Bevacizumab-induced laryngeal necrosis

Tumor angiogenesis is the main target of many modern cancer therapies. Two strategies have been developed to inhibit vascular endothelial growth factor (VEGF) signaling, which restricts tumor growth by limiting new blood vessel development. The first strategy involves the use of recombinant monoclonal antibodies, such as bevacizumab, that recognize and bind VEGF directly, thereby preventing receptor binding. The second strategy involves the use of small molecule tyrosine kinase inhibitors that target one or more of the VEGFRs. In the past few years, different anti-angiogenic agents have been approved for the treatment of a variety of solid malignancies and have lead to survival improvements in the treatment of cancer [1].

However, these drugs carry toxic effects related to on-target, vascular effects, such as hypertension, thromboembolism and bleeding [2, 3] but also possibly to off target effects, such as mucositis and skin rash [4]. The mechanisms underlying the toxic effects of these drugs have still not been completely elucidated.

We herein report the first case of spontaneous necrosis of the vocal folds in a patient treated with bevacizumab, which represents an extreme complication of the laryngeal toxicity that we have previously reported with anti-VEGF drugs [5]. We discuss the possible mechanisms underlying this type of toxicity and the directions for future research.

A 46-year-old woman was referred to our institution for treatment of metastatic bronchopulmonary adenocarcinoma with inaugural pericarditis, mediastinal nodes and bilateral adrenal gland metastases. She received gemcitabine and cisplatin for 7 months and then erlotinib. Due to progression, she was included in a phase I trial with a vascular-disrupting agent (inhibitor of tubulin polymerization) associated with carboplatin and paclitaxel for six cycles. Then, she received two cycles of pemetrexed alone, without efficacy, then weekly carboplatin and paclitaxel (Bristol-Myers Squibb, Rueil-Malmaison, France) associated with bevacizumab.

Three weeks after the first administration of weekly paclitaxel–bevacizumab, the patient’s voice suddenly and permanently became hoarse, with episodes of aphony. The patient complained of vocal fatigue, with no odynophonia, dysphagia or dyspnea. Fiberoptic laryngeal examination revealed white plaques on both vocal folds, sparing the anterior commissure and the vocal process. Small telangiectasias were noted on the supraglottic mucosa. No inflammation or other signs of extra-esophageal reflux disease or mucositis were noted, and laryngeal mobility was normal. No laryngeal modifications were visible on computed tomography or on 18-fluorodeoxyglucose positron emission tomography as compared with baseline. Due to the clinical aspect, empiric topical antifungal treatment (fluconazole 100 mg/day p.o.) was administered for 6 weeks, with no effect. To rule out infection or malignancy, suspension laryngoscopy under general anesthesia was carried out.

On microlaryngoscopy, the mucosa and vocal ligament at the middle two-third of the vocal folds had disappeared, symmetrically sparing the anterior commissure and the mucosa at the posterior aspect of the vocal fold at the level of the vocal process (Figure 1). An excisional biopsy of the left vocal fold was carried out, revealing a necrotic aspect of the underlying vocalis muscle (Figure 2). The postoperative course was uneventful, and voice was no worse after the biopsy.

Histopathological analysis revealed necrosis, edema and a polymorphic inflammatory infiltrate with predominately neutrophils. There was no fungal or bacterial infection on microscopic or microbiological analysis and no malignancy. Follow-up has shown no change in voice or in the clinical aspect of the larynx. The metastatic disease is currently stable with gemcitabine–bevacizumab.

Voice is made possible by the vibration of the mucosa, which is independent of the underlying vocal ligament and vocalis muscle due to the presence of a loose connective tissue layer called the superficial lamina propria (or Reinke’s space) just under the mucosa. The blood vessels vascularizing the mucosa are found in this space. Normally, these vessels cannot be macroscopically individualized, but in inflammatory and neoplastic diseases, vascular dilatation and neovascularization are clearly visible through the mucosa [6].

In our previous report, we reported dysphonia associated with a whitish atrophic aspect of the vocal folds, with a rigid thin mucosa and a decrease in the mucosal wave in patients treated with various anti-angiogenic drugs [5]. The first pathophysiological hypothesis for the spontaneous glottic necrosis that we report now is that the glottic capillaries may be particularly sensitive to VEGF inhibition and undergo regression as has been observed in other adult organs such as the pancreatic islet cells, thyroid, adrenal cortex, choroid plexus and the trachea [2, 7, 8]. Baffert et al. showed that the capillaries in the adult mouse trachea decreased by 19% after 7 days of treatment and by 30% after 21 days of treatment. VEGF inhibition induced endothelial apoptosis and a migration of pericytes to surviving vessels. An empty basement membrane remained as a ‘skeleton’ after endothelial apoptosis, persisting for 2 weeks and serving as a scaffold for vascular regeneration after VEGF inhibition was stopped.
Figure 1. Microlaryngoscopic aspect of the necrosis of the vocal folds.

Figure 2. Microlaryngoscopic aspect of the underlying necrotic vocal ligament and vocalis muscle.

Kamba et al. [7] tested different VEGF-inhibiting approaches and found that all produced capillary regression in the aforementioned tissues in adult mice. The percent loss of capillary density varied among the organs, with a higher loss in thyroid and pancreatic islets, and also varied somewhat among the different VEGF inhibitors employed.

These particularly sensitive capillaries have been shown to express high levels of VEGFR-2 and -3 and have endothelial fenestrations, as compared with non-sensitive capillaries [7, 9]. Capillary regression with VEGFR inhibition is reversible, with re-growth occurring over 1–2 weeks for the adult mouse thyroid and tracheal mucosa [7, 8]. In our previous study, dysphonia was also reversible, with voice recovering during the inter-dose period [5].

Effects of anti-VEGF therapies on the nasal mucosa have also been reported, with edema, inflammation, vascular dilatation and telangiectasis [10], which can even lead to spontaneous nasal septal perforation [11]. Docetaxel in itself has been found to carry endothelial toxicity, and two nasal septal perforations have been reported in patients treated with docetaxel alone [12]. In our previous report, three patients had been treated with a combination of docetaxel–cisplatin–5-fluorouracil–VEGF trap [5]. A recent phase III trial combining docetaxel with VEGF trap in non-small-cell lung cancer has reported at least 10% clinical dysphonia [13].

Nasal septal perforation is an already well-known clinical entity, which can even lead to spontaneous nasal septal perforation [11]. Docetaxel in itself has been found to carry endothelial toxicity, and two nasal septal perforations have been reported in patients treated with docetaxel alone [12]. In our previous report, three patients had been treated with a combination of docetaxel–cisplatin–5-fluorouracil–VEGF trap [5]. A recent phase III trial combining docetaxel with VEGF trap in non-small-cell lung cancer has reported at least 10% clinical dysphonia [13].

Nasal septal perforation is an already well-known clinical entity in the absence of VEGF inhibition and can be caused by traumaism such as surgery and cocaine use. Isolated vocal fold necrosis, on the contrary, is not a known clinical entity and, to our knowledge, this is the first report of this entity. Apoptosis of the capillaries in the superficial lamina propria could theoretically lead to necrosis of the vocal folds due to the fact that there is no other vascular supply to the vocal fold mucosa or vocal ligament. The supraglottic mucosa, however, is vascularized by submucosal capillaries in closer connection to the underlying arterioles and venules, which may explain the isolated effect at the glottic level.

A second target for toxicity are the organelles situated at each end of the vocal fold, called the maculae flavae containing a type of fibroblast, stellate cells, that synthesizes the extracellular matrix [14, 15]. Degeneration of the stellate cells occurs with aging [16] and they are more sensitive to radiation than other fibroblasts [17]. It is unknown whether these cells express VEGFR, but an effect on these cells may also explain the abnormalities observed in our patients. The sparing of the anterior and posterior parts of the vocal folds may be related to the fact that the maculae flavae are located in these areas, with the superficial lamina propria between them, and that the vascularization and homeostasis of the anterior commissure, the posterior commissure and the supraglottic larynx are different from those of the vocal folds.

Submucosal injection of bevacizumab associated with laser photoangiolyis is a promising new treatment of recurrent laryngeal papillomatosis [18], but laryngeal complications such as seen in the present study have not been noted using this treatment.

This is the first report of spontaneous vocal fold necrosis induced by anti-angiogenic drugs. The particular qualities of glottic capillaries may explain their increased sensitivity to VEGF inhibition, but the expression of VEGF in the larynx and the exact mechanism of this toxicity are still unknown. The laryngeal toxicity of anti-VEGF therapies may be underreported due to limited awareness of this rare side-effect, and further studies will be needed before any treatment can be proposed.

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disclosure

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references


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