Cureus

Open Access Case Report

DOI: 10.7759/cureus.26780

Perforation of the Nasal Septum in a Colorectal Cancer Patient Treated With Aflibercept: A Case Report

Review began 07/04/2022
Review ended 07/10/2022
Published 07/12/2022

Javier David Benitez Fuentes [1, 2] , Alfonso Lopez de Sa Lorenzo [2] , Alberto Elpidio Calvo Elias [3] , Carmen Toledano Rojas [2] , Monica Granja Ortega [2]

1. Health Research Institute of the Hospital Clínico San Carlos (IDISSC), Hospital Clínico San Carlos, Madrid, ESP 2. Medical Oncology, Hospital Clinico San Carlos, Madrid, ESP 3. Internal Medicine, Hospital Clinico San Carlos, Madrid, ESP

Corresponding author: Javier David Benitez Fuentes, javierdavidbenitezfuentes@gmail.com

Abstract

Aflibercept is an antiangiogenic agent used in patients with metastatic colorectal cancer who have progressed to a first-line oxaliplatin-based regimen. The main adverse effects (AEs) of antiangiogenic agents are fatigue, asthenia, anorexia, hypertension, proteinuria, urinary tract infection, diarrhea, and neutropenia. Other AEs, such as hemorrhage, thromboembolic events, and gastrointestinal perforation, are much less frequent. Nasal septal perforation caused by antiangiogenic agents is even rarer. The published literature on this subject is scarce. Here, we report the case of a 54-year-old male with metastatic colorectal cancer undergoing treatment with leucovorin, fluorouracil (5-FU), irinotecan, and aflibercept who presented with epistaxis and nasal congestion. An otolaryngologist performed a rhinoscopy that revealed a perforation of the nasal septum. Aflibercept was withdrawn first, and local treatment was applied with lubricant and antibacterial lotions. It was considered a non-life-threatening side effect, and given the high risk of not continuing treatment in this patient with a recent recurrence, aflibercept was reintroduced in combination with leucovorin, 5-FU, and irinotecan. The patient continued local treatment and follow-up with medical oncology and otolaryngology with gradual improvement of symptoms. Follow-up was discontinued due to disease progression and death after 16 months of the event.

Categories: Oncology
Keywords: skin and mucosal toxicity, a case report, antiangiogenic drug, adverse event, nasal septum perforation, colorectal cancer, aflibercept

Introduction

Aflibercept is a recombinant fusion protein formed by portions of the vascular endothelial growth factor (VEGF) binding sites to the extracellular domains of human VEGF receptors 1 and 2, fused to an Fc portion of human immunoglobulin G1 (IgG1) [1]. VEGF is an essential regulator of angiogenesis, primarily activated by hypoxia, and overexpressed in several malignancies, including colorectal cancer. VEGF plays an important role in tumor vascularity, proliferation, progression, invasion, and metastasis [2]. Aflibercept performs its function by binding to various angiogenic molecules, preventing their binding to their native receptors of the VEGF family and thus acting as an antiangiogenic agent. It is indicated, in combination with FOLFIRI (leucovorin, 5-FU, irinotecan), in patients with metastatic colorectal cancer who have progressed to a first-line oxaliplatin-based regimen [1].

Regarding the most frequent adverse events (AEs) related to antiangiogenic drugs, we find fatigue, asthenia, anorexia, hypertension, proteinuria, urinary tract infection, diarrhea, and neutropenia. Also described but less frequent, there are thromboembolic and hemorrhagic events as well as fistula in any location [3]. In the published literature on the use of antiangiogenic drugs, it has been found that perforation of the nasal septum can also occur, the compound with the most data regarding this is bevacizumab [4-5]. It has been hypothesized that this AE could be due to the nasal cartilage being poorly vascularized, in addition to the argument that these drugs may further compromise the sparse vasculature of this tissue [4].

Here we present the case of a 54-year-old man diagnosed with colorectal cancer stage IV treated with FOLFIRI (leucovorin calcium (calcium folinate), 5-fluorouracil, and irinotecan) and aflibercept who presented with nasal septum necrosis and perforation during the treatment.

Case Presentation

We describe the case of a 54-year-old Slavic male with no previous medical records. In January 2019, he was diagnosed with acute appendicitis. The patient underwent an urgent appendicectomy. Pathologists found no signs of malignancy in this first surgery. In March 2019, he was hospitalized with the chief complaint of abdominal pain associated with fever. A computed tomography (CT) scan revealed multiple intra-abdominal abscesses in the right iliac fossa. A second urgent surgery was performed. The surgical

How to cite this article
Benitez Fuentes J, Lopez de Sa Lorenzo A, Calvo Elias A, et al. (July 12, 2022) Perforation of the Nasal Septum in a Colorectal Cancer Patient Treated With Aflibercept: A Case Report. Cureus 14(7): e26780. DOI 10.7759/cureus.26780

team detected an abscessed mass on the hepatic flexure of the colon with perforation to the retroperitoneum and abdominal cavity. The surgeons then performed a right hemicolectomy, drainage, and ileocolic anastomosis. Pathology showed a poorly differentiated enteroid adenocarcinoma pT4apN1c, stage IIIB, wild-type RAS, BRAF V600E mutation.

In May 2019, the patient started adjuvant therapy with capecitabine and oxaliplatin, withdrawing oxaliplatin after the third cycle due to moderate-severe nausea and diarrhea. He received seven cycles until October 2019. A follow-up CT in November 2019 showed disease recurrence in the right iliac fossa confirmed in a positron emission tomography CT in December 2019. The patient then started therapy with FOLFIRI plus aflibercept, reporting epistaxis and nasal congestion after five cycles. The subject had no previous history of nasal pathology, hypertension, or hemorrhagic diathesis. The Medical Oncology team then contacted the otolaryngology department for further evaluation.

Rhinoscopy examination by otolaryngology showed a large perforation involving the cartilaginous nasal septum surrounded by necrotic mucosa, as can be seen in Figure *1*.

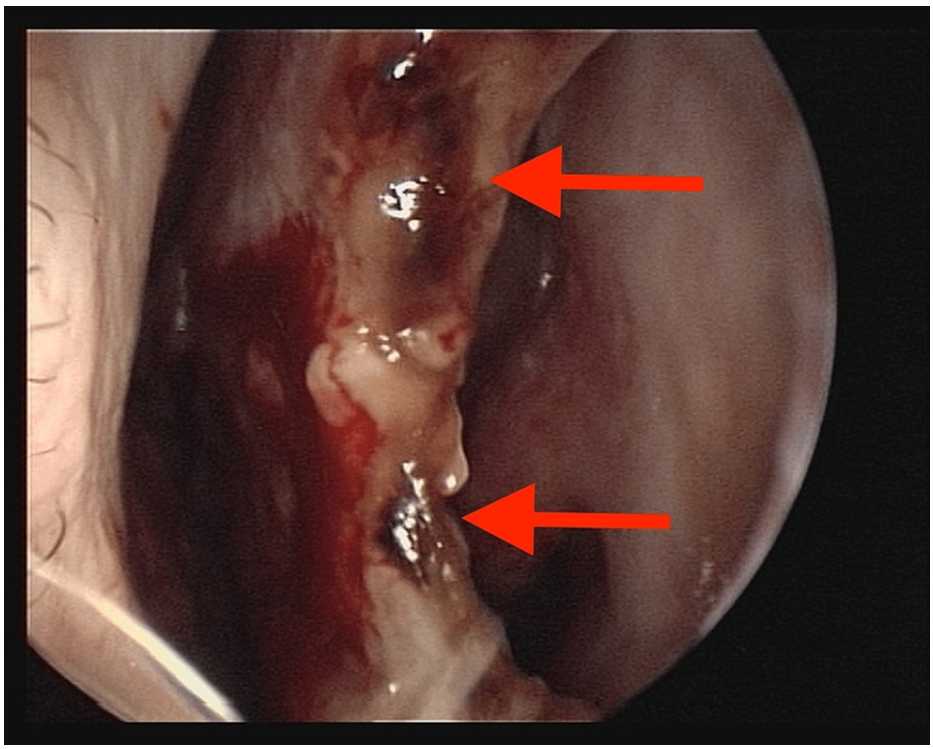

FIGURE 1: Nasal septum perforation

Perforation of the nasal septum seen at rhinoscopy with necrotic-appearing tissue (red arrows)

Otolaryngologists performed multiple biopsies that showed no infectious, granulomatous, or malignant cause of perforation. They then started the patient on local treatment with lubricant and antibiotic lotions to avoid bacterial infection and improve symptoms.

With all these pathology results, aflibercept was withdrawn first. We considered this a non-threatening side effect and because of the high risk of discontinuing antineoplastic treatment in this patient, we reintroduced aflibercept in combination with FOLFIRI. The patient gradually improved the local symptoms without complete resolution of the perforation during otolaryngology rhinoscopy monitoring. However, after 16 months, follow-up was discontinued due to disease progression and death.

Discussion

Nasal septum perforation is a clinical entity usually related to medical fields such as traumatology, infectious diseases, and substance abuse [6]. However, in cancer patients, it is an atypical entity. In this population, this AE is most seen with antiangiogenic treatment, particularly with bevacizumab [4-5].

A literature search of PubMed found few case reports published of septum perforation with bevacizumab [7-16]. The scientific literature regarding the incidence of this complication is scarce. One study found that five subjects (7%) out of 70 metastatic breast cancer patients treated with bevacizumab developed nasal

septum perforation [5]. Another study on metastatic colorectal patients found that one subject (1%) out of 100 metastatic colorectal cancer patients developed this AE [4].

In addition, in one article about two cases, we found evidence that docetaxel may also be associated with nasal septal perforation [17].

The management of this entity is not clearly defined. It remains mainly symptomatic in most cases. Treatment is usually based on local measures, intranasal hydration, lubricant, antibiotic lotions, and hemostatic agents in the event of epistaxis. Surgical intervention is seldom needed, as this complication is usually controlled and successfully treated with local measures, especially in patients with poor prognoses [4-5]. There is no evidence for discontinuing antiangiogenic treatment. Therefore, a case-to-case approach has to be done, balancing the risks of withdrawing versus the benefits of continuing treatment. In our case, we decided to continue therapy with aflibercept due to the sole pelvic implant, excellent performance status, and absence of significant toxicities other than nasal septum necrosis.

Only another case report regarding nasal septum perforation related to aflibercept therapy has been published. The article reports a 58-year-old metastatic colorectal cancer patient with nasal septum perforation treated with FOLFIRI plus aflibercept. The subject had no previous history of nasal pathology. Rhinoscopy evaluation revealed a perforation of the inferior portion of the nasal septum. He was started on topical treatment with resolution of epistaxis. Aflibercept was then restarted with no new episodes of epistaxis or other bleeding complications. Follow-up evaluations showed a persistent lesion with progressive epithelization and resolution [18].

Conclusions

Nasal septum perforation is a rare complication of antiangiogenic treatment usually associated with bevacizumab. In this case report, we show what, to our knowledge, is the second case report of aflibercept-related nasal septum complication. This case report, along with the previously published one, shows that conservative treatment of the lesion and restarting therapy with aflibercept might be appropriate measures.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. The Comité de Ética del Medicamento e Investigación Clínica (Ethics Committee) of Hospital Clínico San Carlos issued approval 22/082-E. The Comité de Ética del Medicamento e Investigación Clínica (Ethics Committee) of Hospital Clínico San Carlos approved this study. Written informed consent was obtained from the patient for the publication of clinical details and clinical images. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

Data are available on reasonable request to the corresponding author.

References

1. Van Cutsem E, Tabernero J, Lakomy R, et al.: Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol. 2012, 30:3499-506. 10.1200/JCO.2012.42.8201
2. Rapisarda A, Melillo G: Role of the VEGF/VEGFR axis in cancer biology and therapy. Adv Cancer Res. 2012, 114:237-67. 10.1016/B978-0-12-386503-8.00006-5
3. Saif MW, Relias V, Syrigos K, Gunturu KS: Incidence and management of ZIv-aflibercept related toxicities in colorectal cancer. World J Clin Oncol. 2014, 5:1028-35. 10.5306/wjco.v5.i5.1028
4. Ramiscal JA, Jatoi A: Bevacizumab-induced nasal septal perforation: incidence of symptomatic, confirmed event(s) in colorectal cancer patients. Acta Oncol. 2011, 50:578-81. 10.3109/0284186X.2010.537692
5. Mailliez A, Baldini C, Van JT, Servent V, Mallet Y, Bonneterre J: Nasal septum perforation: a side effect of bevacizumab chemotherapy in breast cancer patients. Br J Cancer. 2010, 103:772-5. 10.1038/sj.bjc.6605828
6. Pereira C, Santamaría A, Langdon C, López-Chacón M, Hernández-Rodríguez J, Alobid I: Nasoseptal perforation: from etiology to treatment. Curr Allergy Asthma Rep. 2018, 18:5. 10.1007/s11882-018-0754-1
7. Taira Y, Shimoji Y, Nakasone T, Arakaki Y, Nakamoto T, Kudaka W, Aoki Y:A case of nasal septal perforation caused by bevacizumab for advanced cervical cancer. J Obstet Gynaecol Res. 2021, 47:833-7. 10.1111/jog.14589
8. Rodriguez CA, Martin T, Lozano R, Gomez A, Cruz JJ: Spontaneous nasal perforation in a bevacizumab-

treated patient with metastatic breast cancer. Breast J. 2017, 23:745-6. 10.1111/tbj.12913
9. Geltzeiler M, Steele TO: Nasal septal perforation secondary to systemic bevacizumab. Am J Otolaryngol. 2017, 38:354-5. 10.1016/j.amjoto.2017.01.018
10. Petrelli F, Cabiddu M, Barbara C, Barni S: A patient presenting nasal septum perforation during bevacizumab-containing chemotherapy for advanced breast cancer. Breast Cancer. 2011, 18:226-30. 10.1007/s12282-011-0255-8
11. Power DG, Kemeny NE: Nasal septum perforation and bevacizumab. Med Oncol. 2011, 28:89-93. 10.1007/s12032-010-9464-9
12. Marín AP, Sánchez AR, Arranz EE: Nasal septum perforation in a breast cancer patient treated with bevacizumab. Ann Oncol. 2009, 20:1901-2. 10.1093/annonc/mdp451
13. Burkart CM, Grisel JJ, Hom DB: Spontaneous nasal septal perforation with antiangiogenic bevacizumab therapy. Laryngoscope. 2008, 118:1539-41. 10.1097/MLG.0b013e31817c4296
14. Ruiz N, Fernandez-Martos C, Romero I, Pla A, Maiquez J, Calatrava A, Guillem V: Invasive fungal infection and nasal septum perforation with bevacizumab-based therapy in advanced colon cancer. J Clin Oncol. 2007, 25:3376-7. 10.1200/JCO.2007.12.0006
15. Traina TA, Norton L, Drucker K, Singh B: Nasal septum perforation in a bevacizumab-treated patient with metastatic breast cancer. Oncologist. 2006, 11:1070-1. 10.1634/theoncologist.11-10-1070
16. Fakih MG, Lombardo JC: Bevacizumab-induced nasal septum perforation. Oncologist. 2006, 11:85-6. 10.1634/theoncologist.11-1-85
17. Tan TH, Stevenson B, Yip D: Docetaxel-induced nasal septal perforation. Intern Med J. 2006, 36:471-2. 10.1111/j.1445-5994.2006.01105.x
18. Alkan A, Yücel L, Mızrak D, Akbulut H: Aflibercept-related nasal septum perforation. Asia Pac J Clin Oncol. 2017, 13:e179-80. 10.1111/ajco.12320