Volume 20 Number 6
June 2014

Case Presentation

Cutaneous thrombogenic vasculopathy associated with bevacizumab therapy

Maija Kiuru MD PhD[1, 2], Mark Schwartz MD[3], and Cynthia Magro MD[1]

Dermatology Online Journal 20 (6): 9

Department of Pathology and Laboratory Medicine[1] and Surgery[3], Weill Cornell Medical College, New York, NY; Department of Pathology[2], Memorial Sloan-Kettering Cancer Center, New York, NY

Correspondence:

Maija Kiuru
Division of Dermatopathology, Department of Pathology and Laboratory Medicine
1300 York Avenue, Room F309
New York, NY 10065
Phone: 212-746-6434
Fax: 212-746-8570
mhk2003@nyp.org
kiuru.maija@gmail.com

Abstract

Bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor (VEGF), is an angiogenesis inhibitor used to treat a variety of cancers, including lung, colon, cervical, ovarian, and renal cancers as well as glioblastoma. A significant adverse effect associated with its use is one of thromboembolic events. We report a case of a 74-year-old male with diagnosis of glioblastoma multiforme treated with partial resection, radiation, temozolomide, and bevacizumab. He presented to a plastic surgeon with a several week history of asymptomatic crusted hemorrhagic ulcers and purpuric patches on the lower legs shortly following the initiation of bevacizumab. A biopsy showed an occlusive pauci-inflammatory thrombogenic vasculopathy associated with ischemic epidermal and dermal changes and accompanied by extensive vascular C5b-9 (complement C5b-9 membrane attack complex) deposition. Bevacizumab has been associated with thrombotic complications including atypical hemolytic uremic syndrome and arterial and venous thrombosis. C5b-9 may be the factor most important in the mechanism of vascular thrombosis given the extent of deposition in our index case. Thrombotic events in the skin associated with bevacizumab therapy are without precedent and dermatologists should be aware of this potential complication.

Keywords: bevacizumab, vascular endothelial growth factor, vasculopathy, thrombosis, cutaneous side effect

Case synopsis

The patient was a 74-year-old male with a history of glioblastoma multiforme treated with partial resection, radiation, temozolomide, and bevacizumab. He presented to the plastic surgeon with a several week history of multiple asymptomatic heme-crusted ulcers and purpuric patches on the lower legs (Figure 1) that had developed shortly after starting bevacizumab therapy. The patient did not have any prior history to suggest a thrombophilic state as revealed by the lack of any history of recurrent deep venous thromboembolic events, symptoms of pulmonary embolism and/or strokes. Owing to the unusual clinical presentation, a biopsy was performed of one of the ulcers.

The biopsy showed an ulcer with supervening marked degenerative changes of the epidermis and within the dermis (Figure 2A). There was extensive necrosis of the eccrine coil. In the deeper-seated vessels of the dermis and extending into the subcutaneous fat a striking pauci-inflammatory thrombogenic vasculopathy accompanied by intravascular papillary endothelial cell hyperplasia was observed (Figure 2B). There was concomitant lipomembranous fat necrosis.

To better evaluate the nature of the thrombotic diathesis, a series of immunohistochemical stains were conducted. There was extensive vascular deposition of C3d (complement C3d), C4d (complement C4d), and C5b-9 (complement C5b-9 membrane attack complex) (Figure 3). The foci of lipomembranous fat necrosis were also highlighted by the C5b-9 stain.

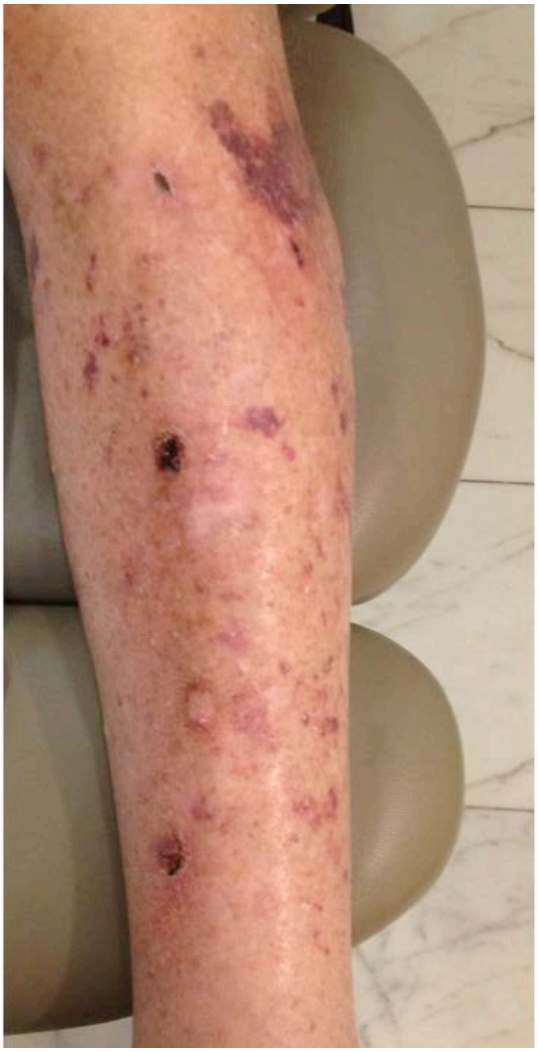

Figure 1

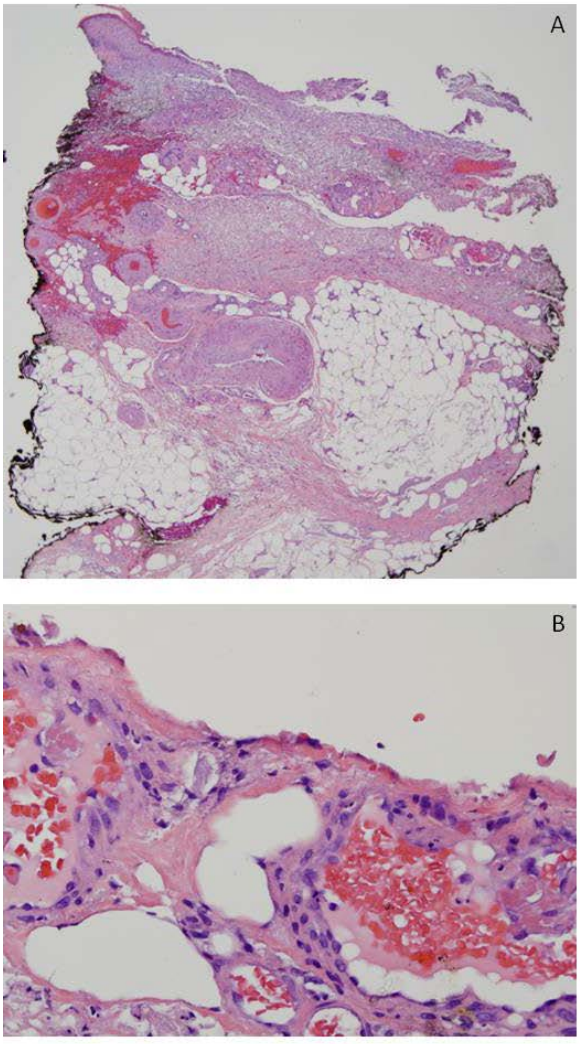

Figure 2

Figure 1. Clinical presentation of heme-crusted ulcers involving the lower extremities.

Figure 2. A biopsy shows epidermal and dermal necrosis associated with a thrombotic diathesis (A). Vessel is occluded with thrombus (B).

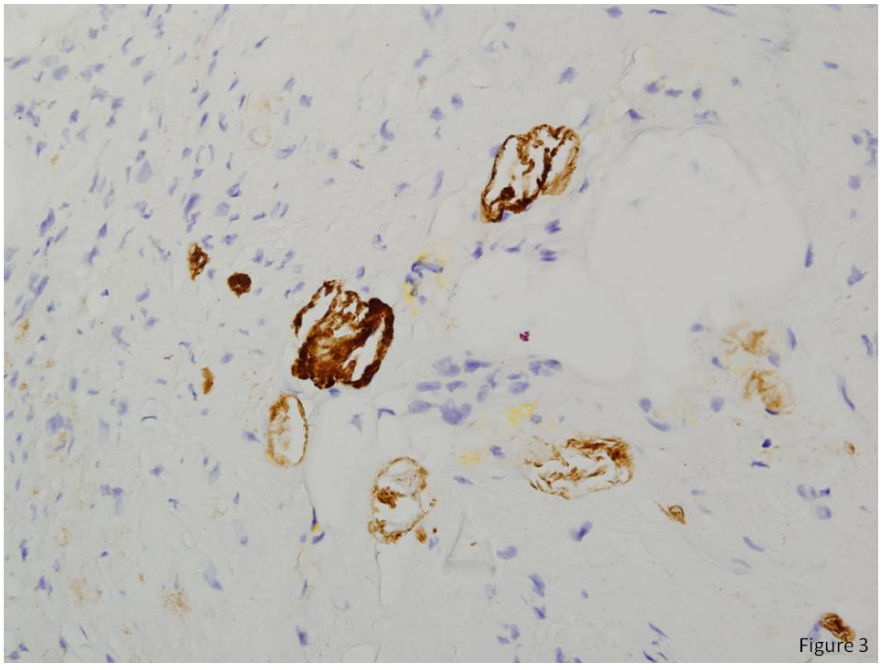

Figure 3

Figure 3. The thrombotic process is associated with extensive deposits of C5b-9 in the microvasculature.

Discussion

We have presented a case of a multifocal ulcerating pauci-inflammatory thrombogenic vasculopathy temporally associated with bevacizumab therapy. We postulate a role for the administration of bevacizumab in the pathogenesis of this multifocal ulcerative process.

Bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor (VEGF), is an angiogenesis inhibitor used to treat a variety of cancers, including lung, colon, and renal cancers, as well as glioblastoma multiforme [1, 2, 3, 4]. Bevacizumab binds directly to VEGF extracellularly preventing interaction with VEGF receptors on the surface of endothelial cells [5]. Given the dependency of certain tumors on angiogenesis, it is most effective in those tumors that are highly dependent upon an adequate vascular supply. Often combined with other chemotherapy, it improves response and survival in certain cancer types, including advanced cervical cancer [6]. Given the inhibitory effects on neovascularization, intraocular diseases associated with the formation of new vessels, such as age-related macular degeneration and diabetic retinopathy, may also benefit from bevacizumab intervention [7]. In addition to bevacizumab, there are many other drugs that target the VEGF pathway and angiogenesis, including other VEGF ligands, VEGFR blockers, and tyrosine kinase inhibitors, such as sunitinib and sorafenib, that block VEGF-induced cellular signaling [8].

Although bevacizumab has a defined role in medical treatment, it is not without complications as is well exemplified by this case. Bevacizumab therapy is associated with an increased risk of a number of toxicities, including hypertension, hemorrhage, and thrombosis [6, 9]. Thrombotic complications are significant and can include arterial thrombosis, venous thrombosis, including portal vein, superior vena cava, and internal jugular vein thrombosis, renal thrombotic microangiopathy, and hemolytic uremic syndrome (HUS) [10, 11, 12, 13, 14, 15, 16]. In most of the reported cases, the patients received combination chemotherapy. The onset of thrombotic complications ranged from shortly after initiation of therapy to a few months after the first cycle [17, 18].

The mechanisms for thrombosis in the setting of bevacizumab therapy is multifactorial and may include direct endothelial cell injury, production of endothelial nitric oxide, increased platelet aggregation, and activation of the FcγRIIa platelet receptor [19, 20]. Perhaps one of the critical mechanisms, however, is one related to a lack of replenishment of endothelial cells given the critical role of vascular endothelial cell growth factor in endothelial cell survival and growth. In particular any reduction in the potential pool of endothelial cells needed to replenish dying endothelial cells will result in a thrombotic diathesis and may also contribute to other forms of arteriopathy, most notably the obliterative fibrointimal arteriopathy of lupus erythematosus and scleroderma (16). In essence, the inhibition of VEGFR activation by anti-VEGF antibodies and by the inhibition of the VEGF intracellular signaling pathway would be highly deleterious to normal endothelial cell function, survival, and replenishment. C5b-9 may be the factor most involved in the mechanism of vascular thrombosis, at least based on the extent of deposition in our index case.

The differential diagnosis of a multifocal ulcerative process in the skin associated with a pauci-inflammatory thrombogenic vasculopathy encompasses defects in anticoagulation, hyperviscosity states, and endothelial cell dysfunction. These include hypercoagulability owing to factor V Leiden, deficiency of protein C, protein S, or antithrombin C, presence of antiphospholipid antibodies, cryopathies, and elevated homocysteine levels. In addition, drugs such as warfarin, heparin, and enoxaparin can cause microvascular thrombosis. Although the thrombotic complications of bevacizumab in other organ systems are well known, an ulcerating thrombotic diathesis involving the skin is without precedent and dermatologists should be aware of this potential complication.

References

1. 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 Jul;349(5):427-434. [PMID 12890841]
2. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004 Jun;350(23):2335-2342. [PMID 15175435]
3. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol. 2004 Jun;22(11):2184-2191. [PMID 15169807]
4. Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med. 2007 Dec;357(26):2666-2676. [PMID 18160686]
5. Ferrara N, Hillan KJ, Gerber HP, et al. Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. Nat Rev Drug Discov. 2004 May;3(5):391-400. [PMID 15136787]

6. Tewari KS, Sill MW, Long HJ, 3rd, et al. Improved survival with bevacizumab in advanced cervical cancer. N Engl J Med. 2014 Feb;370(8):734-743. [PMID 24552320]
7. Veritti D, Lanzetta P. Triple therapy for anti-vascular endothelial growth factor nonresponders in neovascular age-related macular degeneration: impact of different photodynamic therapy parameters. Ophthalmologica. 2013 230(3):131-137. [PMID 23948986]
8. Saif MW. Anti-VEGF agents in metastatic colorectal cancer (mCRC): are they all alike? Cancer Manag Res. 2013 5103-115. [PMID 23807861]
9. Keefe D, Bowen J, Gibson R, et al. Noncardiac vascular toxicities of vascular endothelial growth factor inhibitors in advanced cancer: a review. Oncologist. 2011 16(4):432-444. [PMID 21441297]
10. Schutz FA, Je Y, Azzi GR, et al. Bevacizumab increases the risk of arterial ischemia: a large study in cancer patients with a focus on different subgroup outcomes. Ann Oncol. 2011 Jun;22(6):1404-1412. [PMID 21115602]
11. Donadon M, Vauthey JN, Loyer EM, et al. Portal thrombosis and steatosis after preoperative chemotherapy with FOLFIRI-bevacizumab for colorectal liver metastases. World J Gastroenterol. 2006 Oct;12(40):6556-6558. [PMID 17072991]
12. Verschraegen CF, Czok S, Muller CY, et al. Phase II study of bevacizumab with liposomal doxorubicin for patients with platinum- and taxane-resistant ovarian cancer. Ann Oncol. 2012 Dec;23(12):3104-3110. [PMID 22851407]
13. Eremina V, Jefferson JA, Kowalewska J, et al. VEGF inhibition and renal thrombotic microangiopathy. N Engl J Med. 2008 Mar;358(11):1129-1136. [PMID 18337603]
14. Hurwitz HI, Saltz LB, Van Cutsem E, et al. Venous thromboembolic events with chemotherapy plus bevacizumab: a pooled analysis of patients in randomized phase II and III studies. J Clin Oncol. 2011 May;29(13):1757-1764. [PMID 21422411]
15. Frangie C, Lefaucheur C, Medioni J, et al. Renal thrombotic microangiopathy caused by anti-VEGF-antibody treatment for metastatic renal-cell carcinoma. Lancet Oncol. 2007 Feb;8(2):177-178. [PMID 17267332]
16. Furuyama H, Fuji H, Okumura S, et al. [A case of recurrent colon cancer developed thrombosis in superior mesenteric vein after chemotherapy]. Gan To Kagaku Ryoho. 2013 May;40(5):659-661. [PMID 23863595]
17. Uy AL, Simper NB, Champeaux AL, et al. Progressive bevacizumab-associated renal thrombotic microangiopathy. Clinical Kidney Journal. 2009 2(1):36-39. [PMID
18. Togashi Y, Kim YH, Masago K, et al. Pulmonary embolism due to internal jugular vein thrombosis in a patient with non-small cell lung cancer receiving bevacizumab. Int J Clin Oncol. 2011 Aug;16(4):444-446. [PMID 21116671]
19. Kamba T, McDonald DM. Mechanisms of adverse effects of anti-VEGF therapy for cancer. Br J Cancer. 2007 Jun;96(12):1788-1795. [PMID 17519900]
20. Verheul HM, Pinedo HM. Possible molecular mechanisms involved in the toxicity of angiogenesis inhibition. Nat Rev Cancer. 2007 Jun;7(6):475-485. [PMID 17522716]