CLINICAL VIGNETTE

The Effects of Sorafenib on Wound Healing

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Introduction

The negative impacts of chemotherapeutic agents on wound healing have been well documented. However, the effect of wound healing caused by newer agents such as small molecule inhibitors and Immunotherapeutics designed to inhibit vascular growth factors including sorafenib, sunitinib, bevacizumab, and levantinib have not yet been described in detail.[1] While VEG-F inhibitors are theoretically proposed to inhibit wound healing, given our knowledge of normal physiology and the role of VEG-F in vascularization of healing wounds. However, there is minimal research on the impact of these medications on microvascular development and wound healing for patients on these medications. In this case report, a patient with hepatocellular carcinoma treated with sorafenib developed a leg wound without clear etiology which deteriorated despite multiple wound care modalities and improved only upon discontinuation of sorafenib, suggesting a role for sorafenib in wound healing.

The Case

A 67-year-old male has liver biopsy establishing the diagnosis of Childs Pugh Class B hepatocellular carcinoma (HCC) and found to have locally advanced multifocal HCC without evidence of distant metastatic disease. He was a long-term nursing home resident with a medical history of hypertension, post-traumatic stress disorder, current tobacco use, underlying dementia, cirrhosis secondary to ethanol and untreated hepatitis C infection, and chronic leukopenia with thrombocytopenia secondary to hypersplenism and cirrhosis. He was assessed by oncology and felt to be a poor candidate for radiofrequency ablation, transarterial chemoembolization, and orthotopic liver transplantation. He was treated palliatively with low dose Sorafenib, 200 mg BID, for 4 months, which was limited due to hyperbilirubinemia secondary to hepatic toxicity. He also received lactulose and rifaximin for hepatic encephalopathy.

One month after initiation of sorafenib, the patient noticed a wound on his left medial shin, which he described as a "pebble" that opened and grew larger. The wound was painless and not associated with fever or chills. He denied trauma to the area and denied having similar wounds in the past. He did not report the wound to his nursing team for a month. He spoke up when the wound began to deteriorate into an ulceration. The wound care team noted a 2.0 x 2.1 x 0.2 cm circular wound to the anterior LLE with a mix of smooth red tissue, slough, and eschar with edematous purple-red erythema to periwound skin (Figure 1).

The differential included a ruptured abscess versus a traumatic injury and recommendations were made for daily cadexomer covered with alldress. However, one week later, the wound significantly progressed to 2.6 x2.5 x 0.3 cm with edematous margins and increased necrotic tissue in wound bed (Figure 2). The site had soft eschar, slough, and smooth red tissue and small seropurulent drainage. Recommendations for wound care changed to use of cavilon wipe to periwound area and santyl application to the wound bed and coverage with moistened gauze for enzymatic debridement and improved healing. Two weeks after initial presentation, the wound progressed further, and now measured 3.0 x 3.2 x 0.2 with mixed slough and eschar to wound bed, marginal edema, mild malodor from site, and new complaints of pain from the patient (Figure 3). Silvadene was started due to the lack of improvement with other treatments and increased signs and symptoms of infection.

Given rapid deterioration of the wound and this patient's history of HCC and the use of sorafenib, dermatology, vascular surgery, and plastic surgery were consulted for assessment of the site. Dermatology felt the wound was most likely venous in origin given the location in the medial shin, though there was some concern for an arterial process given the depth of the ulcer. Vascular surgery, performed venous and arterial doppler ultrasound, which showed no evidence of venous insufficiency or arterial etiologies and the patient was found to have a normal ankle/brachial index bilaterally. There was no evidence for DVT. Plastic surgery, deemed the patient to be a poor candidate for a local flap or skin grafting over the wound given the history of poor healing and his current smoking.

A malignant process such as metastasis versus impaired wound healing due to the sorafenib versus wound infection were considered. Wound culture revealed *Citrobacter freundii* complex, widely susceptible *Staphylococcus aureus*, and *Corynebacterium* species. X-rays of the leg showed no evidence of osteomyelitis. The patient was treated with levofloxacin 500 mg PO daily for 7 days to treat his wound infection. Pressure dressings were also initiated. Within one week despite antibiotics and appropriate pressure dressings, the wound had worsened to 5.0 x 6.5 x 0.3 with mixed slough/eschar and smooth red tissue with irregular wound margins and hyperpigmented periwound skin with moderate purulent drainage (Figure 4).

The decision was made to discontinue the sorafenib and observe the wound for improvement. Within less than 1 week of discontinuation of the sorafenib, the patient's wound had begun to improve. The size decreased to 4.5 x 6.0 x 0.3 cm, there was increase in healthy smooth red tissue with reduced slough, and the wound was free of eschar (Figure 5). From this point, the wound continued to improve and healthy red granulation tissue began to form and grow over the next month. At latest visit the wound is 2x2.5x0cm with smooth red tissue (Figure 6).

Discussion

This patient presented with a non-healing atypical vascular wound to the left lower leg. Despite a number of treatments, the wound continued to deteriorate. Even though there was no evidence that sorafenib impacted wound healing this case presents empirical evidence that it interfered with wound healing. The wound etiology remains unclear; it presents as venous stasis or mixed vascular but vascular surgery ruled out vascular insufficiency. Although there is some evidence that sorafenib can increase the risk for arthrosclerosis, hypertension, and arterial thrombus formation, there is little evidence of its effects on wound healing and wound infection management. However, there is some evidence of vascular side effects which may be the underlying cause of the patient's leg wound.[1]

Conclusion

This case highlights the need for further study on the impact of sorafenib and similar medications on wound healing. Because sorafenib interferes with angiogenesis it likely also interferes with capillary formation and blood flow to open wounds. In this case report, stopping sorafenib improved the wound significantly (Figure 7). This suggests that sorafenib should be avoided in patients with non-healing wounds, and that non-healed wounds should be closely monitored when a patient is taking sorafenib. Further research is needed on the impact of sorafenib on wound healing.

Figures

Figure 1: Picture of wound on initial assessment (1/19/18)

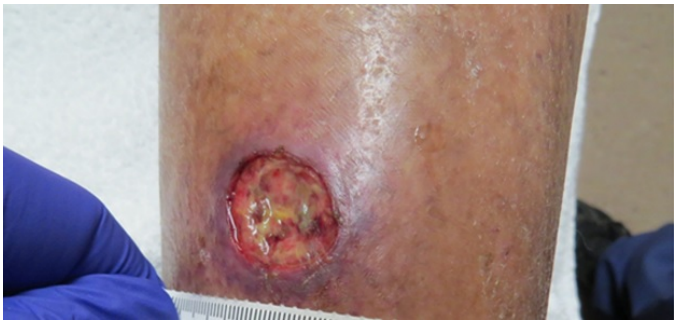


Figure 2: Wound after 1 week

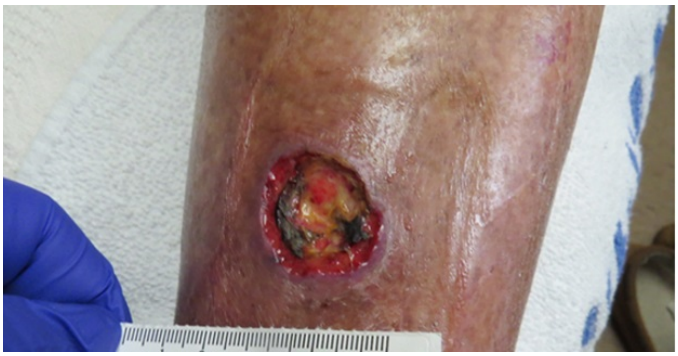


Figure 3 Wound continues to deteriorate

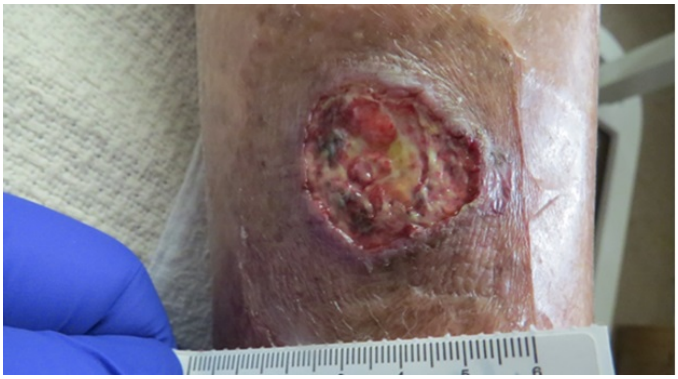


Figure 4 Wound just before holding sorafenib on 3/28/18

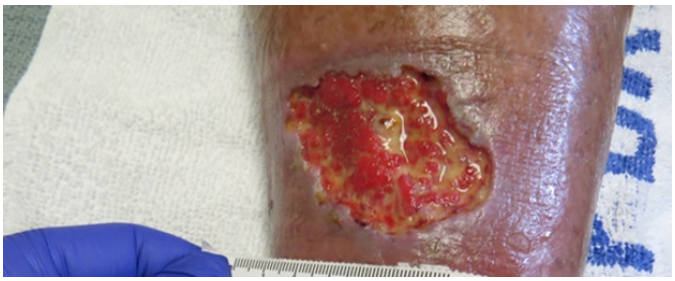


Figure 5

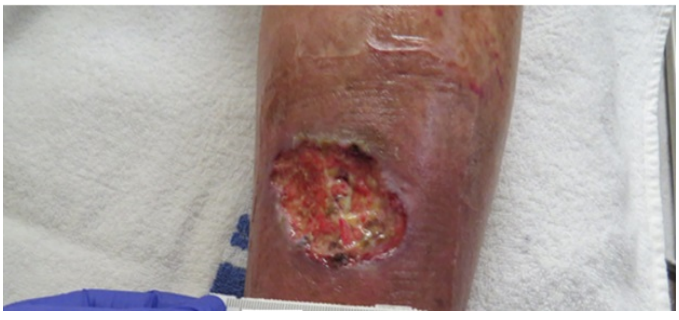


Figure 6: Wound at submission

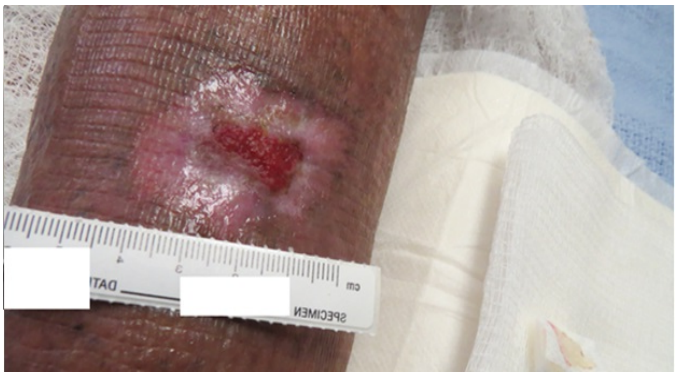
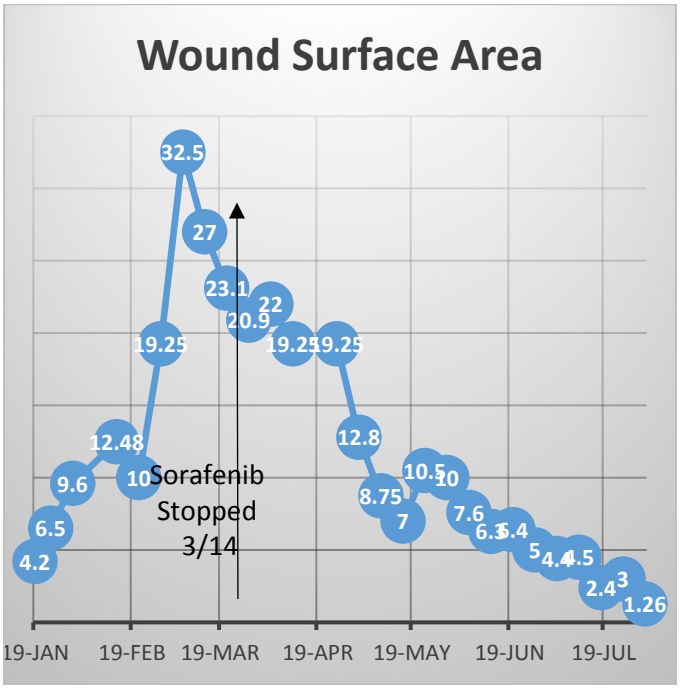


Figure 7: Graph of wound surface area over time



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1. **Touyz RM, Herrmann SMS, Herrmann J**. Vascular toxicities with VEGF inhibitor therapies-focus on hypertension and arterial thrombotic events. *J Am Soc Hypertens*. 2018 Jun;12(6):409-425. doi: 10.1016/j.jash.2018.03.008. Epub 2018 Mar 21. Review. PubMed PMID: 29703600.

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