








# Crizotinib-Related Aseptic Abscesses in Lung Adenocarcinoma and *ROS1*-Gene Rearrangement: A Case Report

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## Abstract

### Keywords

- ▶ aseptic abscesses
- ▶ crizotinib
- ▶ lung cancer
- ▶ *ROS1* rearrangement
- ▶ kidney cysts

Crizotinib is a multi-tyrosine kinase inhibitor (mTKI) with efficacy in treating c-ROS oncogene 1-positive non-small cell lung cancer (NSCLC). The association between this TKI and the development of renal cysts is well established, although data on the formation of aseptic abscesses is scarce. We report a case of a patient with *ROS1*-positive NSCLC treated with crizotinib who developed multiple renal and extrarenal cysts and aseptic abscesses associated with a quick resolution of these lesions after the discontinuation of the TKI therapy. We aim to report a rare presentation of a drug-related adverse event with an unusual behavior.

## Introduction

The *ROS1* proto-oncogene is responsible for encoding a tyrosine kinase receptor. Rearrangements of this gene are identified in approximately 1 to 2% of patients with non-small cell lung cancer (NSCLC) and characterize a specific molecular subgroup. Crizotinib is a multi-tyrosine kinase inhibitor (mTKI) with action on neoplastic cells with rearranged anaplastic lymphoma kinase (ALK) molecule, mesenchymal-epithelial transition factor (c-MET), and *ROS1* tyrosine kinase receptor, and it has been proven to be effective in patients with advanced *ROS1*-positive NSCLC.<sup>1</sup> The incidence of renal cysts reported for patients on therapy with crizotinib varies between 9 and 16%, most commonly in the Asian population.<sup>2,3</sup> Here we report a case of a woman with metastatic NSCLC and *ROS1*-gene rearrangement, who developed cysts and aseptic mastoid and retroperitoneal abscesses during the treatment with crizotinib.

The present study was approved by our institutional review board (IRB), and the informed consent form was applied. Ethics committee number: 5.654.638.

## Case Presentation

A 78-year-old caucasian female, non-smoker, with stage-IVA lung adenocarcinoma and *ROS1*-gene rearrangement initiated first-line treatment with crizotinib 250 mg orally bid, with subsequent dose reduction due to anemia. After 4 months, she developed mastoiditis, with a significant reduction of right auditory acuity and imbalance, not responsive to antimicrobials. Fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) showed increased radiopharmaceutical uptake in the mastoid region and right tympanic cavity and a partial response in tumor lesions (pulmonary lymphangitis, mediastinal lymph node and pleural metastases). Because of

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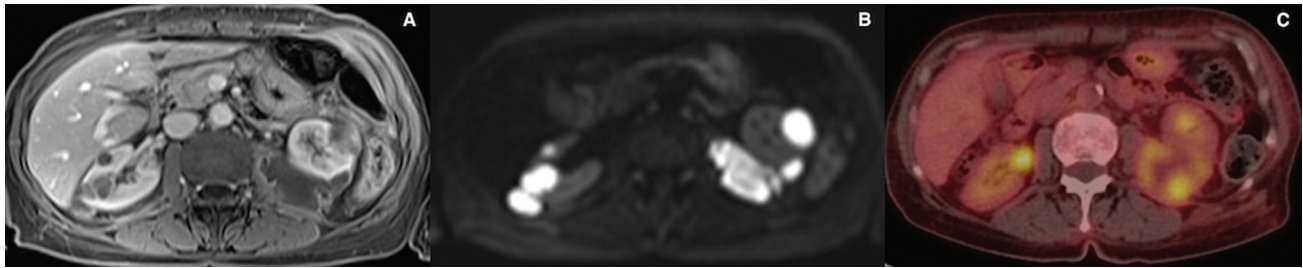
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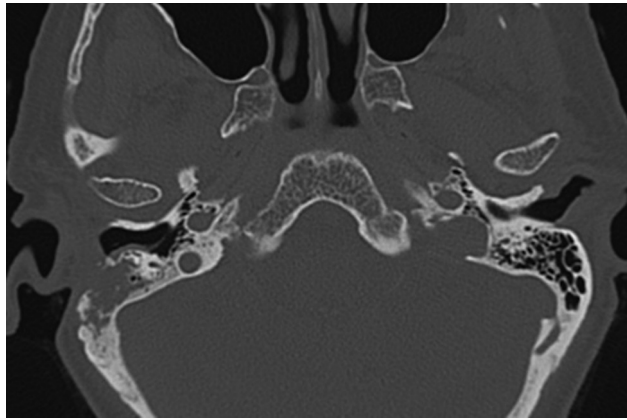
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**Fig. 1** (A) Postcontrast T1-weighted magnetic resonance imaging (MRI), (B) diffusion-weighted imaging and (C) Positron-emission tomography-computed tomography (PET-CT) of the abdomen demonstrate cystic lesions in both kidneys and a larger lesion in the left psoas muscle. The lesions present peripheral postcontrast enhancement and hypermetabolism and the cystic contents show marked restricted diffusion.



**Fig. 2** Mastoid computed tomography demonstrates a destructive lesion in the right mastoid cells, associated with a soft-tissue mass.

refractoriness to clinical treatment, after 2 months, she was submitted to tympanomastoidectomy, which confirmed chronic otitis media, negative bacterial culture, and absence of malignancy.

In the next 6 months, she developed new simple renal cysts and an expansive lesion in the retroperitoneum (►**Fig. 1**) along the left renal fascia, extending to the psoas muscle, and the biopsy revealed necrosis and absence of malignant cells.

One month later, she had relapsed mastoiditis associated with a soft-tissue mass, and a local abscessed area (►**Fig. 2**) and imaging studies revealed new renal, pancreatic, ovarian, and uterine cervix cystic lesions. Crizotinib was discontinued, and a partial improvement in the inflammatory parameters and lesions was observed. After 2 months without

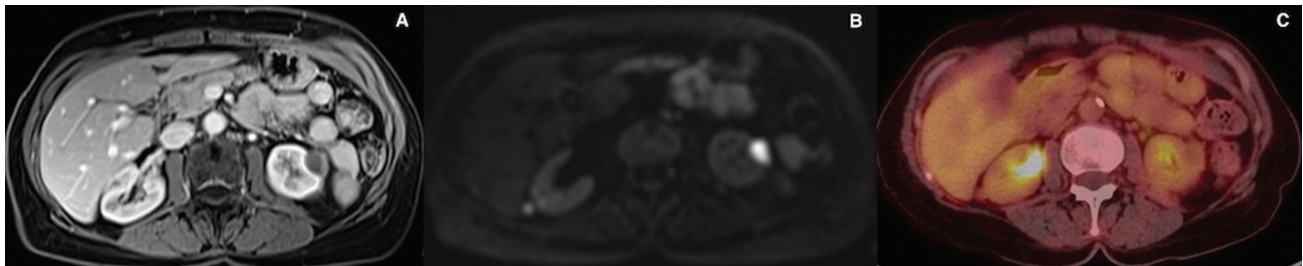
treatment, the intrathoracic disease progressed, and lorlatinib was introduced.

Five months after discontinuation of crizotinib, there was a marked regression of the renal lesions, and of the retroperitoneal expansive formation (►**Fig. 3**), resolution of the mastoid inflammatory process, and stability of the other cystic lesions.

## Discussion

The molecular mechanism of the crizotinib-associated cystogenesis is unknown and does not seem to be directly linked to the inhibition of ALK, ROS1, and c-MET.<sup>4</sup> Some physiological mechanisms could explain the cystogenesis, as the c-MET pathway, which has the hepatocyte growth factor (HGF) as a ligand and mediates the development of cysts in the renal tubular epithelium. However, some authors believe that inhibition of focal adhesion kinase (FAK) could be involved in this process<sup>4</sup> and others associate the vascular damage caused by crizotinib as a promoter of the inhibition of the FAK/forskolin (FSK)/sarcoma (Src) pathway and consequent upregulation of the extracellular signal-regulated kinase (ERK) and mechanistic target of rapamycin (mTOR) pathways, leading to renal cyst genesis.<sup>4</sup>

In a retrospective radiological analysis, the median time to diagnose renal cysts was 6.6 months (1.2–15.2 months) from the start of targeted therapy<sup>3</sup>; and the usual presentation is simple and asymptomatic cysts.<sup>3</sup> Nonetheless, complex cysts, symptomatic masses, and aseptic renal abscesses have been described.<sup>3–5</sup> Our researches only found a case



**Fig. 3** (A) Postcontrast T1-weighted magnetic resonance imaging (MRI), (B) diffusion-weighted imaging and (C) Positron-emission tomography-computed tomography (PET-CT) of the abdomen demonstrate important reduction of the cystic lesions in both kidneys and in the psoas muscle, with only a small lesion remaining in the left kidney after 5 months of crizotinib discontinuation.

report involving an extrarenal abscess.<sup>4</sup> Data suggest that the crizotinib-associated renal cysts development is related to more prolonged progression-free survival (PFS) in patients with NSCLC and ALK rearrangements.<sup>6</sup> Our patient showed an excellent response to treatment, however she needed treatment interruption and did not reach the expected median duration of response and PFS based in the data of the ALK mutated NSCLC population.

Cyst regression often occurs without intervention and even with maintenance of crizotinib,<sup>6</sup> although discontinuing the drug is a strategy.<sup>4,6</sup> We chose to interrupt the targeted therapy, considering that the patient had extensive and progressive cystic disease associated with retroperitoneal abscess, and recurrent mastoid abscess with a reduced dose of crizotinib (200 mg bid).

Alectinib, a more selective and potent TKI of the crizotinib family, was not clearly related to the development of cysts and aseptic abscesses, although a case has been reported of a patient with ALK-positive NSCLC who developed complex renal cysts during treatment with this TKI.<sup>6</sup> Our patient started a second line with lorlatinib, which did not interfere with the resolution of cysts and abscesses.

## Conclusion

The development of renal cysts and aseptic abscesses related to the use of crizotinib is a rare adverse event but may become more frequent due to greater access to targeted therapies. More studies are needed to unravel the pathophysiology, determine the risk factors, and improve the management of this complication.

### Authors' Contributions

TOS: collection and assembly of data, conception and design, data analysis and interpretation, final approval of the manuscript, and writing of the manuscript; CNB: collection and assembly of data, final approval of the manuscript, writing of the manuscript, provision of study materials or patient; MZ: final approval of the manuscript, and writing of the manuscript; NC: final approval of the manuscript, and writing of the manuscript; AAOS: final approval of the manuscript, and writing of the manuscript; JAON: collection and assembly of data, final

approval of the manuscript, and writing of the manuscript; CB: collection and assembly of data, conception and design, data analysis and interpretation, final approval of the manuscript, and writing of the manuscript

### Clinical Trials

None.

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### Conflict of Interests

The authors have no conflict of interests to declare.

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The patient involved in this case report gave her informed consent authorizing use and disclosure of her health information.

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