Clinics in Oncology

Case Report
Published: 29 May, 2019

Ulceration of Steroid-Induced Striae Distensae in a Patient with a Rare Brain Tumor on Bevacizumab

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Abstract

Bevacizumab, a Vascular Endothelial Growth Factor (VEGF) inhibitor, is approved for recurrent glioblastoma and various metastatic cancers. VEGF plays an important role in angiogenesis and wound healing and thus, the use of Bevacizumab has been associated with dehiscence, ecchymosis, surgical site bleeding, and wound infection. A unique side-effect of Bevacizumab is the ulceration of steroid-induced striae distensae in patients treated for brain tumors, mainly glioblastoma. Here we report for the first time the case of a young female who presented with ulcerated striae while on treatment with Dexamethasone and Bevacizumab for anaplastic hemangiopericytoma, a rare malignancy of the central nervous system.

Introduction

Systemic glucocorticoids interfere with collagen type I and III synthesis and degradation in the dermis leading to side effects such as delayed wound healing and skin atrophy [1-3]. Striae distensae develop due to dysfunction of the extracellular matrix components responsible for strength and elasticity, namely fibrillin, elastin, and collagen and have been linked to pregnancy, adolescence, chronic steroid use, obesity, and Cushing syndrome [4-6].

The vast majority of patients with brain tumors are prescribed corticosteroids, most frequently dexamethasone, to reduce peritumoral vasogenic edema and control associated signs and symptoms [7]. Thus, these patients are prone to development of striae distensae. In 2009, FDA approved Bevacizumab, the first Vascular Endothelial Growth Factor (VEGF) inhibitor, for recurrent glioblastoma, the most common type of malignant brain tumor in adults [8,9].

Bevacizumab is a recombinant humanized monoclonal IgG antibody, which binds VEGF-A and does not permit its binding on the endothelial cell receptors VEGFR-1 (Flt-1) and -2 (Flk-1 or KDR) (3). Thus, VEGF, expressed in many tumor cells, cannot stimulate proliferation of endothelial cells, resulting in inhibition of angiogenesis and vascular hyper permeability, and consequently, tumor progression [10-12]. In addition, changes in the local vasculature and interstitial pressure mediated by the VEGF-inhibitor Bevacizumab favor the delivery of other chemotherapeutics to the tumor [13].

Given the importance of VEGF in mediating wound healing, various related abnormalities have been observed in patients on Bevacizumab, such as dehiscence, ecchymosis and surgical site bleeding, and wound infection [14-16]. Bevacizumab was first approved for metastatic colorectal cancer, later for recurrent or metastatic non-small cell lung cancer, metastatic renal cell carcinoma and more recently for recurrent or metastatic cervical cancer, epithelial ovarian, fallopian tube, and primary peritoneal cancers [17]. Interestingly, most wound healing abnormalities have been reported in patients with colorectal cancer and brain tumors [15]. Here we report for the first time a case of a 32-year old female with anaplastic hemangiopericytoma, a rare meningeal tumor arising from pericytes surrounding the endothelial cell lining of capillaries and venules, who presented with ulceration of abdominal striae while on treatment with corticosteroids and Bevacizumab [18].

Case Presentation

A 32-year old female diagnosed with left hemisphere hemangiopericytoma, anaplastic type (stage 3), presented with a three-week history of painful, crusted ulcerations on the abdomen and thighs. On physical examination, the patient had four round ulcerations localized on the large striae

OPEN ACCESS

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Received Date: *02 May 2019*
Accepted Date: *24 May 2019*
Published Date: *29 May 2019*

Citation:
Pilitsi E, Wang S, Braniecki M, Tsoukas ML. Ulceration of Steroid-Induced Striae Distensae in a Patient with a Rare Brain Tumor on Bevacizumab. Clin Oncol. 2019; 4: 1619.

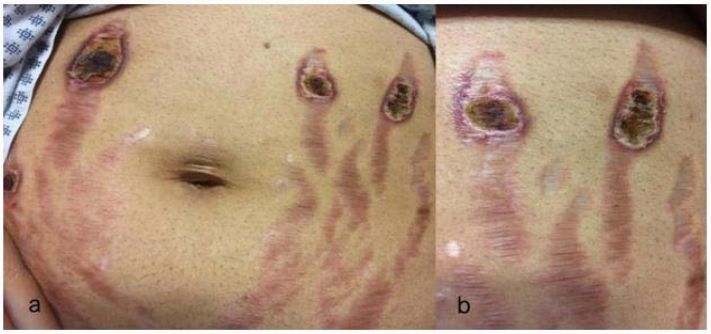

Figure 1: a) Four round ulcerations localized on the large striae on the abdomen. **b)** Close-up view of two of the ulcerations.

Table 1: Cases of ulceration within steroid-induced striae associated with use of Bevacizumab.

Patient's age (years), gender	Diagnosis	Chemotherapeutic regimen	Concurrent corticosteroid use	Management of ulcerations	Outcome	Reference
38, M	Glioblastoma multiforme	Irinotecan, Bevacizumab	Dexamethasone	wound care; Bevacizumab and Irinotecan discontinued	Partial improvement prior to death	[23]
47, F		Temozolomide, Bevacizumab		wound care with wet to dry dressings and triple antibiotic ointment; Bevacizumab	No improvement prior to death	
				Discontinued		
43, F		Temozolomide, Bevacizumab		Wound care; Bevacizumab discontinued	Slow healing	
23, M	Anaplastic astrocytoma	Etoposide, Bevacizumab		Wound care with petrolatum	Complete	
				41% and Lidocaine ointments; Bevacizumab discontinued*	Healing after 2 months	
47, M		Irinotecan, Bevacizumab	high dose systemic steroids	wound care; Bevacizumab discontinued	Slow partial healing prior to death	[30]
29, M	Grade III Glioblastoma	Irinotecan, Bevacizumab	Methylprednisolone	wound care with hydrogel dressings; Bevacizumab	Complete healing after	[24]
				discontinued	1 month	
32, M	Glioblastoma multiforme	Etoposide, Bevacizumab	Dexamethasone	wound care with dressing changes	Partial improvement	[25]
29, F	Glioblastoma multiforme	Temozolomide, Bevacizumab	Dexamethasone	wound care with white petrolatum and nonstick dressings; Bevacizumab	Improvement after 1 month	[26]
				discontinued		
15, F	Gliomatosis cerebri	Bevacizumab	Prednisolone	wound care with dressing;	No improvement	[27]
				opiates for pain; Bevacizumab discontinued		
14, M	Supratentorial Glioblastoma	Bevacizumab and Irinotecan	Dexamethasone	Wound care with dressing changes; opiates for pain;	No improvement prior to death	[28]
				Bevacizumab and Irinotecan discontinued		
11, NR	Astrocytoma	Bevacizumab	Dexamethasone	Diltiazem cream 2% twice daily	Complete healing	[29]
NR, M‡	NR	NR	NR	NR	NR	[22]

*Dexamethasone had already been tapered off a month prior to Bevacizumab discontinuation
‡This case was part of a retrospective chart review. Individual patient information was not provided
Abbreviations: F: Female; M: Male; NR: Not Reported

on her abdomen and three on the striae on her thighs (Figure 1a, 1b). The ulcerations had rolled hyper pigmented to violaceous borders with overlying crust and necrotic eschar. The striae had been present on her abdomen, upper arms, and thighs for the last two years. The patient reported a stretching sensation on the skin for the past four weeks followed by the development of the ulcerations. There were no preceding lesions other than striae prior to ulcer formation and no history of trauma or pressure on the affected areas. The lesions were not self-induced. In addition, the patient had moon facies and central obesity. The review of systems was positive for aphasia, impaired mobility, right-sided hemiparesis, and allodynia related to the underlying malignancy. Vital signs were within normal limits. The magnitude of the ulceration-related pain necessitated IV morphine administration. Since her diagnosis of hemangiopericytoma in 2014, the patient had undergone multiple treatments including surgical resections, radiation therapy, and chemotherapy. At the time of the presentation, she was on Bevacizumab and Dexamethasone. The patient's family and social history were unremarkable. Complete blood count, comprehensive metabolic panel, and coagulation studies (PT/INR, PTT, Protein C and S, antiphospholipid antibodies) did not reveal any abnormalities. Blood cultures as well as serologic blastomyces and histoplasma antigen testing were negative.

Since initial tests were inconclusive, we obtained a biopsy of one of the abdominal ulcerations. Histopathologic examination after hematoxylin-eosin staining revealed an artificially detached and displaced fragment of the epidermal edge of the ulcer and an associated necrotic, purulent crust (Figure 2a). In the dermis, there was a mild neutrophilic inflammatory infiltrate; there was no evidence of vasculitis, micro thrombi, or other pathological findings. No lobular or septal inflammation of the subcutaneous fat was noted.

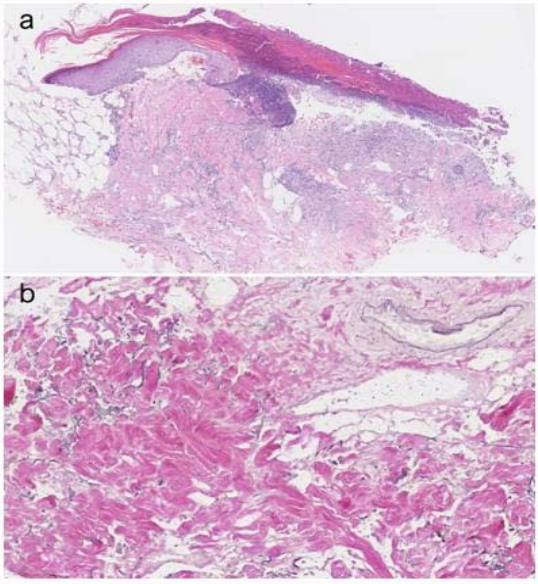

Figure 2: a) Hematoxylin-eosin stain revealing an artificially detached and displaced fragment of the epidermal edge of the ulcer and an associated necrotic, purulent crust. In the dermis, there is a mild neutrophilic inflammatory infiltrate. **b)** Elastic stain showing fragmentation, clumping, and areas of diminished elastic fibers.

A gram stain highlighted surface colonization with gram positive cocci, while PAS and AFB stains were negative. An elastic stain showed fragmentation, clumping, and areas of diminished elastic fibers, findings consistent with striae (Figure 2b). A bacterial culture of the tissue specimen returned positive for coagulase negative staphylococcal species, most likely a contamination, while the fungal tissue culture came back negative.

An underlying infectious etiology was initially considered due to the patient's immunocompromise. However, the physical exam and the history of combined treatment with Bevacizumab and Dexamethasone suggested the diagnosis of ulcerations within steroid-induced striae associated with Bevacizumab (Table 1). Given the progression of the disease despite multiple treatment efforts, the patient elected to pursue hospice care. Therefore, Bevacizumab was discontinued, and appropriate wound care led slowly to improvement of the ulcerations. The pain also subsided requiring less aggressive analgesia. Unfortunately, the patient passed away due to the underlying malignancy before complete healing of the ulcerations was achieved.

Discussion

Hemangiopericytomas commonly originate from lower extremities, retro peritoneum/pelvis, lung/pleura, but also meninges, where they are characterized by particularly challenging features such as local invasion, metastasis, and high recurrence rate [18,19]. Surgical removal is the treatment of choice for localized disease, while radiotherapy is offered for advanced cases [20]. Bevacizumab decreased tumor size and progression free survival in advanced, recurrent and metastatic hemangiopericytoma, therefore it is used off-label [20,21]. Poor wound healing is a known side effect of Bevacizumab, with the median duration on treatment prior to abnormalities being 72 days and the majority of patients being on concomitant chronic steroid use for about 252 days [22]. Other cutaneous side effects of Bevacizumab are painful hand-foot syndrome, exfoliative dermatitis, skin discoloration, and xerosis [17].

Twelve cases of ulceration within striae in patients treated for brain tumors with Dexamethasone and Bevacizumab have been reported thus far [22-30]. Our patient's clinical presentation was similar to the previously published cases with ulcerations strictly confined to the striae. This is the first case involving an underlying Central Nervous System (CNS) hemangiopericytoma, since all previous cases involved other CNS malignancies (mostly glioblastoma). The most common regimen was the combination of Bevacizumab plus Irinotecan, a Topoisomerase I inhibitor, but also etoposide, a plant alkaloid/topoisomerase II inhibitor, temozolomide, an alkylating agent, or even Bevacizumab alone were used in addition to systemic steroids. Bevacizumab is known to cause skin fragility and poor wound healing as compared to the aforementioned chemotherapeutic agents, thus the ulcerations were attributed to it. In most of the cases, Bevacizumab was discontinued and in 7 of the cases, wound care resulted in significant improvement to complete resolution after 1 to 2 months [23-26,30]. The rest of the cases did not exhibit significant improvement, although in 5 of the cases, patients died shortly after drug discontinuation due to progression of the underlying malignancy [23,27,28]. In two cases, Bevacizumab was continued; wound care resulted in partial improvement of the ulcerations prior to patient's death in the first case and application of diltiazem cream 2% daily in complete healing within 4 weeks in the latter [25,29].

Chronic administration of high doses of corticosteroids increases skin fragility, while rendering the epidermis prone to striae development and sensitive even to minor trauma. In addition, chronic steroid use causes Cushingoid phenotypic characteristics, such as moon facies and central obesity, which were evident in the present case [31]. Furthermore, radiation and chemotherapy employed for brain tumors impair wound healing [22]. It is hypothesized that addition of Bevacizumab can weaken the skin even further and/or result in ulceration after minor trauma or friction which cannot heal via inhibition of VEGF [25]. The striae are particularly susceptible to ulceration due to their rich vasculature. Bevacizumab impairs the function of endothelial cells potentially causing thrombotic events and necrosis within striae [26].

Therefore, it is crucial to prescribe the lowest effective dose of systemic corticosteroids to decrease chances of toxicity. Patients on chronic steroids should also be evaluated for delayed wound healing risk factors and educated properly about the side effect profile prior to Bevacizumab administration [22,25]. If striae are already present before therapy initiation, adequate moisturizing and trauma protection should be proposed. All patients on Bevacizumab plus steroids should be monitored for early detection of ulceration [23]. This is a rare complication, but increases morbidity and decreases quality of life; therefore high clinical suspicion is required. Ulceration should be addressed with proper wound care including use of dressings (silicone-based or hydrocolloid) with silver foam if signs of infection are present [23]. Recently, diltiazem cream 2% showed very promising results in a pediatric patient in whom Bevacizumab could not be discontinued [29]. Diltiazem most likely led to complete healing of the ulcerations via improving blood flow [29]. Particularly in cases in which Bevacizumab cannot be discontinued, diltiazem might be an ideal solution, but further studies are needed to confirm its effectiveness and mechanism of action [29]. Nevertheless Bevacizumab should be discontinued upon development of wound

dehiscence and withheld for at least 28 days prior to and after an elective surgery, until complete wound healing [17].

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