Case Report

Renal complication of crizotinib:
Crizotinib-associated complex renal cyst

Warissara Jutidamrongphan, M.D.
Pimporn Puttawibul, M.D.
From Department of Radiology, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand.
Address correspondence to W.J. (e-mail: warissara.jut@gmail.com)

Abstract
Crizotinib is one of the first-generation tyrosine kinase inhibitors targeting anaplastic lymphoma kinase (ALK) and was recently found to be associated with the development of complex renal cysts with an inconclusive explanation up to this time. Hereby, we discuss the hypothesis of crizotinib-associated complex renal cyst development and coexisting renal impairment after initiation of the treatment in a 75-year-old man with ALK-positive non-small cell lung cancer whose complex renal cysts evolved after initiation and cessation of crizotinib treatment. The coexistence as renal impairment persisted even after switching from crizotinib to ceritinib.

Keywords: Crizotinib, Non-small cell lung cancer, Complex renal cyst, ALK inhibitor.

Introduction
Non-small cell lung cancer is the most common form of lung cancer, accounting for 85% of the cases. [1] It is commonly found at an advanced stage by the time of diagnosis. Therefore, systemic therapies take part in major roles as the treatment of choice [2,3]. Crizotinib is a first-in-class, oral, small-molecule tyrosine kinase inhibitor of anaplastic lymphoma kinase (ALK), ROS1 and c-MET kinases [4].

In randomized trials involving patients with ALK-positive advanced NSCLC (PROFILE 1007, PROFILE 1014, and PROFILE 1029), crizotinib has proved to be effective over the standard single-agent chemotherapy with pemetrexed or docetaxel in extending progression-free survival[5] and pemetrexed plus platinum chemotherapy in the previously untreated universal [4,6] and especially Asian patients [7]. Subsequently, it has been approved to be the standard treatment of advanced ALK-positive NSCLC in many countries.

Despite plenty of advantages, crizotinib consequently discloses several adverse effects including gastrointestinal complaints, visual disturbances, interstitial lung disease, impaired renal function, and complex renal cyst [5,7–13]. The development of such complex renal cysts, or so-called crizotinib associated renal cysts (CARCs), has been reported to be observed in 4% of patients treated with crizotinib [14], and showed more incidence, particularly in the Asian population [11,14,15]. The imaging features of this matter should be recognized and not be mistaken for new metastasis or disease progression. Therefore, we would like to introduce a case study of a patient in our center with ALK-positive NSCLC treated with crizotinib and later on, developed multiple bilateral complex renal cysts despite achieving a good therapeutic response.

Case study

A 75-year-old man was pathologically diagnosed with non-small cell adenocarcinoma of the left upper lung. His chest CT scan showed advanced primary lung cancer with pleural and mediastinal nodal metastases, at least stage IVa or T3N2M1, together with a few simple hepatic cysts but no renal lesion. According to an ALK gene rearrangement in his tumor proved by fluorescence in situ hybridization (FISH) and immunohistochemistry, he received crizotinib treatment as the first-line therapy one month later and achieved a good therapeutic response.

On the CT scan taken at 43 days after the initiation of crizotinib, bilateral complex cystic lesions, seen as the mixed solid-cystic component with the thick, enhancing wall, emerging in both kidneys together with diffuse esophagitis and a few esophageal ulcers, were discussed for the most likely cause of the crizotinib side effect. Therefore, crizotinib was ceased. There was no further investigation or invasive procedure needed at the time. After 22 days of supportive treatment for esophagitis and ulcers, the gastrointestinal side effect improved. Thus, crizotinib was continued for 57 more days. Meanwhile, bilateral complex cystic lesions progressed in size and number. More aggressive characteristics were depicted as conglomeration together with newly developed hyperdense internal content, measured about 40 HU, thick wall enhancement, invasion into right iliopsoas muscle and surrounding fat inflammation. Simultaneously, the renal function was also impaired noted as creatinine rising and GFR drop. Eventually, crizotinib was once again ceased. Considering the effective therapeutic response of ALK-targeted therapy in this patient, ceritinib, one of the second-generation ALK inhibitors, was chosen as an alternative therapy after cessation of crizotinib for 21 days. The course of development from CT findings can be seen in Figure 1.

The bilateral complex cystic lesions and surrounding inflammation had gradually regressed within 66 days after cessation of crizotinib. The primary lung cancer also showed partial response whereas the renal function remained progressively and permanently impaired. In this regard, ceritinib was terminated after 23 days of treatment. After all, the patient was deemed to developed chronic kidney disease. The ultrasonography of the kidneys at 206 days after cessation of crizotinib showed neither residual complex cyst nor obstructive uropathy. Only small-sized ones in both kidneys were evident in Figure 2. The stable simple hepatic cysts remained unchanged all along.

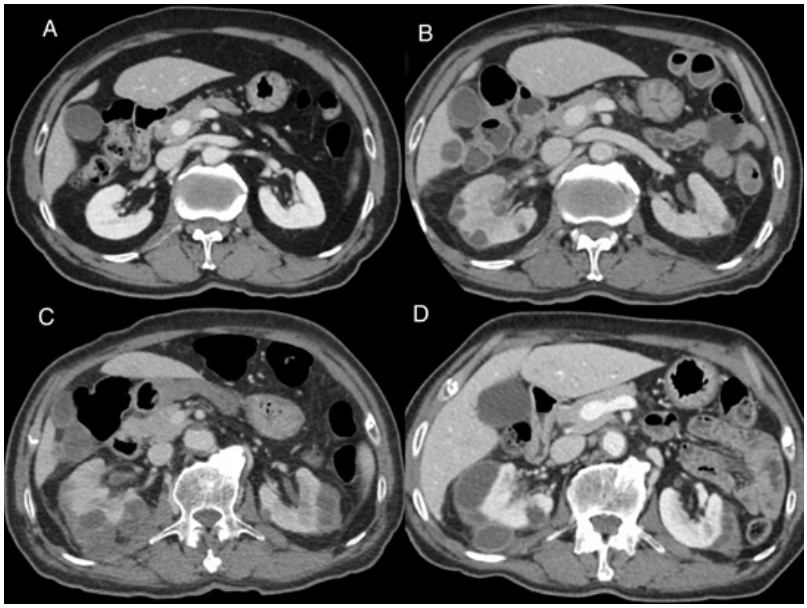

Figure 1: *Serial body CT scan revealed (A) No abnormal lesions before the introduction of crizotinib, (B) Development of bilateral complex cystic lesions at 43 days later. (C) Further growth of a complex cystic lesion extending from the right kidney to the iliopsoas muscle was still observed at 60 days after the first manifestation of bilateral complex cystic lesions. (D) The complex cystic lesion slightly decreased in size and showed less aggressive features at 66 days after cessation of crizotinib.*

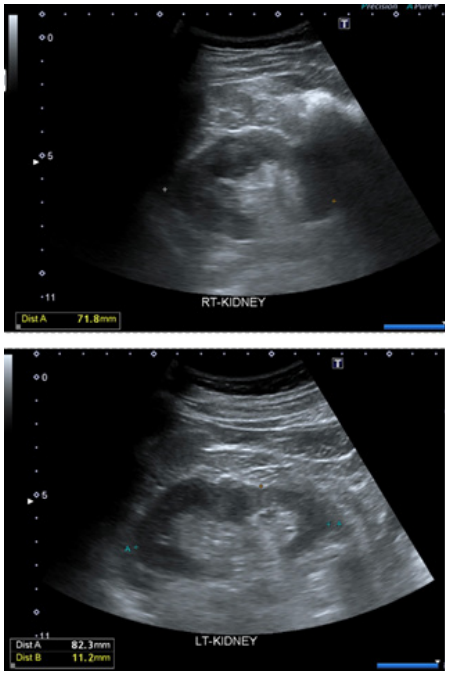

Figure 2: *Ultrasonography of the kidneys at 206 days after cessation of crizotinib revealed completely resolved complex cysts, left with only small-sized ones in both kidneys.*

Discussion

In the general population, renal cysts are deemed to be acquired from diverticula in distal convoluted and collecting renal tubules [16]. They are so common that over 50% of patients of more than 50 years old have at least one simple renal cyst [17,18]. Cystic lesions can be divided into simple and complex and accordingly categorized by Bosniak classification, based on computed tomographic characteristics. Some features, for instance, extensive calcification, septa with the irregular wall, thicker than 1 mm, solid portion, hyperdense fluid, irregular contour, contrast enhancement or evidence of inflammation separate complex from simple, benign cysts [19,20]. The categories IIF-IV correspond to complex cysts with increasing possibility of malignancy [11,13]. Crizotinib has been reported not only relating to the progression of existing renal cysts but also boosting the development of new renal cysts in the patients treated with crizotinib [12] with a higher incidence in the Asian population [12,18,21,22]. A series from Taiwan found evolved renal cysts in up to 22% of patients receiving this remedy [23]. As they usually develop septations or mixed cystic-solid appearances [15], the CARCs can also get complicated by rupture, infection and abscess formation [24,25], especially when prolonged neutropenia can also be a coexisting side effect of crizotinib[25], reported in about 9-14% of Crizotinib-treated patients participating in clinical trials [26]. They can even occur in conjunction with systemic inflammatory response, fever, and circulatory shock. Local extension into adjacent psoas muscle can also occur and require percutaneous drainage procedures to relieve the symptoms. However, most patients are usually able to continue crizotinib with only dose adjustment. Such aggressiveness together with complex features makes these CARCs mimicking metastatic disease and that makes it crucial to acknowledge this entity. Otherwise, patients could be misdiagnosed for infection or metastasis from lung cancer despite a good response of the primary lung cancer [27]. In order to differentiate between a malignant and benign lesions in most cases, positron emission tomography (PET) is proved to be useful by observing fluorodeoxyglucose (FDG) uptake. This process indicates abnormally increased metabolic activity and suggests more of the malignant origin. The CARCs,

unfortunately, have been reported to show FDG uptake as well[28] in spite of the aspiration and biopsy results showing benign xanthogranulomatous inflammation with negative bacterial culture and no evidence of malignant cell from the cytology [15].

Many patterns of CARCs progression have been described in the past decade. The most well-known pattern is that the renal cyst has shrunk after discontinuation of crizotinib or changing to alectinib [7,22,28]. The symptoms of coexisting systemic inflammation also improved after switching the medication [28]. However, there are also those whose CARCs shrank despite continued treatment with crizotinib and achieved a good therapeutic goal. Therefore, the degree of complexity of CARCs has reportedly no correlation with the malignant potential [12]. In our case study, the CARCs progressed within 43 days after the first cycle of crizotinib treatment and started to regress within 66 days after cessation of crizotinib.

The exact mechanism of CARCs is yet to be elucidated. Crizotinib is the first clinically available inhibitor of several tyrosine kinase receptors including ALK, c-MET and c-ROSC oncogene 1 [29]. Two main hypotheses have been proposed for the explanation, relating to hepatocyte growth factor and MET pathway (HGF-MET pathway) or testosterone levels. MET and HGF, which is a ligand of the MET receptor, are known to promote cystogenesis [7,30]. The usage of crizotinib causing inhibition of c-MET should cause cyst regression but the result is paradoxical. Yasuma et al [7] concluded in the recent study comprised of an in vivo experiment in mice. They suggested that there was no evidence of significant activation of Mapk/Erk or Stat3 pathway which was the HGF-mediated activation in the mice treated with crizotinib. The second hypothesis was depicted in the preclinical studies investigating the correlation between testosterone and polycystic kidney disease. The testosterone levels were found to influence the progression of renal cystic change in male and female rats with autosomal dominant polycystic kidney disease (ADPKD) [31,32]. Therefore, the imbalance of gonadal hormones may play some roles in the development of the complex renal cyst[25]. Crizotinib has been found to reduce testosterone

levels in patients with such levels returning to normal after discontinuance of Crizotinib [33]. This hypothesis provides opportunities for future researchers to explore its possibility.

Together with CARCs, renal impairment is one of the side effects of crizotinib which our case study also confronted. The study from the University of Colorado mentioned the reversible decrease of mean GFR by 23.9% compared to baseline in the first 2 weeks of therapy and that 84% of the patients recovered renal function after the cessation of therapy [23,34]. It was thought to be due to a defect in tubular excretion of creatinine rather than an actual drop in GFR. However, in the FAERS analysis, 88 cases of renal impairment were also noted [35]. Yasuma et al [7] again proposed that fibrosis and impaired renal function of the mice's kidneys during crizotinib therapy may be explained by blockade of the protective and anti-fibrotic activity of the HBF-c-MET pathways in the kidneys causing high mRNA expression of collagen I, abnormal glomerular expansion and increased interstitial collagen deposition.

In general, esophageal disorders like esophagitis, ulcer or reflux esophagitis were reported in about 20% of the 255 patients, but only 11% were attributed to crizotinib [36]. The coexisting diffuse esophagitis and a few esophageal ulcers had completely improved after supportive treatment despite the aggressive development of the bilateral renal cysts, which progressed in the same direction as a few previous case reports mentioned. The mechanism of the gastrointestinal side effect is still not well demonstrated. While Camidge et al [8] mentioned the role of ALK in the development of guts of other organisms, the exact function of the ALK is not well-known in humans. The recent study also suggested that the predominance of gastrointestinal side effects may be due to the anti-ALK effects in these tissues [37].

The coexisting hepatic cyst has also been reported to evolve together with the CARCs, regarding the aforementioned hypothesis [11,38]. However, our case study revealed no coincident complex feature development of the stable hepatic cyst in the baseline and follow-up CT, seen in Figure 3.

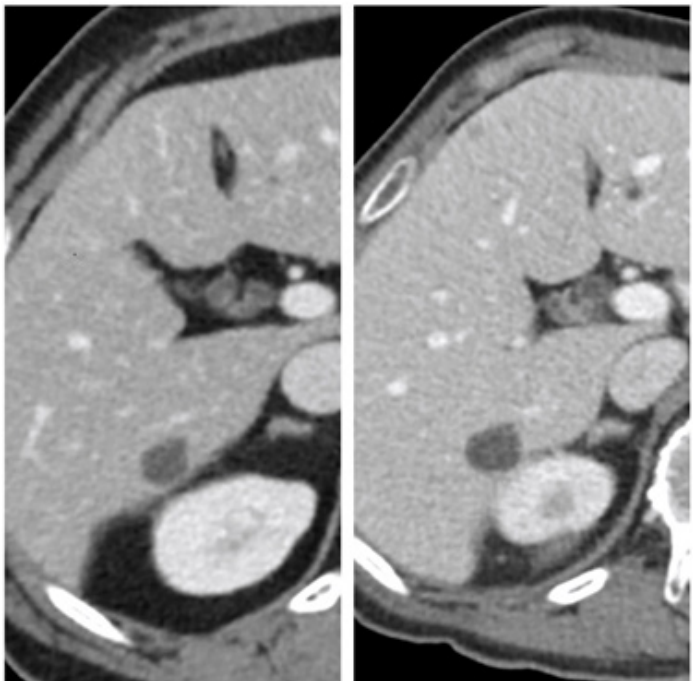

Figure 3: *Stable hepatic cyst on the baseline CT compared with the follow-up CT at 43 days after the initiation of crizotinib*

In conclusion, knowledge and prompt recognition of CARCs may help avoid the unnecessary invasive procedure, such as biopsy or drainage, and suboptimal treatment of lung cancer.

References

1. Dela Cruz CS, Tanoue LT, Matthay RA. Lung cancer: epidemiology, etiology, and prevention. Clin Chest Med 2011; 32:605-44.

2. Binder D, Hegenbarth K. Emerging options for the management of non-small cell lung cancer. Clin Med Insights Oncol 2013;7:221-34.

3. Ettinger DS, Bepler G, Bueno R, Chang A, Chang JY, Chirieac LR, et al. Non-small cell lung cancer clinical practice guidelines in oncology. J Natl Compr Canc Netw 2006;4:548-82.

4. Nishio M, Kim DW, Wu YL, Nakagawa K, Solomon BJ, Shaw AT, et al. Crizotinib versus chemotherapy in Asian patients with ALK-positive advanced non-small cell lung cancer. Cancer Res Treat 2018;50:691-700.

5. Shaw AT, Kim DW, Nakagawa K, Seto T, Crinó L, Ahn MJ, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 2013; 368:2385-94.

6. Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 2014;371:2167-77.

7. Yasuma T, Kobayashi T, D'Alessandro-Gabazza CN, Fujimoto H, Ito K, Nishii Y, et al. Renal Injury during Long-Term Crizotinib Therapy. Int J Mol Sci 2018;19:pii:E2902. doi: 10.3390/ijms19102902.

8. Camidge DR, Bang YJ, Kwak EL, Iafrate AJ, Varella-Garcia M, Fox SB, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. Lancet Oncol 2012;13: 1011–9.

9. Di Girolamo M, Paris I, Carbonetti F, Onesti EC, Socciarelli F, Marchetti P. Widespread renal polycystosis induced by crizotinib. Tumori 2015;101:e128–31. doi: 10.5301/tj.5000338.

10. Heigener DF, Reck M. Crizotinib. In: Martins UM, editor. Small molecules in oncology. Berlin: Springer; 2014. p. 197–205.

11. Lin YT, Wang YF, Yang JC, Yu CJ, Wu SG, Shih JY, et al. Development of renal cysts after crizotinib treatment in advanced ALK-positive non-small-cell lung cancer. J Thorac Oncol 2014;9:1720–5.

12. Schnell P, Bartlett CH, Solomon BJ, Tassell V, Shaw AT, de Pas T, et al. Complex renal cysts associated with crizotinib treatment. Cancer Med 2015;4:887–96.

13. Souteyrand P, Burtey S, Barlesi F. Multicystic kidney disease: a complication of crizotinib. Diagn Interv Imaging 2015;96:393-5.

14. XALKORI U.S. Physician prescribing information [Internet]. New York, Revised 2016 March. [Cited 2019 Jan 15]. Available from: http://labeling pfzercom/ShowLabeling aspx.

15. Cameron LB, Jiang DH, Moodie K, Mitchell C, Solomon B, Parameswaran BK. Crizotinib Associated Renal Cysts [CARCs]: incidence and patterns of evolution. Cancer Imaging 2017;17:7.

16. Baert L, Steg A. On the pathogenesis of simple renal cysts in the adult. A microdissection study. Urol Res 1977;5:103-8.

17. Tada S, Yamagishi J, Kobayashi H, Hata Y, Kobari T. The incidence of simple renal cyst by computed tomography. Clin Radiol 1983;34:437–9.

18. Klempner SJ, Aubin G, Dash A, Ou S-HI. Spontaneous regression of crizotinib-associated complex renal cysts during continuous crizotinib treatment. Oncologist 2014;19:1008–10.

19. Bosniak MA. The current radiological approach to renal cysts. Radiology 1986;158:1–10.

20. Jia JB, Lall C, Tirkes T, Gulati R, Lamba R, Goodwin SC. Chemotherapy-related complications in the kidneys and collecting system: an imaging perspective. Insights Imaging 2015;6:479–87.

21. Liaw CW, Palese M, Fabrizio LD. A complex renal cyst in a patient on crizotinib: case report. Urology 2019;131:21-3.

22. Okubo K, Sato A, Nakamoto K, Hatanaka Y, Isono M, Hatanaka M, et al. Bosniak category III renal cysts caused by crizotinib in an anaplastic lymphoma kinase gene-rearranged non-small cell lung cancer patient. Urology 2018;121:e3–4. doi: 10.1016/j.urology.2018.08.008.

23. Jhaveri KD, Wanchoo R, Sakhiya V, Ross DW, Fishbane S. Adverse renal effects of novel molecular oncologic targeted therapies: a narrative review. Kidney Int Rep 2016;2:108–23.

24. Chan WY, Ang MK, Tan DS, Koh WL, Kwek JW. Imaging features of renal complications after crizotinib treatment for non-small-cell lung cancer: a case report. Radiol Case Rep 2016;11:245–7.

25. Yoneshima Y, Okamoto I, Arimura-Omori M, Kimura S, Hidaka-Fujimoto N, Iwama E, et al. Infected complex renal cysts during crizotinib therapy in a patient with non–small cell lung cancer positive for ALK rearrangement. Invest New Drugs 2015;33:510–2.

26. Kim DW, Ahn MJ, Shi Y, De Pas TM, Yang PC, Riely GJ, et al. Results of a global phase II study with crizotinib in advanced ALK-positive non-small cell lung cancer (NSCLC). ASCO Meeting Abstracts [abstract]. J Clin Oncol 2012; 30(15 Suppl):7533.

27. Eiamprapaporn P, Mungwatthana N, Twinprai P, Sookprasert A, Chindaprasirt J, Ahooja A, et al. Crizotinib-associated renal cysts in anaplastic lymphoma kinase-positive lung cancer patients: A single-center experience. Urol Int 2019; Sep 3:1- 4. doi: 10.1159/000502664.

28. Taima K, Tanaka H, Tanaka Y, Itoga M, Takanashi S, Tasaka S. Regression of crizotinib-associated complex cystic lesions after switching to alectinib. Intern Med 2017;56:2321-4.

29. Christensen JG, Zou HY, Arango ME, Li Q, Lee JH, McDonnell SR, et al. Cytoreductive antitumor activity of PF-2341066, a novel inhibitor of anaplastic lymphoma kinase and c-Met, in experimental models of anaplastic large-cell lymphoma. Mol Cancer Ther 2007;6(12 Pt 1):3314-22.

30. Horie S, Kano M, Kawabe K, Mikami Y, Okubo A, Nutahara K, et al. Mediation of renal cyst formation by hepatocyte growth factor. Lancet 1994;344:789-91.

31. Jayapalan S, Saboorian MH, Edmunds JW, Aukema HM. High dietary fat intake increases renal cyst disease progression in Han: SPRD-cy rats. J Nutr 2000;130:2356–60.

32. Cowley BD Jr, Rupp JC, Muessel MJ, Gattone VH 2nd. Gender and the effect of gonadal hormones on the progression of inherited polycystic kidney disease in rats. Am J Kidney Dis 1997;29:265-72.

33. Weickhardt AJ, Rothman MS, Salian-Mehta S, Kiseljak-Vassiliades K, Oton AB, et al. Rapid-onset hypogonadism secondary to crizotinib use in men with metastatic nonsmall cell lung cancer. Cancer 2012; 118:5302-9.

34. Brosnan EM, Weickhardt AJ, Lu X, Maxon DA, Barón AE, Chonchol M, et al. Drug-induced reduction in estimated glomerular filtration rate in patients with ALK-positive non-small cell lung cancer treated with the ALK inhibitor crizotinib. Cancer 2014;120:664–74.
35. Jhaveri KD, Sakhiya V, Wanchoo R, Ross D, Fishbane S. Renal effects of novel anticancer targeted therapies: a review of the Food and Drug Administration Adverse Event Reporting System. Kidney Int 2016;90:706-7.

36. Srivastava N, VanderLaan PA, Kelly CP, Costa DB. Esophagitis: a novel adverse event of crizotinib in a patient with ALK-positive non-small-cell lung cancer. J Thorac Oncol 2013;8:e23–4. doi: 10.1097/JTO.0b013e31827e2451.

37. Jalil AA, Craig J, Bajaj R, Spurling T. Severe ulcerative esophagitis induced by crizotinib therapy. ACG Case Rep J 2014;1:82-4.

38. Halpenny DF, McEvoy S, Li A, Hayan S, Capanu M, Zheng J, et al. Renal cyst formation in patients treated with crizotinib for non-small cell lung cancer-incidence, radiological features and clinical characteristics. Lung Cancer 2017;106:33–6.