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Oncology

Lithium-induced Nephrotoxicity: A Case Report of Renal Cystic Disease Presenting as a Mass Lesion☆

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ABSTRACT

Lithium is an effective therapeutic agent used in the management of bipolar disorder. However, lithium is also associated with several side effects, including renal toxicity. We present a case of a symptomatic cystic mass lesion in the kidney of a patient who had a history of lithium therapy for the management of bipolar disorder.

Introduction

Lithium is an effective therapeutic agent used in the management of bipolar disorder. However, lithium is also associated with several side effects, including renal toxicity. Chronic tubulointerstitial nephropathy is the predominant form of chronic renal disease secondary to lithium. In addition, the development of renal cysts is highly characteristic of lithium toxicity, occurring in up to 40% of cases.[1]

We present a case of a symptomatic multicystic mass lesion in the kidney of a patient who had a history of lithium therapy for the management of bipolar disorder.

Case presentation

A 45-year-old gentleman presented to the emergency department with frank hematuria. Imaging was performed, which revealed a left enhancing multicystic renal mass (Fig. 1). Renal function was normal, and there was no significant family history. The patient had a history of long-term lithium treatment for bipolar affective disorder.

The patient underwent a left nephrectomy. Macroscopic examination revealed a 35-mm cystic mass in the lower pole of the kidney (Fig. 2). There were no solid areas identified, and the background kidney was unremarkable.

Histologic examination showed the lesion to be composed of multiple variably sized cysts lined by bland cuboidal epithelium, with less prominently dilated cystic spaces present more diffusely (Fig. 3). There was no evidence of malignancy. The background renal parenchyma showed approximately 15% glomerulosclerosis, mild interstitial fibrosis, chronic interstitial nephritis, and arterial nephrosclerosis.

Immunohistochemistry was performed which showed CAM5.2 positivity within the cystically dilated area as well as within the cystic tubules, suggesting that these regions are of distal nephron origin.

Discussion

Lithium is a therapeutic agent used in the prophylaxis and treatment of mania, hypomania, and depression in bipolar disorder.[1,2] The efficacy of lithium for treating mania was discovered in 1949, making it the first medication specifically developed for the treatment of bipolar disorder.[1] Lithium remains in widespread use in the management of bipolar disorder today. Lithium has a narrow therapeutic to toxic ratio and therefore requires monitoring of serum lithium concentrations.[3] Although lithium is an important and highly effective agent, it is associated with many acute and long-term adverse effects.[3] A frequent side effect of lithium is renal toxicity.

Lithium is excreted almost entirely by the kidneys and is freely filtered by the glomeruli. A small fraction is reabsorbed in distal parts of the nephron through the epithelial sodium channel.[3] Lithium, unlike sodium, is not exported from the cell and accumulates intracellularly, which results in dysregulation of the vasopressin-regulated water channel, aquaporin 2 (AQP2), which is

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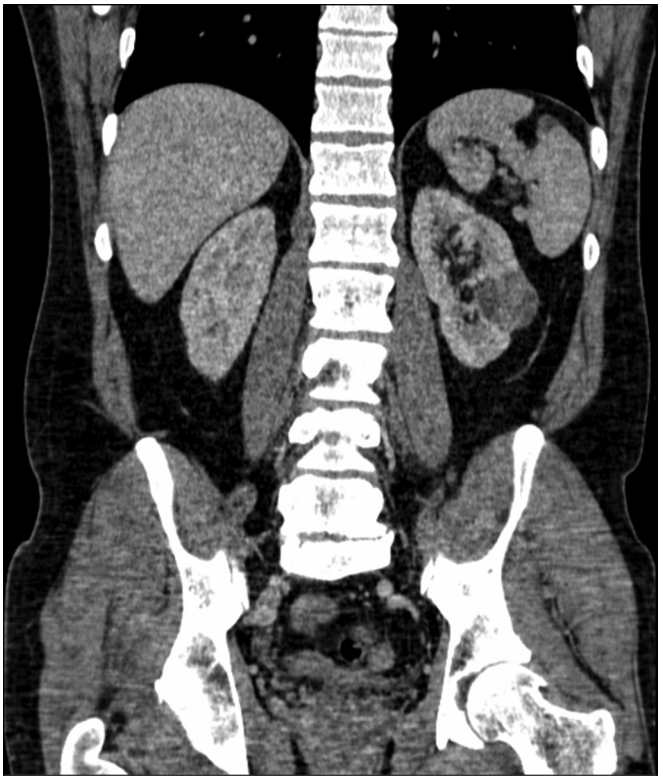

Figure 1. Computed tomography scan showing enhancing multicystic renal mass.

expressed on the apical plasma membrane of the principal cells of the collecting duct.[3]

Nephrogenic diabetes insipidus is the most common renal side effect of lithium therapy. Nephrogenic diabetes insipidus occurs in up to 20%-40% of patients on lithium therapy.[1] Long-term lithium ingestion can lead to resistance to antidiuretic hormone, resulting in polyuria and polydipsia, which can result in significant volume depletion. Lithium enters and accumulates in the principal cells of the collecting duct, where it promotes the inhibition of glycogen synthase kinase 3, an enzyme that controls the transport of water and sodium via AQP2 and epithelial sodium channel, respectively.[1,3] This results in the cell becoming at least partially insensitive to the

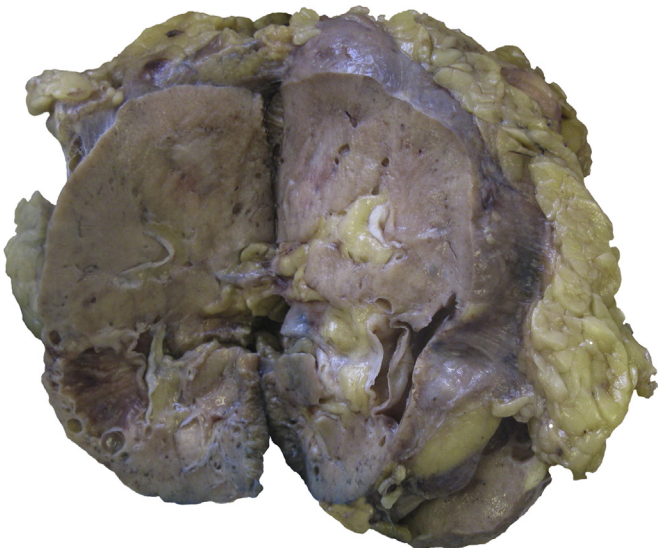

Figure 2. Nephrectomy specimen showing cystic lesion.

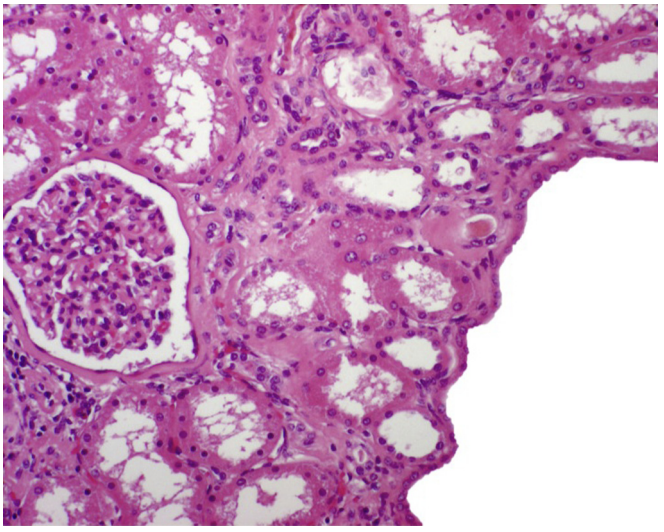

Figure 3. Cystic lesion lined by bland cuboidal epithelium.

actions of vasopressin and aldosterone, thereby interfering with the ability of the cell to increase water permeability. Furthermore, by downregulating AQP2, this leads to an additional decrease in concentrating ability.[2]

Lithium therapy may also result in glomerular toxicity and focal segmental glomerulosclerosis has been reported in up to 50% of renal biopsies from patients on lithium therapy.[2]

The predominant form of chronic renal disease associated with lithium therapy is chronic tubulointerstitial nephropathy (CTIN). The histologic findings in patients with lithium-induced CTIN include tubular atrophy and interstitial fibrosis, which are typically out of proportion to the degree of glomerulosclerosis and vascular disease.[2]

In addition to the relatively nonspecific findings of CTIN, the presence of tubular cysts is highly characteristic of lithium toxicity, occurring in up to 62.5% of cases, with a lesser degree of tubular dilatation occurring in an additional 33.3% of biopsies.[1,2] In a study by Markowitz et al,[2] immunohistochemical and lectin staining revealed tubular cysts of predominantly distal tubular and collecting duct origin. This finding is not unexpected based on the predominantly distal nephron toxicity of lithium.

In our case report, histologic examination of the kidney showed the lesion to be composed of multiple, variably sized cysts, lined by bland cuboidal epithelium. Immunohistochemistry studies revealed CAM5.2 positivity within the cystically dilated area as well as within the cystic tubules, suggesting that these regions are of distal nephron origin. This is in keeping with the previous studies, which have demonstrated the tubular cysts to be of distal and collecting tubular origin.[2]

In most cases, lithium-induced renal cysts appear as multiple bilateral microcysts (measuring from 1 to 2 mm) on magnetic resonance imaging.[4] Imaging in our case showed a multicystic enhancing renal mass, the differential diagnosis for which included renal cell carcinoma. A biopsy was not performed, and the patient underwent a left nephrectomy. Histology showed a complicated cystic lesion with no evidence of malignancy.

Recently, research has suggested that prolonged lithium therapy is not only associated with cyst formation but can also lead to the formation of adenomas and carcinomas.[5] In a study by Rookmaaker et al, they reported 6 cases of lithium-associated tumors, all of which were of collecting duct origin, similar to the origin of the benign cystic lesions.[5] This highlights the importance of adequate sampling of renal lesions in a patient with a history of lithium therapy to rule out the presence of a neoplastic lesion.

Conclusion

Long-term lithium therapy is associated with renal toxicity. The present case report highlights the risk of development of complicated renal cysts due to lithium therapy. Lithium-induced renal cysts can present as symptomatic mass lesions on imaging, the differential diagnosis for which includes renal cell carcinoma. It is important to consider lithium nephrotoxicity in histologic examination of renal lesions in a patient with a history of bipolar disorder and lithium therapy.

Consent

Informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of interest

All the authors declare that there are no conflicts of interests regarding the publication of this article.

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