American Journal of Case Reports

ISSN 1941-5923
© Am J Case Rep, 2017; 18: 842-846
DOI: 10.12659/AJCR.904416

Received: 2017.03.19
Accepted: 2017.04.28
Published: 2017.07.31

Systemic Bevacizumab for Recurrent Respiratory Papillomatosis: A Single Center Experience of Two Cases

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Manuscript Preparation E
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Conflict of interest: None declared

Case series
Patient: Male, 87 • Male, 63
Final Diagnosis: Recurrent respiratory papillomatosis
Symptoms: Cough • dyspnea
Medication: —
Clinical Procedure: —
Specialty: Pulnonology

Objective: Unusual clinical course

Background: Recurrent respiratory papillomatosis (RRP), caused by human papillomavirus (HPV), is the most common benign neoplasm of the larynx and central airways. RRP has a significant impact on quality life and high annual costs to healthcare. Currently, there is no cure for RRP, leading to repeated debulking operations for symptomatic palliation. Various local adjuvant therapies have also been studied with mixed efficacy. HPV oncogene products increase expression of vascular endothelial growth factor (VEGF) providing a potential target for treatment of RRP. Bevacizumab, a recombinant monoclonal antibody that inhibits VEGF, has shown efficacy in patients with localized disease.

Case Report: We present two cases of extensive airway and parenchymal RRP successfully managed with systemically administered bevacizumab, a recombinant monoclonal antibody that inhibits VEGF.

Conclusions: Bevacizumab has shown efficacy in patients with localized disease, but here we illustrate the potential of bevacizumab for patients with extensive parenchymal burden as well as provide a brief review of the literature.

MeSH Keywords: Antibodies, Monoclonal, Humanized • Papilloma • Papillomavirus Infections • Respiratory Tract Infections

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/904416

Background

Recurrent respiratory papillomatosis (RRP), due to human papillomavirus (HPV) subtypes 6 and 11 [1], can cause recurrent growth of exophytic papillomas throughout the tracheobronchial tree. Squamous papilloma is the most common benign neoplasm of the larynx, affecting four in 100,000 children and 1.8 per 100,000 adults [2]. Over time, transformation to squamous carcinoma can occur in RRP at a rate of 2% to 4% [1,3]. Despite being a benign disease, RRP often has a significant impact on quality of life due to laryngeal disease and airway obstruction resulting in the need for serial surgical procedures to remove the papillomas [4].

Currently, there is no cure for RRP, apart from excision. Surgical debulking to preserve airway patency may be performed with CO_2 lasers or the use of endoscopic microdebriders as first-line treatment. However, papillomas often recur. A US survey reported in 1995 showed that RRP required an average of 4.4 procedures per year (19.7 per lifetime) with annual costs at that time estimated to be $150 million [5]. Adjuvant therapies, in addition to surgery, including cidofovir [6] and HPV vaccination [7], have not proven to be effective.

HPV viral oncogene products E6 and E7 have been shown to increase vascular endothelial growth factor (VEGF) via interactions with hypoxia inducible factor 1-alpha (HIF-1alpha) [8]. VEGF is known to play a significant role in the development of papilloma and may be a molecular target for the treatment of RRP [8]. Bevacizumab (Avastin) is a recombinant humanized monoclonal antibody that binds and inhibits VEGF by preventing receptor activation. Although not currently approved by the US Food and Drug Administration (FDA) for RRP, preliminary studies have demonstrated the efficacy of bevacizumab in the treatment of localized upper airway RRP using both intralesional and systemic administration [9–14].

We present the clinical course of two patients with extensive central airway and lung parenchymal RRP who were successfully treated at our center with systemic administration of bevacizumab.

Case Report

Case 1

In 2013, an 87-year-old retired physician with a history of chronic obstructive pulmonary disease (COPD), presented with chronic cough, stridor, and dyspnea. The patient was immunocompetent. Computed tomography (CT) of the chest showed left upper lobe collapse. Bronchoscopy and biopsy showed a benign papilloma that was associated with HPV 6. The patient underwent HPV vaccination and remained stable until 2015 when he developed worsening dyspnea. He required five bronchoscopies with debridement over the next 24 months but had significant post-procedural complications, including an admission to the intensive care unit (ICU) for severe bronchospasm and cardiac arrest.

Previous treatments had little effect and included intralesional cidofovir and an endobronchial stent, which was placed in the left lower lobe bronchus, to prevent obstruction from the papilloma that was extending from the left upper lobe bronchus. On initiation of bevacizumab treatment, the patient developed stridor. Computed tomography (CT) of the chest prior to bevacizumab treatment showed left upper lobe collapse with abrupt obstruction of the left upper lobe bronchus, as well as a heterogeneous left upper lobe mass. Bronchoscopy showed complete obstruction of the left upper lobe bronchus with papilloma (Figure 1).

Systemic bevacizumab was initiated at a dose of 5 mg/kg every two weeks. Within one week his cough and dyspnea improved and his stridor resolved. Following five cycles of bevacizumab treatment, it was agreed with the patient to decrease the treatment interval to every six weeks. After six courses of bevacizumab treatment, imaging showed a significant decrease in the left upper lobe mass and bronchoscopy demonstrated a patent left upper bronchus (Figure 1).

Following treatment, the patient was able to perform his activities of daily living without assistance. He developed two episodes of small volume hemoptysis several months into treatment, which resolved. Following treatment, he had no laboratory abnormalities and did not require further surgical interventions. At the time of writing this case report, the patient continues treatment with bevacizumab, 5 mg/kg every six weeks.

Case 2

A 63-year-old male flight engineer with a history of COPD and hypertension was diagnosed with HPV-11-associated RRP, initially involving the larynx; he was immunocompetent. He underwent six surgical interventions eventually requiring a short-term tracheostomy to facilitate further interventions, the last one being in 2005. The patient remained stable until 2011 when he developed worsening dyspnea and cough. CT showed extensive involvement of the tracheobronchial tree with papillomas, as well as right-sided cystic and nodular lesions. The patient required multiple surgical debulking procedures, but with minimal disease control. At the time of initiation of bevacizumab treatment, in April 2016, he was unable to work because of labored breathing and hoarseness.

Adjuvant therapies were discussed with the patient, but considering his extensive disease burden and parenchymal

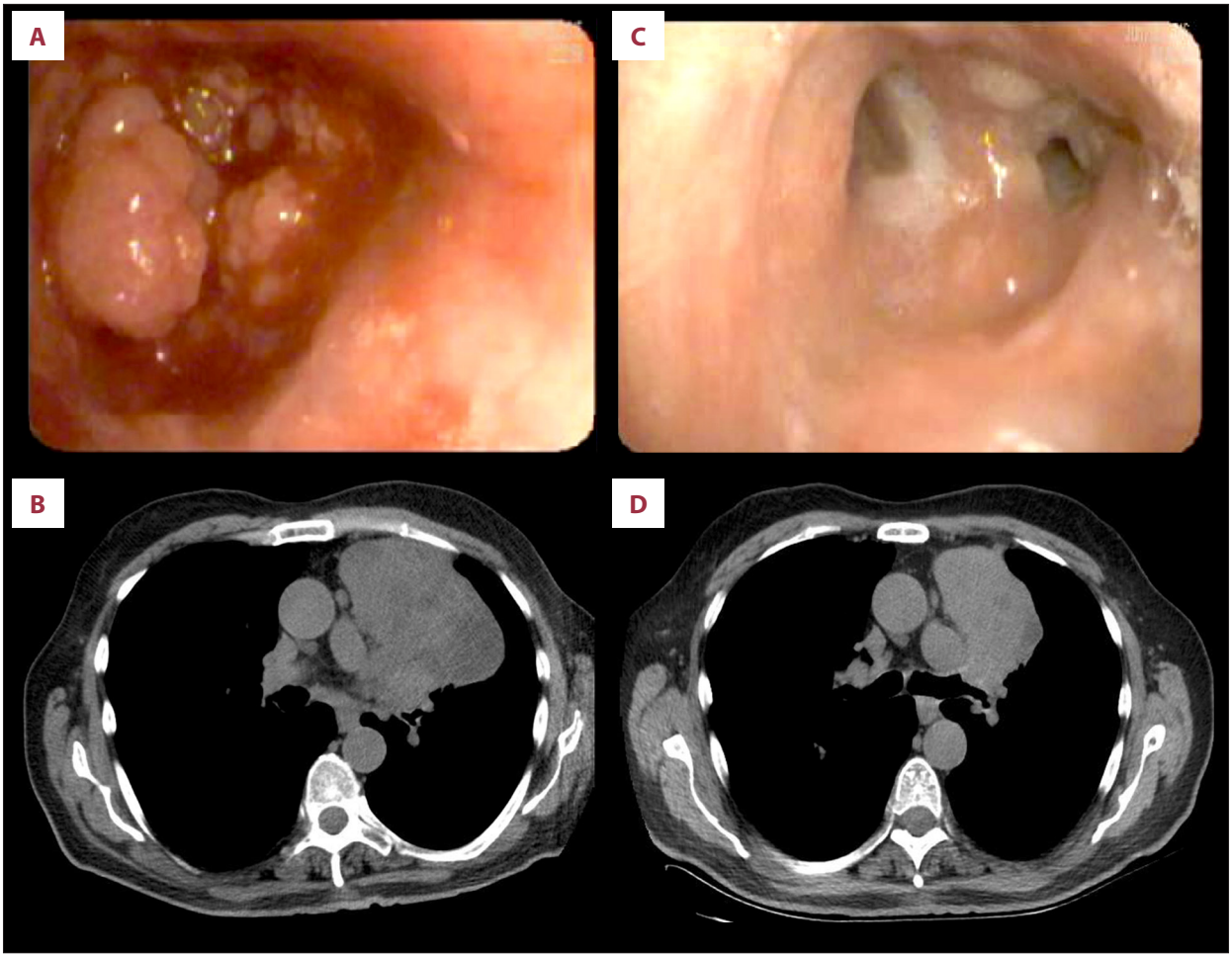

Figure 1. Case 1: Endoscopic and computed tomography (CT) images prior to and 16 weeks following treatment with bevacizumab. (**A**) Case 1: Endoscopic image prior to initiation of systemic bevacizumab treatment. (**B**) Case 1: CT image prior to initiation of systemic bevacizumab treatment. (**C**) Case 1: Endoscopic image 16 weeks after initiation of systemic bevacizumab treatment. (**D**) Case 1: CT image 16 weeks after initiation of systemic bevacizumab treatment.

involvement, systemic bevacizumab treatment was initiated. At this time, imaging showed a cavitating mass of the right lower lobe with endoluminal nodularity and narrowing of the trachea (Figure 2). Bronchoscopy showed a 40% obstruction of the trachea with papilloma. Treatment with bevacizumab, 10 mg/kg every two weeks, was begun. After one course of treatment, the patient described reduced hoarseness and reduced dyspnea. Repeat bronchoscopy after the second course of bevacizumab treatment showed no evidence of tracheal obstruction by papilloma. By December 2016, CT imaging showed that parenchymal involvement was reduced, including reduction in the size of the cavitating mass in the right lower lobe, which had been suspicious for malignancy (Figure 2). At the time of presentation of this case report, he is working full time, with only a mild increase in his blood pressure, which required no change to his antihypertensive regimen. He remains on 10 mg/kg bevacizumab, every three weeks, and has not required further treatment.

Discussion

These two case reports illustrate rapid and sustained improvement of extensive central airway and lung parenchymal RRP using systemic bevacizumab. Previous reports have shown efficacy with both local and systemic bevacizumab treatment. Zeitels et al. reported the use of intralesional bevacizumab in the diseased vocal folds of ten patients [9]. Doses of bevacizumab were administered in conjunction with 532-nm pulsed potassium titanyl phosphate (KTP) photoangiolytic laser treatment [9]. The study demonstrated improved voice assessments and reduced disease burden following treatment [9].

Previous studies have shown that local adjuvant treatment with bevacizumab has resulted in a reduction of RRP disease burden with increasing dosing [10–12]. These previous studies represented the first use of local bevacizumab as an adjuvant treatment [10–12]. In 2009, Nagel et al. presented a case

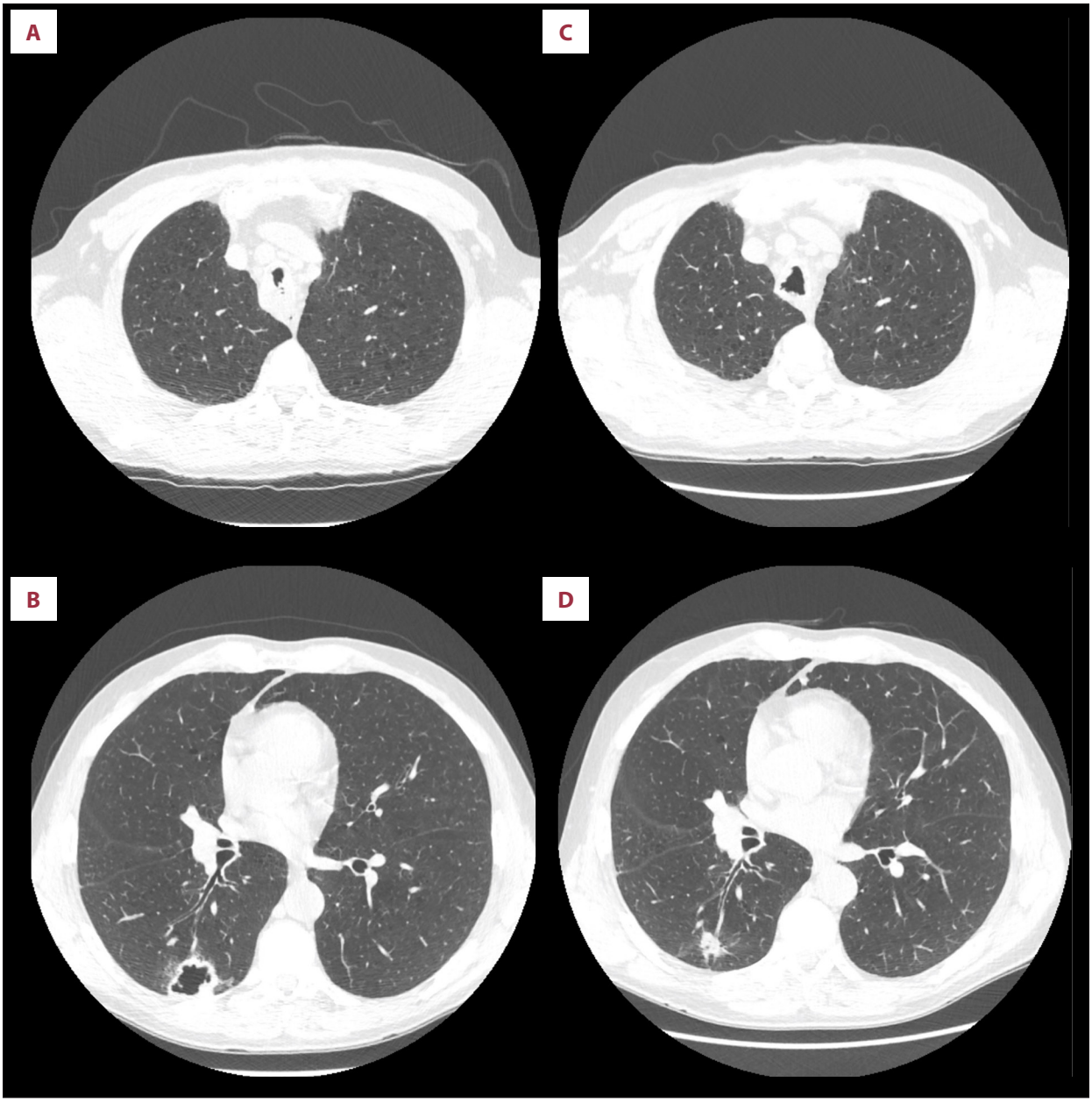

Figure 2. Case 2: Computed tomography (CT) images of upper and lower lung fields prior to and 8 months following treatment with bevacizumab. (**A**) Case 2: CT image of the upper lung fields prior to initiation of systemic bevacizumab treatment. (**B**) Case 2: CT image of the lower lung fields prior to initiation of systemic bevacizumab treatment. (**C**) Case 2: CT image of the upper lung fields, 8 months after initiation of systemic bevacizumab treatment. (**D**) Case 2: CT image of the lower lung fields, 8 months after initiation of systemic bevacizumab treatment.

of a patient who received systemic bevacizumab therapy and demonstrated postponement of the requirement for further local interventions [13]. Mohr et al. presented a single-center study of five patients who cumulatively required 18 procedures in the preceding 12 months [14]. After receiving doses ranging from 5–15 mg/kg for three to 16 courses, a sustained therapeutic effect was seen in all five patients including patients with lung parenchymal involvement [14]. Only one patient required interventional treatment due to a malignant transformation during the 12 months following treatment [14].

Side effects of bevacizumab treatment include hypertension, renal failure, proteinuria, bleeding, and bowel perforation [15]. New opportunities exist for systemic therapeutic modalities in the treatment of RRP and are supported, for example, by preclinical studies that have targeted epidermal growth

factor receptor (EGFR) [16], and ongoing clinical trials to determine the efficacy of anti-PD1 (NCT02632344) and anti-PD-L1 (NCT02859454) therapy for RRP.

Conclusions

The two cases presented of RRP have shown a favorable response to systemic bevacizumab therapy, with both cases showing extensive tracheobronchial disease beyond that previously described. In conclusion, we have shown that bevacizumab (Avastin) may reduce the need for recurrent surgical debridement in advanced cases of RRP. Further studies are needed to determine optimal dosing frequency and duration of therapy for bevacizumab in the treatment of RRP.

Conflicts of interest

There are no conflicts of interest.

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