Cancer Chemother Pharmacol (2010) 66:409–412
DOI 10.1007/s00280-010-1291-3

SHORT COMMUNICATION

Spontaneous bilateral pneumothorax in metastatic renal cell carcinoma on sunitinib therapy

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Received: 12 November 2009 / Accepted: 12 February 2010 / Published online: 5 March 2010

Abstract Bilateral spontaneous pneumothorax is a rare occurrence in patients with both primary and metastatic lung cancer. Pneumothorax occurring as a complication of vascular endothelial growth factor receptor (VEGFR) inhibitor therapy has not been previously described in the medical literature. Sunitinib malate is a VEGFR inhibitor approved for the treatment of advanced renal cell carcinoma. We present a patient with metastatic renal cell carcinoma manifested as bilateral pulmonary nodules who developed a bilateral spontaneous pneumothorax 3 weeks after initiation of sunitinib therapy. We believe that sunitinib therapy resulted in necrosis of multiple pleural-based pulmonary nodules with central cavernization and ultimately rupture with bronchopleural fistula formation. Based on this experience, we advise that practitioners exercise caution when prescribing anti-VEGFR therapy in patients with pleural-based pulmonary metastases and recognize that the efficacy and toxicity of these agents may be closely linked.

Keywords Sunitinib · Pneumothorax · Renal cell carcinoma · Pulmonary metastasis

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Introduction

Secondary pneumothorax is defined as pneumothorax that develops as a result of diverse pulmonary abnormalities. Secondary spontaneous pneumothorax occurring in the setting of cytotoxic chemotherapy for pulmonary metastatic disease is a well-described clinical situation that has been reviewed by previous authors [1, 2]. Interestingly, the primary conclusion from one report was that histology seems to be the predominant factor in susceptibility to pneumothorax with sarcomas and germ cell neoplasms predominating [1]. Importantly, the development of pneumothorax was not invariably related to tumor response.

Simultaneous secondary spontaneous pneumothorax is a rare clinical event and has been reviewed in several series previously [3, 4]. Of the fifty-two cases between both reports, only four were due to neoplastic disease. Data regarding antineoplastic therapy details, response information, or serial CT data were not provided. No patient with neoplastic disease had carcinoma.

Gefitinib, an epithelial growth factor receptor (EGFR) small molecule inhibitor, has been recently reported to cause bilateral spontaneous secondary pneumothorax in a patient treated for bilateral bronchogenic adenocarcinoma [5]. The mechanism by which the pneumothorax occurred is uncertain as no follow-up CT or response data were included in this report.

Sunitinib malate (Sutent®; Pfizer, New York City, NY) is an oral multitargeted receptor tyrosine kinase inhibitor approved for use in advanced renal cell carcinoma. There are no previous published reports of secondary spontaneous pneumothorax in patients with pulmonary metastases treated with any vascular endothelial growth factor (VEGF) inhibitor therapy. We present a patient with metastatic renal cell carcinoma and pulmonary nodules

developing bilateral secondary spontaneous pneumothorax on sunitinib.

Case report

A 43-year-old white male was diagnosed with metastatic renal clear cell carcinoma after gross hematuria led to computed tomography (CT) of chest and abdomen demonstrating a 10.5 cm right renal mass invading the inferior vena cava (IVC) with numerous bilateral pulmonary nodules (Fig. 1). The patient was a lifelong nonsmoker without preexisting lung disease. A radical nephrectomy with IVC thrombectomy was performed, revealing Fuhrmann grade III clear cell, renal cell carcinoma invading the right renal vein and inferior vena cava. A bone scan and CT of brain with intravenous contrast were negative, and he was staged as T3N0M1. He was classified as poor risk based on the Memorial Sloan Kettering Cancer Center prognostic stratification of advanced renal cell carcinoma with three predictors of shortened survival on initial assessment: high serum calcium and lactate dehydrogenase, and low hemoglobin [6].

He elected to undergo treatment with high-dose aldesleukin (interleukin-2). The patient was able to tolerate ten and six doses of interleukin-2 at 720,000 IU/kg/dose on cycles one and two, respectively.

Three weeks after completing interleukin-2, the patient developed ataxia, and an MRI of the brain was obtained. This revealed multiple enhancing foci in the cerebellum and vermis that were consistent with metastatic renal cell carcinoma, although biopsy was not obtained. Dexamethasone at a dose of 8 mg every 8 h was initiated. The patient underwent an uncomplicated course of whole brain radiotherapy to 35 Gy and the ataxia improved.

A chest CT 4 weeks after completing interleukin-2 revealed a mixed response with complete resolution of some nodules with appearance of new nodules (Fig. 2). Sunitinib was initiated at 75 mg by mouth daily to account for the interaction with high-dose dexamethasone.

Twenty-one days after the initiation of sunitinib, the patient presented to the outpatient clinic with a 10-day history of shortness of breath, pleuritic chest pain, and nonproductive cough. Vital signs were the following: temperature 97.8°F, heart rate 91 beats/min, respiratory rate 26/min, blood pressure 148/110 mmHg, and pulse oximetry 92% on room air. Physical examination revealed increased respiratory effort and decreased breath sounds bilaterally. Arterial blood gas on room air revealed a pH of 7.43, P_{CO_2} 31 mmHg, P_{O_2} 84 mmHg, and H_{CO_3} 20 mEq/L. Chest CT with pulmonary embolism protocol revealed large bilateral pneumothoraces with multiple thin-walled cystic areas (Fig. 3, arrow: ruptured cyst).

The patient was hospitalized, cardiothoracic surgery was consulted, and bilateral tube thoracostomy was performed. Sunitinib was discontinued. Bilateral talc pleurodesis was performed without complication after a recurrence of pneumothorax with removal of the right chest tube. The patient was discharged 2 weeks after admission with instructions to restart sunitinib. Three weeks after discharge, the patient was seen in the office without respiratory complaint. A follow-up chest CT demonstrated fully inflated lungs bilaterally with numerous thin-walled cystic structures at the sites of previous lung nodules (Fig. 4). At this point, the patient had taken a total of 6 weeks of sunitinib at 75 mg oral daily. He received 3 weeks prior to the pneumothorax, a 2-week break while hospitalized, and three more weeks prior to the follow-up chest CT. A repeat MRI of the brain demonstrated response of previously described lesions without new abnormalities.

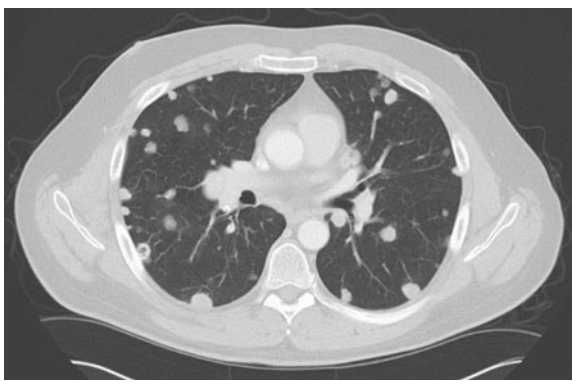

Fig. 1 Chest computed tomogram demonstrating multiple bilateral pulmonary nodules at diagnosis

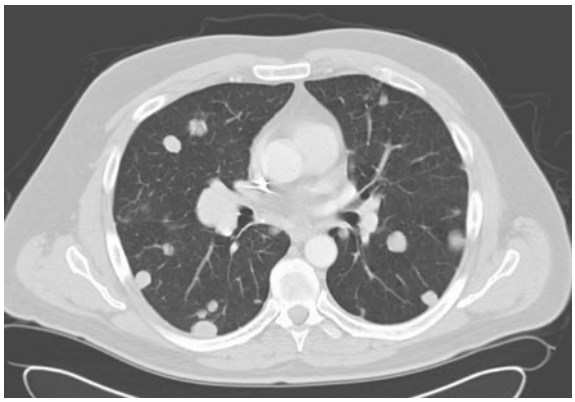

Fig. 2 Chest computed tomogram demonstrating mixed response to interleukin-2 prior to sunitinib initiation

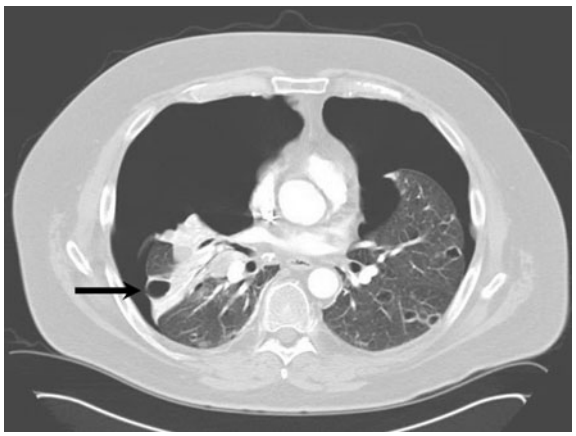

Fig. 3 Chest computed tomogram demonstrating bilateral pneumothorax with multiple cysts at prior sites of nodules after 3 weeks of sunitinib therapy (*Arrow*: ruptured cyst)

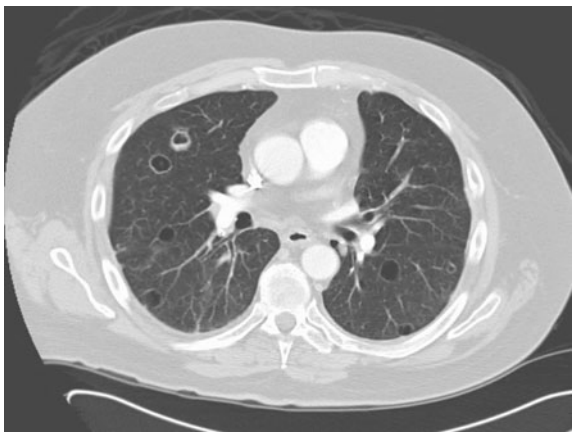

Fig. 4 Chest computed tomogram performed after lung re-expansion and six total weeks of sunitinib therapy demonstrating multiple cavernized lung nodules

Discussion

Renal cell carcinoma has rarely been associated with pneumothorax. We are only aware of one recent report of secondary spontaneous pneumothorax occurring in two patients on temsirolimus therapy for renal cell carcinoma with pulmonary metastases [7]. In both cases, purulence and infectious bacteria were found in the pleural space. The authors speculate that temsirolimus may have caused hypoxic necrosis of the pulmonary metastases by inhibition of tumor angiogenesis, which may have resulted in susceptibility to anaerobic bacterial infection.

The package insert of sunitinib contains no information regarding pneumothorax as an adverse event [8]. Section 6.6 of the package insert, the post-marketing experience, mentions cases of fistula formation associated with tumor necrosis and/or regression. It is known that fistulae and perforations have been reported with each of the VEGF inhibitors currently available clinically [9–11], and these forms of toxicity may be related to the pneumothorax found in our case. Unpublished information from a Pfizer® medical liaison reveals one case of death due to treatment-related pneumothorax in a patient on sunitinib for advanced platinum refractory non-small cell lung carcinoma.

We do not believe that the pleural-based metastases and pneumothorax are two independent and incidental processes, as our patient had no smoking history or pre-existing structural pulmonary disease. Importantly, the patient had no hair follicle lesions or pre-existing pulmonary cysts to suggest Birt-Hogg-Dube syndrome, which is characterized by renal cell carcinoma and development of pneumothoraces. Three primary mechanisms have been proposed by other authors to explain spontaneous secondary pneumothorax in patients with pulmonary metastases [12]. Tumor necrosis, either spontaneous or therapy-related, of subpleural nodules with bronchopleural fistula formation is the most likely mechanism in our patient's case. Other explanations include: a check-valve mechanism with compression of either proximal or distal airways by tumor nodule or air leak due to pulmonary infarction from tumor embolus. Because of the lack of significant residual pulmonary metastatic nodules remaining after sunitinib initiation, a check-valve mechanism in this case is unlikely. A CT with pulmonary embolism protocol demonstrated no intravascular thrombus or pulmonary infarction, although the possibility of bilateral distal vessel small-volume tumor embolism cannot be entirely excluded. Pulmonary arterial catheterization with wedge aspiration cytology was not performed in this case.

We interpret the changes seen in Figs. 2, 3 and 4 to be a rapid, dramatic response to sunitinib in which multiple pulmonary metastatic lesions underwent cavernization, likely due to inhibition of angiogenesis with resultant central tumor necrosis. We cannot completely rule out any remaining effect of the prior interleukin-2 in our patient. However, given that the CT assessment 4 weeks after interleukin-2 showed mixed response without any significant cavernization, and the patient subsequently was receiving lympholytic doses of dexamethasone, we believe that the changes seen represent an effect of sunitinib. Indeed, complete response was reported in 11 of 375 (3%) of patients in the sunitinib arm of a randomized phase III trial comparing sunitinib versus interferon alfa in untreated metastatic renal cell carcinoma [13]. In addition, several groups have reported similar dramatic responses in selected patients with pulmonary metastases due to renal cell carcinoma treated with VEGF inhibition [14, 15]. Interestingly, the CT changes of renal cell carcinoma pulmonary nodules in a patient treated with interferon followed by sorafenib appear strikingly similar to our case in a recent report by German investigators [14].

In summary, we report a patient with renal cell carcinoma with numerous pulmonary metastases who developed spontaneous bilateral pneumothorax 3 weeks after the initiation of sunitinib therapy. Indeed, the efficacy and toxicity of this medication and perhaps anti-VEGF therapy in general appear to be intimately related in certain clinical circumstances. Based on this experience, it is recommended that practitioners exercise caution when initiating sunitinib therapy in patients with renal cell carcinoma who have multiple pleural-based pulmonary metastases. Clinicians should consider periodic chest radiography and discuss with patients the importance of rapid notification if a change in pulmonary symptoms occurs.

Conflict of interest statement None.

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