Epistaxis Secondary to Panitumumab in a Patient with Colon Cancer

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Abstract. *Epidermal growth factor receptor inhibitors (EGFRIs) have become an integral part of therapy for many types of solid malignancy, including colorectal cancer. The drug class has proven to be effective without causing many of the side-effects associated with chemotherapy or other growth factor receptor inhibitors. Epistaxis, a common side-effect of Vascular Endothelial Growth Factor inhibitors, is rarely noted with EGFRIs. We report on one patient, a 51-year-old man with metastatic colon cancer, who developed severe epistaxis with the use of panitumumab. We discuss the other reported cases of EGFRIs causing epistaxis and hypothesize on possible mechanisms by which this drug class might cause mucosal bleeding.*

Epidermal growth factor receptor inhibitors (EGFRIs) are currently one of the major targeted therapies used as treatment for solid organ tumors. The first EGFRI approved by the Food and Drug Administration was gefitinib, which was put on the market in 2003. Since then, a number of other agents have been developed, such as erlotinib, cetuximab, lapatinib and panitumumab. While the drug class has proven to be both highly effective and non-toxic, it can still demonstrate profound side-effects. One of the major organs negatively affected by EGFRIs is the skin and mucosa. EGFR is expressed in the basal layer, keratinocytes, hair follicles, and sweat glands, resulting in the drug targeting the skin and causing most patients taking the drug to incur at least one dermatological side-effect, such as a papulo-pustular rash, xerosis, pruritis, nail, hair or mucosal changes (1).

A rare dermatological side effect of this drug class is epistaxis. The rarity of this side-effect is noteworthy, as some other growth factor receptor inhibitors, particularly those of vascular endothelial growth factor receptors (VEGFRs), are known for causing frequent epistaxis, which can sometimes be quite severe. A meta-analysis looking at side-effects of bevacizumab demonstrated a relative risk of 2.07 for any bleeding, reporting less severe types of bleeding (such as epistaxis) as being more frequent (2). In another large European study, bleeding was noted in 38.2% of patients on bevacizumab, and epistaxis was the most common type of bleeding (3). As a direct result of these and other studies, bevacizumab and other VEGFRIs come with a blackbox warning of possible hemorrhage and gastrointestinal bleeds. Epistaxis is listed as a common side-effect (4). Unlike VEGFRIs, EGFRIs do not come with the same warning.

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Case Report

Our patient represents one of the few reported cases presented with epistaxis while on an EGFRI. He was a 51-year-old Ecuadorian male with a history of metastasis from colon carcinoma originally diagnosed in 2007, at which time the tumor was resected and he was treated with oxaliplatin, 5-fluorouracil plus leucovorin (FOLFOX-4) for 12 cycles. He completed this therapy in November 2007. In April 2009, he developed an intra-abdominal recurrence (confirmed by exploratory laparotomy and biopsy) and metastasis, which was treated with 5-fluorouracil, leucovorin, irinotecan (FOLFIRI), and cetuximab. The patient completed this regimen in July 2009. The patient then moved to the United States and presented to the emergency department in October 2009 with abdominal pain. He was found to have a recurrent lesion in the pancreatic head abutting the stomach measuring 3 cm by 5 cm by 5 cm. An endoscopic ultrasound was performed, and the biopsy was consistent with primary colorectal cancer. The patient was treated with mitomycin C and 5-fluorouracil plus leucovorin at days 1, 2, 3 every 21 days for two cycles. This last cycle was completed on December 2009. Despite treatment completion, the patient continued to have abdominal pain, and therefore systemic chemotherapy was held and the patient was treated with a palliative course of external beam radiation therapy. He received a total dose of 30 Gy in 10 fractions, which he completed in February 2010 with significant improvement in his pain.

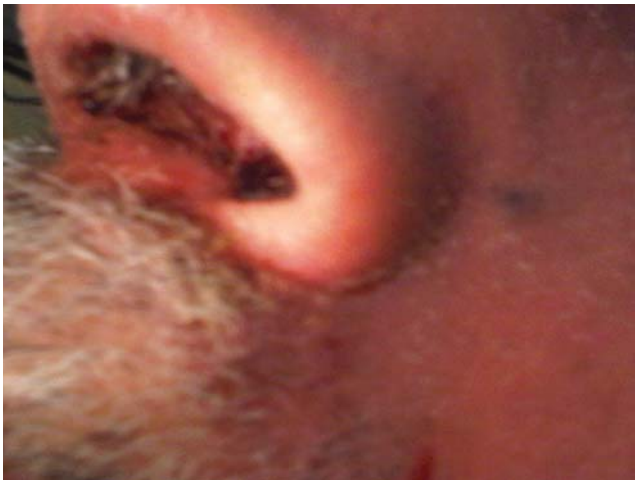

Figure 1. *Mucocutaneous rash around the nares and nasolabial fold.*

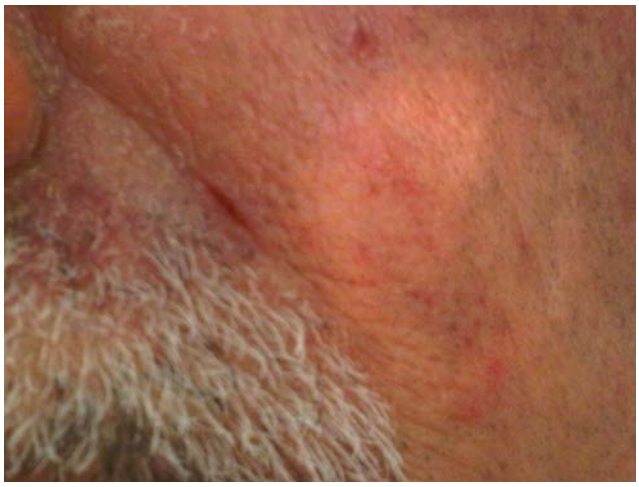

Figure 2. *Epistaxis visualized within the nares.*

Due to improvement in his performance status secondary to better pain control, he was enrolled on a phase I study including irinotecan in combination with PHY906, a Chinese herbal drug. Despite treatment, in June 2010 a repeat computed tomography (CT) scan showed progressive disease at the end of four cycles (eight weeks), evidenced by increased size of pulmonary metastasis, as well as increased size of the necrotic air-containing mass in the head of the pancreas. The chemotherapy regimen was changed to panitumumab, an EGFRI inhibitor manufactured by Amgen. The recommended dose is 6 mg/kg administered IV over 60 min every 14 days, and the blackbox warnings are infusion reaction and a dermatologic reaction, as discussed above (5).

By August 2010, the patient had undergone two cycles of panitumumab at the recommended dose of 6 mg/kg with minimal toxicity except grade 1 rash (Figure 1). After cycle number 3, he presented with the more unusual side-effect of epistaxis (Figure 2). Panitumumab was held, and he was started on doxycycline, which resulted in an improvement in both the rash and epistaxis within a week. Panitumumab was then restarted at a lower dose of 3 mg/kg, which he was able to tolerate for the full 4-month treatment without further side effects.

Discussion

Our patient thus demonstrates both a common as well as an uncommon side effect of panitumumab, the rash and epistaxis respectively. Although rare, a literature search reveals a few other reported instances of epistaxis associated with EGFRIs. A French study noted rhinitis and epistaxis in patients treated with mammalian target of rapamycin (mTOR) inhibitors and EGFRIs (6). Another study looking at the use of gefitinib in treating three cases of lung adenocarcinoma noted that one of the three suffered from massive alveolar hemorrhage on treatment, demonstrating a possible association of EGFRI with bleeding (7).

Part of an explanation for bleeding and epistaxis associated with EGFRI use is likely related to the association between EGFR activation and mucin production. EGFRs have been demonstrated to be present in airway goblet cells, which are instrumental in producing mucin (8). Mucin acts to lubricate the mucosa, and is therefore essential for hydrating nasal epithelial cells (9). Thus, an EGFRI would likely result in dryer epithelial cells, which could in turn cause epistaxis. Another hypothesis regarding the pathophysiology of epistaxis in association with EGFRIs relates to the fact that EGFR shares many common pathways with VEGF, and studies suggest that inhibition of EGFR results in down-regulation of VEGF6.

No matter the pathogenesis, our case report serves as an unusual example of EGFRIs causing epistaxis severe enough to result in a modification of the patient's treatment dose. This case suggests that bleeding or epistaxis should perhaps be listed as a potential medication side-effect in order to warn providers prior to use. It also highlights how novel these targeted agents are, and how some rare side-effects may still be coming to light.

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