Case Report

Safe Use of Systemic Bevacizumab for Respiratory Recurrent Papillomatosis in Two Children

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Recurrent respiratory papillomatosis can be a devastating condition for a child, with severe consequences. Currently, there is no proven successful medical treatment. We describe the use of systemic bevacizumab to treat two children affected by aggressive recurrent respiratory papillomatosis. Respiratory symptoms and quality of life improved dramatically in both patients, without observing any toxicity. The only complication was mild proteinuria. Systemic bevacizumab is a promising adjuvant treatment in aggressive recurrent respiratory papillomatosis in children. It is effective and well tolerated. Further studies are needed to establish the optimal dosing frequency and duration of therapy.

Key Words: Respiratory papillomatosis, laryngeal papillomatosis.

INTRODUCTION

Recurrent respiratory papillomatosis (RRP), also called laryngeal papillomatosis due to the strong predilection of the larynx, is characterized by the development of exophytic proliferative papillomas caused by the human papillomavirus, which affects the tracheobronchial tree. Squamous papilloma is the most common benign neoplasm of the larynx, affecting four per 100,000 children and 1.8 per 100,000 adults, and transformation to squamous cell carcinoma can occur at a rate of 2% to 4%. Despite being a benign disease, RRP often has a significant impact on the quality of life due to laryngeal disease and airway obstruction, resulting in the need for serial surgical procedures to remove the papillomas. The management of aggressive RRP is a real challenge, especially in children.

Currently, there is no cure, so surgical excision and debulking of the lesions to preserve airway patency have been the main treatment modalities to control the disease. Bevacizumab is a recombinant, humanized, monoclonal immunoglobulin G antibody that inhibits angiogenesis by neutralizing all isoforms of human vascular endothelial growth factor-A (VEGF), blocking their binding to VEGF receptors. It blocks the development of the blood supply to the tumor, thereby helping to slow its growth. In 2009, intralesional bevacizumab was reported to control laryngeal papillomatosis, and more recently, there have been publications reporting on the use of systemic bevacizumab in the management of aggressive RRP. The purpose of this article was to present our experience with intravenous bevacizumab for the treatment of aggressive RRP in two children.

CASE REPORT 1

The first case is an 8-year-old boy from Cuba who was first diagnosed with RRP when he was 15 months old and required a tracheostomy tube 1 month later due to severe obstruction of the upper respiratory tract. In Cuba, he had 10 surgical procedures for debridement of laryngeal lesions and was also treated with interferon-α injections for a period of 2 years without any clinical improvement. In June 2012, following a CT scan he was diagnosed with laryngotracheal RRP, with extension to the carina. In August 2012, when he was 3 years old, he was transferred to the Son Espases Universitary Hospital, Palma, Spain.

During the first year he underwent multiple surgical procedures, including debridement of laryngeal and...
tracheal papillomas by microdebrider along with intra-
mucosal injection of cidofovir. In May 2013, computed
tomography (CT) showed bilateral pulmonary spread of
the papillomatosis (Fig. 1), with multiple solid and cystic
nodules, atelectasis secondary to airway obstruction, and
bronchiectasis, and he began treatment with interferon-α
for 1 year and was immunized with Gardasil (Merck &
Co., Kenilworth, NJ). During this treatment period,
patient care was complicated by infection and the coloni-
zation of pulmonary lesions by *Pseudomonas aeruginosa*,
which caused multiple hospital admissions and the need
for prolonged antibiotic treatments. We performed
monthly tracheobroncoscopies and a CT scan every
6 months. After initial improvement of the pulmonary
disease observed on the CT scan in November 2013, a
new CT scan was performed 6 months later showing a
progression of the disease; therefore, systemic bevacizu-
mab treatment was planned. In June 2014, after a multi-
disciplinary committee discussion and hospital approval,
the patient was given his first dose of endovenous bevaciz-
umab at 10 mg/kg along with bronchoscopy and surgical
debridement. The family underwent extensive counseling
about the risks related to the treatment and its off-label
use for this indication. The next bronchoscopies and infu-
sions of bevacizumab were performed at 4-week intervals
for the first 6 months, and after obtaining significant
improvement that was confirmed on a CT scan (Fig. 2),
the time between infusions was increased gradually by
2 weeks until an 8-week interval was reached. After a
total of nine doses of bevacizumab, the patient was decan-
nulated successfully, but the treatment was interrupted
because of the appearance of proteinuria. In August and
September 2015, the patient needed two new surgical
procedures to remove the laryngeal lesions, so at 4-week
intervals bevacizumab infusion was begun again and
maintained for 6 months. In January 2016, a positron
emission tomography–computed tomography scan was
performed. It showed multiple nodular lesions, with no
sign of infection or malignancy. After this period, we
gradually increased the time between bevacizumab infu-
sions by 2 weeks to reach the current (April 2018)
10-week interval between bevacizumab infusions, and
from September 2015, no more surgical procedures were
necessary. During the follow-up, the patient needed sev-
eral hospital admissions and antibiotic treatments due
to recurrent respiratory infections. Proteinuria was the
only drug-related complication observed. Other more com-
mon complications, such as hypertension and thrombosis
(all reversible with drug discontinuation), were not
observed.

**CASE REPORT 2**

The second case is an 11-year-old girl from the
Ukraine who in 2013 was diagnosed with RRP at the age
of 6 years. For the next 3 years she underwent 46 surger-
ies in her country, including two temporal tracheosto-
mies, with the last operation taking place in October
2016. In November 2016, at the age of 9 years, she was
transferred to Son Espases University Hospital for
another surgery. Presurgical examination showed papillo-
matosis lesions affecting the laryngeal surface of the

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**Fig. 1.** Case 1. Computed tomography (CT) scan (May 2013) showing bilateral pulmonary spread of papillomatosis. (a) Axial CT scan.
(b) Coronal CT scan.

**Fig. 2.** Case 1. Axial Computed tomography (CT) scan 6 months after treatment with bevacizumab (January 2015) showing bilateral pulmonary nodules with reduction of inflammation signs.
epiglottis, both ventricular bands and vocal cords, as well as extension to the medial third of the trachea. She also presented with supraglottal anteroposterior synechia and stenosis of the posterior commissure, with subsequent limitation of movement of the vocal cords and obstruction of the air flow (Fig. 3).

In November 2016, we performed papillomatosis lesion removal with a microdebrider and glottal dilation with positive postoperative progress. Only 3 weeks after the surgery, she started receiving systemic bevacizumab at an initial dose of 5 mg/kg due to a poor electrocardiogram (EKG), with augmentation of the subsequent dose to 7 mg/kg because of good tolerance and clinical improvement of the patient. The infusions of bevacizumab were made at 3-week intervals, and every infusion (a total of eight infusions were performed) was preceded by a fibrolaryngoscopy that ruled out the appearance of new lesions throughout the treatment. No significant toxicity problems were observed during and after the treatment. The patient showed important clinical improvement, and no more surgical procedures have been necessary.

**DISCUSSION**

The treatment of aggressive RRP is challenging, especially in children, where multiple surgical procedures may be necessary to control the airway permeability. Even though the role of adjuvant therapy has been proposed,8 no stabilized protocol exists for the management of severe RRP. Only three reports on the use of systemic bevacizumab in children have been published (Table I). The authors observed satisfactory results, with a reduction in the need for surgery, improvement of quality of life,5,7,9 with no severe toxicity. However, it is important to note that all of the studies were small, with limited treatment duration and short follow-up.

In this article, we present two children with aggressive RRP who received systemic bevacizumab due to significant disease progression, with a follow-up of 4 years and 19 months, respectively. Both patients showed rapid improvement of respiratory symptoms. In the first case, decannulation was possible after receiving nine doses, and the only complication was mild proteinuria. Laryngeal papillomatosis recurrence occurred after suspending the treatment, and it is currently being maintained with 10-week intervals between infusions. The second child underwent eight doses of systemic bevacizumab, with 3-week intervals between infusions, resulting in excellent control of the lesions without any toxicity, and currently, the treatment has been suspended without evidence of recurrence.

Bevacizumab has no effect on the viral DNA and mechanisms of apoptosis, but presents a direct antiangiogenic action that affects tumor growth5 and is responsible for the therapeutic effect.9 It is responsible for reduction of the lesions’ size and the improvement of airway permeability, without eradicating the viral infection and risk of recurrence after suspending the treatment. On the first patient, we used a 10-mg/kg dosing schedule, which is recommended for adults in most case reports published in the literature. In the second case, we used a lower dose of 7 mg/kg because of a poor electrocardiogram report, and achieved satisfactory results. However, the long-term effects of the medication, which appears to require continued dosing to keep the papilloma under control, is not yet known, and there is little information about the best protocol to use because of the lack of clinical trials. Some insight might come from the use of systemic bevacizumab as a maintenance therapy for neurofibromatosis 2, where it is used as a nonsurgical modality for skull base schwannomas.10 More data may come from the treatment of Rendu-Osler-Weber disease, where lower doses of systemic bevacizumab are currently being used to treat refractory bleeding.11,12 Even with the limitations of this study, we report the use of systemic bevacizumab in two children without major complications and with a positive effect on respiratory symptoms during a follow-up of 4 years and 19 months, respectively.
CONCLUSION

Systemic bevacizumab is a promising adjuvant treatment in resistant and aggressive RRP in children. Further studies are needed to determine the optimal dosing frequency and duration of therapy.

BIBLIOGRAPHY


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**TABLE I.** Case Reports of Children Treated With Systemic Bevacizumab.

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>Dose, mg/kg</th>
<th>La</th>
<th>T</th>
<th>Lu</th>
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<th>Treatment Interval</th>
<th>Response</th>
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La = larynx; Lu = lungs; T = trachea.