



# Imaging findings of renal toxicity in patients on chronic lithium therapy

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## ABSTRACT

Lithium salts are the mainstay of treatment of bipolar disorder. However, the therapeutic index of lithium is narrow, and severe side effects may be seen. Nephrotoxicity is the most important side effect, which may progress to chronic renal failure. In this pictorial essay, we present ultrasonography, computed tomography, and magnetic resonance imaging findings of renal toxicity secondary to chronic lithium use. We believe that imaging could be extremely helpful for the evaluation of renal toxicity and may even detect preclinical stages of renal parenchymal injury. A combination of different imaging modalities may help clarify findings detected on one modality.

Lithium salts are the mainstay of treatment of bipolar disorder, providing highly successful symptomatic relief. Despite the highly effective utilization in treatment of this disorder, the therapeutic index of lithium is narrow, requiring close follow-up of patients to avoid lithium toxicity. Nephrotoxicity is a well-known side effect of chronic lithium use (1, 2). Acute renal failure may also be observed in the setting of acute drug toxicity, and manifests with altered mental status and other neuropsychiatric symptoms (3).

Despite several comprehensive reviews of medical renal disease associated lithium toxicity (1–4), to the best of our knowledge, little has been reported regarding the broad spectrum of renal imaging findings associated with chronic lithium use. A recently published study describes the utility of magnetic resonance imaging (MRI) in identifying the cystic changes of the kidney from lithium-induced toxicity (5). In this essay, we evaluated ultrasonography (US), computed tomography (CT) and MRI findings associated with lithium-induced nephrotoxicity.

## Pathophysiology and clinical symptoms

Renal toxicity of lithium may present in three main categories: acute toxicity, nephrogenic diabetes insipidus (NDI), and chronic renal disease that may eventually necessitate hemodialysis and ultimately lead to renal transplantation.

NDI is the most frequently encountered side effect of lithium use and is characterized by the inability of the kidneys to concentrate urine. Patients experience polyuria and polydipsia that may lead to significant volume defects (3). NDI may be anticipated in approximately 40% of patients (6). The interference of lithium with the antidiuretic hormone is thought to be the underlying pathophysiology (7). Whether lithium toxicity is reversible if detected at this point is unclear; however, it is generally believed that there is an irreversible point during the progression of the disease (7). Patients are treated with amiloride and offered support for treatment (4).

Acute lithium intoxication may be detected in patients on chronic lithium therapy or in lithium naïve individuals. The main treatment in these cases is hemodialysis (8).

Chronic renal disease may ultimately result in permanent failure of renal function (9), which is the most concerning complication of lithium use. The hallmarks of pathologic findings are tubular atrophy and interstitial fibrosis. The presence of tubular cysts measuring up to 1 to 2 mm is also commonly seen in biopsy specimens of patients with lithium-induced chronic renal failure (3, 10, 11). These cysts are detected most abundantly in zones of atrophy and interstitial fibrosis, scattered in the

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Received 16 October 2012; revision requested 22 November 2012; revision received 4 December 2012; accepted 3 January 2013.

Published online 21 February 2013  
DOI 10.5152/dir.2013.097

cortex and medulla (3). The cysts may be innumerable or scarce, and to the best of our knowledge, no predictive criterion regarding the required specific number of cysts has been reported (5). These cysts are thought to originate from the distal and collecting tubules (5).

### Imaging findings of renal toxicity

US is the most commonly used imaging modality for the evaluation of kidney disorders. It is easy to apply and free of radiation, and the need for patient cooperation is minimal. Most importantly, intravenous contrast to increase the diagnostic accuracy is not required. These features make US the most popular imaging modality in patients with abnormal kidney function. CT and MRI have also been utilized in the work-up of these patients, and several imaging findings have been described, such as cysts, hyperdense foci in CT, and complex kidney lesions.

#### Cortical echogenicity

Cortical echogenicity is a notoriously unreliable imaging finding in the discrimination of the underlying patho-

logic progress, but a very good indicator of medical renal disease and underlying renal parenchymal injury. The amount of renal echogenicity appears to correlate with the plasma creatinine level; however, this should be confirmed in large patient series (Fig 1). Interestingly, in most of our patients, the size of the kidneys was not reduced, even in patients with severely increased parenchymal echogenicity and plasma creatinine levels. Renal size may be a good diagnostic clue for differentiating lithium toxicity from other chronic parenchymal diseases that mostly result in renal atrophy. This finding was also observed on MRI in a previous study (5, 12).

US, coupled with Doppler, may be extremely helpful for the detection of other potential underlying reasons for kidney dysfunction, i.e. polycystic kidney disease, hydronephrosis, and renal vascular stenosis. In experienced hands, US is very informative for the radiologist.

#### Parenchymal kidney cysts

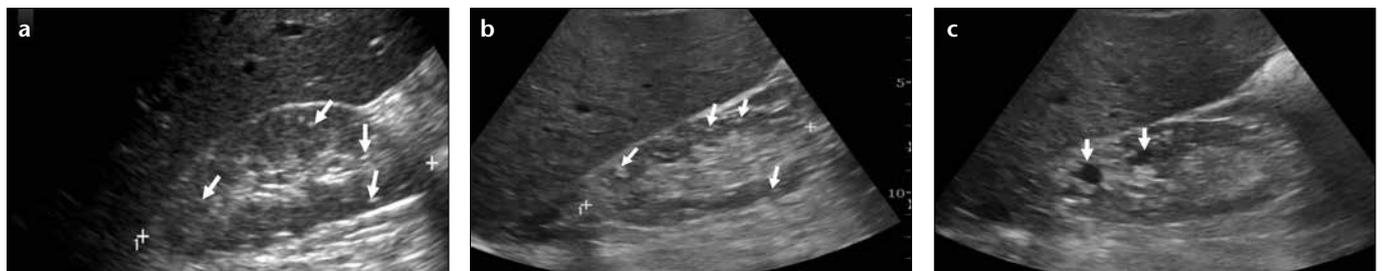
Kidney cysts are one of the well-known imaging findings of chronic lithium nephrotoxicity. They are gen-

erally very small, measuring between 1 and 2 mm, with larger cysts being the exception rather than the rule. The cysts may sometimes be hard to appreciate; however, punctate hyper-echogenic foci sometimes seen scattered throughout the parenchyma may likely represent microcysts below the resolution of US (Fig. 2). MRI is more sensitive compared to other cross-sectional imaging modalities in the evaluation of these cysts. They can easily be appreciated as hyperintense foci on T2-weighted sequences scattered in the renal parenchyma (Fig. 3). Use of contrast material may be helpful to evaluate the nature of these cysts and to rule out complex lesions.

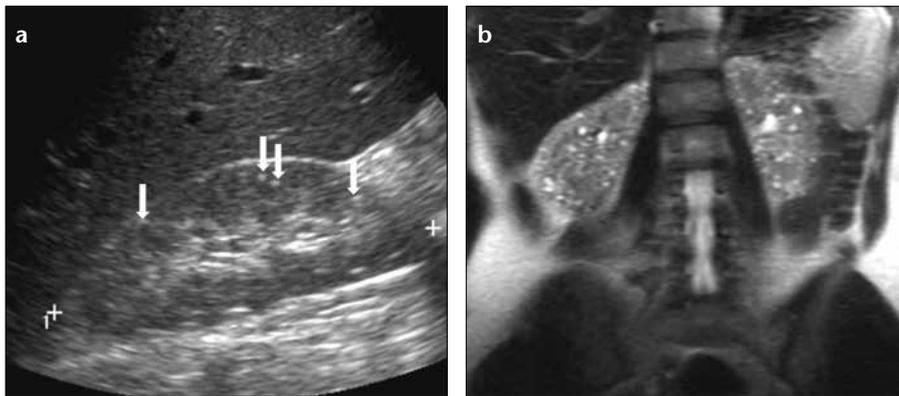
These cysts do not demonstrate any preferential location within the parenchyma and may be detected in both the cortex and medulla, which may be another diagnostic clue (Fig. 4). They are almost always very small at the time of detection compared to the cysts detected in polycystic kidney disease. They may also be detected on contrast-enhanced CT studies as punctate hypodense foci scattered throughout the kidney parenchyma. However,



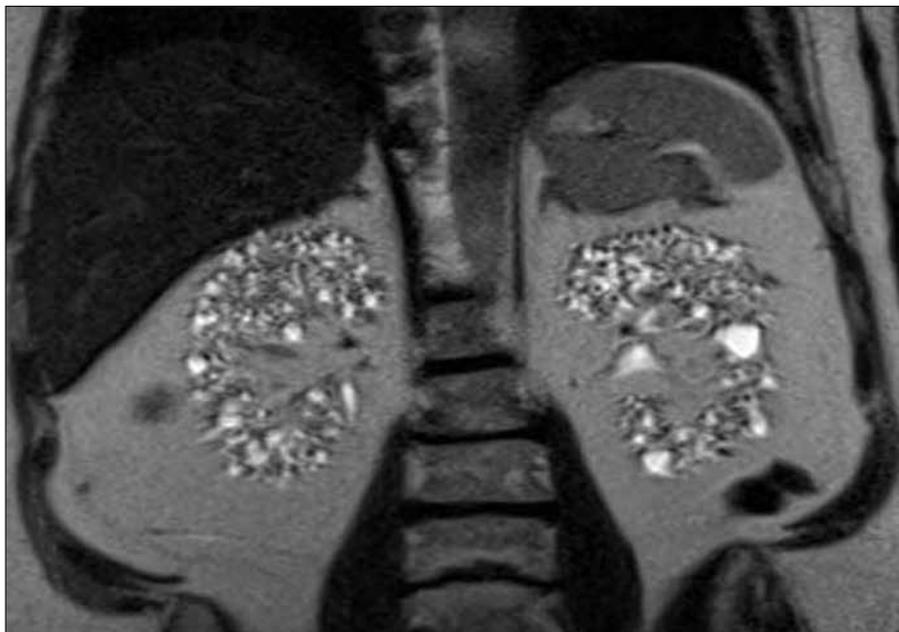
**Figure 1.** a–c. Gray-scale US images demonstrate mild (a), moderate (b), and severe (c) increase of the renal parenchymal echogenicity in three different patients on lithium therapy. Creatinine levels were 1.4 mg/dL, 2.5 mg/dL, and 3.6 mg/dL, respectively. Patient with a creatinine level of 3.6 mg/dL was on hemodialysis for two years, with a history of 15 years of lithium use. Note that the overall kidney size is not grossly affected.



**Figure 2.** a–c. US images demonstrate moderate increase in parenchymal echogenicity in two different patients (a, b, arrows). Also note mild parenchymal atrophy in the second patient (b). The creatinine values were 2.2 mg/dL and 2.9 mg/dL, respectively. Cysts may sometimes be large enough to detect with US (c, arrows). Also note the scattered punctate echogenic foci in the same patient.



**Figure 3. a, b.** A 52-year-old male on chronic lithium therapy for nine years, with a serum creatinine level of 1.9 mg/dL. US image (a) shows moderately increased kidney echogenicity with scattered echogenic punctate foci in the parenchyma (arrows), likely representing cysts under the resolution of US. Corresponding T2-weighted coronal MR image (b) demonstrates innumerable tiny cysts scattered throughout the kidney parenchyma. Patient's creatinine level was 1.5 mg/dL, and was slightly elevated at the time of the study.



**Figure 4.** Typical diffusely scattered T2 hyperintense cysts in both the cortex and the medulla on a coronal MR image in a 45-year-old patient with a history of chronic lithium use.



**Figure 5. a–c.** Coronally reformatted contrast enhanced CT (a) in a 32-year-old patient with multiple tiny hypodense foci in both the cortex and medulla of the kidneys (arrows). US image of the same patient (b) demonstrates several tiny hyperechoic foci (arrows), with no increase in parenchymal echogenicity. Cysts can be better visualized on axial fat suppressed T2-weighted MR image (c). The patient's serum creatinine level was normal (1.1 mg/dL), and he was asymptomatic. We believe that these findings represent early lithium nephrotoxicity; however, there is no histological confirmation. A biopsy was not performed given the absence of clinical findings and normal creatinine values.

they are extremely difficult to detect on noncontrast CT studies due to their small size (Fig. 5).

We believe that mild echogenicity increase with or without the presence of tiny, hardly detectable, punctate hyperechoic foci on US may be a sign of underlying renal parenchymal injury, even in the setting of normal serum creatinine levels and absence of clinical findings.

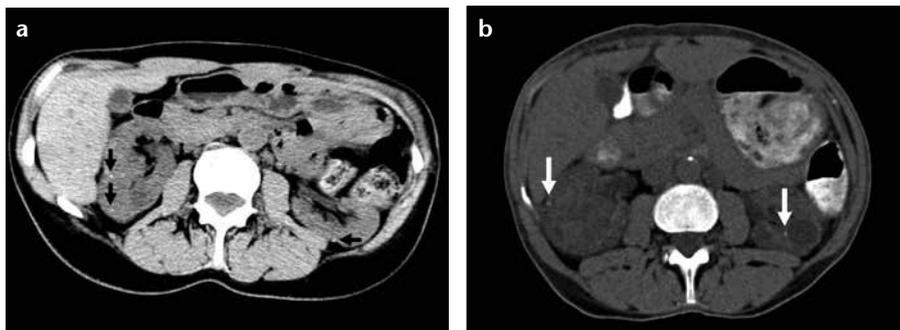
#### *Parenchymal punctate hyperdense foci*

On CT, similar to MRI, multiple cysts that are 1 to 2 mm in size are seen. However, MRI is far more effective in the demonstration of the cysts. Another interesting finding observed on the CT scans of several patients was renal parenchymal punctate hyperdense foci (Fig. 6). These may represent viscous aggregates in the renal tubules, calcification or hyperdense cysts. However, this should be further evaluated in the future on tissue samples obtained after biopsy or transplant.

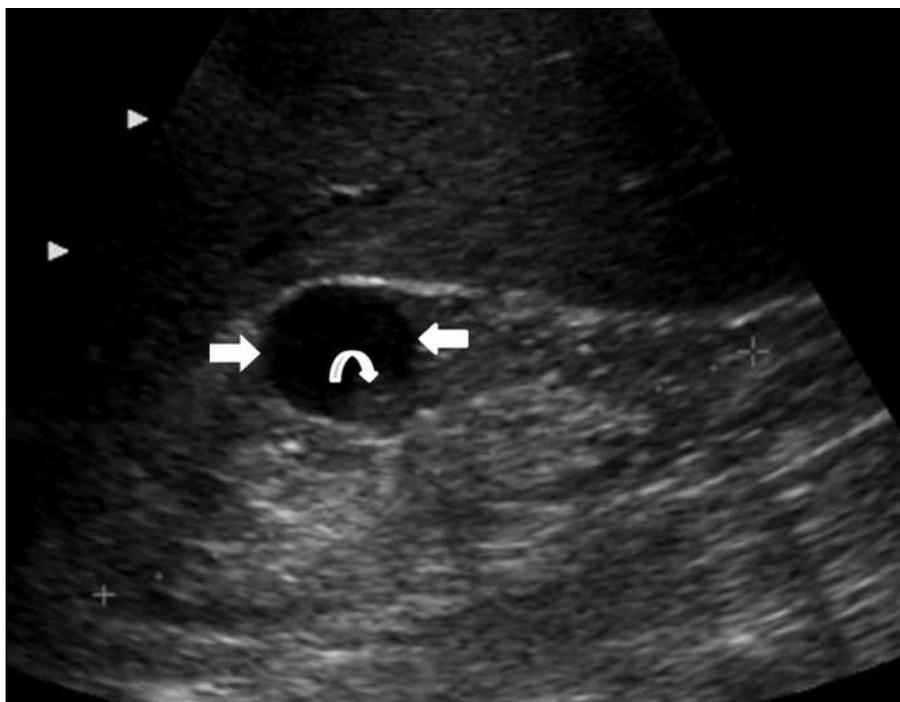
These hyperdense foci may also correspond to the echogenic foci detected on US. It is important to note, however, that we detected bright foci in the US of some patients who did not have the hyperdense foci in their subsequent noncontrast CT scans. Some patients with hyperdense foci on CT also had no corresponding echogenic foci on US, which led us to believe that these foci may be representing cysts beyond the resolution of US.

#### *Complex kidney lesions*

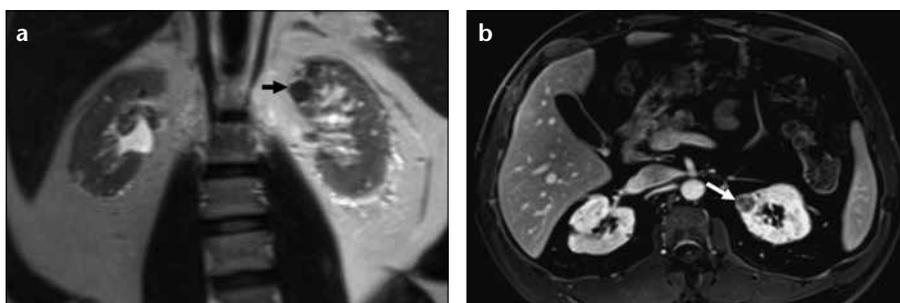
Complex kidney lesions may be observed in patients with lithium neph-



**Figure 6. a, b.** Axial noncontrast-enhanced CT scan of two different patients who are 42 (a) and 37 (b) years old with chronic renal failure due to prolonged lithium use. There are several punctate hyperdense foci in the kidneys of both patients (a, b, arrows). Also note multiple cysts of varying sizes.



**Figure 7.** A 57-year-old patient with chronic lithium toxicity. US showed a 2-cm cyst (straight arrows) in the right kidney with a solid nodule (curved arrow). Patient declined biopsy or any intervention for further treatment. The lesion was stable in appearance on the follow-up studies. Also note the diffusely increased echogenicity of the kidney (arrowheads), another common finding in lithium toxicity.



**Figure 8. a, b.** A 49-year-old patient with a history of chronic lithium use and biopsy proven renal cell carcinoma of the left kidney. Coronal T2-weighted MR image (a) shows a hypointense lesion in the upper pole of left kidney (a, arrow). Spoiled gradient echo postcontrast axial T1-weighted image (b) of the same lesion (arrow) shows enhancement consistent with a solid lesion. This lesion was treated with radiofrequency ablation. No evidence of local recurrence or metastasis was seen at the two-year follow-up.

rotoxicity. The increased incidence of renal neoplasms in patients with chronic lithium therapy is a subject of debate (Fig. 7); however, it is reasonable to be more attentive for a possible neoplastic process and not to be dismissive and overwhelmed given overabundance of findings. Fig. 8 shows a patient who developed renal cell carcinoma after long-term local tumor control subsequent to radiofrequency ablation.

## Conclusion

All cross-sectional imaging modalities appear to be useful in the detection of the effects of the chronic lithium nephrotoxicity. Although MRI seems to be the best modality for the detection of small cysts, US and CT also have roles in the assessment of these cysts. An effort should be made to detect echogenic foci in the kidneys on US that probably represent tiny cysts beyond the resolution of US. The severity of renal parenchymal echogenicity also seems to correlate well with the plasma creatinine values and degree of parenchymal injury. Even in patients with normal creatinine values, increased echogenicity of the kidney parenchyma, though mild and potentially subjective, may be noted, which may represent a subclinical level of renal injury. Although there is no conclusion regarding any cause and effect relationship between chronic lithium nephrotoxicity and kidney malignancy, CT or MRI must be liberally used for further evaluation of the complex lesions detected on US.

We believe that several indicative imaging findings are present for the renal lithium toxicity, and that the role of the radiologist is important in the detection of these early findings, surveillance, and follow-up of the patients. Cross-sectional imaging with US, CT, and MRI seems to be useful, either alone or complementary with each other, in early diagnosis or possibly even in prevention. Studies with larger patient series are needed to investigate the prevalence, evolution of the imaging findings, and time it takes to get renal failure in this patient group, all of which may have a significant impact on planning treatment.

### Conflict of interest disclosure

The authors declared no conflicts of interest.

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