Gut and Gastroenterology

CASE REPORT

# Fatal Pneumothorax Caused by Lung Cavitation Associated with Regorafenib Therapy in Metastatic Colorectal Cancer

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## Abstract

Regorafenib is an oral tyrosine kinase inhibitor indicated for the treatment of metastatic colorectal cancer and it has various adverse effects. We report a case of fatal pneumothorax caused by lung cavitation associated with regorafenib therapy in a 56-year-old Japanese man who was diagnosed of metastatic colorectal cancer. The patient, who had failed first- and second-line chemotherapy after surgery performed 3 years ago, received regorafenib 160 mg orally once daily. After 3 weeks of regorafenib therapy, he suddenly developed fever and productive cough. Chest radiograph and computed tomography demonstrated multiple cavitary lesions in his both lungs. He was diagnosed as lung abscess of pseudomonas aeruginosa due to the regorafenib-induced tumor cavitation. He was administered appropriate antibiotics and regorafenib was withheld for prompt resolution of tumor necrosis. Half dose of regorafenib was administered again after 1.5 months of withdrawal. Six months after discharge his general condition became worse again, and he died of respiratory failure after disclosing pneumothorax due to the communication between the cavity and the pleura. Only one case of pneumothorax following regorafenib therapy has ever been reported. This case illustrates a rare and critical disease presentation along with a unique drug adverse event.

**Keywords:** Pneumothorax, Lung cavitation, Regorafenib, Colorectal cancer

## Abbreviations:

mCRC : Metastatic colorectal cancer

SSP : Secondary spontaneous pneumothorax

EGFR : Epidermal growth factor receptor

VEGF : Vascular endothelial growth factor

## Introduction

Regorafenib is an oral tyrosine kinase inhibitor [1] that approved for use in refractory metastatic colorectal cancer (mCRC) [2], locally advanced gastrointestinal stromal tumor treated with imatinib and sunitinib [3], and unresecatble hepatocellular carcinoma following progression on sorafenib [4]. It potently blocks the activity of several protein kinases involved in the regulation of tumor angiogenesis (VEGFR1–3 and TIE2), oncogenesis (KIT, RET, RAF1, BRAF, and BRAFV600E), and tumor microenvironment (PDGFR and FGFR) [1]. It was demonstrated that daily 160 mg of regorafenib in mCRC prolonged overall survival and progression-free survival, comparing to best supportive care [2]. Although regorafenib has a range of adverse effects, which are mostly moderate and manageable, interstitial pneumonia has been known as a life-threatening but infrequent adverse event [2]. We report a case of lung cavitation led to pneumothorax as a rare and severe adverse event of regorafenib. Although cavitation might signify therapeutic response [5], pneumothorax should never be overlooked before being in fatal condition.

## Case Presentation

A 57-year-old man was admitted to our hospital with chief complaints of intermittent fever and productive cough for a few days. The patient became dyspneic acutely with signs of respiratory infection. His past medical history included angina pectoris and Duke's B adenocarcinoma of the rectum with multiple lung metastases and he had undergone recto-sigmoidectomy with colostomy formation 34 months previously (stageIVa T4aN2bM1a). He subsequently had been referred for chemotherapies. Bevacizumab had not been used by his medical history of coronary artery disease. As

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his tumor was a mutant-type for KRAS (Kirsten rat sarcoma viral oncogene homolog), cetuximab and panitumumab had not been prescribed. Since his tumor became refractory to fluorouracil, oxaliplatin and irinotecan, he started oral regorafenib 160 mg once daily 3 weeks ago. At that time he was in good performance status and had no sign of pulmonary infection.

Laboratory findings were normal except for a highly raised white blood cell count (322 x $10^4$ /L) and C-reactive protein level (22.93 mg/dL). Serum carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 showed high levels of 2841.2 ng/mL and 337.3 U/mL respectively.

Chest radiograph demonstrated a large cavitary lesion surrounded by ground-glass opacities in the right upper lobe of the lung (Figure 1B). Bilateral small consolidations worsened in size and numbers, in comparison to those in the radiograph of 6 months ago (Figure 1A). Chest computed tomography (CT) demonstrated that diffuse interstitial infiltrates containing air-bronchograms encircled various size of cavities throughout both his lungs (Figure 2B). Chest CT taken 6 months before admission showed no evidence of pneumonia but sporadic small tumor cavitations (Figure 2A).

While chemotherapy-associated interstitial pneumonia was proposed at first, differential diagnoses of the lung cavitation included bacterial, viral or fungal pneumonia, and/or tumor necrosis due to regorafenib.

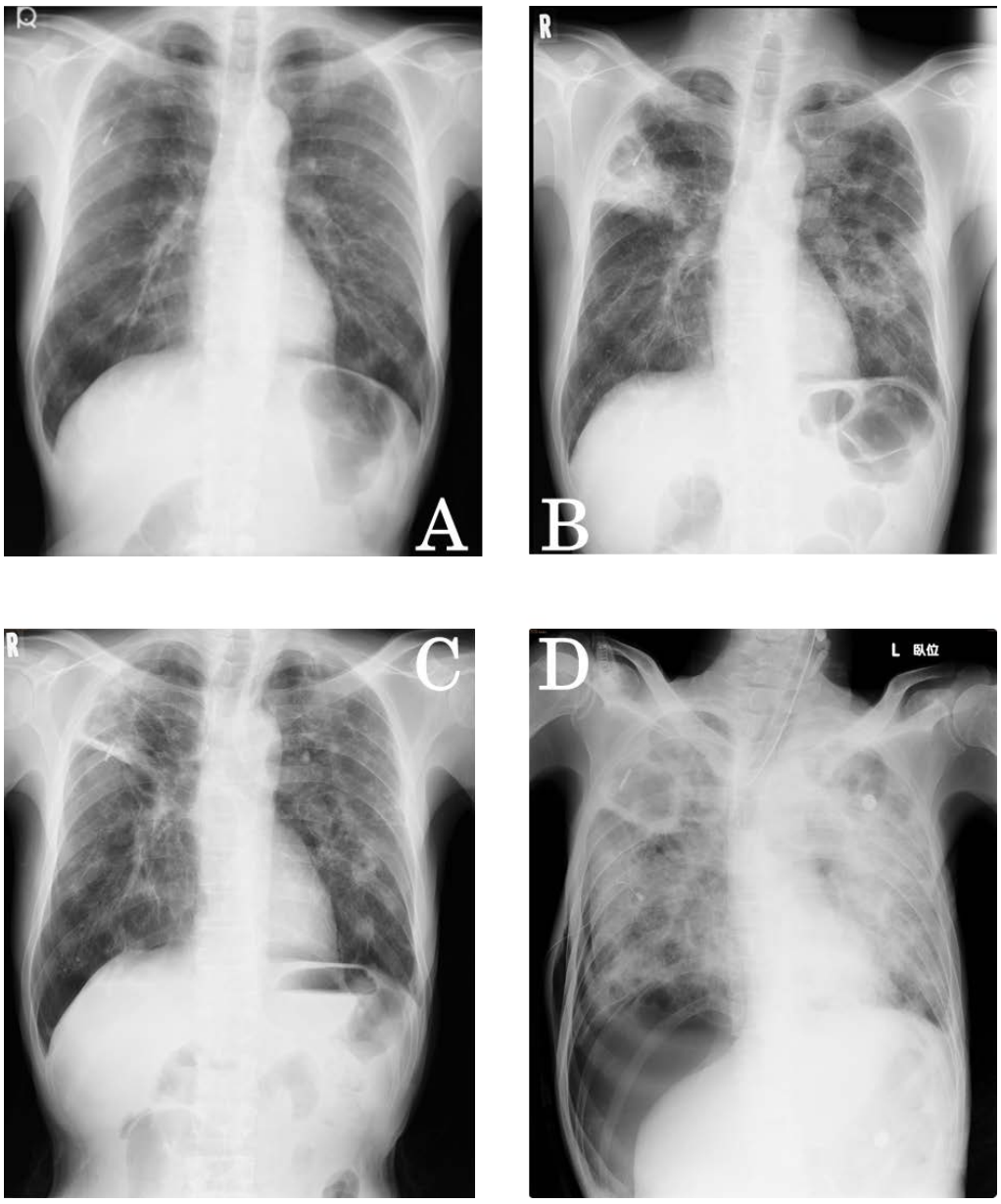


**Figure 1:** Chest radiograph demonstrating bilateral small consolidations 6 months ago (A), a large cavitary lesion surrounded by ground-glass opacities in the right upper lobe on admission (B). Cavitary lesions were not getting worse after 3months of discharge (C). He died of respiratory insufficiency after disclosing a pneumothorax due to lung metastases 6 months after discharge (D).

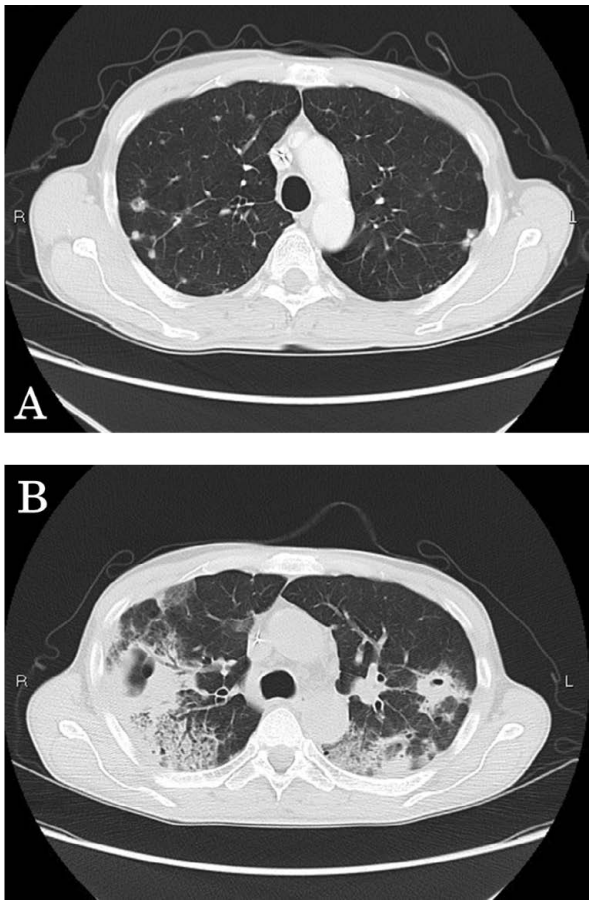


**Figure 2:** Chest CT demonstrating bilateral small consolidations 6 months before admission (A), various size of cavitary lesions throughout both lungs that were encircled by diffuse interstitial infiltrates containing air bronchograms (B).

Regorafenib was withheld because the patient developed expectoration and dyspnea. An empiric antibiotics therapy with cefepime of 4g/day and pazufloxacin of 1000mg/day was started. After the isolation of pseudomonas aeruginosa from his sputum culture, high-dose of 4g/day ceftazidime was administered for 14 days and resulted in the resolution of fever, dyspnea and interstitial changes on chest radiograph. He was discharged 19 days after admission with oral antibiotics.

Half dose of regorafenib was administered again after 1.5 months of withdrawal. For 3 months after his discharge, he had no subjective symptoms and the cavitary lesions were not getting worse in chest radiograph (Figure 1C). Six months after discharge lung lesions worsened again and disclosed pneumothorax due to the communication between the cavity and the pleura (Figure 1D). Although positive pressure ventilation was induced after thoracic drainage and tracheal intubation, air leak worsened and he was died of respiratory failure.

## Discussion

Regorafenib is an oral tyrosine kinase inhibitor indicated for the treatment of mCRC, blocks the activity of several protein kinases involved in angiogenesis, oncogenesis, metastasis, and tumor immunity. The administration of regorafenib can improve overall survival and progression-free survival in patients with mCRC following all approved therapies [2]. Forty one percent of the patients received regorafenib were in disease control (partial response + stable disease) in CORRECT trial, however, only 1% of them achieved objective tumor response. Thus regorafenib was considered to provide clinical benefit, in part by inducing disease stabilization rather than tumor shrinkage [2]. Regorafenib is almost free from the classical toxicities associated with cytotoxic chemotherapy. The most frequent grade 3 or higher adverse events are skin toxicity, fatigue, diarrhea, anorexia, voice changes, thyroid abnormalities and hypertension. Although these adverse events may affect regorafenib dosing and impact patients' well-being [6], they are not life-threatening like regorafenib being cytostatic rather than cytokilling.

The occurrence of regorafenib-related interstitial pneumonia is known as a serious adverse event but remains infrequent [7]. The patients, who develop respiratory symptoms during regorafenib therapy, should be taken attention to having opportunistic pulmonary infection or regorafenib-related interstitial lung disease.

We report a case of fatal pneumothorax caused by lung cavitation as an atypical presentation of a regorafenib-related pulmonary adverse event, on the basis of the relationship between the exposure of regorafenib and the clinical outcome. Lung cavitation is relatively rare in oncology patients. Metastatic lung cancer can cavitate less frequently than primary lung cancer and cavitation in metastatic cancer has been in 4% [8]. Bevacizumab was reported to be associated with cavitation in primary and metastatic lung cancer. Tumor cavitation appeared in 12-24% of primary lung cancer receiving bevacizumab in combination to platinum based chemotherapy [9]. Cavitation was thought to be secondary to central necrosis due to vascular endothelial growth factor (VEGF) inhibition and signify therapeutic response [10]. Eighty one percent of cavitating primary lung cancers were associated with over-expression of epidermal growth factor receptor (EGFR) [11]. The high level of EGFR expression might be associated with rapid growth, central necrosis and cavitation. Although the mechanism of regorafenib in lung cavitation is difficult to ascertain, it might result from central necrosis caused by angiogenesis inhibition or arterial thrombosis due to VEGF inhibition like bevacizumab. In the subset analysis of CORRECT trial, a significant association between the experience of lung cavitation and the favorable clinical outcome was reported [5], however, it remains controversial. Currently, no validated molecular biomarkers are available to predict outcome with regorafenib treatment. Moreover, cavitation has been linked to infection, bleeding and pneumothorax.

Spontaneous pneumothorax can occur secondary to a variety of pulmonary disorders. Cancer-related secondary spontaneous pneumothorax (SSP) is a rare complication of chemotherapy for metastatic cancer, accounting for 0.05% of all pneumothoraxes [10, 12]. The incidence of SSP in osteosarcoma patients treated with apatinib was reported to be 25.9% (14/54) and as an effective prognostic marker [13]. In colorectal cancer, only one case of SSP following regorafenib therapy has ever been reported [14], although there were several cases associated with bevacizumab [15]. Lung cavitation caused by regorafenib may be an indicator of good prognosis, however, the case developing SSP may have a poor prognosis. The necessity of temporary withdrawal or dose reduction of regorafenib is unknown. But it is doubtful that cavity formation would be used to decide when to stop treatment. Physicians have to beware the signs of pneumothorax especially in patients with regorafenib related to sub-pleural tumor cavitation.

## Conclusions

Lung cavitation led to pneumothorax can occur following regorafenib therapy. Appropriate antibiotics and temporary discontinuation or dosage reduction of regorafenib can be considered. It is important to carefully monitor respiratory symptoms in all patients who are receiving regorafenib, as early diagnosis and timely intervention are critical in managing regorafenib induced lung cavitation and pneumothorax.

## Consent for publication

Informed consent for the publication was obtained from the patient's family.

## Competing interests

All authors have no conflict of interest to report.

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