Crizotinib is a first generation tyrosine kinase inhibitor for ALK gene positive nonsmall cell lung cancer (ALK + NSCLC). The FDA approved its use in 2011. There has been a recent recognition of crizotinib-associated renal cysts (CARCs).

We present a case of a patient who was on crizotinib therapy for lung cancer who was admitted for sepsis and also noted to have a complex renal cyst.

CASE PRESENTATION

A 53-year-old woman with a history of NSCLC (completed pemetrexed/cisplatin chemotherapy and radiation therapy, started crizotinib in 2014 for ALK gene positive pathology) presented to the emergency department with dizziness, malaise, and dyspnea which had progressively worsened over several weeks. Additionally, the patient complained of fluctuating constipation and diarrhea. A computed tomography (CT) scan of the abdomen and pelvis showed a large complex right renal mass (Fig. 1). Imaging 2 months prior revealed no definite right renal mass (Fig. 2).

On hospital day 1, the patient triggered a sepsis protocol with fever and hypotension. Interventional radiology was consulted for emergent drain placement into a now presumed renal abscess. After drain placement, an efflux of 30cc purulent fluid was noted. Despite drainage, the patient continued to have fevers with hypotension. Infectious disease was consulted and recommended antibiotics consisting of ceftriaxone and metronidazole for coverage of anaerobic superinfection.

The drain had minimal output and was removed on hospital day 6. Repeat CT scan showed no significant change in the right renal cyst (Fig. 3). The decision was made by infectious disease to observe the patient off antibiotics. The patient continued to have fevers and hypotension. Ultimately, all cultures (urine culture, multiple blood cultures, fluid anaerobic culture, fluid Gram stain, fluid fungal and calcofluor, and AFB stains) revealed no growth. Clostridium difficile and gastrointestinal stool pathogen tests were also negative. The patient required blood transfusions for anemia despite no obvious source of bleeding; the drain output was never sanguineous. During the hospitalization, the patient was also diagnosed with (1) microscopic colitis and was started on total parenteral nutrition, (2) left upper extremity deep vein thrombosis (started on enoxaparin), and (3) heparin-induced thrombocytopenia (started on fondaparinux). The decision was made to change to alectinib based on review of the literature, and suspicion that the renal cyst may be associated with crizotinib use.

On hospital day 20, the patient was stable for discharge. At 1 month follow-up, the symptoms of irregular bowel movements, fevers, and fatigue were still present but improved. Diet was slowly advanced while tapering parenteral nutrition. A CT scan was repeated 6 weeks later as an outpatient which showed a small residual soft tissue opacity in the right kidney (Fig. 4).

DISCUSSION BY MICHAEL PALESE, MD AND LARRY DI FABRIZIO, MD

The initial differential diagnosis included the following. A renal metastasis from the patient’s primary lung cancer, with her general malaise attributed to progression of the malignancy. Given that lung cancer tends to metastasize to the brain and bone and that renal metastases are extremely rare, this was quickly ruled out. The possibility of a renal abscess was more likely and initial therapies were directed toward this diagnosis. As the patient’s condition did not improve, CARC was suspected and treated as a diagnosis of exclusion. The patient’s clinical condition warranted active treatment while waiting for the cyst to “regress” after the switch to alectinib. Finally, the possibility of a primary renal cell cancer was investigated, but the rapidity of onset made this diagnosis also unlikely.

Tyrosine kinase inhibitors for ALK are a relatively new class of targeted treatment for NSCLC. They are generally well tolerated and have different adverse effects from conventional cytotoxic chemotherapy. ALK inhibitors such as crizotinib, a first generation.
ALK inhibitor, are very effective against ALK+ NSCLC, and patients are usually maintained on this therapy long term. Thus, careful monitoring and treatment of adverse effects is needed. Most adverse events are minor and grade 1 or 2 (occurrence 10%-60%): visual disturbances, nausea, vomiting, diarrhea, and fatigue. The serious adverse effects that are grade 3 or 4 are much more rare (<5%): hepatotoxicity, neutropenia, QTc prolongation, and pneumonitis. Most of these more serious adverse effects are managed with temporary holding of crizotinib. Pneumonitis is the only adverse effect that requires permanent cessation at any grade. Complex renal cysts are also seen very infrequently.

Second and third generation ALK inhibitors were developed to address the issue of cancer resistance development to crizotinib. Resistance usually occurs 1-2 years after initiation of crizotinib. Second generation ALK inhibitors include alectinib, ceritinib, and brigatinib; these have been shown to be effective after crizotinib resistance. Lorlatinib is a third generation ALK inhibitor that is currently undergoing clinical trials and shows promising results.

This patient’s clinical course may represent an extreme systemic inflammatory response as an adverse effect of crizotinib with a CARC. Crizotinib was switched to the second generation ALK inhibitor, alectinib, early in the hospital course with gradual improvement and resolution of the CARC over a period of weeks. Taima et al presented a case report of a 56-year-old man with a similar presentation with fever, weight loss, anemia, and hypoproteinemia. This patient was switched to alectinib, and the mass regressed with clinical improvement. Renal biopsy results showed granulomatous inflammation without malignancy. Chan et al reported on a 68-year-old woman with a CARC with a long hospital course and multiple drainage procedures that were all negative for malignancy and infection. The CARC had locally invaded into the retroperitoneum, involving the psoas and abdominal wall as far as the subcutaneous tissue. Numerous antibiotics and antifungals did not improve the clinical situation. Ultimately, discontinuation of crizotinib led to resolution of all the collections. Of note, Chan et al reports from a radiologic perspective without mention of the patient’s specific clinical course (ie, details such as vital signs and lab values), and thus we do not know if this patient had the same systemic inflammatory response.

![Figure 1. Initial CT with contrast. Large right complex renal cyst. Several liver masses, biopsied in the past, negative for malignancy.](image1)

![Figure 2. PET CT noncontrast from 2 months prior. No definite right renal mass.](image2)

![Figure 3. CT with contrast 1 week after presentation. Drain removed, no significant change in the right complex renal cyst.](image3)

![Figure 4. CT with contrast 6 weeks later as an outpatient. Marked resolution of prior large renal mass. Residual crescentic perinephric soft tissue opacity measuring 2.2 cm.](image4)
Most CARCs resolved spontaneously or had benign evolution in a study of 35 patients who were continued on crizotinib therapy. The authors noted 12 patients with complex changes in the cysts, and 4 patients with imaging that was falsely concerning for malignancy or abscess. They found no apparent renal impairment based on serum creatinine levels with CARCs. Lin et al studied 23/32 patients with preexisting renal cysts (all Bosniak 1) prior to crizotinib therapy. In total they found 6 of those patients with increased cyst complexity after crizotinib and 1 patient with new development of a renal cyst. There was regression of these cysts with cessation of crizotinib.

The pathophysiology of CARCs remains elusive. Crizotinib is a nonspecific tyrosine kinase inhibitor with targets for ALK and MET. MET and hepatic growth factor (HGF), a ligand of MET, have been involved in renal cyst formation. One would expect crizotinib, being an inhibitor of MET, to lead to the inhibition of renal cyst formation. Paradoxically, it appears to lead to the opposite of its observed clinical effect. In fact, the HGF-MET pathway is a potential candidate for the treatment of renal cell carcinoma. Ultimately, the development of renal cysts may be related to the interaction with HGF and MET, but this concept requires further research to clarify the exact mechanism.

Since most CARCs are benign, practitioners may be able to follow the CARCs with repeat imaging, serum creatinine, and careful monitoring while continuing crizotinib. Should the patient develop symptoms, then it may be prudent to switch crizotinib to a different ALK inhibitor such as alectinib. While the newer ALK inhibitors were intended to target the cancer resistance to crizotinib, they can also be used when a patient cannot tolerate the adverse effects of crizotinib. CARCs are only recently being reported on in the literature; much of the literature consists of case reports and small, retrospective studies. Future research is needed to more comprehensively characterize CARCs and the rare and extreme systemic inflammatory response.

CONCLUSION
A minority of patients on crizotinib develops renal cysts, and even fewer of these CARCs are symptomatic. However, there needs to be a high index of suspicion for CARCs if the patient has the pertinent relevant history and does not improve with the traditional treatment for sepsis. Recognition and switching the tyrosine kinase inhibitor to an alternative medication such as alectinib is the main treatment decision. With prompt recognition, such patients would only further require supportive care and thus avoid invasive procedures.

References