid is unessential for oxalate nephropathy in a two cases of purslane-induced oxalate nephropathy [20]. The prescription of steroid remains controversial. A previously study suggested that sodium bicarbonate could be used to alkalinize the urine and reduce crystallization [21,22]. However, the role of alkalization also remains controversial, as oxalate is pH independent [14]. When AKI is caused by secondary oxalate nephropathy, supportive treatment remains the most significant therapeutic approach [23]. A review asserted that oxidative stress played a pivotal role in intervening hyperoxaluria and hyperoxaluria associated with deposition of calcium oxalate crystals that required administration of angiotensin II receptor blockers, and NADPH oxidase or NLRP3 inflammasome inhibitors [24]. The outcomes of secondary oxalate nephropathy vary remarkably. A retrospective cohort study confirmed that 81.0% of the patients experienced normal renal function after recovery [10], while most studies mainly demonstrated that approximately 50% of patients experienced kidney failure during the follow-up [8]. Our patients both developed AKI. Once they were admitted to our hospital, we promptly initiated hemodialysis, sodium bicarbonate and low-dose glucocorticoids. Notably, with the adverse effects of large doses of steroids we prescribed low-dose steroid which surprisingly promotes prognosis. Fortunately, their liver function fully recovered and renal function was eventually recovered after 6 months. Thus, when oxalate nephropathy occurs, treatment with low-dose of steroids can serve as one of the effective therapeutic options.

Conclusion

Dimethyl oxalate-induced secondary oxalate nephropathy is a devastating trigger of AKI, accompanying by poor prognosis. Furthermore, the diagnosis is can be remarkably challenging due to various factors, one of which is the potential rejection of kidney biopsy by patients. Moreover, there may be situations where the laboratory lacks the necessary resources to conduct this procedure. After diagnosis, treatments mainly include dialysis and glucocorticoids. This study highlighted the significance of recognizing dimethyl oxalate-induced secondary oxalate nephropathy in AKI patients who exposed to dimethyl oxalate. Early detected and appropriate management of the condition could lead to a positive outcome and prevent it from progressing to end-stage renal disease. Additionally, if there are no absolute contraindications, it is advisable to consider renal biopsy. Hemodialysis and low-dose glucocorticoids play prominent roles in reducing mortality rate. To our knowledge, this study described is the first cases that dimethyl oxalate-induced secondary oxalate nephropathy and the diagnosis was confirmed by kidney biopsy. Furthermore, the results highlighted importance of physicians being knowledgeable about the diagnosis and implementing effective strategies for secondary oxalate nephropathy induced by dimethyl oxalate.

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