Duke Head and Neck Surgery & Communication Sciences
Duke University School of Medicine

Delayed Postoperative Cerebrospinal Fluid Rhinorrhea in Patients on Bevacizumab

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Introduction

Bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, is commonly used as an adjunct chemotherapy agent for a variety of cancers. However, VEGF inhibition has been associated with delayed surgical wound healing.[1,2] For intracranial tumors, bevacizumab has been associated with spontaneous formation of pseudomeningocele.[3] In the nasal cavity, it has been linked to spontaneous nasal septal perforation.[4]

Despite various reports of adverse effects of bevacizumab, delayed spontaneous cerebrospinal fluid (CSF) rhinorrhea after skull base surgery has not been described. The purpose of this study is to describe two cases of delayed CSF leak in patients who underwent endoscopic skull base surgery.

Case 1

48F underwent craniotomy and stereotactic radiation (SRS) for a frontal atypical meningioma WHO grade 2. Due to recurrence, she underwent second craniotomy and SRS 18 months later.

Six months after this, she started *bevacizumab 7.5 mg/kg IV q3 weeks for 3 doses* due to increased enhancement within and around the radiation field consistent with recurrent disease. Shortly after completing treatment, she developed left sided rhinorrhea positive for beta trace protein. MRI shown in Figure 1.

She underwent endonasal endoscopic CSF Leak Repair **of** left cribriform skull base defect with nasal floor free mucosal graft and started on acetazolamide.

Postoperative course was uneventful and one month after surgery, patient was started back *on bevacizumab 5 mg/kg IV q3 weeks* one month after surgery. CSF rhinorrhea recurred a month later (2 months postoperative). This revealed near-complete necrosis of the graft on endoscopy.

Bevacizumab was held for three months in preparation for revision surgery. During this time, the patient noted resolution of rhinorrhea. Endoscopy revealed granulation tissue reaction at prior defect site with spontaneous resolution of CSF leak. (Figure 2)

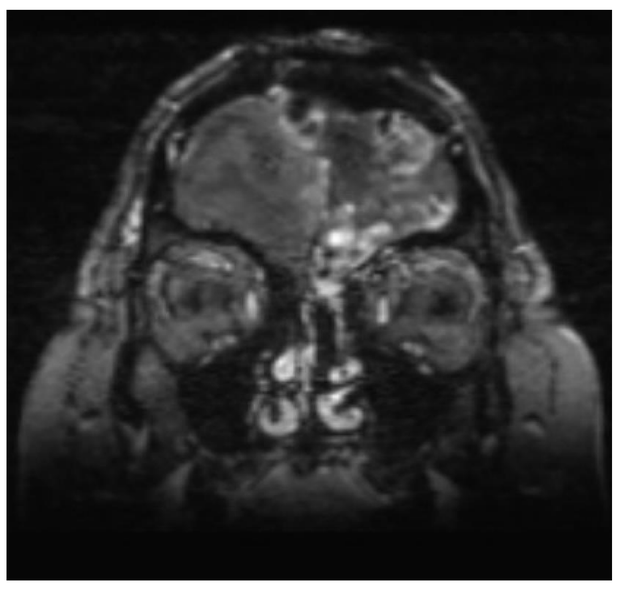

Figure 1. MRI at time of CSF rhinorrhea of left cribriform

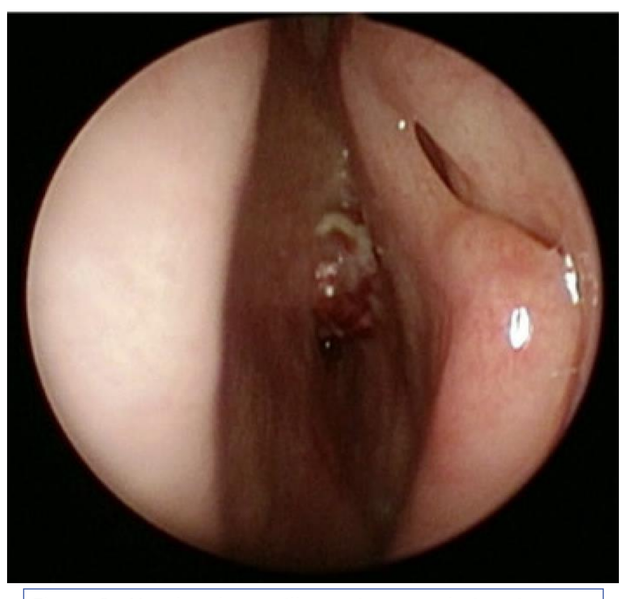

Figure 2: Nasal endscopy illustrating granulation tissue at the left cribriform at prior defect site with no evidence of CSF leak

Case 2

67M with a long-standing history of an ACTH secreting pituitary adenoma diagnosed over twenty years ago. He underwent multiple resections followed by chemotherapy and radiation during this time. No CSF rhinorrhea was reported following surgeries. He then started *bevacizumab 7.5 mg/kg IV q3 weeks.*

Two months later, the patient presented to the ED with new onset left sided temporal headache, fevers, and intermittent clear rhinorrhea. He was diagnosed with CSF leak of the sella.

Initial endonasal endoscopic repair with abdominal fat was performed. This revealed a sellar CSF leak with surrounding fibrinous tissue, atrophic mucosa, and necrotic bone. CSF rhinorrhea resolved and pneumocephalus improved during the first month after surgery. A month later, the patient developed CSF rhinorrhea and underwent repair with nasoseptal flap followed by middle turbinate flap.

Discussion

- Both patients underwent skull base surgery several years prior for intracranial tumors with adjuvant radiation and bevacizumab. While no CSF leak was encountered at the time of initial surgery, patients developed delayed spontaneous CSF rhinorrhea within 1-2 months of starting bevacizumab. Bevacizumab likely caused tissue ischemia and necrosis of an already devascularized skull base.
- For the first patient, the skull base defect healed spontaneously upon cessation of bevacizumab after initial failure of free mucosal graft repair. However, the second patient required multiple reconstructive surgeries due to overall poor vascularization of the nasal cavity.

Conclusions

- We present two cases from a tertiary academic institution which demonstrate the possibility of delayed spontaneous CSF leak in patients on bevacizumab who underwent prior skull base resection.
- This phenomenon is likely to increase as the indications for bevacizumab expand.
- Management of this entity is unclear, but our cases suggest that difficulty of repair due to devascularization of the nasal cavity including the septum. At the same time, cessation of bevacizumab can lead to spontaneous resolution.

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