

STEWART BLUEFARB SYNDROME: REVIEW OF THE LITERATURE AND CASE REPORT OF CHRONIC ULCER TREATMENT WITH HEPARAN SULFATE MIMETIC (CACIPLIQ 20®)

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Abstract:

Stewart-Bluefarb syndrome, also known as acroangiokeratosis or pseudo-Kaposi, is a condition rarely encountered. It involves skin lesions that are clinically similar to Kaposi sarcoma but are histologically different, and are usually secondary to an underlying arterio-venous fistula. Treatment of this disease usually involves the correction of the underlying vascular abnormality, with the mainstay of therapy ranging from compression devices for venous stasis, limited oral medications (dapson, erythromycin), and local wound care including topical steroids. Different methods of treatment showed varied success but none is ideal. We report a case of a lower extremity ulcer in a 22 year old male recently diagnosed with Stewart-Bluefarb syndrome successfully treated with Heparan Sulfate MIMETIC (Caciqliq 20®) (OTR3, Paris, France).

Key Points:

Stewart Bluefarb is a disease rarely encountered
Caciqliq20® has been used successfully in the treatment of Stewart Bluefarb Syndrome

Introduction:

Stewart Bluefarb syndrome is a congenital disease associated with multiple lower extremity arteriovenous shunts and acroangiokeratosis [1]. It is categorized under the group of “Acroangiokeratosis” that includes benign diseases with skin lesions clinically resembling Kaposi’s sarcoma, thus the name “pseudo-Kaposi’s sarcoma”, but histologically different. They can be distinguished by histology and by their expression of several markers including the CD34 antigen [2]. Stewart Bluefarb Syndrome (SBS) is associated with congenital and acquired arterio-venous malformations [1] in contradistinction to acroangiokeratosis of Mali secondary to chronic venous insufficiency of other several etiologies [3].

The pathophysiology of SBS is not very well understood. It is believed that the increase in venous pressure resulting from the multiple arterio-venous malformations may stimulate proliferation of endothelial cells [4]. A recent report claims that the arterio-venous steal syndrome with distal ischemia may cause endothelial proliferation by inducing a local increase in vascular endothelial growth factor [5]. Moreover, mast cells have been shown to play a role in the proliferation of endothelial and perivascular cells under conditions of ischemia [6]. Several other processes including partially impaired

venous flow and disturbed innervations of vessels play a critical role in the pathogenesis of venous insufficiency induced ulcers [7].

SBS Treatment is necessary to prevent further complications, including bone demineralization, destruction of soft tissue, hemorrhage, wound infection, and even heart failure [13,14]. Conservative treatment includes compression, limb elevation, and care of associated ulcers, infections, and other wound complications [4]. The ideal treatment, however, should address the underlying vascular malformation, though this is often not possible due to the very distal and multiple arterio-venous fistulas commonly present. Unfortunately, surgery correcting macroscopically detectable fistulas can lead to increased ulceration or other complications. Occasionally, limb amputation may be necessary [4].

Vascular surgery is indicated in cases involving functional impotence, refractory pain, recurrent infection, bleeding, or cardiac decompensation [8,9]. Selective embolization with different particles (Gelfoam (Pharmacia and Upjohn Company Michigan,USA), Ivalon (Ivalon Inc., San Diego, USA), acrylates, amino acids, alcohol, etc) may be a valid alternative [10, 11, 12]. Brenner et al. [10] and Smiddy et al. [13] claimed that ultrasound-guided sclerotherapy, embolization and surgery are indicated in selected patients who have single and localized AVM. Uterman et al. [15] described successful long-term treatment of a case of SBS with a single AV fistula using polyvinylalcohol embolization. Many reports, however, described temporary relief for few years with coil embolization of the associated arterio-venous fistula after which signs of venous insufficiency recurred [16]. Zutt et al. [1], Turk et al. [17], and Klode et al. [18] stated that the congenital malformation characterized by numerous small arterio-venous connections make surgical treatment difficult. Conservative treatment with bed-rest, limb elevation and compression bandages in addition to medical therapy are probably the best available therapeutic options [7].

Medical and conservative therapy with dapsonein, in combination with leg elevation and compression devices [19], or with oral erythromycin [20] has shown limited benefits in some cases with ulcer regression. We describe an easy and none invasive successful treatment of a SBS patient presenting with chronic leg ulceration with heparan sulfate (Cacipliq20®).

Case report:

A 22 year old male construction worker developed six months prior to presentation a non traumatic ulcers over the left lower extremity at the level of the medial and lateral malleoli. The ulcers enlarged gradually to 3x2 cm over the medial malleolus (Fig. 1A) and 5x4 cm over the lateral malleolus (Fig. 1B). The patient was seen by several physicians and was treated conservatively with several topical wound care preparations including silver sulfadiazine, MEBO (Julphar, Ras Al Khaimah, UAE), Promogran (Johnson&Johnson medical, New Jersey, USA) as well as others to no avail. On presentation, the involved limb showed evident signs of venous insufficiency with mild hypertrophy suggestive of Klippel-Trenaunay-Type syndrome [21]. Lower limb ulcers were clean with no foul smell or excessive discharge. There was also bluish

discoloration around the ankle and dorsal foot area with multiple dilated tortuous superficial veins. The skin exhibited also changes similar to dermatitis (dryness, itchiness, scaling). A wound biopsy was performed. It showed epidermal ulceration with surrounding epidermal pillars without atypia. The dermis showed noticeable fibrovascular proliferation around superficial and medial plexi accompanied by lymphoplasmocytary inflammatory infiltrate without any giant cells. There were also clusters of hemosiderin-laden macrophages. The vessels contained a prominent endothelium with clusters of extravasated erythrocytes. All these findings are indicative of an angio-endothelial reaction with arterio-venous anomalies compatible with a Pseudo-Kaposi syndrome of the Stewart Bluefarb type. The patient was started on Caciqliq20® applied twice per week to both wounds for 5 minutes each and then covered with a moist clean gauze that was changed on daily basis after cleaning the wound with soap and water. After the first application there was a noticeable decrease in pain and tenderness of both ulcers. Two weeks later the ulcers started to epithelialize from the edges (Fig. 1C& 1D) and both completely healed by week 4 (Fig. 1E&1F). After that the patient was maintained on skin moisturizer and compression stockings and showed no recurrence after 3 months of follow up despite his return to his regular job and daily activities.

Discussion:

Glycosaminoglycans (GAG) are a group of molecules that are present both intracellularly such as syndecan and glypican and extra-cellularly such as perlecan and argin. They are classified according to the size of the oligosaccharide component and the amount of sulfation they contain [22,23]. These GAG's have been found to be crucial for intra and inter-cellular processes including neurodegeneration [24], angiogenesis [25], inflammation [26,27,28], cardiovascular diseases [29], cancer [30], and infectious diseases [31,32]. Heparin and heparan sulfate are GAG's that are known to be involved in the anticoagulation process by binding anti-thrombin [23,33]. The activity of heparin and heparan sulfate has been recently expanded to include wound healing due to their ability to bind, activate and immobilize a variety of growth factors, chemokines and metalloproteinases [34,35]. This activity has been further confirmed by the studies that have shown that OTR4120, a molecule similar to heparin but with much less anticoagulant activity [36], can enhance wound healing in experimental animal models following peripheral nerve injuries [37], skin burns [38], chronic ulcers [39], and cutaneous wounds [40].

Among the numerous wound healing modulation strategies for the treatment of chronic non-healing wounds, replacement of GAG's in the extracellular matrix to prevent further tissue damage may be a pertinent approach [41]. Caciqliq20®, a synthetic bioengineered Heparan Sulfate mimetic, applied topically will replace heparin sulfate usually deficient in chronic wounds and restores extracellular matrix scaffold, thus allowing key interactions with growth factors to occur [41]. Interestingly, due to the fact that Caciqliq20® is resistant to endoglycosidase and by binding to heparin binding sites that become vacant after heparanase activation and heparin desintegration, it is an efficient agent for extracellular matrix restoration [41,42,43].

Earlier studies have demonstrated the effect of heparan sulfate both in vitro and in vivo [41]. In vitro, it enhances angiogenesis by modulating vascular endothelial growth factor (VEGF) and collagen-type expression via fibroblast growth factor 2 (FGF-2) and transforming growth factor β 1 (TGF- β 1) [44,45,46,47]. As for in vivo, heparan sulfate was shown to promote angiogenesis, in ischemic cardiac and skeletal muscles [44,45], improve wound healing, decrease inflammation and improve wound quality in mice with skin ulcers [47,48]. The first reported use of Caciqliq20® in humans for the treatment of 15 chronic arterial ulcers were presented in 2008 by Barritault et. al. [49]. One month after treatment initiation, there was a 12-100% decrease in ulcer size with net reduction in pain as reported by the patients. During the course of this study, two patients died due to their primary disease and one patient had to undergo limb amputation [49]. In 2011, Groah et. al. presented their experience with Caciqliq20® treatment of chronic ulcers of 2.5-10 years duration and showed that 22% of the patients participating in their study had complete healing in one month with significant reduction of pain[41]; those who did not benefit had associated comorbid conditions such as spinal cord paralysis and were considered as high risk for recurrence. Nevertheless, they were able to show that in this high-risk group, there was still improvement in wound healing and pain score at least for the first three sessions of treatment [41].

We have observed similar pain reduction in the treatment of chronic sickle cell ulcers with heparan sulfate mimetic (Caciqliq20®). Pain significantly decreased by 80% as measured with the visual scale 2 weeks only from the first application of Caciqliq20®. Groah et. al. postulated that this decrease in pain level might be related to a decrease in the level of inflammatory mediators in the wound, but this hypothesis still awaits confirmation.

Due to the unsuccessful treatment of the patient ulcers with numerous wound-care preparations and modalities and encouraged by our experience in treating a chronic lower extremity sickle cell ulcer with complete healing after 4 weeks, we have elected to use Caciqliq20® for the treatment of the Stewart Bluefarb ulcer. Although the follow up is short, yet the patient was able to regain full activity and return to his previous job with no difficulty.

To our knowledge, this is the first case report using Caciqliq20® for treating Stewart-Bluefarb chronic ulcers. It must be noted though that heparan sulfate mimetic treatment of chronic ulcer is no guarantee against recurrence as long as the underlying disease has not been corrected; it is only a topical wound care modality successful in achieving complete wound healing where other modalities have failed.

References:

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