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Impaired wound healing secondary to bevacizumab

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

1 | INTRODUCTION

Bevacizumab is an angiogenesis inhibitor that targets the vascular endothelial growth factor A (VEGF-A) receptor. It was first approved in 2004 for the treatment of metastatic colon cancer. Since then, bevacizumab has shown successful response in Kaposi sarcoma, including the acquired immunodeficiency syndrome-associated disseminated type, 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 descriptions. Here, we present a case of a non-healing wound in a patient on long-term bevacizumab therapy with histopathology description.

2 | 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 4 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 4 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. On presentation to our clinic, there was a 2.5 cm × 1.5 cm ulcer with undermining

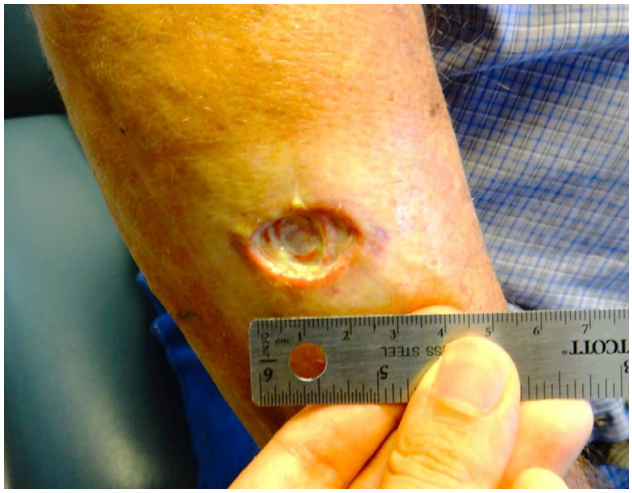

FIGURE 1 Bevacizumab-associated wound-healing failure: 2.5 cm × 1.5 cm punched-out ulcer is seen with undermining borders and purulent discharge on the right dorsal mid-forearm

Key Messages

- bevacizumab therapy inhibits angiogenesis and can lead to non-surgical wound-healing complications
- an examination of histopathology demonstrates diminished dermal regeneration and surface reepithelialisation, providing a possible aetiology for bevacizumab's effect on wound healing
- an awareness about this presentation can prevent unnecessary work-up and lead to appropriate treatment for patients

borders and purulent discharge (Figure 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 5 mg/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 reepithelialisation and insufficient connective tissue regeneration to fill the underlying dermis without inflammation (Figure 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 tumour 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.

3 | 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

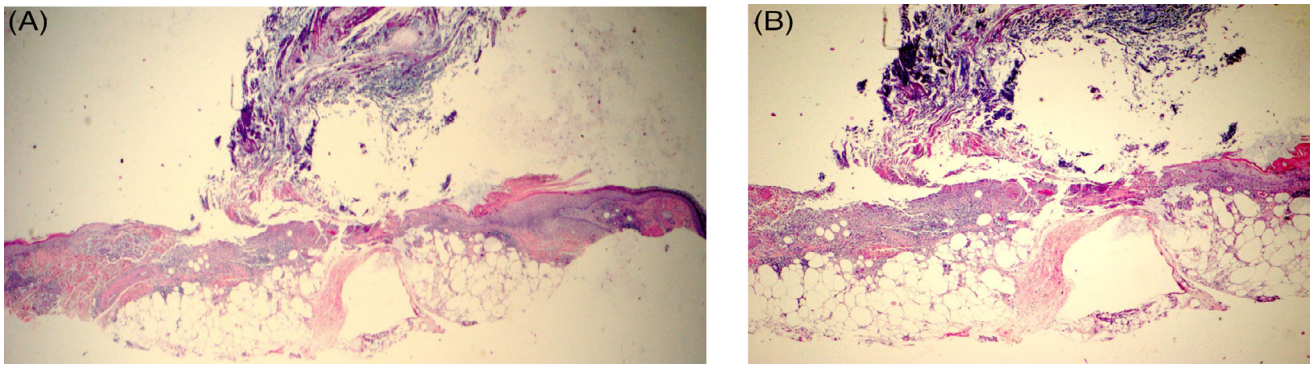

FIGURE 2 Histopathology of bevacizumab-associated wound-healing complication. A, At lower magnification (H&E, ×20), the ulceration is not associated with appropriate dermal connective tissue regeneration, and the subcutaneous fat is pushing into the reticular dermis. B, At higher magnification (H&E,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

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 be 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 neovascularisation 1 week following treatment compared with untreated controls.[6] Further characterisation of wound margins after bevacizumab treatment demonstrated 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. Histopathological examination in animal studies has focused on quantifying blood vessel development in anti-VEGF treated groups, demonstrating 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 case's histopathology findings present the lack of dermal regeneration in patients on bevacizumab along with the lack of reepithelialisation on the surface. During wound healing, neovascularisation 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, 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 reepithelialisation in our patient. Thus, it appears that the defective angiogenesis leading to the lack of dermis regeneration and reepithelialisation 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 well known that oxygen supply to ischaemic wounds accelerates wound healing by up-regulating 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 the healing of bevacizumab-associated WHC is not yet described. 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, HBO treatment may be considered for similar cases. Additional studies are needed to further characterise the mechanism of bevacizumab-associated WHC.

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CONFLICT OF INTEREST

The authors have no conflict of interest to disclose

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