Capmatinib-Induced Pseudo–Acute Kidney Injury: A Case Report
Arjunmohan Mohan and Sandra M. Herrmann

We present a case of pseudo–acute kidney injury (AKI) following capmatinib therapy in an 84-year-old man with combined non–small cell (adenocarcinoma) and small cell lung cancer with MET exon 14–skipping mutation. His past medical history was significant for chronic kidney disease stage 3 with a baseline serum creatinine (Scr) of 1.6 mg/dL rising to 2.44 mg/dL (estimated glomerular filtration rate [eGFR] 24 mL/min/1.73 m²) while on capmatinib. Scr improved to 1.84 mg/dL with the cessation of capmatinib but rose again to 2.22 mg/dL upon resumption of therapy. Further investigation with cystatin C and renal iothalamate clearance showed that despite fluctuation in Scr levels, there was not much variation in GFR calculated using these methods. Urinalysis and urinary protein-creatinine ratio were unremarkable. Treatment with capmatinib was continued at reduced dose and a third instance of rise in Scr was observed, followed by a spontaneous return to baseline. Thus, MET inhibitor therapy can result in an asymptomatic rise in Scr, and it must be distinguished from AKI with more accurate non–creatinine-based methods to evaluate GFR. This could spare such patients from invasive diagnostic tests, such as a kidney biopsy, and premature cessation of prognostically important cancer therapies.

Introduction
Non–small cell lung cancer (NSCLC) accounts for about 80%–85% of all lung cancer cases. A recently studied oncogenic driver in NSCLC is MET, a tyrosine kinase receptor. Capmatinib is a highly selective, potent, small molecule type Ib MET inhibitor with proven antitumor activity. The US Food and Drug Administration (FDA) granted accelerated approval for its use in metastatic NSCLC with MET exon 14–skipping mutations on May 6, 2020.

Targeted therapies have proven to be effective because of their specificity in targeting of cancer cells while sparing the other cells of their toxic effects. Nephrotoxicity is a significant adverse effect, as it limits the efficacy of treatment. These drugs can affect any part of the nephron and result in hypertension, electrolyte disturbances, and acute kidney injury (AKI).

Delaying the recognition of drug-induced AKI may affect overall patient outcomes. Therefore, prompt diagnosis is critical to decide whether to withhold therapy momentarily versus altogether discontinuing it. Herein, we present a case of pseudo-AKI secondary to capmatinib administration.

Case Report
An 84-year-old man was diagnosed with combined non–small cell (adenocarcinoma) and small cell lung cancer with MET exon 14–skipping mutation, with intracranial metastasis. He underwent gamma knife resection of the metastatic brain lesions followed by 4 cycles of carboplatin-etoposide chemotherapy, initially with 60%–80% of full dose, with subsequent dose reductions in each cycle considering his age and pre-existing chronic kidney disease (CKD) presumed secondary to long-standing hypertensive kidney disease.

Eight months after the last cycle of chemotherapy, the patient developed locally progressive and recurrent metastatic disease and he was started on capmatinib 400 mg twice daily. His past medical history was remarkable for tobacco use, gout, hyperlipidemia, paroxysmal atrial fibrillation, hypertension, and CKD stage 3, with serum creatinine concentration (Scr) ranging between 1.3 and 1.6 mg/dL. The corresponding estimated glomerular filtration rate (eGFR) before treatment was 39 mL/min/1.73 m² (calculated by the CKD Epidemiology Collaboration [CKD-EPI] creatinine equation). He was on allopurinol, atorvastatin, spironolactone, levetiracetam, losartan, and metoprolol at the time of the inception of capmatinib therapy.

Within 1 week of receiving capmatinib, his Scr increased to 2.44 mg/dL with a corresponding drop in eGFR to 24 mL/min/1.73 m². Capmatinib was withheld for 3 days, and Scr improved to 1.84 mg/dL. The medication was restarted, and 2 weeks after resuming, Scr was elevated again (to 2.22 mg/dL, corresponding to eGFR of 26 mL/min/1.73 m²). He was referred to the Division of Nephrology and Hypertension and underwent a comprehensive evaluation. He had no complaints of nausea, vomiting, dizziness, or any pain. He was normotensive and clinically euvolemic as per physical examination. Imaging revealed no evidence of obstructive uropathy or any other cause of AKI. Capmatinib was withheld for 5 days and Scr declined to 1.62 mg/dL, which was within his baseline range.

Furthermore, urinalysis was bland with no active sediments and a normal urinary protein-creatinine ratio of 0.13 mg/mg. As the deterioration in eGFR correlated with the introduction of capmatinib and resolved with the removal of the drug, the question arose if this was a case of AKI or pseudo-AKI related to MET inhibitors.
investigation with cystatin C clearance and renal iothalamate clearance showed that despite fluctuation in Scr, there was not much variation in GFR calculated using these methods (Fig 1). His urinalysis continued to be unremarkable throughout. The patient experienced no other adverse events and his blood pressure readings did not vary meaningfully from his pretreatment values at any point.

After we ruled out an AKI, capmatinib was restarted at a reduced dose of 200 mg twice a day. Scr increased to 2.2 mg/dL before it leveled out eventually. Seven weeks into follow-up, his Scr was 1.52 mg/dL.

**Discussion**

We report a case of pseudo-AKI in the setting of an advanced metastatic NSCLC positive for MET exon 14–skipping mutation treated with capmatinib. MET exon 14 alterations occur at a prevalence of around 3% in adenocarcinomas and about 2% in other lung neoplasms. Patients with these mutations face a poor prognosis, making these mutations attractive therapeutic research targets. Tyrosine kinase inhibitors with activity against MET receptors include crizotinib, cabozantinib, capmatinib, and tepotinib, among many others. These tyrosine kinase inhibitors have better efficacy when compared to conventional chemotherapy in terms of objective response rate, progression-free survival, and disease control rate. However, the overall survival has not been found to be significantly different between tyrosine kinase inhibitor–and conventional chemotherapy–treated groups owing to various confounding factors.

Clinical trials that compared the efficacy of MET inhibitors in NSCLC suggest that capmatinib had a higher objective response rate in treatment-naïve patients (71.4%) versus pretreated patients (39.1%). Capmatinib also demonstrated higher objective response rates when compared to crizotinib (9.1%) for MET exon 14–skipping mutations. A phase I clinical trial established that a copy number of 6 or greater for the MET gene and the MET exon 14–skipping mutation are reliable biomarkers for the use of capmatinib. According to the phase 2 clinical trial GEOMETRY mono-1, the most common adverse reactions were peripheral edema, nausea, fatigue, and vomiting. Clinically significant adverse reactions (occurring in <10% of patients) included interstitial pneumonitis/interstitial lung disease, AKI, pruritus, urticaria, and cellulitis. The most common laboratory abnormalities were decreased
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Target</th>
<th>Kidney AEs</th>
<th>Mechanism</th>
<th>Management</th>
<th>Considerations With Pre-existing Reduced CLcr</th>
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<tbody>
<tr>
<td>Capmatinib</td>
<td>MET</td>
<td>- ↑ Scr (62%)</td>
<td>- MATE1 and MATE2K inhibition</td>
<td>- Grade 2 &amp; 3 AE&lt;sup&gt;a&lt;/sup&gt;: withhold and resume at reduced dose</td>
<td>- Starting dose modification not recommended for CLcr ≥ 30 mL/min - CLcr &lt; 30 mL/min not studied</td>
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<tr>
<td></td>
<td></td>
<td>- Peripheral edema (52%)</td>
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<td>- Grade 4 AE&lt;sup&gt;a&lt;/sup&gt;: discontinue drug</td>
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<tr>
<td>Crizotinib</td>
<td>c-MET, ALK, ROS 1</td>
<td>- AKI (ATN, arterial myocyte vacuolization)</td>
<td>- OCT and/or MATE 1 inhibition</td>
<td>- Grade 3&lt;sup&gt;a&lt;/sup&gt;: Temporarily withhold until Scr ≤ 1.5× ULN, then resume at reduced dose</td>
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<td></td>
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<td>- ↑ Scr</td>
<td>- c-MET inhibition in the nephron</td>
<td>- Grade 4&lt;sup&gt;a&lt;/sup&gt;: Discontinue drug</td>
<td>- CLcr ≥ 30 mL/min: No modification required - CLcr &lt; 30 mL/min: 250 mg, 1×/d</td>
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<tr>
<td>Alectinib</td>
<td>ALK, LTK, GAK, RET</td>
<td>- Peripheral edema (15%-22%)</td>
<td>- OCT and/or MATE 1 inhibition</td>
<td>- Grade 3&lt;sup&gt;a&lt;/sup&gt;: Temporarily withhold until Scr ≤ 1.5× ULN, then resume at reduced dose</td>
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<td></td>
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<td>- ↑ Scr (26%)</td>
<td></td>
<td>- Grade 4&lt;sup&gt;a&lt;/sup&gt;: Discontinue drug</td>
<td>- CLcr ≥ 30 mL/min: No modification required - CLcr &lt; 30 mL/min: Data not available</td>
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<td></td>
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<td>- AKI (ATN, MCD, crescentic GN)</td>
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<td></td>
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<td>- Progressive kidney function decline</td>
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<td>Cabozatinib</td>
<td>c-MET, VEGFR, RET, ALK, KIT, TRKB, FLT3, and TIE-2</td>
<td>- Hypertension</td>
<td>- Inhibition of VEGF signaling pathways</td>
<td>- HTN that is not adequately controlled with therapy: withhold and continue at reduced dose</td>
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<td></td>
<td></td>
<td>- AKI (MCD, GN, TMA)</td>
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<td>- Hypertensive crisis or HTN despite adequate therapy: discontinue drug</td>
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<td>- ↑ Scr</td>
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<td>- NS: discontinue drug</td>
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<td>- No starting dose modification is recommended</td>
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<td>Ceritinib</td>
<td>ALK, IGF-1R, INSR, STK22D</td>
<td>- Peripheral edema (8%)</td>
<td>- Hypophosphatemia</td>
<td>- Grade 3&lt;sup&gt;a&lt;/sup&gt;: HTN despite optimal therapy: withhold drug, then resume at same dose</td>
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<td>- ↑ Scr (58%)</td>
<td>(36%)</td>
<td>- Grade 4&lt;sup&gt;a&lt;/sup&gt; or recurrent grade 3&lt;sup&gt;a&lt;/sup&gt; HTN: discontinue drug</td>
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<td></td>
<td></td>
<td>- Hypophosphatemia</td>
<td>Kidney failure (2%)</td>
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<td>Tepotinib</td>
<td>MET</td>
<td>- Peripheral edema (23%)</td>
<td>- HTN (32%)</td>
<td>- Grade 4&lt;sup&gt;a&lt;/sup&gt; or recurrent grade 3&lt;sup&gt;a&lt;/sup&gt; HTN: discontinue drug</td>
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<tr>
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<td>- ↑ Scr (6%)</td>
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<td>- HTN (32%)</td>
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<tr>
<td>Brigatinib</td>
<td>ALK, ROS1</td>
<td>- Peripheral edema</td>
<td>- Hyponatremia</td>
<td>- Grade 3&lt;sup&gt;a&lt;/sup&gt;: HTN despite optimal therapy: withhold drug, then resume at same dose</td>
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<td></td>
<td></td>
<td>- HTN (32%)</td>
<td>- Hyponatremia</td>
<td>- Grade 4&lt;sup&gt;a&lt;/sup&gt; or recurrent grade 3&lt;sup&gt;a&lt;/sup&gt; HTN: discontinue drug</td>
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<td></td>
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<td></td>
<td>- Hyponatremia</td>
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<td>- CLcr ≥ 30 mL/min: No modification required - CLcr &lt; 30 mL/min: reduce dose by ~50%</td>
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Abbreviations: AE, adverse events; MET, mesenchymal epithelial transition; MATE, multidrug and toxic compound extrusion; ALK, anaplastic lymphoma kinase; AKI, acute kidney injury; ATN, acute tubular necrosis; TMA, thrombotic microangiopathy; OCT, organic cationic transporter; MCD, minimal change disease; VEGF, vascular endothelial growth factor; ULN, upper limit of normal; NS, nephrotic syndrome; GN, glomerulonephritis; Scr, serum creatinine; HTN, hypertension.

<sup>a</sup>The Common Terminology Criteria for Adverse Events (CTCAE) v4.0 by the National Cancer Institute was used to grade the adverse events.
albumin level, increased Scr, decreased lymphocytes, and elevated liver enzymes. Of these, Scr elevation was observed in 62% of all patients. However, a severe increase (grade 3 or 4 as per CTCAE [Common Terminology Criteria for Adverse Events] v4.0) leading to discontinuation of the drug was reported only in 0.3% of the study group.6

The Naranjo adverse drug reaction probability scale helps evaluate the causality of adverse reactions by a drug.7 This patient yielded a score of 7, meaning that the pseudo-AKI is probably linked to the drug. This is further reinforced by the fact that the elevation in Scr coincided with drug administration, improved with withdrawal, and reappeared upon restarting the medication. Of note, the patient was not on any other medications that are known to affect Scr except for losartan, but the dose was maintained throughout this period. The decision to reduce the dose of capmatinib to 200 mg twice a day was taken by the oncologists based on the manufacturer’s official prescribing information, which recommends withholding capmatinib until the adverse event has resolved, then resuming at a reduced dose.8

It could be argued that the combination of carboplatin(etoposide induced a subclinical kidney injury before the first rise in Scr. However, a recent AKI is unlikely, as these were discontinued 8 months back. Also, an underlying CKD could predispose the patient to a more profound rise in serum Scr because lower GFR increases tubular creatinine secretion.9 An unremarkable urinalysis, normal ratio of urine retinol-binding protein to urine creatinine, and higher values of GFR calculated by cystatin C and renal iothalamate clearance than that calculated from the Scr values all point toward a pseudo-AKI rather than a true AKI. Since cystatin C is produced by all nucleated cells, its levels in the blood and urine are more stable than creatinine. Therefore, it is a potentially more accurate method of eGFR assessment and a better prognosis marker.10 It is also an inflammatory marker and its increase does not necessarily correlate with a worsening of eGFR.11 Hence, it should be evaluated with caution in patients with cancer.

A probable explanation for this reversible increase in Scr could be the inhibition of renal transporters—multidrug and toxic extrusion protein 1 and 2-K (MATE1 and MATE2-K)—by capmatinib.12,13,14 Approximately 10%-40% of Scr is cleared through active tubular secretion by MATE and organic cation transporter, in addition to glomerular filtration.14 The pharmacokinetic profile of capmatinib is similar to the anaplastic lymphoma kinase inhibitor crizotinib. In a retrospective study by Brosnan et al on the renal effects of crizotinib, it was observed that Scr was elevated significantly by the end of week 2 of treatment and then leveled out.15 In all these patients, there was a corresponding drop of Scr-derived eGFR (by a mean of 23.9%). Discontinuation of crizotinib was associated with improvement in eGFR to 84% of the baseline levels in 16 of the 38 patients.16 We hypothesize that capmatinib could have affected Scr in a similar fashion. We also believe that this is a class effect that includes other kinase inhibitors like crizotinib and tepotinib that have activity against MET (Table 1). A kidney biopsy would aid further in this distinction, but it was avoided, as the laboratory and clinical parameters suggested a pseudo-AKI.

In conclusion, Scr elevation was chronologically linked to capmatinib administration on 2 occasions, probably owing to the competitive inhibition of creatinine secretion in the renal tubules. Capmatinib was granted accelerated approval by the FDA because of its superior efficacy in MET exon 14–skipping NSCLC and its ability to penetrate the blood-brain barrier, making it a promising drug for intracranial metastatic disease. A kidney biopsy would be the diagnostic test of choice to evaluate the etiology of AKI but before AKI develops, non–creatinine-based estimates of GFR such as use of cystatin C and iothalamate clearance could help distinguish it from the pseudo variant.13 It is the role of the onco-nephrologists to weigh the benefits of continuing therapy against its risks to prevent unwarranted discontinuation of the medication, which could compromise the overall outcome.

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Support: Dr Herrmann is supported by National Institute of Health K08 DK118120 from the NIDDK and by Mary Kathryn and Michael B. Panitch Career Development Award. Funders did not have any role in the decision to submit for publication.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Patient Protections: The authors declare that they have obtained consent from the patient reported in this article for publication of the information about him that appears within this Case Report.

Peer Review: Received January 20, 2021. Evaluated by 3 external peer reviewers, with direct editorial input from an Associate Editor and a Deputy Editor. Accepted in revised form April 17, 2021.

References


