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Short communication

Renal cyst formation in patients treated with crizotinib for non-small cell lung cancer—Incidence, radiological features and clinical characteristics

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ABSTRACT

Treatment with the ALK inhibitor crizotinib has been associated with complex renal cyst formation in patients with non-small cell lung cancer (NSCLC). Using patients treated with crizotinib, we aimed to evaluate the incidence of renal cyst formation, to identify risk factors for cyst formation and to provide a radiological description of cyst characteristics. Patients with ALK-positive NSCLC treated with crizotinib were retrospectively identified from an institutional database. Computed tomography (CT) imaging performed prior to and during crizotinib treatment was retrospectively reviewed to assess the size and complexity of pre-existing cysts, new cysts, and enlarging cysts. Demographic data including age, sex, ethnicity, smoking history and length of treatment were also recorded. Data from 60 patients with NSCLC treated with crizotinib at our institution between 6/5/2009 and 7/1/2015 were collected. 57 had CT imaging before and during treatment. Mean length of imaging follow-up was 18 months. 9 (16%) patients had cysts which enlarged or developed de novo during treatment. 2 (4%) patients developed complex renal cysts (1 of these patients also developed complex hepatic cysts). Female gender ($p = 0.008$) and the presence of renal cysts on baseline scans ($p = 0.044$) were significantly associated with cyst formation or growth. Renal cyst formation or growth occurred in 16% of crizotinib-treated patients. Women and those with pre-existing cysts were at greatest risk. Although the potential causal relationship between crizotinib use and renal cyst formation has yet to be fully defined, it is important for radiologists and clinicians to be aware of this finding.

1. Introduction

Renal cyst formation in patients receiving crizotinib for the treatment of NSCLC was first noted in early-phase trials of this drug [1]. Although the putative role that crizotinib may play in renal cyst formation has not yet been fully defined, crizotinib use has been linked to the growth of pre-existing cysts, and the development of new complex and simple cysts in several patients with NSCLC [1,2]. Cyst formation in this setting has been associated with a longer duration of crizotinib treatment [2], Korean ethnicity [1] and a history of having received previous anticancer medical therapy [2].

Renal cysts are a common and mainly incidental radiological finding [3]. When found on computed tomography (CT) they are frequently classified using the Bosniak classification of renal cysts as either simple or complex [4,5]. The large majority of lesions are either Bosniak category 1 or 2 lesions which are benign and require no follow up. Bosniak category 2F lesions are probably benign, but require follow up, while complex cysts falling into Bosniak category 3 and 4 are frequently surgically managed [5]. Most cysts are simple and considered benign [3], however those classified as complex have an increased risk of malignancy [6].

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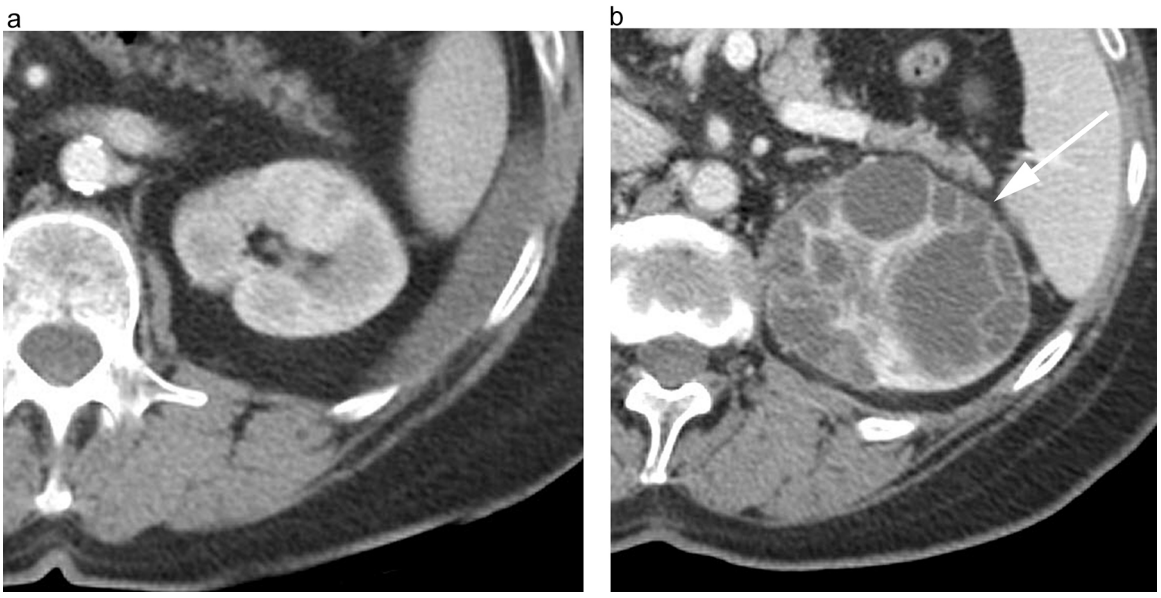

Fig. 1. (a) and (b) Axial post contract CT images of the left kidney in a 68 year old female patient, before crizotinib treatment (Fig. 1a) and 10 months after crizotinib treatment (Fig. 1b). The post treatment image demonstrates the development of a complex cystic lesion with numerous internal septations, some of which were thickened and had measureable enhancement (Bosniak category 3).

We aimed to evaluate the incidence of new renal cyst formation or the growth of pre-existing renal cysts, to identify any risk factors for cyst formation, and to provide a radiological description of cysts that form or progress on crizotinib.

2. Methods

Our institutional review board and privacy board approved this retrospective study. Using institutional databases, we identified crizotinib-treated patients who had CT or Magnetic Resonance Imaging (MRI) of the kidneys both before and after treatment, which were available for review. Clinical information was collected from the electronic medical record.

CT studies obtained at our institution were performed using 16- and 64-MDCT scanners. The protocol, an abdominopelvic survey, included contrast-enhanced acquisitions during the porto-venous phase (80 s following injection) from the diaphragm to the pubic symphysis. 150 mL of contrast material (iohexol, Omnipaque 300, GE Healthcare) was administered at a flow rate of 2.5 mL/s. Reconstructed slice thickness was 5 mm for axial images and 2.5 mm for coronal and sagittal images. Some CT studies included in the analysis were performed at outside institutions.

Pre-crizotinib CTs and all follow-up CTs while patients were on crizotinib were included for analysis. Images were retrospectively reviewed by 2 radiologists using commercially available PACS software (Centricity, GE Healthcare). A cyst was deemed to have increased in size if a lesion increased by $\geq$4 mm.

Cumulative incidence function of renal cyst formation or growth was estimated from time of crizotinib commencement using Gray's method [7], a class of K-sample tests for comparing the cumulative incidence of a competing risk, using death as a competing risk event. Associations between different risk factors and the cumulative incidence function of renal cyst formation or growth were assessed using Gray's and Fine and Gray methods [8], proportional hazards model for the sub-distribution of a competing risk. Duration of crizotinib treatment (log-transformed) was treated as a continuous time-dependent variable to study its association with risk of cyst formation or growth in a competing risk regression.

3. Results

3.1. Patient characteristics and imaging findings

Of 60 patients with NSCLC treated with crizotinib between 6/2009 and 7/2015, 57 had pre and post-treatment CT images which included the kidneys in the field of view. 32 (56%) were female. 41 (72%) were never smokers. 46 (81%) were white, 4 (7%) were black and 7(12%) were Asian. Median age at starting crizotinib treatment was 58 (range 29–87). Mean duration of treatment was 14 months (range 1–67). 7 (12%) patients received crizotinib as first line therapy for lung cancer, while 50 (88%) had received prior chemotherapy for lung cancer.

Twenty-three (38%) patients had baseline renal cysts. Twenty patients had Bosniak 1 lesions, one patient had a Bosniak 2 lesion, and two patients had Bosniak 4 lesions. None of the category 2 or 4 lesions changed during the course of treatment. The mean length of imaging follow-up was 18 months (range 1–73), and the mean number of follow up CTs performed was 7 (range 1–28). Most (46, 81%) patients had baseline CTs with intravenous contrast. The mean number of follow up CTs with contrast was 4 (range 0–16). 43 (75%) had a baseline CT and at least one follow-up CT performed with contrast.

Nine (16%) patients had cysts which enlarged or developed during treatment with crizotinib. Four patients (44%) developed new cysts, while five (56%) developed growth in pre-existing cysts. Eight (89%) were women, mean age was 59 (range 31–81). Two-year cumulative incidence rate (CIR) of cyst change was 19% (95% CI: 7%–31%). The median length of time on treatment before cyst change was 9.9 months (range 1–70).

Two patients (4%) developed complex cysts. A 68 year old woman developed bilateral Bosniak 3 cysts measuring up to 53 mm, first detectable 10 months after crizotinib treatment, and slowly growing in size and complexity until crizotinib was stopped 13 months later (Fig. 1a and b). 2 complex hepatic cysts measuring up to 36 mm developed in the same patient. Both the hepatic and renal lesions regressed after crizotinib was stopped. An 81 year old woman developed left sided Bosniak 2F renal cysts measuring up to 50 mm 5 months after crizotinib treatment was initiated. The cysts were aspirated, yielding fibrous tissue with acute and chronic