A Case of Methicillin-resistant *Staphylococcus aureus* Necrotizing Bronchitis after Radiotherapy in Combination with Axitinib

Hiroki Nakatsumi \(^1\,^2\), Satoshi Watanabe \(^1\), Kazuki Gohara \(^1\), Takafumi Kobayashi \(^1\), Yoshihiro Takeda \(^1\), Kazuo Kasahara \(^1\) and Seiji Yano \(^1\)

**Abstract:**

A 38-year-old man with renal cell carcinoma was referred to our hospital because of a productive cough. He had received radiotherapy for lung metastasis and been treated with axitinib. Bronchoscopy revealed necrosis in the bronchi of the right middle and lower lobes. Culture of the necrotic bronchial specimen revealed methicillin-resistant *Staphylococcus aureus* (MRSA). Although radiotherapy in combination with axitinib carries a risk of causing airway toxicity, MRSA necrotizing bronchitis has not been reported. Physicians should consider the possibility of infectious necrotizing bronchitis if irradiated patients show prolonged respiratory symptoms.

**Key words:** MRSA, necrotizing bronchitis, radiotherapy, axitinib, angiogenesis inhibitor

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**Introduction**

Radiotherapy is widely used for the local control of solitary primary or metastatic lung tumors. Bronchial necrosis is a rare but fatal complication that occurs months to years after radiotherapy (1). Several risk factors have been reported, including external beam radiation therapy, chemotherapy, and lobectomy (2). However, the concurrence of infections is uncommon and can cause severe medical condition in irradiated patients.

We herein report a case of methicillin-resistant *Staphylococcus aureus* (MRSA) necrotizing bronchitis after radiation therapy in combination with axitinib for metastatic renal cell carcinoma.

**Case Report**

A 38-year-old man presented with prolonged productive cough. He was an ex-smoker of 1.5 pack-years. His family history was unremarkable. He had no evidence of MRSA colonization or infection. He had undergone surgery for a left renal tumor two years ago and been diagnosed with renal cell carcinoma with multiple lung metastases (pT4N2M1, stage IV). Nivolumab and ipilimumab were administered as first-line therapy, but his primary tumor and lung metastasis grew early after treatment initiation. He was thus switched to axitinib one year ago. Although the primary tumors were completely reduced by this switch, the lung metastasis in the right hilar region progressed (Fig. 1a). Stereotactic body radiotherapy (SBRT; total 66 Gy/11 Fr) was performed 9 months ago, and axitinib had been continued during the radiotherapy (Fig. 1b). He had hypothyroidism and hypoadrenalism due to immune-related adverse events that were well controlled with medications (Hydrocortisone 10 mg/day, Levothyroxine 75 μg/day).

At presentation, his vital signs were as follows: blood pressure of 132/81 mmHg, pulse rate of 111 beats/min, body temperature of 36.6 °C, and percutaneous oxygen saturation of 94% on room air. Chest auscultation revealed rhonchi at the right mid-zones. The results of blood tests were as follows: white blood cells, 8,100/μL; KL-6, 547 U/mL (nor-
Figure 1. Radiological findings during the clinical course. (a) Chest computed tomography showing pulmonary metastasis from renal cancer before radiation therapy (arrow). (b) A metastatic lung cancer treatment plan. (c) Infiltration appearing in the irradiated areas nine months after radiation therapy. (d) Infiltration worsening even after antimicrobial treatment and steroid administration 11 months after radiation therapy.

Discussion

The present case showed necrotizing bronchitis as well as MRSA infection coinciding with the irradiated area. Although radiotherapy is a common treatment for lung tumors, MRSA necrotizing bronchitis after radiotherapy with angiogenesis inhibitor has not been previously reported. We hypothesized that the combination of radiotherapy and axitinib had caused airway toxicity and further exacerbated the bronchitis due to the persistence of MRSA.

Necrotizing bronchitis is a rare clinical entity that can be caused by viral and bacterial infections, mechanical ventilation, rheumatoid arthritis, and ulcerative colitis (3). It can induce perforation or asphyxiation by necrotic material (4). Severe and fatal cases have been reported as complications of the H1N1 influenza that was pandemic in 2009 (3). It has also been reported as a rare complication of irradiation and is thought to be due to vascular damage resulting in an inadequate blood supply to adjacent airways (5).

Radiation-induced airway toxicity includes superficial vascular changes, lumen narrowing, tracheal necrosis (6), chon-

mal range, <500 U/mL; SP-D, 284 ng/mL (<110 ng/mL); C-reactive protein, 9.72 mg/dL; and procalcitonin, 0.12 ng/mL (<0.05 ng/mL). Chest computed tomography (CT) showed infiltration in the right hilar region (Fig. 1c).

Amoxicillin and levofloxacin were started without any improvement. Oral prednisolone 20 mg per day was administered, considering a diagnosis of radiation pneumonitis; however, the symptoms and chest radiograph findings worsened (Fig. 1d). One month after the first presentation, Bronchoscopy showed necrosis and reddening of the surrounding epithelium in the right middle lobe branch and the right basal branch of the lung (Fig. 2a, b). The culture of the biopsy specimen and a histological analysis revealed necrotizing bronchitis caused by MRSA.

The patient stopped the use of axitinib and was treated with intravenous vancomycin (VCM). His productive cough was relieved, and bronchoscopy showed improvement of the necrosis (Fig. 2c, d). Although the progression of infiltrative shadows was reduced on chest CT, malignant pleural effusion due to renal cancer worsened (Fig. 2e). One month after treatment with VCM, he was transferred to the urology department.
Figure 2. Bronchoscopic and radiological findings during the clinical course. (a, b) Bronchoscopy showing necrosis and surrounding redness and swelling. (c, d) Bronchoscopy revealing improvements in necrosis and vascular regeneration four weeks after the intravenous administration of vancomycin. (e) Chest computed tomography showing suppression of infiltration progression and exacerbation of pleural effusion after the intravenous administration of vancomycin.

drosis (1), esophageal-tracheal fistula (7), and esophageal-pulmonary fistula (8). There have been a few cases of post-radiation infectious tracheobronchitis, including aspergillus (9) and candida (10). The recommended clinical doses for central lung tumors in JROSG10-1 and RTOG0813 are 60 Gy/8 Fr and 50 Gy/5 Fr, respectively (11, 12). Although the present patient received a total of 66 Gy in 11 fractions, the risk of airway toxicity was considered acceptable.

Axitinib is a receptor tyrosine kinase inhibitor of vascular endothelial growth factor (VEGF)-1, VEGF-2, and VEGF-3, and has antiangiogenic activity. Although there are no reports of axitinib, several reports of fistulas have been reported for other VEGF receptor tyrosine kinase inhibitors, such as bevacizumab and sunitinib. In a clinical trial of bevacizumab combined with chemoradiation for lung cancer, the labeling of bevacizumab was changed due to the risk of tracheoesophageal fistula following a warning from the US FDA. There are also reports of fistulas with bevacizumab alone (14) and with bevacizumab administered long after radiation (15). In addition, there has been a report of sunitinib inducing bronchial perforation after radiation in lung metastasis of renal cell carcinoma (16). Thus, the angiogenesis inhibitor axitinib can cause localized necrosis of the bronchial wall.

In this case, the concomitant use of axitinib with irradiation may increase the risk of bronchial necrosis. In addition, oral steroid may also have had an effect on the MRSA colonization. Because no clinical trials have been published combining antiangiogenic therapy with radiotherapy, safety data and the long-term adverse effects are still largely unknown. Thus, physicians should consider strict follow-up of patients treated with angiogenesis inhibitors and irradiation.

Conclusion

To our knowledge, this is the first case of MRSA necrotizing bronchitis induced by radiotherapy in combination with axitinib. Physicians should consider performing bronchoscopy due to the possibility of infection when delayed airway toxicity appears or develops after chest irradiation. Further studies concerning the relationship between radiation and angiogenesis inhibitors are warranted.

The authors state that they have no Conflict of Interest (COI).

References