Leg ulcers in patients with Sickle Cell Disease

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ASCAT
October 11, 2017
London, UK
Disclosures

- Tautona Group: Advisory Board
- Global Blood Therapeutics: Advisory Board, Research funding
- Bayer: Research funding
- Patent application/ IND holder: Topical Sodium Nitrite
Sickle Cell Disease: A Monogenetic Disease with Pleomorphic Manifestations

Vaso-occlusive complications
- Acute pain crises: ischemia of BM
- Acute chest syndrome
- Diastolic cardiomyopathy
- Acute hepatopathy
- Splenic infarction
- Mesenteric ischemia
- Avascular necrosis
- Fat emboli from marrow of long bones
- Multiorgan failure
  - Chronic inflammatory and neuropathic pain

Hemolytic complications
- Chronic anemia, Vasculopathy
- Stroke/HighTCD
- Retinopathy
- Pulmonary hypertension
- Gall stones
- Nephropathy
- Priapism
- Leg ulcers

Inflammatory stimuli:
- WBC activation
- Endothelial cell activation
- Platelet activation
- Proinflammatory cytokine production
- Expression and activation of cell adhesion molecules on endothelial cells, platelets, and leukocytes

Dehydration
Activation of coagulation
Adhesive interactions

Hemolysis
RBC sickling
HbS gelation

Telen M J, Blood 2016;127:810-819
Kato GJ, Steinberg MH, Gladwin MT. JCI, 2017;127:750-760
Why study Leg Ulcers in SCD?

- **Are a marker of disease severity**
  - Associated with PH, renal disease, severe anemia, priapism, ± Stroke, mortality

- **Are a visible model of end organ disease**
  - How does end organ initiate, and progress?
  - Why some patients have more end organ damage than others?
    - Genetic/Epigenetic
    - Psychosocial and environmental factors
  - At which stage is it still reversible?

- **Exemplify the culmination of SCD complications:**
  - Pain, stigma, depression, sleep disruption, poor QOL, linked to poor socioeconomic status

Parent et al, NEJM 2011, Powars, 2005
Serarslan, Clin Exp HTN 2009
Epidemiology: Leg ulcers are common and not declining in prevalence

- CSSCD (1986), 986 patients, heavily weighted toward pediatrics and young adults: Increase with age, only SS
  - 5% < 20 yrs
  - 15% >20 yrs
  - 27% >40 yrs
- Providers survey (2013): 1% prevalence of active ulcers
- Powars, 2005: 14 % (1057 pts)
- Bethesda Cohort (2001-2010), 505 adults (mean age 39 Ulcers, 31 non ulcers):
  > 18 % ulcers or history of ulcers
  > 22% of SS and 9% of SC

Delaney and Minniti CP. Hemoglobin. 2013;37:325-32
Who treats these patients? Very few are seen at wound centers.

- 794 outpatient wounds centers across 32 States
- ~ 200,000 patients with ulcers/year
- 114 centers had at least one SCD (14%)
- 133 unique sickle cell patients with 427 wounds (mean 2.15 wounds/patient)
- Male to Female ratio: 1.2
- Age: 42±2 years (vs. 70.2 for venous ulcers)
Clinical presentation: Patients hematological and Clinical Characteristics

- Second decade of life
- M:F : 1.1  Low BMI (21) ; Tall
- HBSS>>>HBSC/Sbeta thal
- High prevalence of elevated TRV(and RHC proven PH)
- Thrombophilia markers: Low ATIII, low prot. C and S, high VIII, positive LA
- History of DVT’s/PE
- Indices of severe hemolysis: Low Hb, high LDH, high retic
- Low Pulse Ox
- Renal dysfunction: high uric acid, NT-pro-BNP and low serum albumin, proteinuria
- Priapism (men)
What type of ulcers do patients with hemoglobin disorders get?

- **Location:** Lower extremities: mostly ankles >> dorsum of feet >> digits
- Superficial, mean size ~7-10 cm², but can be circumferential
- Abx usually normal, good peripheral pulses
- **Painful:** Pain often precedes ulcer formation/recurrence
- Bilateral in 50% of cases
- Recurrent in 50-60% of cases
- Hyper or hypopigmented skin
- Ankle ankylosis, feet deformities

Senet P, Br J Derm 2017
Minniti AJH 2013, personal observations
# Proposed Sickle Cell Ulcer Stages.

<table>
<thead>
<tr>
<th>Stage 1.</th>
<th>Stage 2.</th>
<th>Stage 3.</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-10 d</td>
<td>7-14 d</td>
<td>2 to &gt;4 wks</td>
</tr>
<tr>
<td>+/- Pain and Itching</td>
<td>+ Pain, burning</td>
<td>+/- Pain, burning, irradiating, stabbing</td>
</tr>
<tr>
<td>Hyperkeratotic but intact skin.</td>
<td>Skin necrotic/ Epidermal color changes.</td>
<td>Skin absent.</td>
</tr>
<tr>
<td>Unclear margins.</td>
<td>May show subcutaneous edges.</td>
<td>Defined margins.</td>
</tr>
<tr>
<td>May be reversible.</td>
<td>Margins appear well defined.</td>
<td>High skin edges.</td>
</tr>
<tr>
<td>Difficult to identify.</td>
<td>Not reversible.</td>
<td>Adherent fibrinous tissue. (yellow/white)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wound enlarges</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate drainage</td>
</tr>
</tbody>
</table>
Proposed stages of SCD ulcer development

Normal Skin

Stage 1

Stage 2

Resolving Stage 1

Stage 3
Proposed Sickle Cell Ulcer Stages.

Stage 1

Stage 2

Stage 3
Clinical Presentation

The “one time” ulcer ~50% of patients with ulcers

- Young age, minimal trauma /insect bite
- Heals within several months with most types of wound care. Occasionally these recur in periods of intense stress and heal promptly
- Physicians may not be aware that their patients have suffered from ulcers unless they ask directly or look carefully at their ankles for scars

The “stuttering” ulcer ~ 25%

- Small, recurrent ulcers, every 6-12 months for many years, seasonal
- Early institution of local wound limits the size and/or duration
- Individuals live in fear of recurrence, but are not severely debilitated from them

The “long standing” ulcer ~ 25%

- Most devastating disabilities, chronic pain, unemployment and depression
- 75% to 80% of patients will eventually heal, in some patients ulcers persists for over 20 years and may never heal
- Larger wounds, often circumferential
- Older patients, many not US born, severe disease, many co-morbidities
### Clinical Features of Leg ulcers in SCD patients

N : 39 ( NIH Cohort)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>M- F</td>
<td>1:1.2</td>
</tr>
<tr>
<td>Age at presentation (yrs)</td>
<td>39 ± 12 (range 20-59)</td>
</tr>
<tr>
<td>Ulcer size (cm$^2$) manual</td>
<td>30± 4.65 (range 0.3-260)</td>
</tr>
<tr>
<td>Depth</td>
<td>0.2 mm( 0.1-0.4)</td>
</tr>
<tr>
<td>Lower extremities ( three dorsum of foot)</td>
<td>L:R=1.3</td>
</tr>
<tr>
<td>Pain scale</td>
<td>7.7 (range 0-10)</td>
</tr>
<tr>
<td>No. of ulcers (median, range)</td>
<td>2.3 (1-10)</td>
</tr>
<tr>
<td>Age of ulcers in months (median, range)</td>
<td>10 (2-300)</td>
</tr>
<tr>
<td>Hydroxyurea therapy (N)</td>
<td>26/39 (70%)</td>
</tr>
<tr>
<td>Chronic transfusion (N)</td>
<td>7/39 (18%)</td>
</tr>
<tr>
<td>Taking daily opioid (N)</td>
<td>35 (90%)</td>
</tr>
<tr>
<td>Current anti-coagulation therapy (N)</td>
<td>11/39 (30%)</td>
</tr>
<tr>
<td>Hospitalization in past 12 months for vaso-occlusive crisis (N)</td>
<td>9</td>
</tr>
<tr>
<td>History of priapism (N of men)</td>
<td>5</td>
</tr>
<tr>
<td>History of pulmonary embolism or deep vein thrombosis (N)</td>
<td>8</td>
</tr>
<tr>
<td>Recurrent</td>
<td>90% (only two new)</td>
</tr>
<tr>
<td>Previous ulcer therapies/patient, mean (Number of therapies)</td>
<td>7</td>
</tr>
<tr>
<td>- Surgical/sharp debridement</td>
<td>36 (92%)</td>
</tr>
<tr>
<td>- Hyperbaric chamber</td>
<td>13/39 (33%)</td>
</tr>
<tr>
<td>- Skin graft</td>
<td>17/39 (40%)</td>
</tr>
<tr>
<td>- Compression</td>
<td>36 (92%)</td>
</tr>
<tr>
<td>- Oral/parenteral antibiotics</td>
<td>19/39 (50%)</td>
</tr>
</tbody>
</table>
Healing Rates

Kaplan-Meier Healing Estimates

Age

Size

Minniti et al. Submitted for publication
A case: SCD PH and Leg Ulcer

- 46 year old African American woman with sickle cell anemia
- Leg and foot ulcers for many years
- Pain crisis twice a year
- Diagnosed PAH, treated with sildenafil with clinical improvement
- Died during pain crisis complicated by sepsis
Another patient

- 27 yr, HBSS, from Ghana, stroke at age 13, with bilateral narrowing MCA, moyamoya, with residual left side weakness, recurrent leg ulcers since age 18, systemic hypertension, and proteinuria. Transfused at the time of the stroke, but not placed on chronic transfusions. Since age 21 on hydroxyurea, Hb ~6 g/dL, TRV between 2.7 and 2.5 m/sec. Stuttering priapism
- Infrequent pain crisis. Pain at ulcer site and peri-wound.
- Full HLA matched brother, but he and his family did not think he needed a transplant, mostly because he had no pain
Pain, quality of life in patients with SCD and ulcers

A prospective analysis of 17 subjects in the Sodium nitrite study, resulted in SF36 scores for patients with leg ulcers lower than patients with SCD of similar age but no leg ulcers.

<table>
<thead>
<tr>
<th>Health Dimension</th>
<th>Baseline</th>
<th>Post-intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Functioning (PF)</td>
<td>37</td>
<td>39.6</td>
</tr>
<tr>
<td>Role-Physical (RP)</td>
<td>37.3</td>
<td>39.9</td>
</tr>
<tr>
<td>Bodily Pain (BP)</td>
<td>33.6</td>
<td><strong>44.5</strong></td>
</tr>
<tr>
<td>General Health (GH)</td>
<td>38.7</td>
<td>39.8</td>
</tr>
<tr>
<td>Vitality (VT)</td>
<td>43.8</td>
<td>49.5</td>
</tr>
<tr>
<td>Social Functioning (SF)</td>
<td>39</td>
<td><strong>46.4</strong></td>
</tr>
<tr>
<td>Role - Emotional (RE)</td>
<td>40.1</td>
<td>43.7</td>
</tr>
<tr>
<td>Mental Health (MH)</td>
<td>46.8</td>
<td>50.1</td>
</tr>
</tbody>
</table>
Pain characteristics, personal observation

- Pain from leg ulceration is distinct from VOC described as burning, stabbing, and irradiating, and often precedes the occurrence or reoccurrence of a new ulcer.
- Size has no relationship to pain intensity, with pain often heralding the occurrence of a new ulcer.
- More intense when the ulcer is exposed to air, or after standing for a long time and at night.
- Interferes with the ability wound care providers to manipulate the ulcer and provide adequate care.
- As ulcers become chronic, pain sometimes, but not always, decreases in intensity and other neurologic symptoms manifest, such as numbing of the toes, changes the nails trophism, alopecia and discoloration, either hypo or hyper pigmentation with iron deposition and chronic venostasis.
Psychosocial: The INSIGHTS trial

- Pain proved debilitating for patients and played a critical role in physical function.
- Participants felt as if their physical function and their ability to walk, run, and play sports was severely compromised.
- Individuals felt isolated from social activities either by others or by themselves to avoid further consequences such as embarrassment.
- Individuals did not seek support from their families as they did not want to be a burden to others; however, many participants found support and comfort through their religious beliefs.
Proposed and simplified mechanism of ulcer formation in patients with sickle cell disease

1. **Predisposing vasculopathy and long-term microvascular injury**
2. **Ischemic insult leads to tissue necrosis, then skin breakdown**
3. **Neuropathy promotes local motor muscle atrophy, alopecia, dry skin, neurogenic inflammation**
4. **Bacterial colonization aggravates local inflammation**
5. **Scar has low tensile strength and underlying vasculopathy progresses**
6. **Heightened pain leads to central sensitization and augments neurogenic inflammation, further impairing healing**
7. **Stress: Physical Psychological Environmental**
My (evolving) concept of Leg ulcer pathogenesis

- Leg ulcer as Complication of “High flow shear damage”
- Leg ulcer as complications of inability to increase blood flow when needed (much like stroke)
- Arterial vs venous etiopatogenesis, more like stroke, renal disease than VOC
Blood vessels occlusion, fibrin deposition in the intima, and microthrombi in biopsies of leg ulcers.
Proposed multi-hit mechanism of chronic leg ulcers in SCD

- **Noxious insult(s) causes breakdown of skin integrity**
  > 50% of patients report a “trauma” before the first ulcer appeared, and the incidence is lower in areas of the world that “cover” (protect?) lower extremities

- **Predisposed individuals**, with underlying vasculopathy, poor nutrition, thrombofilia, hyper-inflammatory response develop an ulcer that heals slowly
  > Mine and other investigators data on demographic association with low BMI, inflammation, thrombotic, hemolytic and vasculopathic markers support this concept

**Upward Arrow**

- **Pain** leads to central sensitization and neurogenic inflammation, high substance P in the skin results in further impairment of wound healing
  > Neurogenic inflammation leads to fluid extravasation, with resulting venous stasis, amplification of inflammatory response, increase in pain and systemic narcotic use and use of topical anesthetic such as lidocaine, which cause vasoconstriction and further decrease blood flow

Can Vasculopathy be reversed?

34 year old AA man with HbSS. Recurrent vaso-occlusive pain crises, acute chest, avascular necrosis of the hips, s/p hip replacement, priapism.

Lower extremity ulcer(s) since age 17, after minimal trauma. Very painful. Never healed. Main reason for requesting bone marrow transplantation: Leg Ulcer

BEFORE matched sib transplant

10 Months after successful engraftment
## Therapies for patients with Sickle Cell Ulcers

<table>
<thead>
<tr>
<th>Systemic treatment</th>
<th>Local wound care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasodilators for systemic hypertension</td>
<td>Debridement</td>
</tr>
<tr>
<td>ACEI/ARB for proteinuria/microalbuminuria</td>
<td>Identify and treat infection</td>
</tr>
<tr>
<td>Hydroxyurea for recurrent pain, ACS, severe anemia</td>
<td>Absorb excess exudate</td>
</tr>
<tr>
<td>Chelation for iron overload</td>
<td>Maintain moist wound surface</td>
</tr>
<tr>
<td>Pulmonary vasodilator and/or diuretics for pulmonary hypertension</td>
<td>Open or excise closed wound edges</td>
</tr>
<tr>
<td>Correction of vitamin D or zinc deficiency</td>
<td>Protect healing wound from infection or trauma</td>
</tr>
<tr>
<td>Supplements for protein-calorie malnutrition</td>
<td>Relieve periwound edema by compression</td>
</tr>
<tr>
<td>Anticoagulation for newly diagnosed DVT</td>
<td>Comfortable footwear</td>
</tr>
<tr>
<td>Psychological support</td>
<td></td>
</tr>
<tr>
<td>Pain control</td>
<td></td>
</tr>
</tbody>
</table>

Minniti C: How I treat, 2015. AJH
Practical suggestions for the hematologist

- Refer to a good wound center
  > Make sure they treat their pain
  > Topical lidocaine/morphine
  > Compression, bed rest
- Optimize SCD care
  > Don’t stop HU, utility of transfusions dubious, unless in very early stages
- Optimize nutrition
- Address depression, psychosocial factors
- PT/OT to avoid frozen ulcers and bone deformities
- Don’t over treat infections, Osteo pretty rare
- Look for other vasculopathic complications
Clinical Trials

- Few prospective trials
- No specific SCD ulcer therapy, usually venous ulcer treatments are utilized
- NO and wound healing well established connection

Infrared Imaging of Ulcer Before and After Nitrite Application

Baseline

mean ± std for 30-min imaging

3.75 cm

Nitrite

Temperature (°C)

Before cream

After cream

Surrounding area

NHLBI / NIBIB Project
Sodium Nitrite Cream decreases pain at the ulcer site

- **Visual analogue scales (VAS) of the study ulcer at each study visit for all subjects.**
- **There is a trend toward decreased VAS score and range.**
Phase 2 trial now open!

- FDA RO1 funded!
- Phase 2, placebo controlled
- 3 months duration, with 2 weeks run in
- End point
  - Size and pain
  - Secondary endpoints; Microbiome changes, QOL
Topical DFO for SCD ulcers: Hypothesis

- Sickle cell patient tissues accumulate iron over time
- Iron destabilizes nitric oxide balance; vessel constrict
  - Poor blood flow
  - Localized pain
  - Increased oxidative stress
- Uncontrolled reactive oxygen species (ROS) and inflammation facilitate chronic wound
- Locally chelates iron, removing it from the tissue
  - Stabilizes nitric oxide balance
    - Vessels dilate, improved flow
  - Reduces ROS
  - Reduces Inflammation
  - Reduces Oxidative stress
CONCLUSIONS

- Leg ulcers in SCD are a “visible early sign” of end organ disease and underlying vasculopathy.
- “The diagnosis of clearly evident clinical conditions such as leg ulcer, osteonecrosis, and retinopathy predicted an increased likelihood of developing a more lethal form of organ damage and earlier death”. Powars 2005
- We are starting to understand the mechanism of formation.
- “HOLISTIC” approach to prevention and care of the patient with leg ulcers.
- Global impact of ulcers deserves a global approach, to be tailored to the different needs and capabilities.
DFO and Hif 1alpha in diabetes

In diabetes, HIF-1α function is compromised by a high glucose-induced and reactive oxygen species-mediated modification of its coactivator p300, leading to impaired HIF-1α transactivation

• Deferoxamine enhances neovascularization and accelerates wound healing in diabetic rats via the accumulation of hypoxia-inducible factor-1α

It Takes a Village

Sickle Cell Awareness Day 2017

Division of Hematology
THANK YOU!
Human studies
Controversial results so far

Topical morphine gel in the treatment of painful leg ulcers, a double-blind, placebo-controlled clinical trial: a pilot study

Salumeh Bastami, Thomas Frödin, Johan Ahlner, Srinivas Uppugunduri

ABSTRACT

Chronic painful wounds, a major health problem, have a detrimental impact on the quality of life due to associated pain. Some clinical reports have suggested that local administration of morphine could be beneficial. The aim of this study was to evaluate the analgesic effect of topically applied morphine on chronic painful leg ulcers. Twenty-one patients were randomly assigned to receive either morphine or placebo in a randomised, placebo-controlled, crossover pilot study. Each patient was treated four times in total. Pain was measured by the visual analogue score (VAS) before application of gel, directly after and after 2, 6, 12 and 24 hours. Although an overall, clinically relevant, reduction of pain was observed upon treatment with morphine, the difference was not statistically significant. Morphine reduced pain scores more than placebo on treatment occasions 1 and 2. The difference was statistically significant only 2 hours after dressing on the first treatment occasion. Thus, our study did not demonstrate a consistent and globally significant difference in nociception in patients treated with morphine. However, the relatively small number of patients included in our study and other methodological limitations makes it difficult for us to draw general conclusions regarding efficacy of topically applied morphine as an effective treatment for some painful ulcers. Further studies are warranted to evaluate the value of topically applied morphine in the treatment of patients with chronic painful leg ulcers.

Key words: Leg ulcers • Morphine • Pain • Topical • VAS
Proposed model leg ulcer pathogenesis

Chronic anemia with hemolysis, high flow
Endothelial damage
(Micro)Vascular Disease
Inflammation

Neuropathy
Motor
Sensory
Autonomic

Muscle atrophy
Decrease in calf pump: stasis

Neurogenic inflammation
Dry Skin, alopecia
Excessive vasocostriction

Chronic/recurrent ulceration

NO scavenging 1
Free iron 2

1. N Conran: Acute hemolytic vascular inflammatory processes are prevented by nitric oxide replacement or a single dose of hydroxyurea. Blood, 126 p711.2015
2. Oqato
“HU has anti-inflammatory effects by inhibiting hemolytic inflammation” N. Conran Blood 2015

- Nitrite concentration increases after oral administration of HU in a dose dependent fashion. C.P. Minniti Lancet Haematology 2014

Scavenging NO causes vascular inflammation and NO donation reverses it.