Nasal septum perforation induced by bevacizumab therapy in patients with breast cancer

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Bevacizumab is a recombinant monoclonal immunoglobulin G1 antibody that selectively binds to vascular endothelial growth factor (VEGF), thus preventing it from binding to the VEGF receptors, VEGFR-1 and VEGFR-2, which leads to the inhibition of angiogenesis.[1] Numerous landmark clinical trials have shown overall and/or progression-free survival benefit with bevacizumab-based chemotherapy regimens for patients with metastatic colorectal,[2,3] lung,[4] breast,[5] and renal cell[6] carcinomas.

Angiogenic growth factors (eg, VEGF) are crucial for normal tissue wound healing.[7] Bevacizumab therapy is associated with a number of vascular complications, including hypertension, proteinuria, thromboembolism, impaired wound healing, bleeding, and gastrointestinal perforations.[8] Nasal septum perforation is a rare and often underrecognized complication of bevacizumab therapy.[9] We report here 2 cases of spontaneous septal perforation in patients who were receiving bevacizumab-based chemotherapy for breast cancer, and provide a literature review to identify risk factors for this complication and to provide management recommendations.

Patient 1

A 62-year-old white woman with newly diagnosed stage I (T1c N0 M0) estrogen receptor (ER) -positive, progesterone receptor (PR) -negative, HER2/neu positive (IHC 3+) invasive ductal carcinoma (moderately differentiated, intermediate nuclear grade) of the left breast, underwent modified radical mastectomy and sentinel lymph node biopsy. She was subsequently enrolled on a clinical trial for HER2/neu-positive, node-positive, or high-risk node-negative breast cancer to either adjuvant chemotherapy plus trastuzumab or to adjuvant chemotherapy plus a trastuzumab and bevacizumab combination.

The patient was randomized to the adjuvant chemotherapy, trastuzumab and bevacizumab arm. She completed her 6 cycles of adjuvant chemotherapy with docetaxel, carboplatin, trastuzumab, and bevacizumab. She tolerated the adjuvant chemotherapy with no significant toxicity. Following 6 cycles of this regimen, the patient noticed nasal congestion and scant blood tinged discharge on blowing her nose but denied any episodes of gross epistaxis. An anterior rhinoscopic examination revealed a 5-mm nasal septal perforation close to Kiesselbach area in the caudal septum.

The patient had no history of intranasal recreational drug use. She denied any recent nasal trauma, surgery, foreign bodies, or digital manipulation. A review of the patient's concurrent medications did not identify an offending agent, except for bevacizumab. She was removed from the study and the bevacizumab was discontinued. Despite conservative management with aggressive moisturization using topical bacitracin ointment, saline nasal washes, and humidifiers, her symptoms did not improve and she underwent surgical

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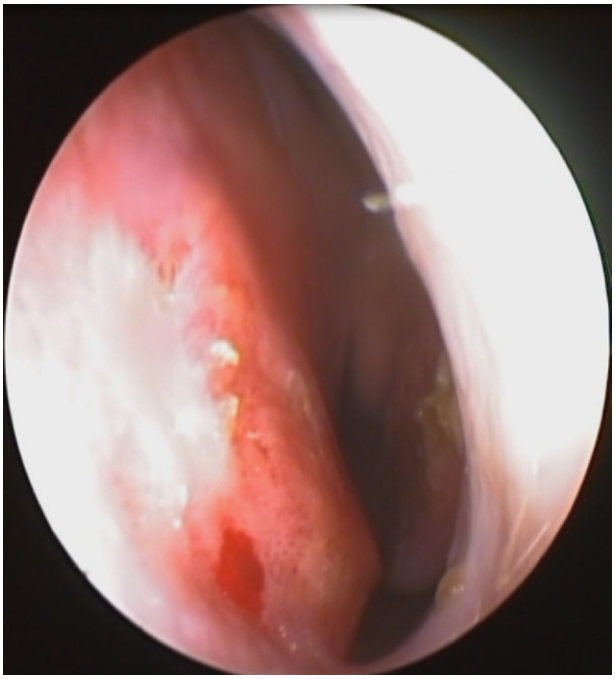

FIGURE 1 Anterior rhinoscopic examination after repair of the septal perforation in the distal part of the septum (Patient 1).

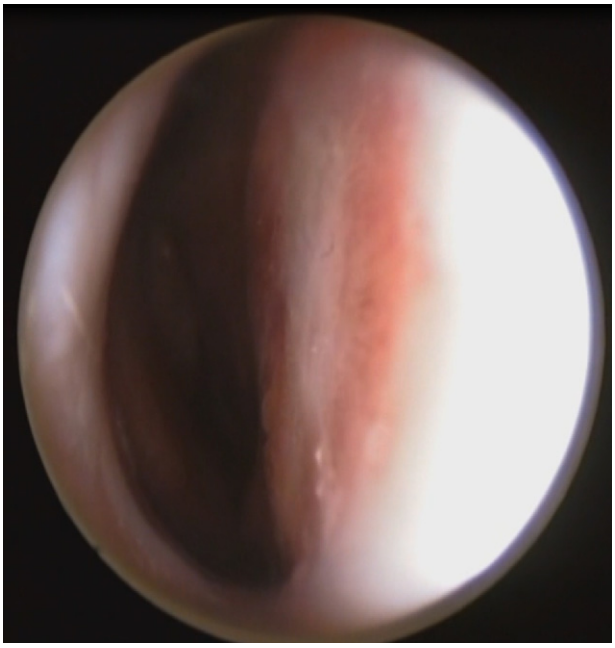

FIGURE 2 Another view of anterior rhinoscopic examination after repair of the septal perforation in the distal part of the septum (Patient 1).

repair of the septal defect (Figures 1 and 2) with resolution of epistaxis.

Patient 2

A 62-year-old woman with stage IIB (T2 N1 M0) ER-positive, PR-negative, HER-2/neu-positive infiltrating ductal carcinoma (moderately differentiated, intermediate nuclear grade) of the right breast diagnosed in September 2001, underwent right modified radical mastectomy in October 2001. She received 4 cycles of adjuvant chemotherapy with adriamycin and cyclophosphamide and was subsequently lost to follow-up. After a hiatus of 4 years, she presented with metastatic disease. She went on to receive several lines of therapies in the metastatic setting.

At the time of her most recent disease progression, the patient was started on a combination of weekly paclitaxel, and bevacizumab on the ECOG 2100 protocol (February 2009-December 2009). She responded well to this treatment, and her disease remained stable for almost a year. After 12 cycles of this regimen, the patient reported frequent episodes of epistaxis. These episodes were not associated with nasal obstruction or congestion. The patient had no history of recurrent sinus infections, intranasal recreational drug use, or trauma. An anterior rhinoscopic examination showed a 3-mm, through-and-through septal perforation in the distal part of the septum (Figure 3). There was ulceration at the periphery of the perforation; however, no crusting or bleeding was noticed.

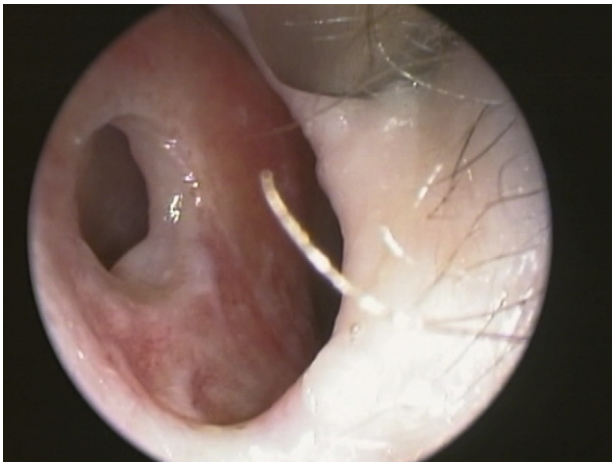

FIGURE 3 Anterior rhinoscopic examination showing a 3-mm, through-and-through septal perforation in the distal part of the septum (Patient 2).

Bevacizumab was discontinued, and the patient responded to conservative management with topical bacitracin ointment and moisturization.

Discussion

Bevacizumab, a direct inhibitor of VEGF, is increasingly being used to treat multiple malignancies. Its inhibition of VEGF-mediated signaling is not selective to tumor microenvironment, so it is not surprising that

TABLE 1 Characteristics of patients developing nasal perforation with bevacizumab therapy

Source	Age, y (Sex)	Cancer diagnosis	Bevacizumab dose	Concurrent chemotherapy	Latency[a]	Presenting symptoms	Management
Traina,[11] 2006	54 (F)	Breast	10 mg/kg every 2 weeks	Paclitaxel (70 mg/m^2 weekly)	12 weeks	Rhinorrhea, epistaxis, nasal irritation	Symptomatic treatment, discontinuation of bevacizumab
Fakih,[12] 2006	53 (M)	Colon	NA	FOLFOX	12 weeks	Epistaxis, septal crusting	Symptomatic treatment, discontinuation of bevacizumab
Ruiz,[13] 2007	53 (M)	Colon	5 mg/kg every 2 weeks	LV5FU	1 year	Pain, epistaxis	Symptomatic treatment, discontinuation of bevacizumab
Burkart,[14] 2008	52 (F)	Ovarian	NA	None	20 weeks	Epistaxis, septal crusting	Sialstic nasal septal button, discontinuation of bevacizumab
Marín,[15] 2009	39 (F)	Breast	NA	Paclitaxel	12 weeks	No symptoms	Symptomatic treatment, discontinuation of bevacizumab
Chaudhary, current study	62 (F)	Breast	1,310 mg	Docetaxel, carboplatin, trastuzumab	18 weeks	Nasal congestion, scant blood tinged discharge	Surgical repair
	62 (F)	Breast	10 mg/kg	Paclitaxel, lapatinib	1 year	Episodic nose bleeds	Symptomatic treatment, discontinuation of bevacizumab

Abbreviations: F, female; FOLFOX, 5FU, leucovorin, oxaliplatin; LV5FU, leucovorin, 5FU; M, male; NA, not available.
[a]Time interval between start of chemotherapy and presenting symptom.

despite its favorable efficacy in various solid tumors,[2-6] the therapy has been associated with a variety of vascular complications.

Black box warnings for bevacizumab include gastrointestinal perforation, impaired wound healing, and hemorrhagic complications that include hemoptysis, gastrointestinal, central nervous system and genital tract bleeding. Although epistaxis has been reported in more than 10% of patients who are treated with bevacizumab, nasal septal perforation is an exceedingly rare complication and its exact incidence rate is unknown. The nasal septum is a sensitive area and any damage or irritation to it requires optimal conditions for healing to occur. The normal process of wound repair requires angiogenesis to provide nutrients, promote granulation tissue formation, and facilitate the clearance of debris. Bevacizumab inhibits VEGF-dependent angiogenesis, including endothelial cell proliferation, which results in suboptimal would healing.[10] It is probable that bevacizumab interferes with the normal mucosal repair mechanisms that are orchestrated in response to irritation or injury not infrequently encountered in the exposed nasal mucosa, hence predisposing patients to this unique vascular complication.

To our knowledge, only 2 cases of nasal septal perforation associated with bevacizumab therapy in breast cancer patients have been reported. A few others have been reported in patients with metastatic colon and ovarian cancer (Table 1).[11-15] The most common presenting signs and symptoms seem to be mild to moderate epistaxis and nasal irritation, congestion, or discharge.[11-15] A few patients developed this complication within the first 3-4 months of therapy initiation,[11,12,14,15] whereas others experienced the complication after 1 year of chemotherapy.[13] Nasal septal perforation was diagnosed in these patients by anterior rhinoscopy, which was performed after the patients complained of nasal symptoms. Although this complication does not seem to be associated with any particular dose or administration schedule of bevacizumab, in both of the patients in our series and 2 patients in previously reported cases,[11,15] the patients were receiving taxanes in addition to bevacizumab. Taxanes, such as paclitaxel and docetaxel, have been shown to suppress smooth muscle-cell and endothelial-cell proliferation.[16] This property of taxanes has been shown to cause substantial impairment in arterial healing characterized by lack of reendothelialization and persistence of

fibrin in drug-eluting stents.[17] In fact, 2 cases of docetaxel-induced nasal septal perforation in patients with breast and metastatic ovarian cancer have been described.[18] This complication is more frequently seen with weekly docetaxel rather than a 3-weekly schedule.[19] It is possible that a combination of bevacizumab and taxanes might be synergistic in impairing wound healing.

In addition to concomitant chemotherapy with taxanes, other possible risk factors for bevacizumab-induced nasal septal perforation include nasal trauma, mucosal dryness, digital manipulation, and intranasal drug abuse. It is noteworthy that bevacizumab applied locally (such as intravitreal injection for choroidal neovascularization for age-related macular degeneration) has not been reported to have systemic effects (nasal septal perforation, bowel perforation).[20] This finding may be the result of a much lower dose (1.23 mg/dose for intravitreal injection vs 10-15 mg/kg per dose for breast, ovarian, and other cancers) or a lack of systemic absorption.[14]

In patients who receive bevacizumab-based therapy (in particular with taxane-containing regimens), any minor nasal symptoms warrant consideration of this complication. The first step in management is to perform an anterior rhinoscopy in all patients with nasal symptoms to look for perforation. If mucosal damage or perforation is present, the bevacizumab should be discontinued to prevent further damage and to allow mucosal healing. Mucosal damage can often be reversed with medical management, but in cases of through-and-through or large perforations, surgical intervention—including a septal button—might be necessary. Conservative management (including aggressive moisturization with topical bacitracin ointment, saline nasal washes, and humidifying) is intended for symptomatic relief and to prevent the perforations from becoming larger, but once a documented perforation is present, spontaneous healing without surgical intervention is unlikely. After the resolution of nasal septal perforation, the decision to restart bevacizumab should be made on a case-by-case basis after discussing the risks and benefits of further bevacizumab therapy with the patient.

References

1. Kim KJ, Li B, Winer J, et al. Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumour growth in vivo. *Nature*. 1993;362(6423):841-844.

2. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med*. 2004;350(23):2335-2342.

3. Giantonio BJ, Catalano PJ, Meropol NJ, et al. High-dose bevacizumab improves survival when combined with FOLFOX4 in previously treated advanced colorectal cancer: Results from the Eastern Cooperative Oncology Group (ECOG) study E3200 [ASCO abstract 2]. *J Clin Oncol*. 2005;23(suppl):S1.

4. Sandler A, Gray R, Perry M, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer [published correction appears in *N Engl J Med*. 2007;356(3):318]. *N Engl J Med*. 2006; 355(24):2542-2550.

5. Miller KD, Wang M, Gralow J, et al. E2100: A phase III trial of paclitaxel versus paclitaxel/bevacizumab for metastatic breast cancer. *Breast Cancer Res Treat*. 2005;94(suppl 1):S6-S6.

6. Yang JC, Haworth L, Sherry RM, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med*. 2003;349(5):427-434.

7. Hom DB, Maisel RH. Angiogenic growth factors: their effects and potential in soft tissue wound healing. *Ann Otol Rhinol Laryngol*. 1992;101(4):349-354.

8. Shord SS, Bressler LR, Tierney LA, Cuellar S, George A. Understanding and managing the possible adverse effects associated with bevacizumab. *Am J Health Syst Pharm*. 2009;66(11):999-1013.

9. Oberg D, Akerlund A, Johansson L, Bende M. Prevalence of nasal septal perforation: the Skövde population-based study. *Rhinology*. 2003;41(2):72-75.

10. Hicklin DJ, Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. *J Clin Oncol*. 2005; 23(5):1011-1027.

11. Traina TA, Norton L, Drucker K, Singh B. Nasal septal perforation in a bevacizumab-treated patient with metastatic breast cancer. *Oncologist*. 2006;11(10):1070-1071.

12. Fakih MG, Lombardo JC. Bevacizumab-induced nasal septum perforation. *Oncologist*. 2006;11(1):85-86.

13. Ruiz N, Fernandez-Martos C, Romero I, et al. Invasive fungal infection and nasal septum perforation with bevacizumab-based therapy in advanced colon cancer. *J Clin Oncol*. 2007;25(22):3376-3377.

14. Burkart CM, Grisel JJ, Hom DB. Spontaneous nasal septal perforation with antiangiogenic bevacizumab therapy. *Laryngoscope*. 2008;118(9):1539-1541.

15. Marín AP, Sánchez AR, Arranz EE. Nasal septum perforation in a breast cancer patient treated with bevacizumab. *Ann Oncol*. 2009; 20(11):1901-1902.

16. Abal M, Andreu JM, Barasoain I. Taxanes: microtubules and centrosome targets, and cell cycle dependant mechanisms of action. *Curr Cancer Drug Targets*. 2003;3(3):193-203.

17. Finn AV, Nakazawa G, Joner M, et al. Vascular responses to drug eluting stents: importance of delayed healing. *Arterioscler Thromb Vasc Biol*. 2007;27(7):1500-1510.

18. Tan TH, Stevenson B, Yip D. Docetaxel-induced nasal perforation. *Internal Med J*. 2006;36(7):471-472.

19. Esmaeli B, Burnstine MA, Ahmadi MA, Prieto VG. Docetaxel-induced histologic changes in the lacrimal sac and the nasal mucosa. *Ophthal Plast Reconstr Surg*. 2003;19(4):305-308.

20. Shaikh S, Olson JC, Richmon PP. Retinal pigment epithelial tears after bevacizumab injection for exudative age-related macular degeneration. *Indian J Ophthalmol*. 2007;55(6):470-472.