CLINICAL VIGNETTE

Complete Response with Systemic Bevacizumab in a Woman with Recurrent Respiratory Papillomatosis

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Recurrent Respiratory Papillomatosis (RRP) is a rare, benign condition caused by the human papillomavirus (HPV). It most commonly affects the larynx but can occur anywhere in the respiratory tract. Despite its benign nature, treatment is often complicated by multiple lifetime recurrences, requiring surgical interventions, prompting a search for other treatments and adjuvant therapies. We report the case of a 59-year-old woman with a history of chronic recurrent severe respiratory papillomatosis requiring recurrent direct laryngoscopy with CO2 laser ablation of papillomas, who was initiated on systemic bevacizumab with complete response.

Introduction

Recurrent Respiratory Papillomatosis affects males and females equally, at a rate of 1.8 per 100,000 adults and 4.3 per 100,000 children in the United States.[1] Average age at diagnosis for juveniles onset RRP is 5 years while adult onset RRP average 37 years.[1] Despite being benign, this chronic disease frequently recurs with significant impact on quality of life, as well as financial impacts. Recurrences result in multiple surgical interventions throughout a lifetime. Severe forms of the condition can cause airway obstruction leading to respiratory distress requiring tracheostomy. Recurrent respiratory papillomatosis is primarily treated with surgical ablation of all visible papillomas with CO2 laser. This is often effective, but each surgery has increased risk of complications, including scaring and stenosis.[2] We describe a patient with complete response with systemic bevacizumab. There was minimal toxicity, and no need for ongoing surgical interventions.

Case

A 59-year-old woman with recurrent respiratory papillomatosis, required surgical ablation with CO2 laser every 3-4 months. She presented with worsening dysphonia over the last year. She had been lost to follow up, and her last surgical ablation was a year prior to presentation at our hospital. Flexible laryngoscopy revealed significant papillomas on the left false vocal cord and the posterior glottis. Bilateral vocal cords were patent along with her airway. She was taken to the OR for gross debulking of the papillomas with biopsy, followed by CO2 laser ablation. Surgical pathology was negative for malignancy, noting multiple fragments of squamous papillomas with focal koilocytic changes, along with focal acute on chronic inflammation. Her hoarseness significantly improved after the ablation.

One month later, the patient returned for repeat endoscopic surveillance. She had recurrent and progressive papillomatous lesions, and again underwent debulking, ablations with CO2 laser. During the procedure, the ENT surgeons injected Cidofovir to the bilateral vocal cords. This has been reported to be effective to slow the underlying papillomatous development.[3] Despite the intraoperative injection of Cidofovir, she had continued to have recurrent papillomas requiring repeat resection and ablation every three to four months. She was then given intraoperative steroid injections to the vocal cords, along with Cidofovir injection. This was more effective, and the patient remained symptom free for five months before repeat ablation. Repeat surgical pathology showed squamous papilloma with low grade dysplasia and she continued to be negative for malignancy. Patient was then given a trial of intraoperative, intralesional injections of Bevacizumab (Vascular Endothelial Growth Factor Inhibitor) but this did not affect the rate of recurrence.

The patient reported significant improvement in dysphonia after each procedure, with slow worsening until her next ablation. She was subsequently referred to medical oncology for consideration of systemic Bevacizumab. She had undergone eighteen resections with CO2 ablation over seven years. She was started on cycles of parenteral Bevacizumab 10mg/kg every 3 weeks. After three cycles of systemic Bevacizumab, endoscopy showed no evidence of recurrent papillomas. She was initially transitioned to Bevacizumab 10mg/kg IVPB every 6 weeks which was extended to every 9 weeks after cycle four. She continues to remain disease free with resolved symptoms. Surveillance includes a flexible laryngoscopy every 2 months and continued clinical assessment for return of symptoms. We plan to transition to Bevacizumab 10mg/kg IVPB every 12 weeks if she remains without disease after cycle seven, with approximately one year of treatment followed by surveillance. She reports no adverse events from bevacizumab other than mild Grade 1 hypertension that was easily controlled with medical management.

Discussion

Recurrent respiratory papillomatosis (RRP) is most commonly caused by HPV 6 and 11, but high risk strains from HPV 16, 18, 31, 33, and 39 have also been identified.[4] Although considered benign, it is associated with a 2% to 4% rate of malignant transformation, particularly with higher risk strains and lung involvement.[2] First line treatment is surgical ablation of all visible papillomas with CO2 laser, when patients develop symptoms from RPR. However, due to the relapsing and remitting nature of this disease, most patients require recurrent ablations as the papillomas frequently return. This is associated with cumulative lifetime risk of general anesthesia and iatrogenic complications. This prompts alternative treatments and adjuvant therapies. These include intralesional Cidofovir, systemic Interferon, and Celecoxib.[5] Prior adjuvant treatments proved either too toxic (particularly systemic interferon), or with limited efficacy.

Over the last decade, bevacizumab, has emerged as safe, effective treatment for RRP. This monoclonal antibody inhibits angiogenesis and tumor growth by targeting vascular endothelial growth factor (VEGF). It is used in patients with RRP and a high burden of disease.[6] VEGF has strong expression in papilloma epithelium in RRP patients.[7] In 2014, Mohr published their initial experience with systemic bevacizumab in five RRP patients. They reported dramatic responses and significant reduction in need for interval surgical debridement.[5] All patients had immediate effect with endoscopic reduction of disease and only one patient with malignant transformation required additional interventional treatment.

A systematic review by Pogoda et. al included 15 studies systemic Bevacizumab for severe RRP, and found 95% of cases (41 out of 43 patients), systemic Bevacizumab considerably prolonged the surgical interval.[8] Nearly 18% (24 out of 43) did not require any surgical intervention for RRP during follow up after initiation of Bevacizumab. The majority of patients in this systematic review had received various prior adjuvant therapies. The most common was Cidofovir (previously given to 26 out of 64 patients).[8] In regard to Bevacizumab dosing, most of these studies used a starting dose of 5-10mg/kg, more commonly 10mg/kg with initial dosing interval ranging from 2-4 weeks. Overall, 44% of patients experienced mild, self-limiting side effects. The most common side effects were proteinuria, epistaxis, headache, and hypertension. Additional retrospective review of 14 adults, reported only 30% of patients required additional procedures after starting Bevacizumab.[9] These patients received median of 8.5 bevacizumab infusions, and all experienced subjective improvement in symptoms (primarily hoarseness and shortness of breath). The majority of patients received Bevacizumab starting doses of 15 mg/kg every 3 weeks, with 42% requiring dose reduction to 10 mg/kg without clinical deterioration.

Best et. al conducted a survey of nine medical centers. The majority of patients received various other adjuvant treatments, and all patients were started on a dose of 5-10 mg/kg, most frequently every 3 week intervals.[5] Seven patients showed partial response, and one patient had a complete response.

Our patient was remarkable with complete response. While this has been previously reported in case reports and retrospective reviews, it remains rare. We believe that systemic Bevacizumab, has great promise in the treatment of severe Recurrent Respiratory Papillomatosis.

Conclusion

Though a benign condition that is generally manageable, Recurrent Respiratory Papillomatosis is a chronic disease frequently requiring lifelong treatment. It has significant quality of life implications - particularly as some patients first get the disease when they are quite young. The average age of onset for adults is 37 years old.[1] Systemic Bevacizumab, in our experience along with systematic reviews, can be a very effective option in patients who have required multiple ablations and surgical interventions. It transformed our patient's chronic disease that used to require four to five surgical interventions per year, along with additional visits and the outpatient infusions typically takes less than 90 minutes. Most importantly, the side effects of bevacizumab are generally mild with less risk than the general anesthesia required for her prior interventions, along with the surgical risks. At this time, the patient has maintained a complete response for over six months with Bevacizumab treatments now spaced out to every 9 weeks with plan for total treatment for 12 months. Given the unique side effects of Bevacizumab, not every patient will be a candidate for treatment; Bevacizumab should be avoided in patients, with history of severe cardiac disease, active thrombosis, hemorrhage, stroke, hemoptysis, or perforation. However, it remains a promising option for patients with Recurrent Respiratory Papillomatosis who have exhausted localized treatments and should be considered in patients requiring multiple procedural interventions.

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