CASE STUDY

The Use of Hyperbaric Oxygen Therapy in the Treatment of Non-healing Ulcers Secondary to Graft-versus-host Disease

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Abstract We present the case of a 69 year-old gentleman with non-healing ulcers of the bilateral medial malleoli as a result of graft-versus-host disease (GvHD). The patient discussed was diagnosed with stage IV mantle cell lymphoma. Over the course of 4 years the patient was treated with autologous stem cell transplant, later reduced-intensity allogeneic stem cell transplant, and finally donor lymphocyte infusion due to recurrence. Following these therapies, the patient developed extensive GvHD that resulted in bilateral non-healing ulcers of the medial malleoli. The patient was seen in the wound care center, and his ulcers were treated with standard care that included off-loading, minor outpatient debridement, macrovascular assessment, and local moist wound healing. Despite this care, the ulcers failed to heal over a 6 month period. The patient underwent adjunctive hyperbaric oxygen therapy (HBO). He healed both ulcers within a month of completing HBO. It is our goal to discuss the pathophysiologic mechanism of non-healing wounds in the setting of GvHD and discuss the potential role of HBO in their treatment. © 2014 Elsevier Inc. All rights reserved.

Introduction

The advent of allogeneic stem cell transplantation for the treatment of hematopoietic and lymphatic malignancies has resulted in the known complication of a unique set of clinical findings that fall under the title of graft-versus-host disease (GvHD). Cutaneous manifestations of GvHD are the most common finding and can range from simple pruritus to chronic and difficult wound development.¹

The theorized process is mediated by donor T cells that, while matched with HLA loci, interact with minor histocompatibility complexes (MiHC) initiating immune mediated damage to host tissues, primarily skin, liver, various mucosa and gastrointestinal tract. Its manifestation requires several factors including intact immunity in the donor graft, host expression of major and minor histocompatibility complexes that are not expressed by the donor, and an inability, often manifested by an immunocompromised state, in host defenses against the malicious effect of donor T cells.²

The unique nature of the underlying pathophysiology of GvHD with a component of micro-angiopathy makes management of chronic non-healing wounds that develop in its course an equally exceptional task. This paper discusses a case of a patient that developed such wounds

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in combination with treatment variables and tissue oxygen levels that were amiable to utilization of hyperbaric oxygen therapy (HBO). The success of this treatment in the healing of his wounds inspired us to present this case and a discussion of adjunctive HBO as a treatment modality under similar circumstances in conjunction with a multidisciplinary approach.

Case Report

The patient was a 68 year old male who presented to our wound care center after two months with a non-healing ulcer on his medial right ankle that was followed by a two week history of a similar ulcer on his left medial ankle. His medical history had been complicated by urologic intervention for prostate cancer diagnosed in 2003 which was shortly followed by a diagnosis of stage IV mantle cell lymphoma in 2004. He completed a course of hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) chemotherapy and rituximab followed by an autologous stem cell transplant which achieved complete remission. In 2007 he experienced his first lymphoma recurrence followed by remission after six cycles of velcade and rituximab. At that time he underwent a reduced intensity autologous stem cell transplant (ASCT) with his sister as the matched donor. This was followed by a second recurrence in 2010 that was successfully treated with bendamustine, rituximab and donor lymphocyte infusion over the course of several months. He had a concurrent medical history that included hypertension, hypercholesterolemia and coronary artery disease. He is a former smoker with an estimated 10 pack year history ended in 1982. He was not a diabetic.

While GvHD manifesting in liver, joint and skin abnormalities had been suspected in the patient since shortly after ASCT, specific diagnosis via skin biopsy was made after presenting in 2011 with elevated alkaline phosphatase, diffuse edema and multiple bullous cutaneous lesions. The histopathologic analysis included sections showing epidermis and a hair follicle with mild lymphocytic infiltrates and a few keratinocytic apoptosis, and dermal-epidermal junction with vacuolar degeneration including marked edema and fibrinous deposition consistent with GvHD. He was started on 40 mg of oral prednisone daily, photophoresis and topical kenalog 0.5% with initial improvement of symptoms.

His more recent presenting ulcers were initially treated by home care with triple antibiotic ointment, daily gauze and cleaning with antibacterial soap twice a week. On physical exam there was no cyanosis or peripheral edema, pulses were 2+ bilaterally with hemosiderin discoloration suggestive of venous stasis in the lower extremities. The wound on the right medial ankle was 1 cm by 0.7 cm and superficial with intact periwound integrity. The left was similar measuring 0.5 cm by 0.5 cm with overlaying black eschar. The left and right ankle-brachial indices (ABI) were

1 and 1.1 respectively. Initial wound management was relatively conservative consisting of off-loading, wound gel with silver component dressing, compression and selective outpatient debridement. Further macrovascular assessment by pulse volume recordings showed no evidence of peripheral arterial disease.

An MRI was obtained as part of his initial care, and it was equivocal for underlying osteomyelitis on the right side. Both infectious disease and orthopedic surgery were consulted. Orthopedic surgery deemed him not to be a surgical candidate either for surgical wound closure or bone debridement. Infectious disease did not recommend systemic antibiotics as there was no definitive evidence of osteomyelitis. Ongoing bio-burden control was achieved with silver component dressing. Conservative wound management was continued.

After approximately six months of this regimen with minimal healing, transcutaneous oxygen measurements of the lower extremities were obtained. These values can be seen in Table 1. The patient was found to have low local tissue oxygenation levels in the absence of peripheral arterial disease suggestive of micro-angiopathy and predictive of non-healing. In addition, the patient had a positive response at 1 atmosphere absolute (ATA) of oxygen suggesting he would be a responder to HBO. Initial consult in hyperbaric medicine recommended HBO for an initial course of 40 treatments at 2 ATA. He continued to be followed weekly in the wound care center with concurrent use of wound gel, gauze and tape dressing. His initial wounds prior to the onset of HBO can be seen in Fig. 1a.

The patient was monitored closely and reassessed frequently. The patient demonstrated a positive response without complete healing at 40 treatments as seen in Fig. 1c. He was extended to a total of 60 treatments. His wound progression during HBO is apparent in Fig. 1b–d. Fig. 1e shows complete healing one month after completion

Table 1 Transcutaneous Oxygen Monitoring Assessment.

Site	P _{tc} O ₂	P _{tc} O ₂	RPI
	Room Air	100% O ₂	
Chest control lead	73		
Lead 1: Dorsum right foot	24	64	0.33
Lead 2: Medial right lower leg	33	89	0.45
Lead 3: Lateral right lower leg	27	56	0.37
Lead 4: Dorsum left foot	23	112	0.31
Lead 5: Medial left lower leg	35	173	0.48
Lead 6: Lateral left lower leg	18	174	0.25

Baseline room air saturation: 96%.

P_{tc}O₂ reference range: >40 mm Hg is normal/adequate perfusion, 35–40 is threshold value sufficient to support O₂-dependent wound healing, <35 is sub-optimal for O₂ dependent wound healing.

RPI, regional perfusion index, reference range: >0.8 consistent with healing, ≤0.4 indicates healing complications.

TCOM values can be affected by skin thickness, edema, and infection.

Figure 1 Right and left medial malleolar ulcers. a) Pre-treatment, three months of conservative wound management. b) After 20 HBO treatments. c) After 40 HBO treatments. d) Completion of 60 HBO treatments. e) One month after completion of HBO.

of HBO. He tolerated HBO well complaining only of mild myopia at the conclusion of therapy.

Discussion

GvHD, Micro-angiopathy, and Non-healing Wounds

GvHD has more recently been characterized based on clinical and histologic classification with the establishment of a distinct staging protocol based on skin, liver and gut involvement, while presenting in acute and chronic forms has been defined historically by an arbitrary cut off of 100 days. It is the cutaneous manifestations that dominate the clinical spectrum of this disease, and Table 2 outlines the clinical and histopathologic stage and grading of acute GvHD.¹

Acute disease characteristics are more closely associated with the MiHC incompatibility and manifest primarily as subtle macular erythema and edema with evolution to bullae with a positive Nikolsky sign in severe cases. With progression to chronic GvHD, the syndrome appears pathologically related to autoimmune disorders, often accompanied by nonspecific autoantibodies.¹

There was high suspicion that an acute on chronic GvHD presentation, otherwise known as overlap syndrome, was the likely wounding event in the synchronously forming malleolar ulcers of this patient. The greater question is the effect that GvHD has on the

pathophysiology of such troubled wound healing and an underlying micro-angiopathic component that provided a template for successful HBO treatment.¹

While there appears to be a well-established role of bone marrow transplant (BMT), GvHD and its treatment in the development of thrombotic micro-angiopathy include varied states of hemostatic abnormality with clinical comparison to thrombotic thrombocytopenia purpura.³ Despite a few transient episodes of elevated LDH, there was no such histopathologic or clinical history that would suggest such a relationship in this patient. That said, more recent review of the literature describes instances of less specific forms of micro-angiopathy and endothelial damage in the course GvHD leading to ischemia and fibrosis.^{4,5}

Tichelli et al compares acute GvHD to the early endothelial injury syndromes including diffuse alveolar hemorrhage, engraftment syndrome, and capillary leak syndrome while noting that the chronic disease results in rarefaction of microvessels caused by the infiltration of alloreactive cytotoxic T cells.⁶ Along with this, there are multiple studies that examine endothelial activation markers in the post-BMT period including von Willebrand factor, thrombomodulin and Fas/Fas-ligand.^{5,7,8} The mounting evidence of angiopathy associated with GvHD and BMT is even further displayed with more qualitative analysis of structural findings including vessel rarefaction, neovascularization, endothelial microparticles and circulating endothelial cells.^{5,8-10}

While the research demonstrates potential vascular damage directly associated with GvHD, the question as to a relationship to poor wound healing has received little to no attention. It is important to note as well that the evidence discussed herein combines the findings in the post-BMT period with and without a definitive diagnosis of GvHD.

TCOMs in HBO

Transcutaneous oximetry (TCOM) currently stands as one of the best modalities available for predicting HBO success in the treatment of non-healing problem wounds.¹¹ P_{tc}O₂ values ≤ 40 mm Hg are typically considered indicative of hypoxia capable of inhibiting wound healing.^{12,13} The levels near the patient’s non-healing ulcers were in this range as documented in Table 1. In addition, these levels improved dramatically while breathing 100% oxygen at 1 ATA. The combination of baseline hypoxia and improvement in response to 1 ATA of 100% oxygen indicated underlying micro-angiopathy and potential positive response to HBO.

Co-morbidity

The use of adjunctive HBO in the management of non-healing wounds directly associated with GvHD is a relatively novel concept. There are early studies into the potential overall antagonizing effect of HBO on GvHD and

Table 2 Clinical Stage and Histologic Grade of Graft-versus-host Disease.

Stage ^a	Presentation
0	GvHD, no rash or skin involvement
1	MPR on <25% BSA w/o associated symptoms
2	MPR or erythema w/pruritus or other associated symptoms on ≥25 and <50% BSA or localized desquamation
3	Generalized erythroderma or symptomatic macular, papular or vesicular eruption with bullae or desquamation on ≥50% BSA
4	Generalized bullae, exfoliative or ulcerative dermatitis
Grade	Histopathologic features
0	Normal epidermis
1	Focal or diffuse vacuolar alteration of basal layer
2	Grade 1 + dyskeratotic squamous cells in the epidermis and/or hair follicle
3	Grade 2 + subepidermal vesicle formation
4	Complete separation of epidermis from dermis

Adapted from Hymes et al.¹

GvHD, graft-versus-host disease; MPR, maculopapular rash; BSA, body surface area.

^aDefinitive clinical staging of acute GvHD requires assessment of liver and gut involvement as well as skin.

its well-established role in the treatment of hemorrhagic cystitis in the wake of BMT and similar immunogenic disorders.¹⁴

Gassas et al describe the only other case of an attempt at utilizing HBO specifically for non-healing wounds in the presence of GvHD.¹⁵ This report discussed a lack of apparent micro-angiopathy on TCOM in a 17 y/o with chronic GvHD after ASCT. This resulted in the decision not to go ahead with HBO. While they share in the use of chronic immunosuppressive treatment, which in and of itself has the potential to hinder wound healing, the main difference between the patient discussed in that study and the one discussed herein is age in years of vasculopathic comorbidity (hypertension, hypercholesterolemia, smoking history) and questionable nutrition status. Along with this, our patient had clinical evidence of venous stasis, but after the decision to go ahead with HBO based on TCOM results there was no reason to undergo venous reflux study as HBO would be indicated under either circumstance.

Secondary Role of HBO in Immune Modulation

Appreciating that chronic GvHD is in many ways pathologically comparable to rheumatic and autoimmune diseases, it is important to discuss the role of HBO in immune modulation. Studies have shown a favorable effect of a hyperbaric environment on minimizing the proliferation of damaging lymphocytes while modulating the biology of cytokines and inflammatory mediators.^{15,16} Transient cytokine down-regulation and growth factor up regulation including the liberation TNF α , endothelins and VEGF with the reduction of PGE2 and COX-2 mRNA is theorized to support healing in a pro-inflammatory state such as GvHD.¹⁶ While we did not establish the presence of immune mediators, inflammatory markers or autoantibodies in our patient, future assessment of non-healing wounds in the presence of GvHD could better establish this role of HBO.

Conclusion

The role of HBO in the management of GvHD maintains significant potential amidst a complicated myriad of treatment variables and pathophysiologic pathways. The patient discussed displayed evidence of micro-angiopathy on TCOM that allowed for successful HBO in the healing of his lower extremity wounds. While there is mounting evidence supporting endothelial damage and angiopathic mechanisms of GvHD, there still remains question as to the specific role this plays in the cutaneous manifestations of the disease. Even further, there is a paucity of research investigating a correlation between these processes, healing status, chronic wounds and their care to include HBO, debridement, and other standard wound care.

TCOM was an accurate indicator of HBO success in this patient, and could serve as a tool to aid in the further study of this disease. This should be considered in the context of a patient's co-morbidities and its impact on wound healing. The effects of HBO likely incorporate a combination of immunologic modulation, vasculogenesis, and endothelial mechanisms of healing.

We set out to discuss and share this patient due to his unique presentation and his success with adjunctive HBO. It is our hope to stimulate and encourage the study of HBO's role in the treatment of GvHD as it relates to chronic non-healing wounds.

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