

Central airway complications following VEGF and chemoradiotherapy in advanced intrathoracic malignancies

Stephanie G. Worrell, Jeffrey A. Hagen, P. Michael McFadden

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INTRODUCTION: Lung cancer is the most common cause of cancer death in both men and women worldwide. Most patients will have advanced disease at the time of diagnosis. This results in many patients being referred initially to oncology and radiation oncologists without ever being a surgical candidate. We report on four patients over three years who developed major central airway complications following treatment with chemotherapy and radiation, with two patients receiving anti-angiogenic chemotherapeutic drugs.

CASE REPORT: Four cases are included in this case series of patients that developed post treatment central bronchopleural fistula after treatment for a

central airway tumor. There were two men and two females, mean age of 65 years. Different techniques, including stenting and the use of extracorporeal membrane oxygenation were required for treatment and stabilization of the airway. There was a 75% mortality in this series.

DISCUSSION: Airway complications resulting in large airway defects are life threatening and difficult to manage. Treatment of these central airway tumors can result in catastrophic complications.

CONCLUSION The cases presented report a complication of concurrent chemotherapy and radiation treatment, with concern for use of vascular endothelial growth factor (VEGF) inhibitors on advanced central and upper airway malignancy.

Key Words: Airway; Lung cancer; Concurrent chemotherapy and radiation; VEGF inhibitors

BACKGROUND

Lung cancer is the most common cause of cancer death in both men and women worldwide. The majority of patients have advanced disease at the time of presentation (1). Combination therapy with chemotherapy and radiation has improved long-term outcomes (2-5).

Bevacizumab and Sorafenib is anti-angiogenic chemotherapeutic drug that specifically inhibit vascular endothelial growth factor (VEGF). Bevacizumab was first introduced for advanced non-small cell lung cancer (NSCLC) in the early 1990s and was found to improve overall survival and patient quality of life (6,7). The addition of radiation therapy has also been associated with improved progression free and overall survival by controlling sites of local disease (2). These therapies while effective may result in catastrophic bronchopleural fistula when administered to patients with central airway tumors. To date, there have been limited case reports of patients with esophagitis who progress to tracheoesophageal fistula formation during therapy with bevacizumab (8).

In our current case series we report on four patients over three years who developed major central airway complications following treatment with chemotherapy and radiation, two of which included a VEGF inhibitor with concurrent radiation.

CASE SERIES

Case 1

A 51-year-old (yo) woman with stage IV NSCLC of the right upper lobe extending in to right main stem bronchus began systemic treatment with Carboplatin, Paclitaxel, and Bevacizumab and concurrent radiation. Three months later she presented to an outside hospital with cough and regurgitation upon drinking liquids. A chest CT scan showed a bronchoesophageal fistula (Figure 1). She was transferred to our center for higher level of care. Bronchoscopy revealed a large defect in the right main bronchial wall. Esophagoscopy showed a large defect in communication with the right main bronchus, 23 cm from the incisors. An 18 mm × 15 cm covered Ultra flex esophageal stent was placed across the defect. A feeding gastrostomy tube was also placed during her hospitalization and she was discharged in good condition.

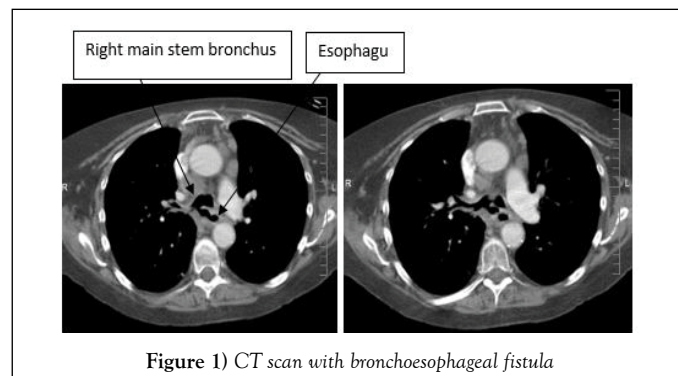


Figure 1) CT scan with bronchoesophageal fistula

Case 2

A 65-year-old female with metastatic renal cell carcinoma, twelve years post nephrectomy, presented to the emergency room with hemoptysis and stridor. CT scan showed a right upper lobe pleural based lesion and a smaller end bronchial lesion. Bronchoscopy and biopsy confirmed renal cell carcinoma. Mediastina radiation and sorafenib, a VEGF inhibitor primarily used for renal cell carcinoma, was then begun. Two and a half years later she presented with progressive dysphagia and increasing shortness of breath. Bronchoscopy revealed a necrotic defect starting proximal to the carina and ending distal to the right main bronchus. Esophagoscopy showed a fistula between the esophagus and the right main bronchus at 25 cm from the incisors. This was covered with a 12 mm × 9 cm ultra-flex esophageal stent. The tumor continued to grow and obstruct the proximal airway. She died of respiratory failure 40 days later.

Case 3

A 58-year-old male with chronic obstructive pulmonary disease (COPD) and recently diagnosed right upper lobe NSCLC, presented to an outside hospital with shortness of breath and was found to have a tension pneumothorax, treated with chest tube. He had just completed 6 weeks of concurrent paclitaxel, carboplatin, and radiation. He continued to have a large air leak after chest tube placement and was transferred to our facility

Division of Thoracic Surgery, Department of Surgery, Keck Medical Center, University of Southern California, 1510 San Pablo Street Los Angeles, California, USA

Correspondence: Dr Michael McFadden, MD, Department of Cardiothoracic Surgery, Keck School of Medicine, University of Southern California, Los Angeles, California, USA, Telephone (323) 442-5849, e-mail mmcfadden@surgery.usc.edu

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TABLE 1
Multiple complications in different patients

Patient	Location of defect	Location of tumor	Type of tumor	Chemotherapy	Radiation	Treatment	Outcome
1	Right mainstem bronchus	Right upper lobe	Stage IV NSCLC	Bevacizumab Carboplatin Paclitaxel	Yes	18 mm x 15 cm covered Ultraflex esophageal stent	Discharged in good condition
2	Right mainstem bronchus	Right upper, middle, and superior aspect of lower lobe	Stage IV Renal Cell Carcinoma	Sorafenib	Yes	12 mm x 9 cm ultraflex esophageal stent	deceased
3	Right mainstem bronchus	Right upper lobe	Stage IV NSCLC	Paclitaxel Carboplatin	Yes	16 mm x 4 cm covered endobronchial stent	deceased
4	Inferior segment of Left upper lobe	Left main bronchus	Stage IV, NSCLC, squamous	Docetaxel Carboplatin	Yes	15 mm x 12 cm ultraflex esophageal stent	deceased

for higher level of care. He displayed tension physiology despite chest tube placement and was emergently taken to the operating room. An attempt at intubation was begun; however, he went into a cardiopulmonary arrest. Extracorporeal membrane oxygenation (ECMO) was initiated and a rigid bronchoscope was placed. A large, 4 cm, hole in the lateral wall of the right mainstem bronchus was visualized with surrounding tumor. A 16 mm x 4 cm covered endobronchial stent was placed across the defect. The air leak immediately resolved and he was endotracheally intubated. He was continued on ECMO until family discussion resulted in decision to remove the ECMO, immediately following removal he went in to cardiac failure and passed away.

Case 4

A 85-year-old male with COPD who initially presented to his primary care doctor with symptoms of sinusitis. On imaging he was found to have a mass consistent with NSCLC in the left hilum with narrowing of the left mainstem bronchus and renal metastasis. He began concurrent taxotere, carboplatin, and palliative radiation and 2 weeks later he presented with dyspnea and hoarseness requiring intubation. Bronchoscopy showed mucosal irregularities in the distal trachea and a wall defect in the inferior division of the left upper lobe. Endoscopy showed a fistulous connection at 29-30 cm and a 15 cm x 12 mm covered ultraflex esophageal stent was deployed. He developed multiple complications including bacteremia, fungemia, and eventually multi-organ failure. He was terminally extubated and passed away two weeks later (Table 1).

DISCUSSION

Lung cancer is the most common cause of cancer death worldwide. In 2014, over 200,000 people in the United States were newly diagnosed with lung cancer and over 150,000 people died from lung cancer (9). Therapy with VEGF inhibitors and radiation therapy in advanced disease have led to improvements in progression free and overall survival (2,6,7). The purpose of VEGF inhibitors is to inhibit angiogenesis to a growing tumor. The known risk factors associated with this treatment include hypertension, bleeding, thromboembolic events, delayed wound healing, infection, and trachea-esophageal fistula (8). These complications can predispose patients with large central airway tumors to progress to bronchopleural fistula. The proposed mechanism by which this occurs is via the tissue necrosis induced by these therapies as the tumor regresses. Additionally, once the tumor necrosis these patients are at a decreased ability to heal these large defects.

Several randomized trials have established the superiority of concurrent chemoradiotherapy compared with chemotherapy alone for advanced lung

cancer (2-5). The side effect most commonly reported with combination therapy is esophagitis. In previous studies the esophagitis has led to tracheoesophageal fistula in some cases due to severe erosion (8). Radiation pneumonitis is a known pulmonary complication of radiation therapy. Therefore, it is not unreasonable to assume that the radiation induced injury to the surrounding tissue may contribute to the formation of bronchopleural fistula.

VEGF inhibitors are more commonly being used in combination with radiation therapy. The mechanism of synergy between the two treatments involves a transient vessel normalization that occurs with VEGF therapy improving radiosensitization (10). VEGF inhibitor therapy causes a transient angiostatic state prior to vessel regression, this is the time in which radiation therapy is most effective (10). This also enhances the ability of the combination therapy to cause tumor necrosis by enhancing the ability to induce tumor hypoxia and cell death.

The cases presented report a complication of concurrent chemotherapy and radiation treatment, with concern for use of VEGF inhibitors on advanced central and upper airway malignancy. While chemotherapy, particularly VEGF inhibitors, and radiation have prolonged survival for patients with advanced NSCLC, they should be used with caution in tumors directly invading the bronchotracheal tree. These complications are all difficult to manage with significant mortality (75% in our series.) The high mortality is secondary to delay in diagnosis and difficulty in treatment.

CONCLUSION

Clinicians should consider pre-treatment stenting across centrally located tumors or even avoidance of VEGF inhibitors in specific patients. There is a need for further investigation in to the true incidence of airway complications associated with concurrent VEGF inhibitor treatment.

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