Characteristics of Oral Mucosal Events Related to Bevacizumab Treatment

IGOR T. GAVRILOVIC,^a YEVGENIY BALAGULA,^b ALYX C. ROSEN,^b VIJAY RAMASWAMY,^c
MAURA N. DICKLER,^d IRA J. DUNKEL,^c MARIO E. LACOUTURE^b

^aDepartment of Neurology, ^bDermatology Service, ^cDepartment of Pediatrics, and ^dBreast Cancer Medicine Service, Memorial Sloan-Kettering Cancer Center, New York, New York, USA

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ABSTRACT

Background. Bevacizumab, a monoclonal antibody targeting a vascular endothelial growth factor (VEGF) protein, has been reported to induce mucosal toxicities. However, the clinical characteristics of these particular toxicities have not been well characterized. We aimed at providing a detailed clinical description of signs and symptoms limited to the tongue mucosa in patients treated with bevacizumab.

Methods. A retrospective review of medical records and clinical photographs was performed with specific attention to clinical presentation, evolution, associated symptoms, concomitant medications, and treatment methods.

Results. In total, four patients presented to the dermatol-

ogy service with clinical findings characterized by multifocal, erythematous circinate and serpiginous erosions on the dorsal tongue surrounded by white hyperkeratotic rims that were temporally related to bevacizumab therapy. Associated increased sensitivity to spicy foods was frequently observed.

Conclusion. These characteristic clinical findings are consistent with geographic tongue. However, large prospective evaluations are necessary to confirm this potential relationship. If bevacizumab is indeed associated with geographic tongue, increased awareness may result in improved reporting and characterization of this particular adverse event. *The Oncologist* 2012;17:274–278

INTRODUCTION

Bevacizumab is a humanized recombinant monoclonal IgG₁ antibody that targets the vascular endothelial growth factor (VEGF)-A protein, interfering with its binding to VEGF receptor (VEGFR)-1 (Flt-1) and VEGFR-2 (KDR) [1, 2]. Disrupting the process of neoplastic angiogenesis, bevacizumab can negatively affect the growth of various tumor types and is used to treat recurrent or metastatic non-small cell lung cancer, metastatic colorectal and breast cancers, renal cell carcinoma, and recurrent glioblastoma [3]. Because VEGFRs are abundantly expressed in normal tissues and intricately involved in regulat-

ing essential functions, multiple adverse events have been described: hypertension, proteinuria, arterial thromboembolic events, cardiomyopathy, hemorrhage, wound complications, gastrointestinal perforation, and reversible posterior leukoencephalopathy syndrome [4]. Mucocutaneous toxicities, however, are significantly less common [5]. Stomatitis has been reported in patients receiving bevacizumab in combination with interferon- α , 5-fluorouracil plus leucovorin, and capecitabine [3]. The addition of bevacizumab to interferon- α resulted in fivefold higher incidences of mouth ulceration (six patients versus none), gingivitis (eight patients versus one pa-

Correspondence: Mario E. Lacouture, M.D., Dermatology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, Rockefeller Outpatient Pavilion Suite 228, 160 East 53rd Street, New York, New York 10022, USA. Telephone: 212-610-0079; Fax: 212-308-0739; e-mail: lacoutum@mskcc.org Received June 13, 2011; accepted for publication November 1, 2011; first published online in *The Oncologist Express* on January 26, 2012. ©AlphaMed Press 1083-7159/2012/\$40.00/0 <http://dx.doi.org/10.1634/theoncologist.2011-0198>

tient), and gingival pain (five patients versus none) [3]. Nevertheless, these mucosal toxicities have not been well characterized. Our goal was to provide a detailed clinical description of signs and symptoms limited to the tongue mucosa in patients treated with bevacizumab. Herein, we describe distinct mucosal surface changes, which are consistent with geographic tongue.

METHODS

In total, four patients, who were identified retrospectively, were referred to the dermatology service from June 2010 to June 2011 for the appearance of tongue lesions attributed to bevacizumab treatment. A review of the medical records of these four patients was performed from the secure electronic health care information system and pertinent data from dermatology and oncology physician and clinic records and laboratory results were recorded. Investigated parameters included the time to onset, clinical presentation, evolution, associated symptoms, concomitant medications, and therapeutic interventions against the adverse event. In addition, the clinical database was accessed to retrieve clinical photographs of these mucosal findings.

REPORT OF CASES

Case 1

The patient was a 16-year-old white female with recurrent anaplastic astrocytoma for which she received intensity-modulated radiation therapy with a total dose of 30 Gy and had been on biweekly bevacizumab (10 mg/kg). Approximately 2 years after starting bevacizumab therapy, the patient reported intermittent asymptomatic patches on her tongue, which subsequently became increasingly painful and were associated with a burning sensation upon exposure to spicy foods. This occasionally interfered with oral intake and made articulation difficult. The use of oral diphenhydramine, bismuth subsalicylate mouthwash, and magic mouthwash containing simethicone and lidocaine provided only partial relief. Although oral ranitidine (150 mg) twice a day and cetirizine (10 mg) daily resulted in resolution, the lesions remained recurrent in nature in the absence of treatment. Physical exam (PE) revealed multifocal, erythematous circinate and serpiginous erosions on the dorsal tongue, surrounded by white hyperkeratotic rims, consistent with geographic tongue (Fig. 1). Concomitant medications administered prior to onset included valproic acid (antiepileptic), propranolol (antihypertensive), rizatriptan (analgesic), and ondansetron (antiemetic). Laboratory testing revealed a hemoglobin (Hgb) level of 10.8 g/dL ($\downarrow$), a mean corpuscular volume (MCV) of 90 fL (normal), a vitamin B₁₂ level of 345 pg/mL (normal), and a folate level of 13.8 ng/mL (normal).

Case 2

The patient was a 50-year-old Asian male with glioblastoma multiforme who was treated with resection, hypofractionated radiation (3,600 cGy), biweekly bevacizumab (10 mg/kg) and temozolomide 100 mg daily for 7 months. After 3 months,

Figure 1. Multifocal, erythematous circinate and serpiginous erosions on the dorsal tongue surrounded by white hyperkeratotic rims, consistent with geographic tongue.

treatment was complicated by tongue lesions and increased sensitivity to some foods and spices. Concomitant medications included levetiracetam (antiepileptic), lansoprazole (gastric protectant), and dexamethasone (anti-inflammatory), but steroids were discontinued several months prior to onset. The lesions spontaneously resolved within 2 months following discontinuation of therapy. As a result of disease progression, biweekly bevacizumab (10 mg/kg) and metronomic temozolomide (100 mg) daily were restarted. After 3 months of therapy, there was recurrence of painful tongue sores exacerbated by exposure to spicy foods. Of note, prior to onset, temozolomide was discontinued and one dose of carmustine (150 mg/m²) was administered. Following tongue manifestations, monthly carboplatin (area under the concentration–time curve, 5) was added to bevacizumab. Treatment with oral fluconazole (100 mg) three times weekly or daily for presumed oral candidiasis was ineffective, and the lesions remained recurrent in nature despite unrelated carboplatin dose reductions. PE demonstrated areas of smooth erythema and loss of filiform papillae with elevated whitish borders (Fig. 2). Laboratory testing revealed a Hgb level of 12.8 g/dL ($\downarrow$), MCV of 102 fL ($\uparrow$), and vitamin B₁₂ level of 300 pg/mL (normal). Parietal cell and intrinsic factor antibodies were negative. As a result of disease progression, bevacizumab was stopped, with a resultant spontaneous complete resolution of the oral lesions.

Case 3

A 55-year-old white male patient with recurrent glioblastoma was receiving salvage therapy with biweekly bevacizumab (10

Figure 2. Areas of smooth erythema and loss of filiform papillae with elevated whitish borders.

mg/kg). Concomitant medications included levetiracetam (antiepileptic), metoprolol (antihypertensive), insulin aspart, lansoprazole (gastric protectant), dexamethasone (anti-inflammatory), and sulfamethoxazole/trimethoprim (antibacterial). He developed asymptomatic mouth sores after a few months of therapy that were treated with oral acyclovir for presumed herpes simplex infection. However, the lesions persisted despite treatment. PE revealed irregular atrophic tongue patches consistent with a diagnosis of geographic tongue. Laboratory testing revealed a Hgb level of 16.3 g/dL (normal), MCV of 90 fL (normal), a vitamin B₁₂ level of 477 pg/mL (normal), and a folate level of 16.4 ng/mL (normal). As of the last follow-up visit, the lesions continued to be recurrent in nature.

Case 4

A 50-year-old white female patient with metastatic breast cancer was treated with bevacizumab (15 mg/kg i.v.) every 3 weeks in combination with letrozole (2.5 mg) orally daily in a feasibility clinical trial. Of note, she was receiving letrozole (hormonal therapy) and leuprolide (hormonal therapy) for approximately 1 year prior to initiation of bevacizumab. After ~8 months of therapy, she reported tongue sores that were sensitive to spicy and acidic foods. PE revealed similar changes, consistent with geographic tongue. Laboratory testing showed a Hgb level of 12.8 g/dL (normal) and MCV of 87 fL (normal). Testing for B₁₂ and folate levels was not performed. The lesions remained recurrent in nature throughout the last 5 years of continued therapy.

DISCUSSION

Geographic tongue, a benign condition characterized by circinate or serpiginous, irregular, well-demarcated, erythematous, patchy erosions surrounded by slightly elevated whitish borders, was first described by Rayer in 1831 [6]. Because of multifocal involvement, the tendency to spontaneously regress and recur in other areas, and variability in the morphology and size of individual lesions, which can occur within hours, days, or weeks, this entity has also been called benign migratory glossitis [7, 8]. Although the most common sites are the dorsal and lateral tongue, involvement of the ventral surface, buccal mucosa, soft and hard palates, and gingiva have uncommonly been reported, which has been referred to as geographic stomatitis [8]. The majority of affected patients are asymptomatic. However, discomfort ranging from foreign body sensation to minimal itching to a severe burning sensation, which may occasionally interfere with eating or sleeping, may occur [8–11]. Moreover, some patients implicate smoking and seasoned or spicy foods as aggravating factors [8]. Conditions associated with painful tongue lesions may include burning tongue or abnormalities of the tongue surface such as median rhomboid glossitis, atrophic glossitis, and geographic tongue. Intraoral squamous cell carcinoma may commonly involve the lateral tongue and progress to nodular or ulcerated tongue lesions and cause pain and discomfort [12]. Oral complications associated with targeted cancer therapies or conventional chemotherapy include mucositis, aphthous-like stomatitis, ulcerations, hyposalivation/xerostomia, dysphagia, pharyngitis, infection, discomfort, and taste alterations [13]. Because the patients' tongue events were related to bevacizumab therapy, this represents a novel entity with the clinical appearance of geographic tongue with painful areas.

Typical geographic tongue tends to persist, characterized by periods of remission and recurrence, and may last for months to years without permanent sequelae such as scarring or malignant transformation [7, 11, 14]. The prevalence of geographic tongue in the population has been reported to be in the range of 0.28%–18.4%, mostly 1%–2.5% [14, 15]. Recently, the point prevalence among U.S. adults was reported to be 1.8% [16]. Although it has been reported to more commonly affect children, other studies failed to demonstrate a significant association [16] whereas others described a possibly greater prevalence with age [7, 15]. Similarly, although both genders have been described as predisposing factors, other studies reported no significant differences [14–16]. Ethnicity is believed to contribute to the development of geographic tongue, which may explain variations in its reported prevalence. However, no statistically significant differences were observed among an Israeli population [15]. In contrast, using a multivariate logistic regression model, geographic tongue was significantly more common in non-Hispanic whites and non-Hispanic blacks than in Mexican Americans in a large U.S.-based population [16].

Erythematous erosions or ulcer-like lesions are a result of loss of filiform papillae. Microscopically, these areas demonstrate a failure of differentiation and absence of filiform papillae, edema, and inflammatory submucosal infiltrate, with neutrophils forming

microabscesses. Elevated borders contain neutrophilic infiltrates and microabscesses, leukocyte invasion, and exfoliation of necrotic cells to the surface layer [7, 14].

The cause of this inflammatory condition has not yet been elucidated. However, multiple studies have suggested potential associations. Diabetes mellitus, hormonal imbalance, nutritional deficiencies, Down syndrome, psychosomatic factors and stress, atopy, (asthma, eczema, hay fever), and pustular psoriasis have all been reported in association with geographic tongue. In fact, some authors believe it to be a mucosal manifestation of psoriasis [14]. Nevertheless, a large population-based case-control study using multivariate analysis failed to show a significant association between geographic tongue and diabetes mellitus, allergy or atopy, and psychological or dermatologic conditions [16]. Interestingly, in that study smoking was shown to be protective. In terms of drugs, lithium has been implicated as a rare inciting factor [17, 18]. No significant association has been determined for antifungal or oral contraceptive use [16]. In contrast, systemic corticosteroids have been shown to have a statistically significant association with geographic tongue (odds ratio, 3.7; 95% confidence interval, 1.5–8.6; p -value = .0004), although the significance of these findings is unclear [16].

To our knowledge, changes clinically consistent with geographic tongue have not yet been described with bevacizumab. The development of geographic tongue in our patients treated with bevacizumab may represent a mechanism-based effect: VEGF is critical for homeostasis of the oral mucosa, as evidenced by its ability to induce dilation and permeability of mucosal vessels, and angiogenesis under physiologic and pathologic oral mucosal conditions, such as wound healing and inflammation. Moreover, VEGF mRNA is constitutively expressed in salivary glands and VEGF is present in the saliva of healthy individuals, adding to its protective and wound-healing abilities [19]. VEGF expression in basal and suprabasal cell layers in a three-dimensional organotypic oral mucosa model was correlated with cell survival, and increased expression of VEGF was stimulated by mechanical compression or damage of the oral mucosa. Antibody-mediated VEGF inhibition results in up to a 69% decrease in human vascular endothelial cell invasion of oral mucosa in vitro, suggesting that VEGF blockade may impede the normal reparative capability of tongue epithelium after subclinical trauma that occurs from speaking or eating, which may account for the alterations seen in our patients.

All patients underwent an evaluation by the treating oncologist prior to therapy initiation, which included an evaluation of past medical history and a PE. There was no history or current evidence of oral mucosal alterations at the time of therapy initiation. The oral mucosal changes appeared at the defined time points indicated in the manuscript, as assessed by the treating oncologist and dermatologist. Therefore, oral mucosal changes were attributed as definitely related to therapy with bevacizumab. Moreover, recurrence upon exposure to bevacizumab and prompt resolution following discontinuation in two separate instances support bevacizumab as an offending agent.

Two of our patients received systemic corticosteroids, but these were discontinued several months prior to manifestation in one patient. Whereas one patient had diabetes mellitus, none of our patients carried a diagnosis of psoriasis or atopy. Although no iron testing was performed on the patients included in this manuscript, the MCV for all patients was within normal limits and the Hgb level was normal in two patients and marginally low in two other patients at the time of presentation.

Although none of our patients presented with aphtha, six of 11 patients on treatment with bevacizumab plus either 5-fluorouracil, leucovorin, and oxaliplatin (the FOLFOX6 regimen) or 5-fluorouracil, leucovorin, and irinotecan (the FOLFIRI regimen) developed aphtha [20]. Moreover, bevacizumab plus docetaxel was shown to cause stomatitis in 2.8%–3.2% of patients, versus 0.4% of patients treated with placebo plus docetaxel [21]. Similarly, paclitaxel plus bevacizumab was shown to cause high-grade (grade ≥ 3) stomatitis in 1.1% of patients, versus 0.6% of patients treated with paclitaxel only [22]. However, the occurrence of aphthous ulcers was not described in either of those studies. None of the patients described in our manuscript presented with aphthous-like lesions. Geographic tongue was the only oral adverse event.

Asymptomatic geographic tongue does not necessitate treatment or bevacizumab interruption, and patients should be reassured about the benign nature and course of this condition. Associated symptoms may be alleviated with topical anesthetic agents, topical or systemic antihistamines, corticosteroids, and anxiolytics [10, 11, 14]. Successful management with topical tretinoin, systemic acitretin, vitamin A acid therapy, and cyclosporin has also been reported in the non-oncologic setting [11, 14].

CONCLUSION

The ephemeral qualities and potential asymptomatic presentation of geographic tongue may present a challenge in documenting changes. This emphasizes the importance of consistent examination of oral mucosa in patients receiving therapy with bevacizumab. If bevacizumab is indeed associated with geographic tongue, greater awareness may result in better reporting and characterization of this particular adverse event.

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AUTHOR CONTRIBUTIONS

Conception/Design: Mario E. Lacouture, Igor T. Gavrilovic, Maura N. Dickler, Ira J. Dunkel, Alyx C. Rosen

Provision of study material or patients: Mario E. Lacouture, Igor T. Gavrilovic, Vijay Ramaswamy, Maura N. Dickler, Ira J. Dunkel

Collection and/or assembly of data: Yevgeniy Balagula, Alyx C. Rosen

Data analysis and interpretation: Mario E. Lacouture, Yevgeniy Balagula, Igor T. Gavrilovic, Vijay Ramaswamy, Maura N. Dickler, Ira J. Dunkel, Alyx C. Rosen

Manuscript writing: Mario E. Lacouture, Yevgeniy Balagula, Igor T. Gavrilovic, Vijay Ramaswamy, Maura N. Dickler, Ira J. Dunkel, Alyx C. Rosen

Final approval of manuscript: Mario E. Lacouture, Yevgeniy Balagula, Igor T. Gavrilovic, Vijay Ramaswamy, Maura N. Dickler, Ira J. Dunkel, Alyx C. Rosen

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