

## Dysphonia after Bevacizumab Rechallenge: A Case Report

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### Key Words

Oncology · Bevacizumab · Dysphonia · Antiangiogenics

### Abstract

Inhibition of vascular endothelial growth factor (VEGF) signaling, an initiator of tumor angiogenesis, inhibits tumor growth and invasion. Bevacizumab, a monoclonal antibody to VEGF, in common use as an adjunct to standard chemotherapy like irinotecan in advanced colorectal cancer, also affects the normal (nontumor) vasculature. Dysphonia or voice changes have been anecdotally reported in patients that have been exposed to antiangiogenics. In this case report, we present an occurrence of severe dysphonia in a 60-year-old male with metastatic colorectal cancer after reintroduction of irinotecan and bevacizumab. To our knowledge, this is the first case of dysphonia associated with bevacizumab rechallenge.

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### Introduction

Reversible dysphonia or voice changes have been associated with antiangiogenic treatments such as bevacizumab, aflibercept, sunitinib, sorafenib, pazopanib, axitinib and regorafenib [1, 2]. As a non-life-threatening condition, vascular endothelial growth factor (VEGF)-related dysphonia may be overlooked and underreported; however, it is an important consideration for quality of life, potentially leading to depression and frustration since the voice is so fundamental for communication and social interaction.

In colorectal cancer, bevacizumab is the most frequently administered biologic agent administered across all lines of therapy even after the development of treatment resistance [3]. In this context, to improve quality of life and decrease the possibility of noncompliance,

it is proportionately more important to heuristically recognize and treat even (formerly) rare side effects when they occur.

### Case

A 60-year-old man treated at Walter Reed National Military Medical Center with metastatic colorectal adenocarcinoma was rechallenged with irinotecan and bevacizumab. The patient improved symptomatically; however, hoarseness of voice and periods of dysphonia/aphonia developed synchronously with bevacizumab and irinotecan re-treatment. Ear, nose and throat specialists were consulted, and endoscopy demonstrated edema and inflammation of the larynx. Interestingly, dysphonia was not a side effect during FOLFOX and FOLFIRI treatment with bevacizumab. Despite the clear clinical benefit, bevacizumab may be temporarily or permanently discontinued to investigate the reversibility of the voice loss.

### Discussion

Bevacizumab, a humanized monoclonal antibody that intercepts VEGF and inhibits angiogenesis, is indicated in the adjuvant setting for the treatment of advanced or metastatic colorectal cancer. However, it may also damage the microvasculature of normal tissue as well as neoplastic vessels, leading to adverse effects. Experimental data from Kamba et al. [4], which demonstrate that anti-VEGF treatment leads to capillary regression in several mouse tissues, including the trachea and laryngeal mucosa, suggest that the mechanism of the clinical dysphonia may be related to disruption of these particularly sensitive capillaries (fig. 1).

Fortunately, however, VEGF receptor-induced capillary regression may be reversible, with regrowth occurring over 1–2 weeks for the adult mouse tracheal mucosa [5]. Case presentations have reported voice recoverability during anti-VEGF inter-dosing periods [6]. Therefore, discontinuation of bevacizumab may similarly lead to reversal of hoarseness in this patient.

We have presented this short clinical vignette for two reasons: (1) because VEGF-induced dysphonia may be an underreported and underappreciated side effect, and (2) because this patient may be a bellwether for the development of formerly rare side effects like dysphonia due to the continual reuse of therapies such as bevacizumab. As life expectancy increases with improved systemic treatment, it will be even more important to minimize side effects for maximal quality of life.

### Statement of Ethics

The research behind this case report complies with the guidelines for human studies. Any subjects have given their informed consent, and the study protocol has been approved by the relevant institute's institutional review board, also known as an independent ethics committee, ethical review board, or research ethics board.

### Disclosure Statement

The authors declare that there exist no conflicts of interest in the publishing of this case report.

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### Potential Avastin effects on larynx vasculature

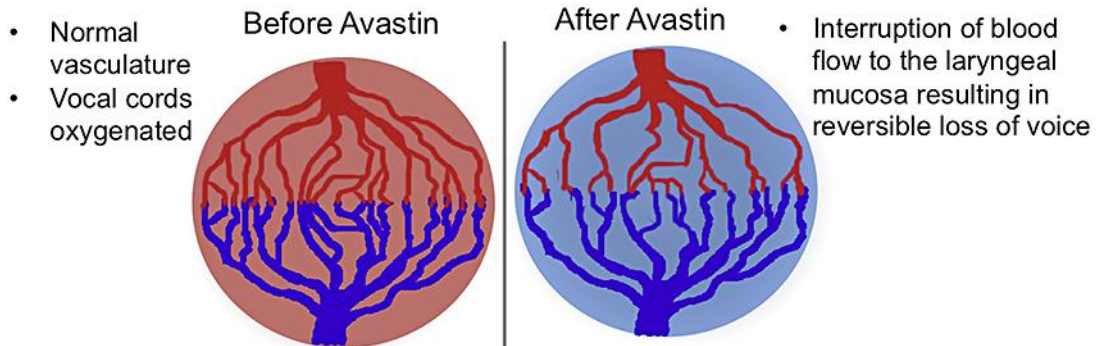


Fig. 1. Potential effects of Avastin on the larynx vasculature.