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Case report

Transient vocal fold lesion and hoarseness associated with the use of ramucirumab: Case report



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ABSTRACT

Introduction: Gastric cancer (GC) is among the leading neoplasms with highest morbidity and mortality in the world. Tumor angiogenesis represents one of important targets of antineoplastic treatment, as it has an important role in cell development and growth.

Case report: Ramucirumab, an IgG1 monoclonal antibody (MoAb), inhibits the angiogenesis pathway by blocking the VEGFR-2 activation. The most common adverse events associated with angiogenic inhibitors are cardiovascular and healing disorders, such as systemic arterial hypertension (HTN), thromboembolism, bleeding, wound healing delay and fistulas. We report a case of vocal fold lesion associated with ramucirumab in a patient with metastatic gastric cancer. The patient presented with transient hoarseness that was related to the exposure to ramucirumab.

Discussion: Laryngeal toxicity due to anti-angiogenic agents is rare. Despite the fact that this adverse event is not a life-threatening complication, it can significantly impair quality of life and should be promptly recognized.

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1. Introduction

Gastric cancer (GC) represents the fifth most common malignancy and the third leading cause of death due to cancer in the world. Currently, chemotherapy regimens based on the combination of fluoropyrimidines and a platinum compound are standard of care in first-line treatment [1]. Based on the result of a randomized phase III trial, ramucirumab plus paclitaxel was approved for second-line treatment of patients with metastatic GC [2].

Anti-angiogenic drugs have been incorporated in the treatment of many neoplasms in the past decades. Neo-angiogenesis is a fundamental process necessary to tumor growth and dissemination. The angiogenesis process relies on the interactions between vascular endothelial growth factor ligands (VEGF) and the respective receptors (VEGFRs) on endothelial and tumor cells [3].

Ramucirumab, an IgG1 monoclonal antibody (MoAb) that inhibits the angiogenesis pathway by blocking the VEGFR-2 activation, is capable of binding itself to the extra-cellular domain of the VEGFR-2 causing a blockade of the ligands: VEGF-A, VEGF-C and VEGF-D. By blocking VEGFR-2 activation, ramucirumab inhibits the

angiogenesis pathway involved in the development and progression of tumor cells [4].

As a result, most common adverse events associated with angiogenic inhibitors are vascular and healing disorders, such as systemic arterial hypertension (HTN), thromboembolism, bleeding, wound healing delay and fistulas [5]. In addition, mucositis and cutaneous rash has been observed in some patients [6]. This report aims to present a situation of vocal fold lesion associated with the use of ramucirumab, which represents an important complication related to laryngeal toxicity and is often neglected due to the rarity of the situation. Although it is not a life-threatening complication, the vocal fold lesions can cause dysphonia and impair the quality of life of patients under treatment.

2. Case report

A 73-years-old, male, was admitted with a history of ulcerated gastric lesion that was diagnosed by upper digestive endoscopy and the biopsy revealed adenocarcinoma, Lauren diffuse subtype, with signet ring cells. The patient had previous medical history of hypertension, hypothyroidism and dyslipidemia, and was on benazepril, atorvastatin, levothyroxin. On 25/04/2016, he underwent partial gastrectomy with D2 lymphadenectomy. The patient was staged as pT2pN2M0 (TNM staging system 8th ed.) [7].

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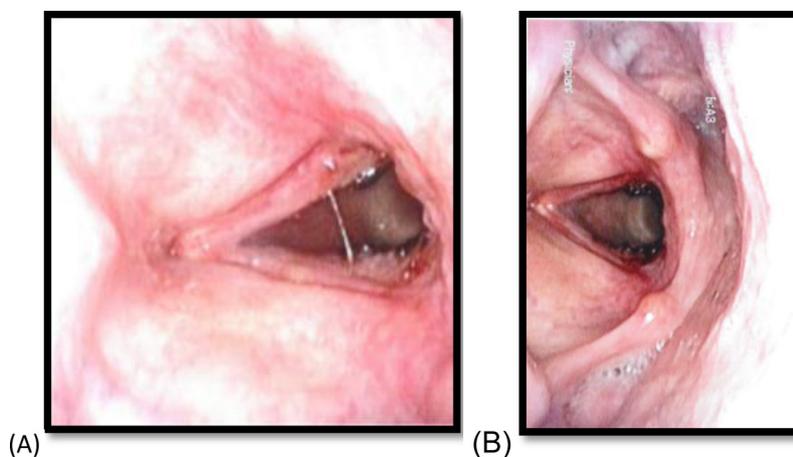


Fig. 1. A and B. Presence of edema, inflammation and hematic crusts on both vocal folds after the third cycle of ramucirumab.

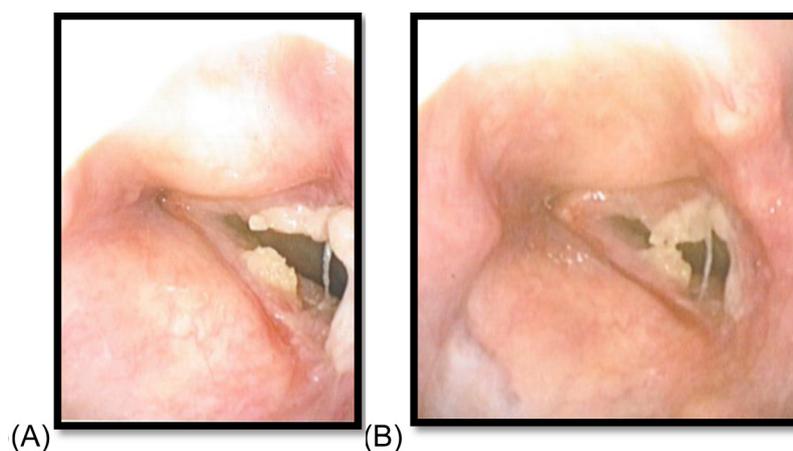


Fig. 2. A and B. Presence of scar areas in the vocal folds containing fibrin after delay of the fourth cycle of chemotherapy.

Initially, the patient received adjuvant chemotherapy with capecitabine + oxaliplatin. However, after completion of 8 cycles of chemotherapy, progression of disease was observed in lymph nodes (peripancreatic, mediastinal and abdominal aortic) and 3 hepatic nodules. For relapsed disease, second-line chemotherapy was started on 12/01/2017 with weekly paclitaxel and every 15-day ramucirumab. After the third cycle of chemotherapy, the patient evolved with dysphonia and was referred for video nasolaryngoscopy on 04/04/2017, which showed the presence of edema, inflammation and hematic crusts on both vocal folds (Fig. 1). After the diagnosis of this complication, the beginning of the fourth cycle was delayed and an interval nasolaryngoscopy was performed.

In the new examination, it was possible to detect scar areas in the vocal folds containing fibrin, corroborating the clinical improvement in the dysphonia reported by the patient on 27/04/2017 (Fig. 2). The same chemotherapy regimen was resumed and it was associated with worsening of the dysphonia, a grade 3 hoarseness being diagnosed [8]. The patient was able to communicate by whispering and had difficulty in keeping talks by the phone and complained of impairment in the quality of life. Due to the potential causality of the event and the use of ramucirumab, this drug was discontinued and the patient was kept on paclitaxel monotherapy on 07/07/2017. After 10 weeks, on 19/09/2017, a new video nasolaryngoscopy was carried out showing a complete resolution of the vocal fold lesions (Fig. 3). After this new discontinuation, the voice quality was reestablished. On October 2017, the patient presented central nervous system (CNS) progression of disease,

received whole brain irradiation, but eventually died on November 2017, due to CNS progression disease.

3. Discussion

Adverse events most frequently associated with the use of ramucirumab are cardiovascular, dermatological, gastrointestinal, genitourinary and hematological. In addition, like other anti-angiogenic agents, the use of ramucirumab may result in hypertension, proteinuria, thromboembolism, perforation of the GI tract, epistaxis and other bleeding events.

The symptom of dysphonia has been observed in the context of oncological treatment during the use of anti-angiogenic drugs, such as bevacizumab, aflibercept, sunitinib, sorafenib, pazopanib, axitinib and regorafenib [9,10]. In recent years, different anti-angiogenic agents have been approved for the treatment of several solid neoplasms and are related to improvement in the survival of patients with many types of neoplasms [11]. Ramucirumab, in association with paclitaxel, significantly increased overall survival when compared to placebo associated with paclitaxel in patients with metastatic gastric adenocarcinoma that progressed after the first-line of chemotherapy [12].

Vocal fold lesions have been previously reported with the use of anti-angiogenic agents, mainly bevacizumab. The lesions are described as vocal fold necrosis and the laryngeal examination reveals pale and atrophic vocal fold mucosae. The onset of the events was temporarily associated with the use of bevacizumab and

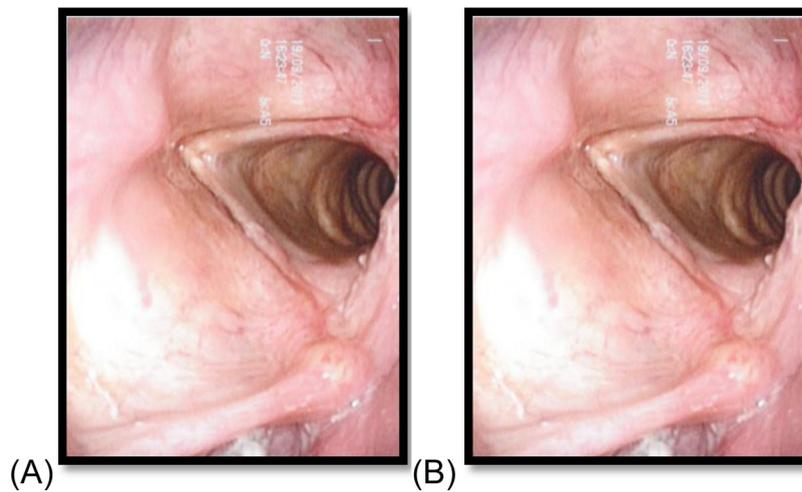


Fig. 3. A and B. Complete resolution of the vocal fold lesions after discontinuation of ramucirumab.

resolved with discontinuation of the drug [9]. One irreversible vocal fold necrosis was reported by Hartl et al. in 2010 [13]. In our case, the patient presented hoarseness after initiation of Ramucirumab and recovered after discontinuation. In a new attempt when the drug was resumed, the patient restarted with the symptoms, and a new discontinuation was necessary, showing a clear association between symptoms and ramucirumab use, as well as the vocal fold lesions as shown in Figs. 2 and 3. The symptom of dysphonia can be graded according to the impairment in daily activities, such as speech and social contact. Our patient complained of limitation to talk by the phone and to communicate to hospital professionals during the treatment.

Treatment with anti-VEGF may cause damage to the mucosa by inhibiting the neo-angiogenesis and disrupting the microvasculature. This may explain the bleeding aspect observed in our patient. Experimental data from Kamba and McDonald [14] have shown that anti-VEGF treatment can lead to capillary regression in various rat upper airway tissues, including trachea and laryngeal mucosa, suggesting that the mechanism of dysphonia is related to the damage of these capillaries. However, this capillary regression induced by anti-VEGF treatment may be reversible, with new capillary growth occurring within 1–2 weeks [5]. Some reported cases have demonstrated vocal recovery during the intermittent period of anti-angiogenic administration [6]. Differently from the classical aspect of vocal fold necrosis with pale lesions, our patient presented with edema, inflammation and hematic crusts with signs of recent bleeding. This type of lesion has not yet been reported with the use of anti-angiogenic agents. One explanation may be related to the fact that our patient was referred to the department of otolaryngology early in the development of the symptoms. A delay in diagnosis could justify the aspect observed in other publications that do not specify the time between the start of symptoms and the nasolaryngeal examination.

4. Conclusion

This report shows a rare and often overlooked adverse event associated with the use of ramucirumab. The exact mechanism of laryngeal toxicity caused by anti-angiogenic agents has not yet been fully investigated or understood. As a result of improvement in survival in many malignancies with routine usage of

anti-angiogenic agents, it is important to be familiar with atypical but specific events. Early recognition of vocal fold lesions during ramucirumab therapy can minimize treatment interruption and it can be translated into improvement in outcomes and quality of life for patients.

Disclosure of interest

The authors declare that they have no competing interest.

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