

Lithium Induced Lamotrigine Toxicity, A Case Report

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Background

- ❖ Nephrotic syndrome is an uncommon form of kidney disease associated with lithium therapy.
 - ❖ Hypoalbuminemia, a sequela of nephrotic syndrome is known to affect bioavailability of protein bound pharmacologic agents.
 - ❖ This case demonstrates the effect of lithium induced nephropathy on serum lamotrigine levels.
 - ❖ Nephrotic syndrome secondary to lithium use is uncommon. Proteinuria generally begins within 1.5-10 months after the onset of lithium therapy with minimal change disease completely or partially resolving in most patients in 1-4 weeks after lithium discontinuation.
 - ❖ Lamotrigine is an anti-epileptic drug absorbed orally with high bioavailability. The drug is approximately 55% bound to plasma proteins. Although lamotrigine's role in binding specifically to albumin is not highly reported in the literature, serum protein contains approximately 55% of albumin.
 - ❖ Factors affecting lamotrigine clearance are age, pregnancy, hormone replacement therapy, and hormonal contraceptives.
- Lamotrigine Toxicity

 - Rash (10%)
 - SJS (.001%)
 - Nausea/Emesis
 - Dizziness
 - Somnolence
 - Myoclonus
 - Tremor
 - Diplopia
 - Dress/multiorgan failure
 - Aseptic Meningitis
 - Hypogammaglobulinemia
 - Cardiac conduction disorder

Case

21-year-old African American male with a past medical history of epilepsy on lamotrigine and Autism Spectrum Disorder on lithium for mood stabilization presented with lethargy, two episodes of non bloody, non bilious emesis, unsteady gait, and bilateral lower extremity edema. The patient did not have a rash.

Several months prior to admission he presented to the outpatient clinic with unsteady gait and was found to have a supra-therapeutic lamotrigine level on a dose of 150mg PO BID. The dose was decreased to 100mg QDay and 150 mg QHS, and the levels returned to normal range.

On admission, initial workup was significant for a serum total protein of 5.7g/dL (Range: 6.0-8.2), serum albumin 1.3g/dL (Range: 3.5-5.0), lithium of 0.78mmol/L and lamotrigine level of 17mcg/mL.

Complete blood count, urine drug screen, and computed tomography of the brain without contrast were unremarkable. A urinalysis revealed protein >300 (Range: Negative) and urine chemistry significant for an elevated microalbumin/cr ratio of 5081ug/mg (Range: 0-25 ug/mg).

Workup for nephrotic syndrome was significant for hyperlipidemia and negative for other causes of nephrotic syndrome, including HIV, ANA, Hep B, Hep C, C3, C4, and Anti-PLA2R antibodies.

There was suspicion for lithium induced nephrotic syndrome and renal biopsy was performed. Light microscopy with PAS, Jones, and H&E stains showed normal glomerular cellularity, mesangium, and capillary walls. Diagnostic electron micrographs showed oversimplification of epithelial foot processes, but normal glomerular basement membrane, consistent with minimal change disease. Lithium was discontinued and lamotrigine was decreased to 100mg twice daily. Patient's gait, N/V, and lethargy eventually improved and was discharged on an alternate mood stabilizer for behavioral modification.

Implications

- ❖ There are no known direct interactions between lithium and lamotrigine
- ❖ To our knowledge, this is the first case of lithium induced nephrotic syndrome complicated by hypoalbuminemia, resulting in lamotrigine toxicity
- ❖ In hypoalbuminemic patients, consider testing free lamotrigine levels, and alternative AEDs/mood stabilizers that are not as highly protein bound
- ❖ In addition, consider routine urinalysis for patients on lithium

Results

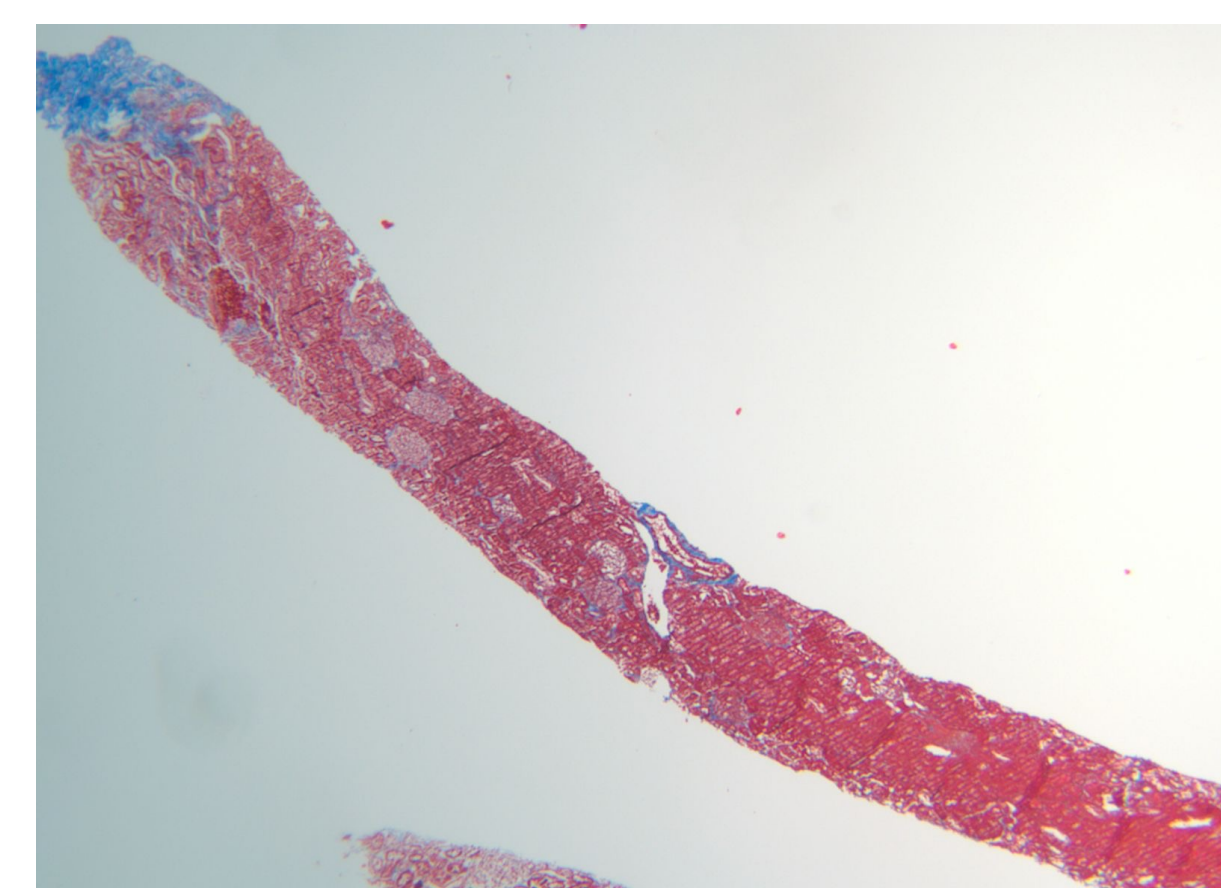


Figure 1. Adequate kidney biopsy sample

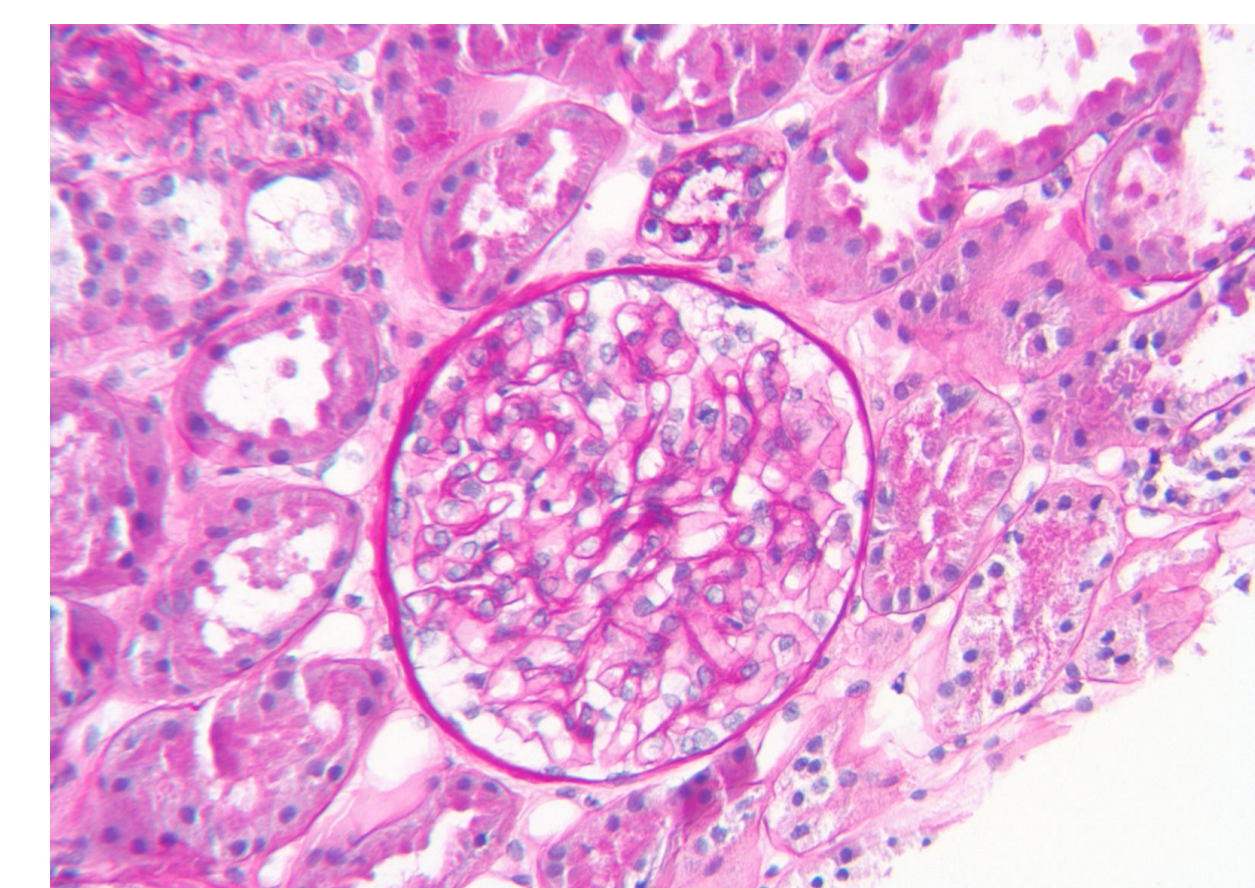


Figure 3. PAS stain

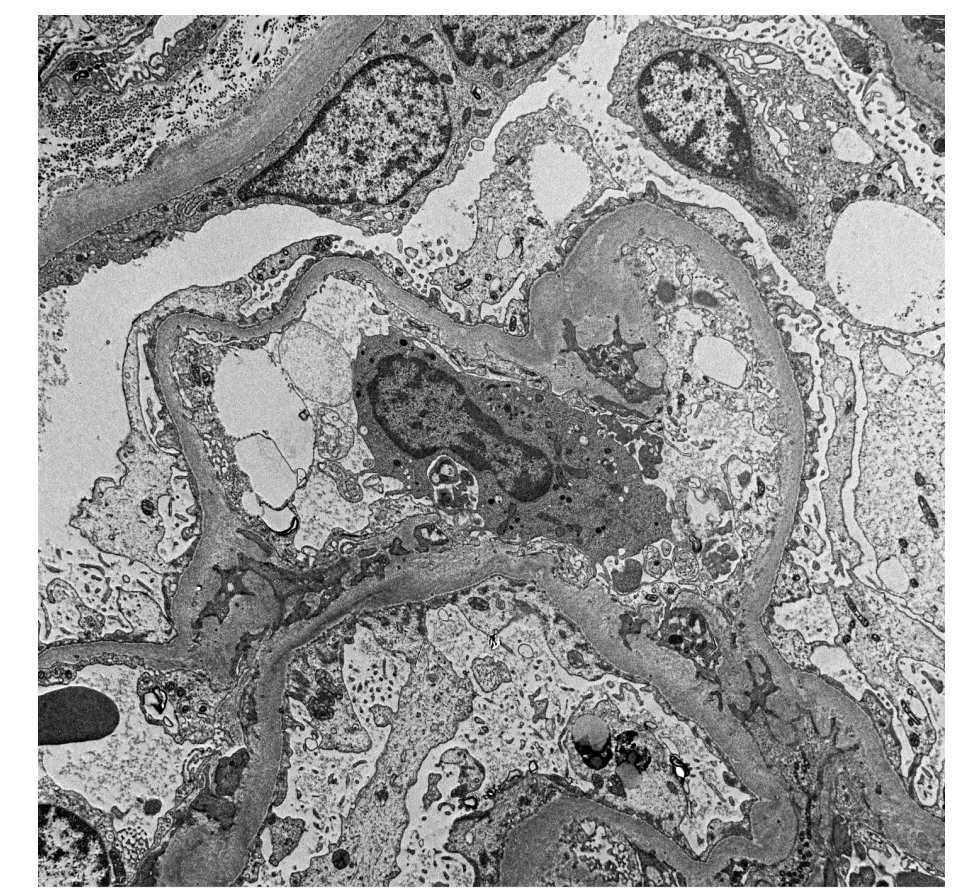


Figure 5. Diagnostic Electron Micrograph

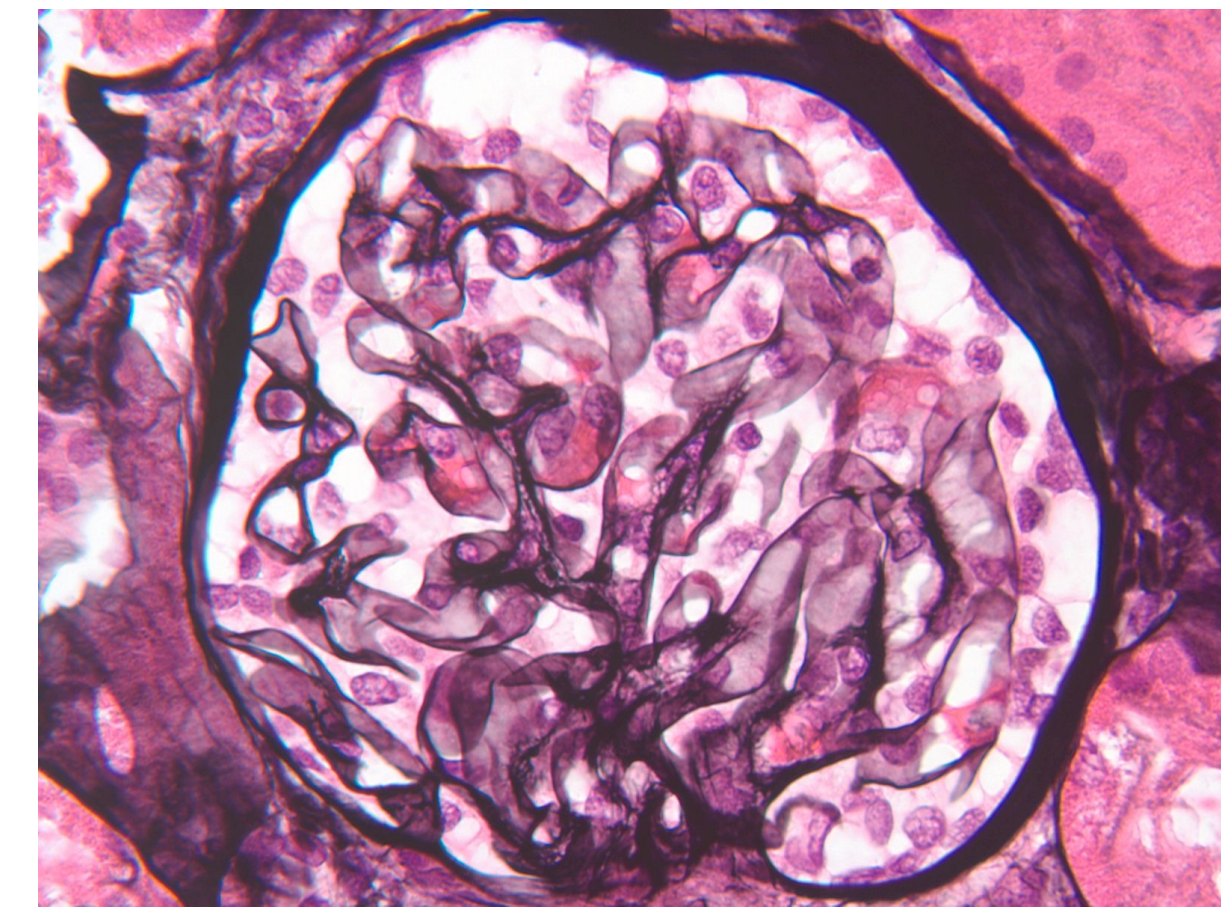


Figure 2. Jones Stain

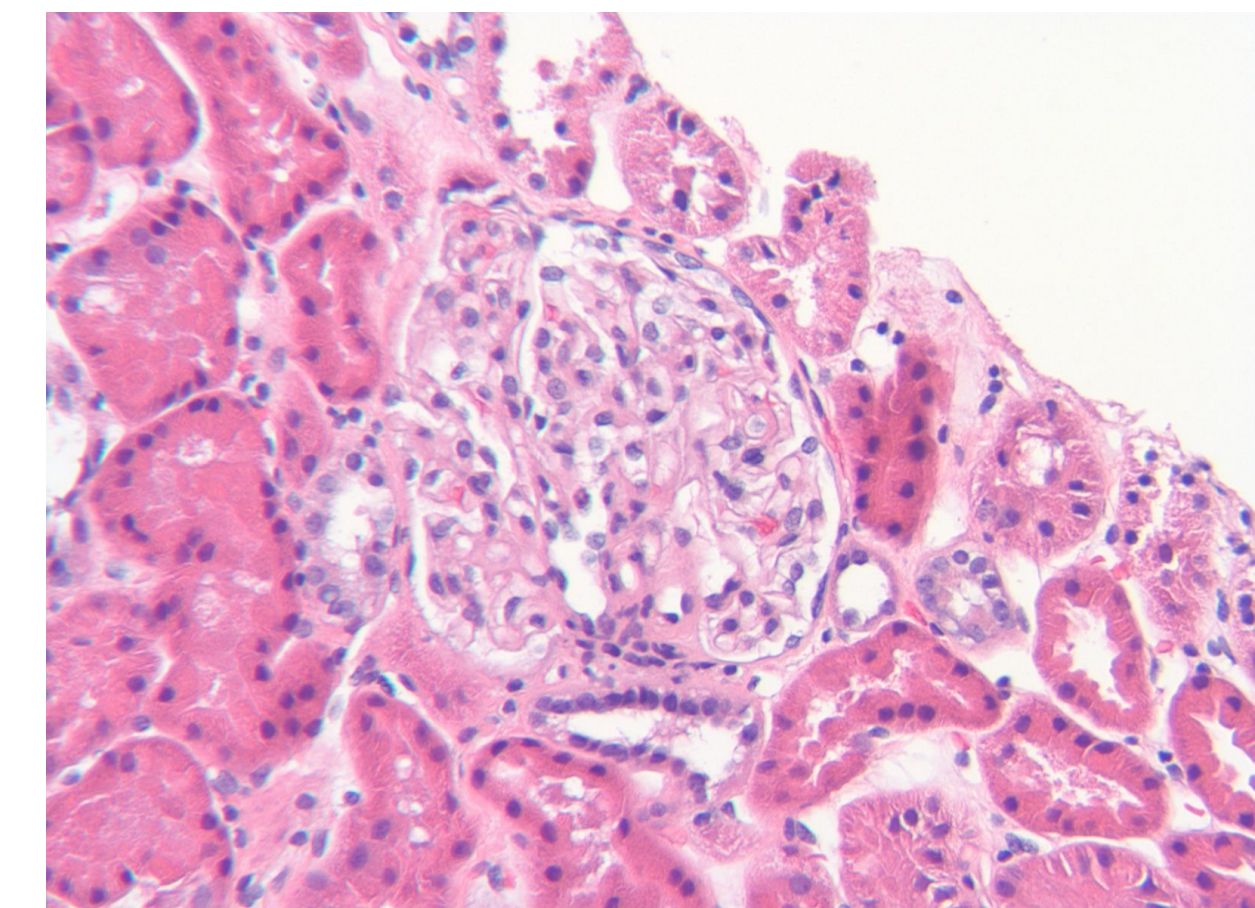


Figure 4. H&E stain

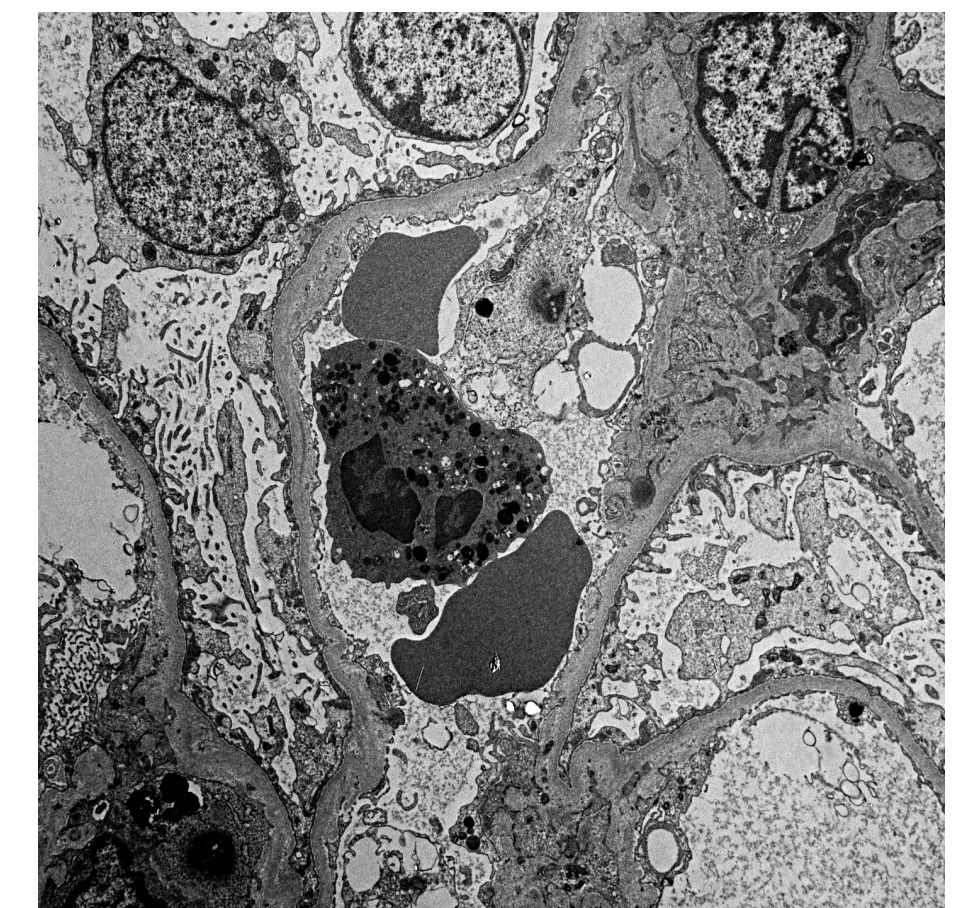


Figure 6. Diagnostic Electron Micrograph

Discussion

We demonstrate that although lithium-induced nephrotic syndrome is rare, it must be considered in cases with patients taking lamotrigine, as protein bound anti-epileptic drugs (AEDs) may show inconsistent serum free levels even at a steady dose. Bioavailability of highly protein bound AEDs such as phenytoin have been shown to be affected by hypoalbuminemia (Montgomery, 2019), but no data suggests this for lamotrigine, although the plasma protein binding of lamotrigine is estimated to be 56% (Rambeck, 1993). Therefore, a significant reduction in plasma protein from nephrotic syndrome can lead to elevated and possibly toxic lamotrigine levels.

Urinalysis

Measured	Baseline	Admission
Specific Gravity	1.012	1.008
PH	7.0	7.5
Protein	Negative	>300

References

- Rambeck, B., Lamotrigine Clinical Pharmacokinetics. Clin. Pharmacokinetics: 25, 433-443 (1993).
- Montgomery, M.C., Predicting Unbound Phenytoin Concentrations: Effects of Albumin Concentration and Kidney Dysfunction. Pharmacotherapy, 39: 756-766 (2019)