Spontaneous Regression of Crizotinib-Associated Complex Renal Cysts During Continuous Crizotinib Treatment

Crizotinib is a multitargeted anaplastic lymphoma kinase (ALK)/c-ros oncogene 1/hepatocyte growth factor receptor tyrosine-kinase inhibitor (TKI) that has been approved for the treatment of advanced ALK-positive non-small cell lung cancer (NSCLC) in the U.S. since August 2011 [1]. According to the package insert of crizotinib, there is a 4% incidence of renal cysts (most of them complex) associated with the use of crizotinib [2]. However, there is no literature on the risk factors for, natural history of, and management of crizotinib-associated complex renal cysts (CACRCs). Here we describe the development and subsequent spontaneous regression of complex cystic renal lesions in a female patient with ALK-positive advanced NSCLC with an ongoing complete response to crizotinib while on continuous crizotinib treatment.

A 49-year-old white female never-smoker was initially diagnosed with locally advanced NSCLC adenocarcinoma in 2004 but subsequently relapsed in 2007. Her tumor was found to harbor an ALK rearrangement by fluorescence in situ hybridization, and she was enrolled on a single-arm crizotinib phase 2 trial (PROFILE1005, NCT00932451). She achieved a complete response and currently has been on continuous crizotinib treatment for more than 3 years. Serial protocol-mandated imaging revealed interval development of new bilateral partially fluorodeoxyglucose (FDG)-avid complex renal lesions approximately 6 months after initiation of crizotinib (Figs. 1A–1I, 2). The patient had no prior history of renal disease. The renal lesions increased in size over a short period of time (Fig. 1B). Although the patient was asymptomatic despite the rapid growth of the complex renal cysts, persistent pyuria and bacteriuria were noted on routine urine analysis. Urine cultures alternately grew out *Escherichia coli*, *Streptococcus viridans*, coagulase-negative *Staphylococcus*, and *Enterococcus faecalis*. She was successfully treated for one episode of urinary tract infection (UTI). Otherwise, the patient remained asymptomatic from these cysts with no decrement in her renal function, increase in urine protein, or development of systemic hypertension. At their maximum size, the radiographic appearance progressed to Bosniak class IIF (multiple thin septae, septa thicker than hairline or slightly thick wall, intrarenal >3 cm, no contrast enhancement). Because of the radiographic appearance and concern for infectious nidus, she was referred to urology for biopsy and resection consideration. Urine cytology was negative, and split differential nuclear furosemide scan to assess each kidney function prior to potential surgical cyst resection revealed normal uptake and excretion of the left kidney but decreased functional tissue volume. Given the clear clinical benefit and radiographic complete response of this patient's underlying ALK-rearranged NSCLC to crizotinib, we decided to continue the patient on crizotinib treatment and monitor with

protocol-specific surveillance imaging because any invasive approach would necessitate temporary crizotinib cessation. On subsequent protocol surveillance scans, spontaneous regression of the complex renal cysts was observed approximately 22 months after initial appearance of renal cysts and 3 months after completion of UTI treatment (Fig. 1B). Patient remains on continuous crizotinib treatment with an ongoing complete response.

Discussion

Crizotinib is the first TKI known to be associated with the generation of complex renal cystic lesions [2]. The incidence of crizotinib-associated complex renal cysts is low (4%), and the etiology, natural history, and most importantly the management of CACRCs is unknown. Given the potential long duration of crizotinib treatment [3], oncologists could be faced with the management of patients with crizotinib-associated complex renal cysts for a long period of time. Although the molecular mechanism(s) of CACRC development is unknown, presumably cessation of crizotinib treatment would lead to regression of complex renal cysts. However, unless crizotinib is discontinued because of disease progression, the current management of these complex renal cysts will depend on the individual patient's clinical course while he or she is still on crizotinib. Here we describe a patient whose crizotinib-associated complex renal cysts regressed spontaneously while on continuous and uninterrupted crizotinib treatment.

Renal cysts are a common incidental radiographic finding, and over 50% of patients age 50 and above have at least one simple renal cyst [4]. Cystic lesions are classified as simple or complex and can be further subdivided into Bosniak categories based on triphasic computed tomography characteristics [5]. The etiology of the majority of complex renal cysts is unknown. Management guidelines have been proposed according to the Bosniak classification based on its malignant risk with surgical resection recommended for Bosniak class III and IV renal cysts [6]. Although crizotinib has been associated with the appearance of complex renal cysts, there is no literature regarding whether these crizotinib-associated complex renal cysts arise de novo, from existing simple renal cysts, or both. Because the natural history of crizotinib-associated complex renal cysts is unknown, whether Bosniak-guided management guidelines for complex renal cysts are also applicable for CACRCs is unknown. The median progression-free survival (PFS) of advanced ALK+ NSCLC patients on crizotinib is 8–10 months [7–9] with a subset of ALK+ NSCLC patients who derived continual clinical benefit with the continuation of crizotinib beyond disease progression reaching a median PFS of 16 months [3]. Hence, ALK+ NSCLC patients can be treated with crizotinib for a prolonged period of time. The clinical context of crizotinib use requires frequent imaging studies, so observation is probably the best approach to CACRC management in asymptomatic patients. Finally, these complex renal cysts are FDG-avid, as shown in our patient case, and can be mistaken for renal metastases; therefore, oncologists should be aware not to mistake crizotinib-associated complex

Figure 1. Serial fused positron emission tomography-computed tomography (CT) and corresponding contrast-enhanced CT demonstrating the development of multifocal complex Bosniak IIF cystic renal lesions. **(A):** Prior to crizotinib treatment. **(B):** Seven months on crizotinib. **(C):** Ten months on crizotinib. **(D, E):** At their maximum diameter, CT images demonstrating thin rim enhancement and multiple cysts with enhancing thin septations and fluorodeoxyglucose avidity at 13 months on crizotinib **(D)** and 15 months on crizotinib **(E)**. **(F):** Eighteen months on crizotinib. **(G):** Twenty-one months on crizotinib. **(H):** Twenty-seven months on crizotinib. **(I):** Thirty-one months on crizotinib.

Figure 2. Graph of the size and time on crizotinib of the complex renal cysts showing development, rapid interval growth, and spontaneous regression of a representative complex renal cystic lesion over a period of 31 months of continuous crizotinib treatment. Abbreviation: N/A, not applicable.

renal cyst development with disease progression. In summary, the natural history of crizotinib-associated complex renal cysts remains unknown, and large-scale longitudinal follow-up studies of these cysts are eagerly awaited to inform optimal management.

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