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REVIEW

Mini review: leg ulcers - a secondary complication of sickle cell disease

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Abstract: Sickle cell disease (SCD) is a group of inherited blood disorders recognized by WHO as a major public health problem. It affects morbidity and mortality of the affected population considerably. Leg ulcer in the lower limbs is a hallmark feature of SCD. Meticulous physical examination, thorough history, laboratory tests, and imaging will lead to proper diagnosis and lead to proper treatment and management of the cases. Although newer treatment strategies have improved the prognostic outcome of SCD, leg ulcers still are a disabling and difficult to treat a complication of the condition. This mini review summarizes this common complication of SCD.

Keywords: sickle cell disease, SCD, leg ulcers, complication

Introduction

Sickle cell disease (SCD) is an autosomal recessive hemoglobinopathy. It is caused by a structural alteration in the β-globin chain on chromosome 11. Glutamic acid in the β-globin chain is substituted to valine.[1] This results in defective hemoglobin S (HbS) that causes red blood cells (RBCs) to sickle. The sickled RBCs manifest in vaso-occlusion (VO), inflammation, ischemia, organ damage, and hemolytic anemia (HA).[2] The patients with SCD have hemoglobin (Hb) variants SS, SC, S-β thalassemia, SOArab, SD and rarely S-Hb genotypes. SCD is one of the most common inherited diseases worldwide.[3] The resultant deformed hemoglobin causes impaired blood flow and diverse symptoms. The symptoms include avascular necrosis of joints such as hip and shoulder, pulmonary hypertension, priapism, life-threatening infections, end-organ failure, and hemolytic anemia. Therefore, patients require regular clinical follow-up to treat the symptoms and secondary complications of the disease.[4,5]

Ulcers, especially in the lower limbs, are common symptoms in SCD patients. Ulceration of the skin and underlying tissues at the medial and lateral ankle may occur in SCD patients. Some of the risk factors associated are trauma, high hemolytic rate, infection, venous incompetence, severe anemia, geographic location. Varying incidence has been reported among different phenotypes and geographical area.[1] The incidence rate of leg ulcers in the adult SCD patients is reported to be up to 75%.[2,6,7] Prevalence is reported to be 8–10% in homozygous patients and more than 50% in patients living in the tropical areas.[8] Recent evidence showing varying prevalence rate across geographical locations is summarized in the Table 1.

Ulcers appear in areas with less subcutaneous tissue and thin skin such as tibialis anterior, the inner or outer malleolar region and less frequently in the instep.

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Table 1 Prevalence rate across geographical locations

Country	Prevalence rate (%)
Jamaica[9]	29.5%
Nigeria[10]	5.9%
Brazil[11]	43%
Sierra Leone[12]	13.2%
Ghana[12]	10.6%
Saudi Arabia[13]	None

The contributory factors to cause leg ulcers in SCD patients include poor skin perfusion due to vaso-occlusion, venous incompetence, minor trauma, decreased oxygenation, microvascular thrombosis, and impaired endothelial function. Although leg ulcers occur commonly, treatment response is poorer than in wounds of other aetiologies making the healing process slower.[5] In addition, mouse models proved the pain at the wound site to be the most prominent differences between SCD wounds and "other wounds" and neurogenic inflammation perpetuate tissue damage.[14]

Pathophysiology

The pathophysiology of leg ulcers in patients with SCD is complex and not fully understood. It is most probably multifactorial, and it is more common in patients with SCD than others.[14,15] Binding of hemolysis-freed hemoglobin to nitric oxide (NO), vasoconstriction; sickling of red blood cells in blood vessels, resulting in vaso-occlusion and impaired oxygen delivery to tissues have been implicated in its pathophysiology.[1,16,17] Endothelial NO receptors initiate vasodilation. Free hemoglobin in SCD due to chronic hemolysis reduces NO bioavailability leading chronic vasoconstriction which in turn contributes to leg ulcers, priapism, and pulmonary hypertension. In addition, leg ulcers in SCD patients are believed to be infrequent in some parts of the world where dominant genetic factors, presence of α-thalassemia and high fetal hemoglobin (HbF) levels, are thought to ameliorate its existence, thereby highlighting a probable role for geographical and environmental factors.[14,15,18]

Classification of leg ulcers

Leg ulcers can be classified as acute and chronic based on the time required for healing. Acute leg ulcer usually heals in less than a month, while chronic leg ulcer, usually persists for at least six months and may last several years. The physiological healing procedure of skin lesions is affected by many factors like general factors, factors associated with the site of the ulcer. General factors affecting the healing include age, vascularization, systemic medication, nutritional status, smoking, primary disease. Factors related to the site are topical agents, infections, necrotic tissue, blood supply and the suitable type of coverage.[5]

In 2016 Minniti and colleagues[14] have proposed three patterns of leg ulcer in patients with SCD:

One-time ulcer

In this pattern, patients develop only one ulcer during their life which heals within a period of a few months. It typically occurs in the second decade of life and may recur in case of stress. These patients have low-frequency pain crises and may have pulmonary and renal complications. Most of the time relation of the complication with the SCD is missed. Hence, it is important that clinicians are meticulous while obtaining patient history.

Shuttering ulcer

In this type, small ulcers that recur every 6–12 months for several years are developed. Although it can be treated easily and is less harmful, the constant fear of recurrence resides.

Chronic, recurrent ulcer

SCD patients develop an ulcer that persists for years and/or ulcers that recur in the same or nearby sites. Chronic, recurrent ulcers cause the most disabling chronic pain, and patients suffer from depression, disabilities, unemployment. Although 75–80% of patients suffering from chronic recurrent ulcers heal, many patients have ulcers for more than 20 years and may never heal. Amputation may be considered in some patients to improve quality of life.

Minniti and colleagues also proposed a stepwise, multifactorial model on how ulcers are formed in SCD patients.[14] They propose that damage to the blood vessels and impaired perfusion in the distal lower extremities are responsible for causing slow-healing ulcers. The blood vessels are damaged due to poor nutrition, poor socioeconomic status, thrombophilia, hyperinflammatory response, and some unidentified causes. The healing process is further delayed as the consequent pain due to the ulcers leads to central sensitization and neurogenic inflammation. Thus, the resulting scar tends to reopen due to low tensile strength and poor perfusion. This vicious cycle continues in SCD patients.

Diagnosis and management

Medical history, thorough physical examination, and laboratory testing and imaging are required for diagnosis. The medical history should include systematic information on treatment attempted, and complications that arose during the treatment. Physical examination should include assessment hypo- or hyperpigmentation of surrounding skin, edema, serous discharge, and thickened fibrinous material, inguinal nodes, hair follicles, pulse oximetry, and wound size. Microscopic analysis of skin biopsies is important evidence revealing an increase in vascularity, vasculopathy with blood vessels occlusion, chronic inflammation, microthrombi, and fibrin deposition in the intima. Laboratory tests with urinalysis, complete blood count and chemistry panel should be performed. These tests will often reveal microalbuminuria and markers of severe chronic hemolysis along with others that will help in the diagnosis.

At present, management of leg ulcers in SCD patients comprise of prevention and treatment. It includes overall disease control, wound care and dressing, debridement and surgical management with skin grafts. To achieve healing a multipronged approach of systemic and local therapy will help. Due to the need for multifaceted treatment collaborative efforts of a hematologist, wound care specialist, surgeon, nutritionist, and social workers are needed for management of the leg ulcers.[14] 14Along with the management of the ulcers, systemic treatment of the SCD and treatment for other identified micronutrient deficiencies should always be continued.

Systemic therapy for leg ulcers in SCD patients should include vasodilators and diuretics, hydroxyurea, ACE inhibitor or ARB, chelation therapy, correction of deficiencies, along with nutritional management, management of pulmonary hypertension, psychological support for stress and depression. Whereas the local therapies should be focused on wound care to achieve healing.

Prevention is the major part of the management strategy for leg ulcer particularly in patients with a history of ulcers. The treatment comprises of debridement, the use of bandages, surgical treatment, infection control, rest and elevation of the affected area.[8] Furthermore, patients, particularly with a prior history of leg ulcers should be educated to avoid the emergency of leg ulcers due to SCD. Avoiding trauma, using cotton socks; wearing comfortable shoes; bug-spray to avoid insect bites; the topical use of moisturizing to avoid exfoliation and skin scarification is part of prevention tactics. Patients should also be educated to seek medical treatment in case of traumas.[5] Patients' participation for prevention and medical team for treatment both are equally important in the management of leg ulcers in SCD patients.

Conclusion

Leg ulceration is an important contributor to the morbidity burden in SCD patients. Many treatment options are available for the management of leg ulcers. But the effectiveness of these treatments has not been yet tested in SCD patients. Hence, prevention and early intervention, therefore, are the basis for the management of this complication. More research is needed to improve treatment and prevent recurrence of the leg ulcer in SCD patients.

Disclosure

The author reports no conflicts of interest in this work.

References

1. Ladizinski B, Bazakas A, Mistry N, et al. Sickle cell disease and leg ulcers. *Adv Skin Wound Care*. 2012;25(9):420–428. doi:10.1097/01.ASW.0000419408.37323.0c
2. Trent JT, Kirsner RS. Leg ulcers in sickle cell disease. *Adv Skin Wound Care*. 2004;17(8):410–416.
3. Driscoll C. Sickle cell disease. *Pediatr Rev*. 2007;28(7):259–268. doi:10.1542/pir.28-7-259
4. Wang WC. The pathophysiology, prevention, and treatment of stroke in sickle cell disease. *Cur Opin Hematol*. 2007;14(3):191–197. doi:10.1097/MOH.0b013e3280ec5243
5. Martins A, Moreira DG, Do Nascimento EM, et al. Self-care for the treatment of leg ulcers in sickle cell anemia: nursing guidelines. *ESC Anna Nery*. 2013;17(4):755–763. doi:10.5935/1414-8145.20130021
6. Vasconcelos A, Prior A, Ferrao A, et al. An Adolescent with sickle cell anemia experiencing disease-related complications: priapism and leg ulcer- a management challenge. *BMJ Case Rep*. 2012;2012:bcr1120115146. doi:10.1136/bcr.11.2011.5146
7. Sauntharajah Y, Vichinsky E. Sickle cell disease: clinical features and management. In: Hoffman R, Silberstein L, Weitz J, editors. *Hematology: Basic Principles and Practice*. Philadelphia: Elsevier Saunders; 2013:548–572.
8. Paladino SF. Ulcera de membros inferiores na anemia falciforme. *ESC Anna Nery*. 2007;29(3):288–290. doi:10.1590/S1516-84842007000300019
9. Cumming V, King L, Fraser R, Serjeant G, Reid M. Venous incompetence, poverty and lactate dehydrogenase in Jamaica are important predictors of leg ulceration in sickle cell anaemia. *Br J Haematol*. 2008;142(1):119–125. doi:10.1111/j.1365-2141.2008.07115.x
10. Olatunya OS, Albuquerque DM, Adekile AD, Costa FF. Evaluation of sociodemographic, clinical, and laboratory markers of sickle leg ulcers among young nigerians at a tertiary health institution. *Niger J Clin Pract*. 2018;21(7):882–887. doi:10.4103/njcp.njcp_4_18
11. Figueiredo MS, Kerbauy J, Goncalves MS, et al. Effect of alpha-thalassemia and beta-globin gene cluster haplotypes on the hematological and clinical features of sickle-cell anemia in Brazil. *Am J Hematol*. 1996;53(2):72–76. doi:10.1002/(SICI)1096-8652(199610)53:2<72::AID-AJH3>3.0.CO;2-0

12. Knox-Macaulay HH. Sickle cell disease in Sierra Leone: a clinical and haematological analysis in older children and adults. *Ann Trop Med Parasitol*. 1983;77(4):411–419. doi:10.1080/00034983.1983.11811730
13. Alsultan A, Alabdulaali MK, Griffin PJ, et al. Sickle cell disease in Saudi Arabia: the phenotype in adults with the Arab-Indian haplotype is not benign. *Br J Haematol*. 2014;164:597–604. doi:10.1111/bjh.12650
14. Minniti CP, Kato GJ. How we treat sickle cell patients with leg ulcers. *Am J Hematol*. 2016;91(1):22–30. doi:10.1002/ajh.24134
15. Minniti CP, Taylor JGVI, Hildesheim M, et al. Laboratory and echocadiography markers in sickle cell patients with leg ulcers. *Am J Hematol*. 2011;86(8):705–708. doi:10.1002/ajh.22065
16. Bowers A, Reid H, Greenidge A, et al. Blood viscosity and the expression of inflammatory and adhesion markers in homozygous sickle cell disease subjects with chronic leg ulcers. *PLoS One*. 2013;8(7):e68929. doi:10.1371/journal.pone.0068929
17. Lopes F, Ferreira R, Albuquerque D, et al. In vitro antiangiogenic affects of hydroxyurea. *Microvasc Res*. 2014;94:106–113. doi:10.1016/j.mvr.2014.05.009
18. Adekunle DA. Mild-phenotype of sickle cell disease: molecular basis, clinical presentation and management recommendations. *Curr Pediatr*. 2005;15(1):57–61. doi:10.1016/j.cupe.2004.10.009