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.

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...
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.

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

*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
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 stain 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 Cushingsoid 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

**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.
References


