

Bronchial Necrosis Following Bevacizumab and Stereotactic Body Radiotherapy for Treatment of Metastatic Breast Cancer

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Abstract

Bevacizumab is an emerging therapy with widespread use in the treatment of advanced malignancies. We describe a young female with metastatic breast cancer that underwent stereotactic body radiation during treatment with bevacizumab after the discovery of a new metastatic focus within the lung parenchyma. Approximately one year later she presented with a progressive foul smelling cough and dyspnea. Bronchoscopy revealed extensive necrotic destruction of the bronchus intermedius. Airway necrosis may be a rare adverse event associated with the use of bevacizumab, especially with concomitant radiotherapy.

Keywords: Bevacizumab; Metastatic breast cancer; Airway necrosis; Bronchoscopy

Introduction

Airway necrosis remains a rare, but potentially fatal problem. Necrosis is described in association with radiotherapy [1,2] but has also recently been described in relation to chemotherapeutic agents utilized for lung cancer [3,4]. Bevacizumab is a recombinant humanized monoclonal antibody that inhibits vascular endothelial growth factor, thereby preventing angiogenesis and tumor growth. When used in combination with antineoplastic agents it has demonstrated a significant survival benefit in several different types of advanced stage malignancies including non-squamous non-small cell lung cancer, colorectal cancer, and breast cancer. Bevacizumab use has been associated with numerous adverse events including spontaneous pulmonary hemorrhage, gastrointestinal perforation, and thromboembolic events [5,6], including a recent report suggesting that airway complications and cavitation may be more common than initially described [3]. We present a case of airway necrosis observed after the use of stereotactic radiotherapy and bevacizumab to treat metastatic breast cancer.

Case

A 32-year-old woman was diagnosed with poorly differentiated invasive ductal carcinoma of her right breast in July 2010. Immunohistochemical analysis was consistent with triple receptor negative and BRCA1 positive disease. She received neoadjuvant chemotherapy (doxorubicin, cyclophosphamide, and paclitaxel) followed by bilateral mastectomies. She appeared to have no evidence of disease on follow-up imaging, however in August 2013 she presented with headaches and imaging demonstrated brain lesions as well as a lung mass (Figure 1a). Transthoracic needle aspiration of the lung mass demonstrated cytology consistent with her previously diagnosed breast carcinoma. She was started on bevacizumab and received stereotactic body radiation therapy in five fractions over 10 days (total of 5000 cGy) to the lung lesion as well as whole brain radiation.

She continued systemic therapy with bevacizumab for over one year without measurable evidence of progressive disease. Chest imaging demonstrated almost complete resolution of her lung mass in August 2014 (Figure 1b). In October 2014 she presented with fevers, dyspnea, and a cough productive of foul smelling sputum. Due to concern for underlying sepsis, chest imaging was performed concerning for a potential airway defect (Figure 1c). Chest imaging revealed evidence of what appeared to be a new right main stem bronchus defect. At this same time she also developed a right-sided pneumothorax requiring chest tube placement, thought to be related to an attempted central

line placement during her initial volume resuscitation. Due to her new pneumothorax, intermittent air leak, and chest imaging findings, bronchoscopy was performed.

Bronchoscopy revealed a large defect of the posterolateral bronchus intermedius with involvement into the orifice of the right upper lobe (Figures 2a and b). Examination of her chest tube under positive pressure revealed no air leak despite suction at -40 cm H₂O. Cultures of endobronchial sampling revealed *Pseudomonas aeruginosa*. She improved clinically and her chest tube was removed without incident two days later. She unfortunately developed further seizures and neurologic decline during her hospitalization, thought to be related to progressive metastatic disease in her brain. She was transitioned to hospice and comfort measures were undertaken, expiring one month after admission.

Discussion

Airway necrosis remains an infrequent finding that may be under-reported. The majority of data regarding incidence and management appears to be from expert opinion and isolated case reports. Symptoms appear to include cough, dyspnea, and in some cases hemoptysis. Imaging features may be subtle but can include airway wall defects, as evident in our case. Depending on location, the presence of a pneumomediastinum or pneumothorax may also exist.

Diagnosis may be suggested with imaging, but can be confirmed by direct endoscopic visualization or with contrast imaging. Treatment options will depend on the underlying severity and overall prognosis of the patient. As colonization is frequently a concern, therapeutic decisions should focus on control and prevention of further infection. Although primary resection with anastomosis is often the preferred option for patients with non-malignant fistulae, in patients with advanced malignancy and limited lifespan this is often inappropriate. Other therapeutic options may include endobronchial stenting to

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Figure 1: Computed tomography of chest (axial images): A) Computed tomography of the chest from August 2013 demonstrating new right sided lung mass, B) Computed tomography of the chest from August 2014 noting almost complete resolution of the lung mass after the use of stereotactic body radiation to the lung mass and maintenance use of Bevacizumab, C) Computed tomography of the chest from October 2014 demonstrating concern for new airway fistula within the posterior portion of the bronchus intermedius as well as the development of a parenchymal infiltrate on the right side.

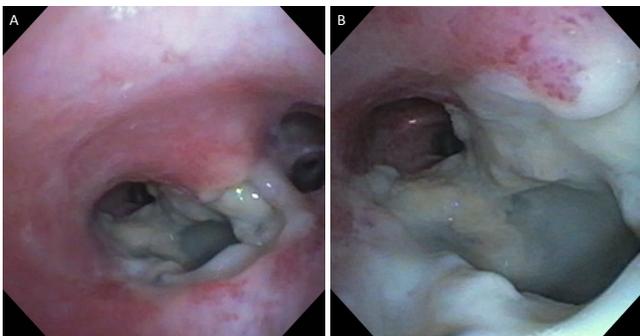


Figure 2: Bronchoscopic images from October 2014: A) View from the entrance of the right main stem bronchi with the right upper orifice at approximately 2 O'clock, the bronchial necrosis/fistula within the middle of the frame, and the bronchus intermedius to the left. Take note that the more lateral portion of the right upper lobe carina appears intact, however the medial portion and the bronchus intermedius appears completely absent. B) View during closer inspection of the necrosis. In this frame, the right upper lobe is out of view at approximately 2-3 O'clock, while the bronchus intermedius is now more visible at about 11 O'clock. Within the center of the picture is the remaining portions of the lateral wall of the bronchus intermedius and to the right was evidence of a cavity full of pus. Cultures were obtained from this area. During the bronchoscopy there was no evidence of an ongoing airleak, suggesting this remained a contained pocket of infection and had not created a bronchial-pleural fistula.

prevent further pulmonary or mediastinal soiling as described more recently by Machuzak et al. [7]. In the absence of the above issues and adequate egress to clear the cavity, long-term treatment with antibiotics may be appropriate and associated with less morbidity, as was elected in this case.

Currently at least four reports have identified seven patients developing airway necrosis and intrathoracic fistula (esophageal, mediastinum, pleura) in the setting of bevacizumab and radiotherapy [4,7-9]. Interesting all these reports involve patients with lung cancer. Bevacizumab has been well-studied in metastatic breast cancer, with no reports of airway necrosis/fistula formation during its phase 3 trial by Miller et al. [10]. Since its introduction, associations with

gastrointestinal perforation and pulmonary hemorrhage have been reported [3,5]. Intrathoracic cavitation (not necessarily airway necrosis) after bevacizumab has been reported with a median time of 1.8 months (range 0.7-6.2 months) [3]. However case reports identifying airway necrosis and fistula formation, while sparse, appear to be reported in the range of 3 weeks to 10 months after bevacizumab therapy [4,7-9]. The exact mechanism for this spontaneous hemorrhage/perforation remains unclear, but some propose impaired neovascularization and resultant dysfunctional wound healing. This may be of particular consequence to an already compromised airway wall following radiation.

Conclusion

Bevacizumab is an antiangiogenic agent used in a variety of neoplastic conditions. It is important for the pulmonary specialist to be aware of its toxicity profile due to serious pulmonary adverse effects that can occur. In addition to the more commonly described complications such as pulmonary hemorrhage, our case suggests that patients treated with bevacizumab may be at risk of developing airway necrosis particularly in those patients also receiving radiotherapy.

Author Contributions

UO and CRG participated in the case collection and manuscript writing of this project. UO and CRG have no conflicts of interest to disclose related to this research.

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