TITLE
Impaired wound healing secondary to bevacizumab

AUTHORS
Ji Won Ahn, MD[1]; Doaa Shalabi, BA[2]; Lilia M Correa-Selm, MD[3]; Bahar Dasgeb, MD[2]; Neda Nikbakht, MD, PhD[2]; Jisun Cha, MD[2,4]

AFFILIATIONS
[1]University of Michigan Hospitals, Department of Dermatology
[2]Thomas Jefferson University Department of Dermatology and Cutaneous Biology
[3]Cleveland Clinic Indian River Hospital, Scully Welsh Cancer Center
[4]Rutgers Robert Wood Johnson Medical School, Department of Pathology and Laboratory Medicine,

CORRESPONDANCE
Jisun Cha, MD,
Thomas Jefferson University,
Department of Dermatology & Cutaneous Biology
833 Chestnut Street Suite 740
Phone: 215-955-6680
Email: jisun.cha@jefferson.edu

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Abstract

Bevacizumab is a monoclonal antibody that exerts its antitumor activity by inhibiting vascular endothelial growth factor (VEGF). Consequently, it suppresses endothelial cell proliferation, vascular permeability, and angiogenesis. This inhibitory effect contributes to tumor size reduction, but causes wound healing delay, specifically during the proliferative phase, in patients receiving bevacizumab. Although surgical wound healing complications associated with bevacizumab have been extensively reported, there is limited literature on peripheral wound healing complications. More importantly, histopathology of bevacizumab-associated wound healing complications has not been described. We present the histopathology findings of a non-healing ulcer in a patient receiving bevacizumab, providing insight into the possible etiology of this drug adverse reaction. Furthermore, our patient's positive response to hyperbaric oxygen suggests its possible use for treatment of bevacizumab associated non-healing wounds.

Keywords: Bevacizumab, Dermal matrix, Epithelialization, VEGF-inhibitor, Wound healing complication

Introduction

Bevacizumab is an angiogenesis inhibitor that targets the vascular endothelial growth factor A (VEGF-A) receptor. It was first approved in 2004 for treatment of metastatic colon cancer. Since then, bevacizumab has shown successful response in Kaposi sarcoma including AIDS associated disseminated form with resolution of lesion assessed histologically and by imaging.(1) It has also been used for various other cancers, including metastatic renal cell carcinoma, glioblastoma, and non-small cell lung cancer.(2) Bevacizumab's inhibitory side effect on wound healing has been described for surgical wounds.(3, 4) However, non-surgical wound healing complications (WHC) have not been reported with detailed histopathology description. Herein, we present a case of a non-healing wound in a patient on long-term bevacizumab therapy with histopathology description.

Case Report

A man in his 70s with a history of metastatic colorectal carcinoma on capecitabine and bevacizumab was referred to our clinic for a persistent painful ulcer on his right forearm. The patient had no previous history of WHC. Eight months prior, the patient noticed a new purple lesion on his right forearm, which was painful and itchy with erosion and occasional bleeding. The patient saw a dermatologist four months after the appearance of the lesion as it failed to heal. A biopsy report described cutaneous ulcer with no further specification. The biopsy site did not heal, and he continued to experience worsening pain for four months. By then, he had been treated with topical mupirocin and clindamycin, intralesional triamcinolone, oral doxycycline, and oral minocycline with no improvement in pain or size of the ulcer. Subsequently, the patient was referred to our clinic to exclude pyoderma gangrenosum. At presentation to our clinic, there was a 2.5x1.5cm ulcer with undermining borders and purulent discharge (Fig 1). Bacterial culture was positive for Corynebacterium species, which was treated with cephalexin, polymyxin-bacitracin ointment and silver sulfadiazine. Upon follow-up visits, the ulcer remained and a greenish discharge from the ulcer was noted. Bacterial culture grew Pseudomonas aeruginosa, for which the patient was treated with topical gentamicin ointment. When no sign of infection was seen at the follow-up visit, intralesional triamcinolone 5mg/mL injection and

clobetasol ointment were given. Nonetheless, the ulcer persisted, with minimal improvement in size and pain level.

Biopsy slides showed a failure of wound healing with improper re-epithelialization and insufficient connective tissue regeneration to fill the underlying dermis without inflammation (Fig 2). The likely cause of the non-healing ulcer was discerned to be the current treatment with bevacizumab, which is known to interrupt surgical wound healing in patients with tumor resection.(3) However, after discussion with the patient's oncologist regarding this concern, the decision was made to continue bevacizumab, as the patient's cancer was controlled on bevacizumab and capecitabine. The patient was referred to a wound care clinic for consideration of hyperbaric treatment that significantly improved the wound healing process and the wound finally closed after 13 weeks of treatment.

Discussion

Bevacizumab is often used as the adjuvant or neoadjuvant treatment of various cancers, including metastatic colorectal cancer, metastatic renal cell carcinoma, glioblastoma, and non-small cell lung cancer.(2) The antibody, by inhibiting the role of VEGF, can cause severe wound healing delay. VEGF has been shown to mediate endothelial-cell-induced coagulation and angiogenic activity during the proliferative phase of wound healing.(5) In fact, surgical WHCs that include dehiscence, surgical site bleeding and infection are well-documented adverse reactions of bevacizumab.(3, 4) Given these complications, it is recommended that bevacizumab is stopped at least 60 days before surgery and restarted 28 days after surgery.

However, non-surgical WHC has limited descriptions in the literature, although a few animal studies have reported peripheral skin WHC in rabbits with short-term exposure to

intravitreal bevacizumab.(5, 6) An initial study observing cutaneous wound healing following intravitreal bevacizumab demonstrated reduced neovascularization one week following treatment compared with untreated controls.(6) Further characterization of wound margins after bevacizumab treatment revealed significantly diminished wound tensile strength in treated groups compared with control.(5)

The histopathology behind bevacizumab-associated WHC has only been described in animal models and briefly in human patients. Histopathologic examination in animal studies has focused on quantifying blood vessel development in anti-VEGF treated groups, revealing diminished numbers of endothelial cells.(5) In one human presentation, histopathology of bevacizumab associated skin necrosis showed vascular thrombosis and infarction of dermal and subdermal layers.(7)

Our cases' histopathology findings present the lack of dermal regeneration in patients on bevacizumab along with the lack of re-epithelialization on the surface. During wound healing, neovascularization during the proliferative phase of wound healing promotes cell proliferation and adhesion that compose the dermal matrix.(8) Given that angiogenesis is disrupted with bevacizumab therapy, dermal matrix regeneration is expected to be diminished, as seen in our patient's histopathology (thin to absent dermis with exposing the subcutaneous fat). As a result, a lack of fibrosis for wound healing and insufficient dermal matrix regeneration are expected. Subsequently, in the lack of fibrosis, the fibroblast derived keratinocyte growth factor, the major stimulator of basal keratinocyte proliferation during wound repair, is presumably reduced.(9)

This is consistent with the lack of basal keratinocytes and disrupted re-epithelialization in our patient. Thus, it appears that the defective angiogenesis leading to the lack of dermis regeneration and re-epithelialization hindered wound healing in our patient.

Hyperbaric oxygen (HBO) has been an effective adjuvant treatment in various wounds including non-healing diabetic and venous insufficiency ulcers, thermal burns and infected wounds.(10) Given our patient's persistent ulcer, HBO was attempted. It is known that oxygen supply to ischemic wounds accelerates wound healing by upregulating growth cytokines, such as fibroblast growth factor and VEGF.(11) Moreover, HBO has resulted in modest effects on angiogenesis and a VEGF abundance in wounds following therapy.(11) Despite our patient's improvement with HBO, the exact mechanism leading to healing of bevacizumab associated WHC is not described yet. However, it can be considered for wounds secondary to bevacizumab therapy.

The clinical course of the patient highlights how important it is for dermatologists to be aware of bevacizumab and its association with peripheral WHC to prevent any unnecessary work up and further morbidities in patients on bevacizumab with non-healing ulcers. From the positive outcome of our patient's wound, hyperbaric oxygen treatment may be considered for the similar cases. Additional studies are needed to further characterize the mechanism of bevacizumab-associated WHC.

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Reviewers:

1. Jichyun Jcon, MD, PhD; jhjconmd@gmail.com

2. N Jourabchi, MD: njourab1@jhmi.edu

3. Duygu Gulseren; duygu_gulsrn@hotmail.com

Abbreviations and Acronyms:

HBO: hyperbaric oxygen

VEGF: vascular endothelial growth factor

VEGF-A: vascular endothelial growth factor A

WHC: wound healing complications

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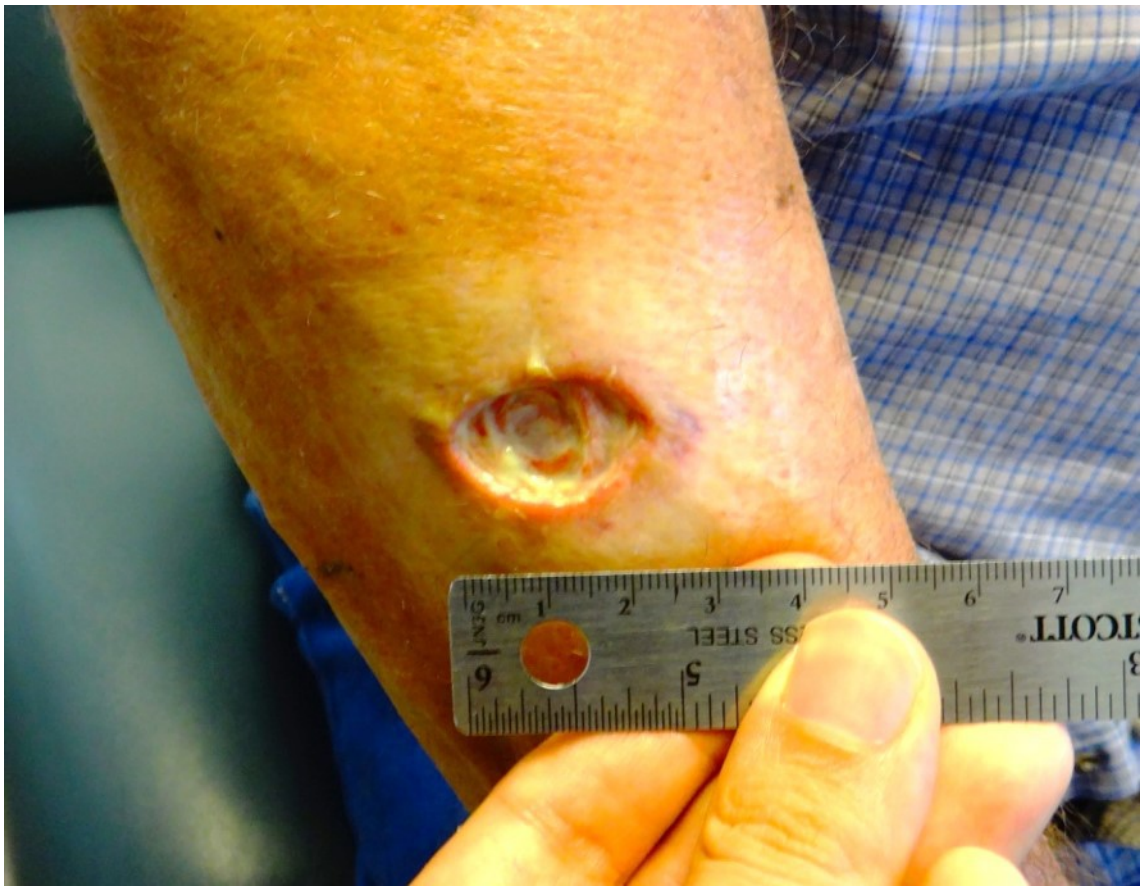
LEGENDS:

Figure 1. **Bevacizumab-associated wound healing failure.** 2.5 x 1.5cm punched out ulcer is seen with undermining borders and purulent discharge on the right dorsal mid-forearm.

Figure 2. **Histopathology of bevacizumab-associated wound healing complication.** A, At lower magnification (H&E, 20X), the ulceration is not associated with appropriate dermal connective tissue regeneration and the subcutaneous fat is pushing into the reticular dermis. B, At higher magnification (H&E, 40X), there is a lack of re-epithelization on the edge of the ulceration and lack of vascularization on the base of the ulceration.



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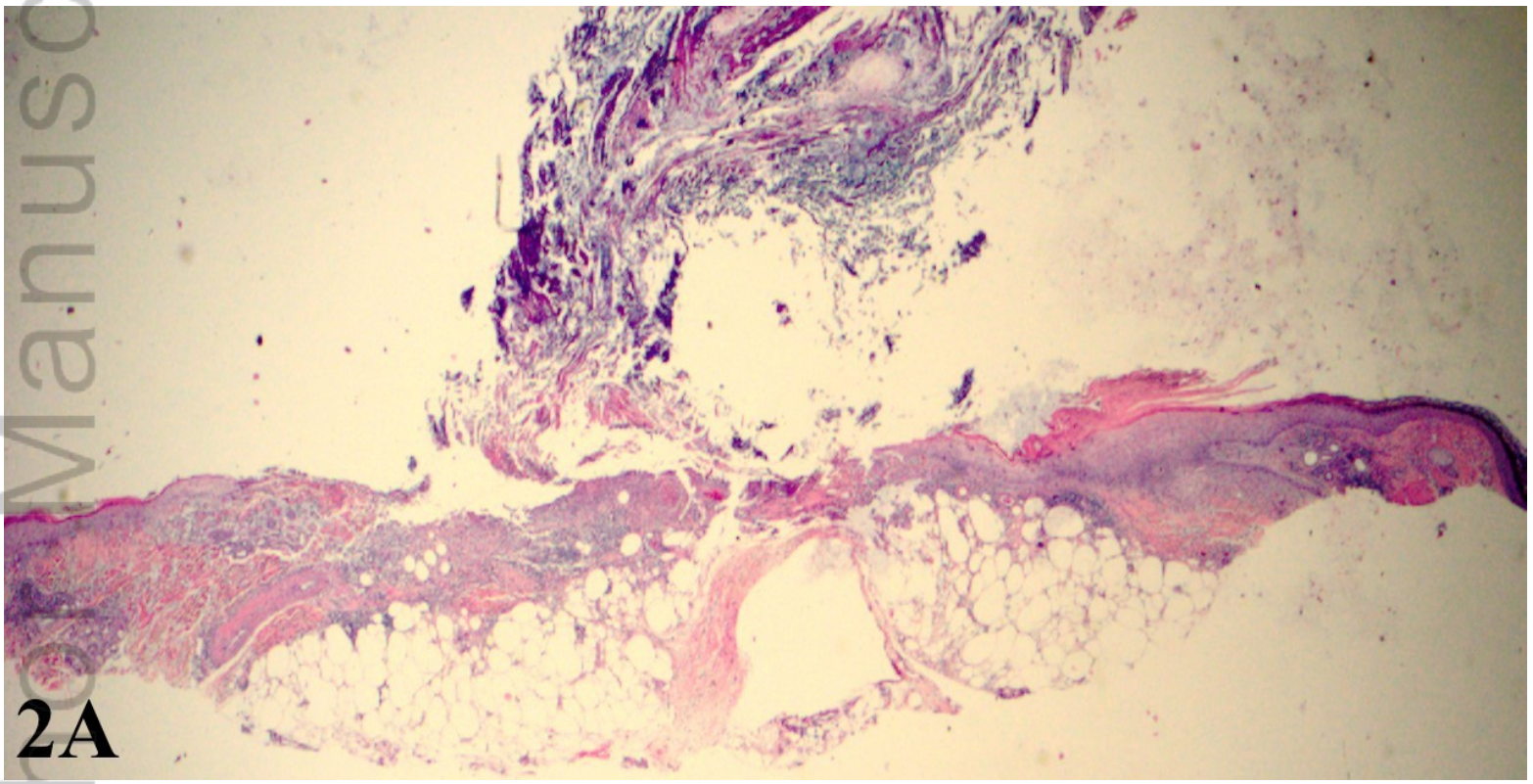

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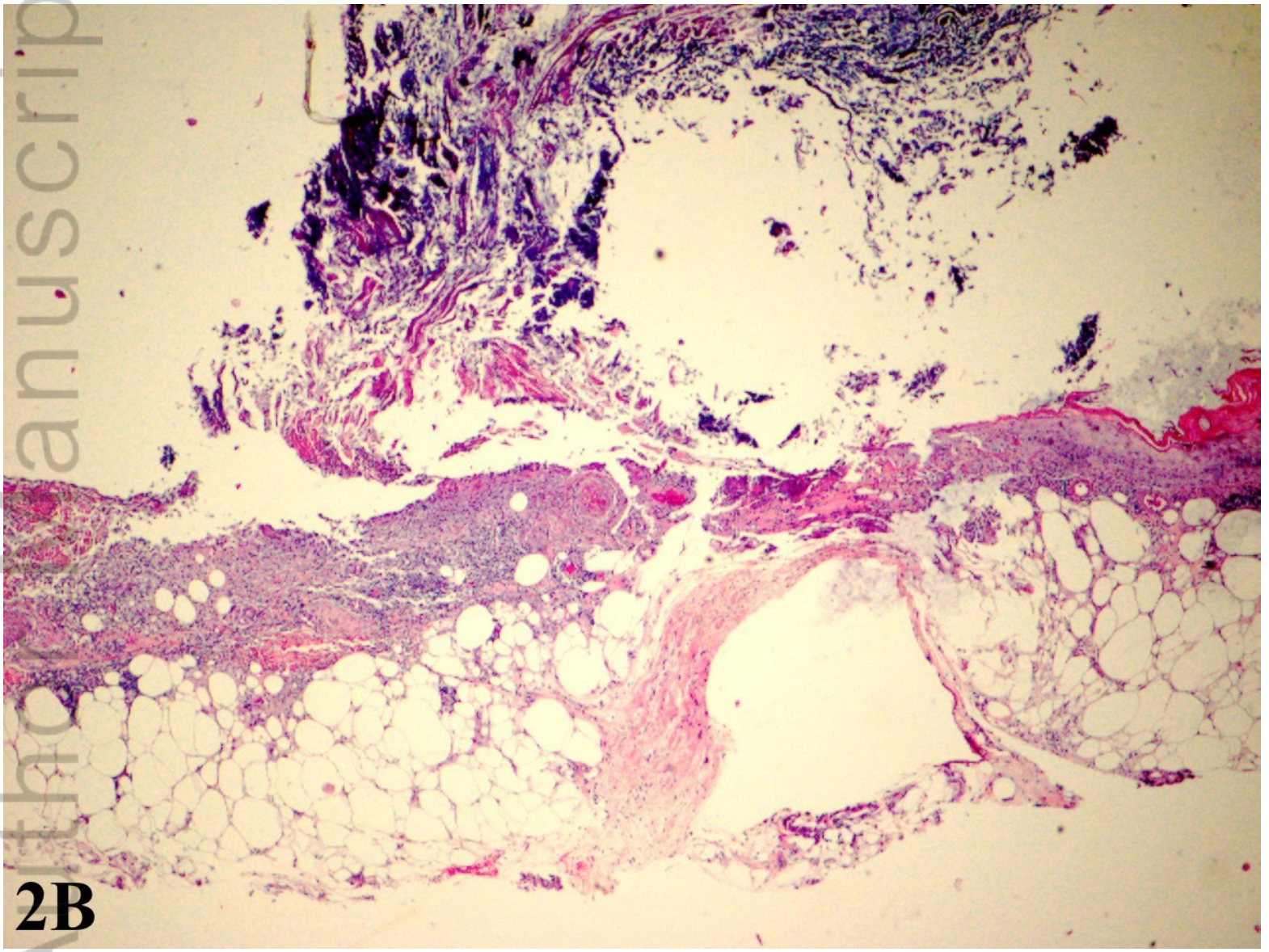

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Key Messages:

- Bevacizumab therapy inhibits angiogenesis and can lead to non-surgical wound healing complications
- An examination of histopathology reveals diminished dermal regeneration and surface re-epithelialization, providing a possible etiology for bevacizumab's effect on wound healing
- An awareness about this presentation can prevent unnecessary workup and appropriate treatment for patients