Pneumothorax and lung metastases cavitation during cabozantinib treatment for metastatic clear cell renal cell carcinoma: A clinical case with literature overview

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Abstract

Cabozantinib is an oral multikinase inhibitor approved for the treatment of advanced renal cell carcinoma. Radiological response evaluation may be difficult because, like other multikinase inhibitors, cabozantinib causes vascularization reduction and, in the lung, it may be associated with metastasis cavitation instead of a pure size reduction. Moreover treatment may be complicated with pneumothorax development, a life threatening condition, that has to be clinically suspected and promptly recognized on imaging.

We present a clinical case of a spontaneous pneumothorax in a patient with metastatic clear cell renal carcinoma treated with cabozantinib.

Keywords: cabozantinib; lung metastases; pneumothorax; computed tomography.

Introduction

Renal Cell Carcinoma (RCC) is the most common renal malignancy, accounting for 3.7% of all new cancers, and Clear Cell RCC (ccRCC) represents the more frequent subtype (75%). Localized disease is treated with partial or radical nephrectomy, heat or cold ablation, or active surveillance, but approximately 20% of patients have Metastatic RCC (mRCC) at diagnosis and require systemic treatment. Target therapies represent a well established option for the treatment of mRCC, and cabozantinib, a multikinase inhibitors of VEGFR2, MET, RET and AXL, has been approved in Europe both for initial therapy in intermediate and poor risk groups, and for second or third-line therapy in all risk groups [1]. The introduction of molecular-targeted therapies, including cabozantinib, poses challenges for the radiological assessment of treatment response and, although Response Evaluation Criteria In Solid Tumors (RECIST) are currently used for the evaluation of therapeutic response to antineoplastic agents, these criteria have shown several limitations. Mainly, RECIST are based only on dimensional changes of tumoral lesions, while tyrosine kinase inhibitors induce first changes in attenuation and necrosis rather than a pure size reduction; moreover in lungs, metastases necrosis could appear as air-filled cavities, and these changes may be misinterpreted on radiological evaluation. Furthermore, in case of a rapid cavitation of lung metastasis, pneumothorax may develop and the radiological assessment could be more complex and doubtful.

We present a clinical case of mRCC treated with cabozantinib, with cavitation of lung metastases and pneumothorax development as hallmarks of drug response.

Clinical case

A 57 year-old man underwent a thoracoabdominal Computed Tomography (CT) for persistent left flank pain, anemia and haematuria. CT demonstrated a very large left renal mass with bilateral lung metastasis and soft tissue lesions (Figure 1); lung lesions were distributed both in the central and subpleural regions (Figure 2). Pathological diagnosis of clear cell RCC was obtained with a percutaneous renal biopsy, and so the patient started a medical therapy with oral cabozantinib 60 mg daily.
One month after starting treatment, he experienced acute chest pain and dyspnea, and so he was admitted to the Emergency Department where chest CT was performed, demonstrating a right pneumothorax and multiple cavitated lung lesions (Figure 3). Interestingly cavitated lesions were noted instead of originally solid lesions (Figure 4), and compared to the baseline CT both renal mass and the others already known soft tissue lesions were smaller and more hypodense due to vascularization reduction (Figure 5). Patient was therefore stabilized, treated with chest drainage placement, and finally discharged home after ten days.

**Discussion**

Cavitation of lung metastases is a known occurrence induced by cancer therapy, especially by antiangiogenic agents, but pneumothorax development is considered a quite rare complication. In a post-hoc analysis of the phase 3 CORRECT study, it is previously reported a 40.9% of incidence of lung metastases cavitation in 85 patients with Metastatic Colorectal Cancer (mCRC) treated with regorafenib [2]; no pulmonary events, such as dyspnea, pneumonia, hemoptysis or pneumothorax were reported. Lim et al. [3] published similar results in a prospective trial including 72 patients with mCRC treated with regorafenib; among 53 patients with lung metastasis, 17 (32.1%) developed cavitation at the first CT evaluation and this radiological sign was associated with better disease control rate. More recently Datar et al. [4] evaluated the incidence of cavitations in 83 patients with thyroid cancer metastases during treatment with antiangiogenic TKIs; authors reported a 12% of cavitations and described two cases of pneumothorax. Marom et al. [5] reported that 17 of 124 (14%) patients who received antiangiogenic therapy for lung cancer developed tumor cavitation, but they did not describe pneumothorax development. In another study by Intariano et al. [6] it was demonstrated a close association between pneumothorax and cavitation of pulmonary nodule, studying 33 patients with lung metastases treated with bevacizumab-sorafenib and low-dose cyclophosphamide, but authors analyzed a pediatric population. In another two studies considering patients with soft tissue sarcoma and treat-
Lung metastases cavitation may be a consequence of cabozantinib treatment, like other anti TKI agents, and from the few available reported cases in this setting, it seems that cavity formation could be associated with therapy response. Moreover spontaneous pneumothorax could be a possible complication during cabozantinib treatment for mRCC, and so both Oncologists and Radiologists have to be aware of this eventuality.

References