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Reminder of important clinical lesson

An adolescent with sickle cell anaemia experiencing disease-related complications: priapism and leg ulcer – a management challenge

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Summary

Sickle-cell anaemia (SCA) is a multi-system disease, associated with episodes of acute illness and progressive organ damage. Disease severity shows substantial variation and it is often a burden for adolescents. Complications such as leg ulcer and priapism have a significant impact on quality of life. There are still no definitive treatment guidelines available. Considering the embarrassing nature of priapism and the dire consequences for erectile dysfunction, it is important to inform patients, parents and providers about the relationship of SCA to prolonged painful erections. This article will review the pathophysiology and treatment options of SCA focusing the complications of leg ulcers, priapism, cholelithiasis and retinopathy. The case study of a 14-year-old boy is used to present a management challenge of multiple SCA-related complications.

BACKGROUND

Sickle cell anaemia (SCA) is an autosomal recessive hereditary haemoglobinopathy. About 5% of the world's population carries the gene, and each year about 300 000 infants are born with major haemoglobin disorders.[1] The public health implications of SCA are clear as it causes either death or disability. The predominant symptom associated with SCA is pain resulting from the occlusion of small blood vessels by abnormally 'sickle-shaped' red blood cells (RBCs).

Priapism is a SCA complication which has a great impact on boys' sexual health. Adolescents with priapism frequently fail to seek medical assistance due to embarrassment and the lack of understanding of the relationship between painful sustained erections and SCA. Early recognition of the different clinical types of priapism and appropriate management can prevent irreversible fibrosis and impotency.

Poor healing of leg ulcers is also a well-described complication of SCA and represents a disabling and chronic repercussion associated with a more severe clinical course. Cholelithiasis and retinopathy are also SCA related complications. Managing adolescents with SCA requires a multidisciplinary approach in a field where treatment options are frequently controversial.

CASE PRESENTATION

A 14-year-old boy from Angola with SCA presented with a 1 year history of a recalcitrant leg wound. The wound was the result of a blow from an iron rod. The patient had undergone a split-thickness skin graft in Angola. As it had been unsuccessful, his parents decided to bring him to Portugal. He was first diagnosed with SCA at the age of 5 and had approximately three sickle cell pain crises per year but he had never been previously followed-up in a sickle-cell clinic. Since the traumatic event he had had limited mobility and had not been attending school.

On examination, there was an 11 cm by 7 cm wound above the left medial malleolus. The wound tissue was >60% thick yellow slough and <40% granulation with copious serous secretions. General examination was otherwise unremarkable except for mild icteric sclerae and a grade 2/6 ejection systolic murmur at the left sternal edge. He was Tanner stage 4 and had a body mass index of 16 kg/m^2.

Further evaluation elicited a 1 month history of waking with painful erections persisting for up to 4 h and that resolved spontaneously. He was not aware of the link between these symptoms and SCA. A multi-disciplinary approach was used to manage his SCA with non-healing traumatic leg ulcer and stuttering priapism.

INVESTIGATIONS

He had a low haemoglobin of 6.9 g/dl with a reticulocyte count of 322 000 (11.5%) and a haematocrit of 20%; a high white cell count of 18×10^9/l with a polymorph cell count of 8×10^9/l (54%); and a high platelet count of 535×10^9/l.

Urine and complete biochemical investigations were all normal with a ferritin level of 143.7 ng/ml; except for a high lactate dehydrogenase (LDH) of 2408 U/l (normal range from 208–378 U/l). Blood cultures were sterile. Chest radiography was normal. At room air, the patient's oxygen saturation was 95% at rest.

High-performance liquid chromatography confirmed homozygous SCA (HbSS) with a quantitative analysis of 73% of HbS and a low HbF of 1.7%. Ultrasonography revealed an atrophic 6 cm spleen and multiple gallstones. Ophthalmologist examination findings were

compatible with a non-proliferative retinopathy of SCA. Echocardiography, pulmonary function study and transcranial doppler ultrasonography were all normal.

TREATMENT

Early intervention regarding the non-healing leg ulcer was bed rest, 16 days of intravenous antibiotics and analgesia. Ulcer management consisted of selective debridement of necrotic tissue and application of an enzymatic debrider covered with fat gauze to prevent adherence of secondary dressing to the wound bed. At the end of the 2nd week of admission he had a split-thickness skin graft.

With respect to the priapism a two-phased management approach was implemented. The first consisted of instructions to drink plenty of liquids, urinate, take a warm bath, undertake physical activity and ask for analgesics. If it did not resolve spontaneously after 3 to 4 h, urgent urological opinion should be sorted.

The second phase of management for priapism started as an outpatient. He underwent a simple RBC transfusion programme consisting of one transfusion every 4 weeks for 8 months. The transfused erythrocytes were leukoreduced and matched the patient for the C, E and K1 antigens. This was also to improve the healing after the split-thickness skin grafts.

Concerning the clinically silent gallstones a conservative management plan was adopted. No therapy for the non-proliferative retinopathy was indicated.

OUTCOME AND FOLLOW-UP

The first month of management of the leg ulcer, with the skin graft was performed as an inpatient. All other management was done as an outpatient with the follow-up of a multi-disciplinary team.

In the beginning of the erythrocyte transfusion programme all his episodes of priapism were stuttering, occurring twice to three times a week and lasting up to 4 h before spontaneously resolving. After the fourth transfusion he started to experience less frequent episodes with shorter durations but it was not until the seventh transfusion that he reported having no more episodes of priapism. Initially his HbS was high at 73% and the reduction to 30% recommended was only achieved after the fourth transfusion. His haemoglobin concentration reached a steady state around 9 mg/dl.

No complication associated to the blood transfusion was observed. Iron stores were fully monitored and at the end of the 8th month transfusion programme ferritin levels did not reach the maximum of 1000 ng/ml.

He is still priapism free on his 4th month of follow-up after the last transfusion.

Regarding his leg ulcer, after the graft an initial improvement and a faster healing were observed around the fourth erythrocyte transfusion. Meanwhile, in the last 2 months recurrence of the ulcer was noticed despite adequate care and follow-up by the plastic surgical team. Another split-thickness skin graft is being taken into consideration.

Since his first admission he has already had a total of 14 months of monthly follow-up and the long-term goals of full closure of the wound and return to school have not yet been observed although successful management of the recurrent priapism was achieved. For the non-proliferative rethinopathy he will have an annual dilated eye examination carried out by an ophthalmologist experienced in retinal disease.

DISCUSSION

It has been 100 years since Herrick published the first medical case report of sickle cell disease (SCD). However, its management and complications are still controversial now.

Although some evidence supports the use of blood transfusion and hydroxycarbamide, to date, no drugs have been developed that specifically target the pathophysiology of this disease.[2]

The term SCD is used to refer to all the different genotypes that cause the characteristic clinical syndrome, whereas SCA, the most common form of SCD, refers specifically to homozygosity for the ⊠S allele.

Homozygous HbSS have the most severe phenotype and can progress with different clinical severity and complications.

SCD is a single amino acid molecular disorder of haemoglobin leading to its pathological polymerisation. The clinical manifestations are driven by two major pathophysiological processes: vaso-occlusion with ischaemia-reperfusion injury and haemolytic anaemia.

Deoxygenation causes HbS to polymerise, leading to sickled erythrocytes. Vaso-occlusion results from the interaction of sickled erythrocytes with leucocytes and the vascular endothelium. Vaso-occlusion then leads to infarction, haemolysis and inflammation; inflammation enhances the expression of adhesion molecules, further increasing the tendency of sickled erythrocytes to adhere to the vascular endothelium and to worsen vaso-occlusion.[2] This vaso-occlusive-viscosity is responsible for complications of disease like acute painful episodes, osteonecrosis of bone and the acute chest syndrome.[3]

Reperfusion of the ischaemic tissue generates free radicals and oxidative damage. The damaged erythrocytes release free haemoglobin into the plasma, which strongly bind to nitric oxide, causing functional nitric oxide deficiency and contributing to the development of vasculopathy.[2] This reduction in levels of nitric oxide alters the balance between vasoconstriction and vasodilation skewing it towards vasoconstriction. Pulmonary hypertension, priapism, leg ulceration and stroke, are all SCA complications that can be linked to the intensity of haemolysis.[3]

Adolescents are at special risk as they can suffer from all the SCA complications either those related to the vaso-occlusive viscosity phenomena as well as those related to haemolysis.[4 5]

In our adolescent we can associate the multiple-disease related complications with some risk factors such as: a low HbF and high platelet count are associated with priapism. Being a male (3:1) and also the lower haemoglobin concentration and lower HbF levels are risk factors for the non-healing leg ulcer. The rate of intravascular haemolysis with permanent high LDH is a risk factor to the cholelithiasis.[4]

The maintenance of high fetal haemoglobin concentrations beyond infancy has long been recognised to ameliorate many aspects of SCD including predicting increased life expectancy and reducing the frequency of both acute pain and leg ulcers.[6 7] The fetal haemoglobin concentration in patients with SCA varies from 1% to 30%, and is inherited as a quantitative genetic trait.[2] In our case we consider

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that a fetal haemoglobin concentration of only 1.7% is our adolescent's main risk factor.

Chronic leg ulcers have been reported to occur in 25% to 70% of adolescent and adult sickle cell patients, depending on the geographic area evaluated and sickle genotype.[4] The events surrounding the initial skin ulceration in SCA suggest two different causes: traumatic or spontaneous. In the traumatic form, there is a clear history of trauma, even involving minor trauma such as insect bites. Those arising spontaneously are believed to represent skin infarction.

Recently, vasculopathic abnormalities and intensity of haemolysis have been recognised as a pathway to end organ damage and complications such as leg ulceration; promoting the non-healing of wounds, especially those in lower extremities.[5 8 9]

Leg ulcers are often associated with a more severe clinical course. Despite the fact that this complication has been recognised since the early times of SCA, there has been little improvement in the efficacy of its management and clinical outcome over the past 100 years.[8] The treatment of leg ulceration is still unsatisfactory and information from controlled clinical trials is sparse. Prevention of trauma is the cornerstone for eviction of chronic leg ulcers in SCA patients.[4 8]

Chronic recalcitrant ulcers are a challenge and techniques include debridement and scrupulous hygiene; iodosorb wound dressing to induce localised proinflammatory cytokines such as tumour necrosis factor and interleukin-6; low-pressure elastic bandage and above-the-knee elastic stockings to improve venous circulation and split-thickness skin grafts can be successful strategies for treating leg ulcers.[10] There is also some evidence for the use of oral administration of zinc sulfate (220 mg three times a day) to promote healing of leg ulcers although we did not use it.[10] The role for regular, long-term blood transfusions in leg ulcers is controversial but some authors do indicate them if ulcers persist despite optimal care.[2 10]

In the case presented, despite all the efforts to achieve a complete long-term healing of the leg ulcer a relapse was observed in the first 10 months after split-thickness skin graft and blood transfusion programme. Our outcome did not come as a surprise as recurrence rates within 2 years, even in successfully grafted and healed ulcers, are documented in literature to be as high as in 80–97% in patients with SCA.[4]

Historically, priapism was thought to be present in 5% to 10% of patients with SCA. A survey was conducted in 1999 to investigate the prevalence of priapism in patients with SCA aged 5 to 20 years. Of the 98 patients surveyed, approximately 27% reported having at least one episode of priapism. The probability of having at least one episode of priapism by age 20 was reported to be 89%. Patients had the average age of 12 when they had their first episode, and the majority of episodes were nocturnal.[11]

There are three kinds of priapism: stuttering priapism (recurrent ischaemic priapism), ischaemic priapism (veno-occlusive, low flow) and non-ischaemic priapism (arterial, high flow).[12]

Ischaemic priapism and stuttering priapism are phenotypic manifestations of SCA.

Stuttering priapism is an uncommon recurrent form of ischaemic priapism consisting of episodes of unwanted, painful erections that typically last for <3 h. It occurs repeatedly with intervening periods of detumescence. If these episodes are not treated, it may evolve into a classic ischaemic priapism and eventually lead to irreversible corporal fibrosis with permanent erectile dysfunction.[13]

The current molecular hypothesis for stuttering priapism in SCA proposes that insufficient basal levels of phosphodiesterase type-5 are available in the corpora to degrade cyclic guanosine monophosphate (cGMP). Nocturnal erections result from normal neuronal production and surges of cGMP. In the context of SCA stuttering priapism, these nocturnal surges in cGMP go unchecked, resulting in stuttering priapism.[12]

The goals of managing stuttering ischaemic priapism are: prevention of future episodes, preservation of erectile function and balancing the risks versus benefits of various treatment options.

There are no definitive guidelines available for the treatment of SCA-related priapism. The evidence consists primarily of case reports, a few small trials and prospective protocols. For the treatment of paediatric acute priapism, conservative measures are initially prudent, but they should not interfere with decisions to proceed to the next level of treatment. For the first 2 h, patients at home should be encouraged to drink extra fluids, urinate, exercise and take oral analgesics if needed.[12–16] These simple steps have occasionally been sufficient enough to produce detumescence. If the priapism continues beyond 2 h, patients should report to the emergency department for further assessment.[14 16] For the next 2 to 4 h, patients should be given intravenous hydration and analgesics, since this often sufficiently resolves the episode. Anxiolytics, such as lorazepam or midazolam, and supplemental oxygen may also be given if needed. If priapism persists beyond 4 h, intracavernosal aspiration of blood and instillation of an α-agonist should be performed under local or regional anaesthesia.[12 13] Phenylephrine and epinephrine appear to be equally safe and efficacious for use in dilute solutions. There is also a new emerging use of phosphodiesterase-5 inhibitors and finasteride with success.[15] Aspiration and irrigation may be repeated as necessary and initial management with intravenous hydration, analgesics, anxiolytics and oxygen should be continued. If the erection continues beyond approximately 12 h, shunt placement should be considered.[13 16] This should be the last option, since rates of impotence are higher, and most paediatric patients respond well to pharmacologic treatments.

Long-term erythrocyte transfusion has an established role in the management of both acute and chronic complications in SCD but its role in priapism is controversial.[2 16] In our case we thought it would be an advantage as transfusion corrects anaemia, decreases the percentage of HbS, suppresses HbS synthesis and reduces haemolysis, all of which are of potential benefit for managing complications.

Stuttering priapism of our adolescent case-report showed resolution after the fourth transfusion and he is priapism free since the seventh transfusion so benefits were observed with the long-term blood transfusion programme.

The key message is that boys with SCA should be alerted regarding the need to seek prompt specialised treatment for any episode of priapism that lasts longer than 2 h. Eighty six per cent of patients with SCA do not spontaneously report complaints regarding intermittent priapism

during regular consultations because of cultural factors, absence of perception of the phenomenon as abnormal especially in children and adolescents, shame or a lack of understanding of the relationship of the phenomenon to SCA.[14] The physician must actively inquire about priapism in the anamnesis of any patient with SCA.

Children with SCA have an increased risk of developing pigment gallstones that initially may be asymptomatic. Their complications are difficult to distinguish from vaso-occlusive abdominal pain and they can sometimes threaten the patient's life. The literature is inconsistent in relation to the best approach to silent gallstones.[17–19] Some recommend an elective laparoscopic cholecystectomy procedure for paediatric patients with SCA to prevent the risk of requiring an emergency cholecystectomy however, our experience together with literature data support an expectant management of clinically silent gallstones in SCA with good outcomes.[17 19]

Sickle retinopathy is common in all forms of SCA and can be of a non-proliferative or a proliferative form. Non-proliferative retinopathy is an occlusion of small blood vessels of the eye and retinal neovascularisation is very common (30% as young as 5–7 years of age) and is usually not associated with defects in visual acuity.[10 20] Some authors recommend treatment with hydroxyurea as it may slow or prevent further vaso-occlusion and have a favourable effect by reducing subsequent neovascularisation.[10]

However, taking into consideration that there is no risk of visual acuity deficiency and that hydroxyurea is also related to worsen the course of leg ulcers, the use of hydroxyurea was not recommended in our patient.[19]

One can not underestimate the substantial impairment of quality of life in adolescents with SCA. In our patient since his traumatic event in Angola 2 years ago his life suffered a complete downturn with school deprivation and emigration in order to look for better healthcare.

Definitely further multicentre randomised clinical trials are required to evaluate the efficacy of different treatment options and to define safe and effective management strategies for multiple SCA related complications in adolescents.

Learning points

- Young people, especially boys from certain ethnic cultures, do not disclose their sexual problems (such as priapism) unless they are asked in a non-judgmental environment.
- The first approach to stuttering priapism is to encourage the patients to drink extra fluids, urinate, exercise and take oral analgesics if needed.
- If the priapism continues beyond 2 h, patients should report to the emergency department for further assessment.
- Prevention of leg ulcers in patients with SCA is better than trying to treat them after they have arisen.

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REFERENCES

1. WHO [Internet]. Executive Board Report: EB117/R3: Sickle-cell Anaemia. Available from: http://www.who.int/nmh/eb117/en/index2.html (accessed 14 February 2012).
2. **Rees DC,** Williams TN, Gladwin MT. Sickle-cell disease. *Lancet* 2010;**376**:2018–31.
3. **Kato GJ,** Gladwin MT, Steinberg MH. Deconstructing sickle cell disease: reappraisal of the role of hemolysis in the development of clinical subphenotypes. *Blood Rev* 2007;**21**:37–47.
4. **Serjeant GR,** Serjeant DE. *Sickle Cell Disease*. Third Edition. Oxford: Oxford University Press 2001.
5. **Siddiqui AK,** Ahmed S. Pulmonary manifestations of sickle cell disease. *Postgrad Med J* 2003;**79**:384–90.
6. **Watson J**. The significance of the paucity of sickle cells in newborn Negro infants. *Am J Med Sci* 1948;**215**:419–23.
7. **Koshy M,** Entsuah R, Koranda A, *et al*. Leg ulcers in patients with sickle cell disease. *Blood* 1989;**74**:1403–8.
8. **Serjeant GR,** Serjeant BE, Mohan JS, *et al*. Leg ulceration in sickle cell disease: medieval medicine in a modern world. *Hematol Oncol Clin North Am* 2005;**19**:943–56, viii–ix.
9. **Hamm R,** Rodrigues J, Weitz IC. Pathophysiology and multidisciplinary management of leg wounds in sickle cell disease: a case discussion and literature review. *Wounds* 2006;**18**:277–85.
10. **Lanzkowsky P**. *Manual of Pediatric Hematology and Oncology*. Fourth Edition. Oxford, UK: Elsevier Inc. 2005:200–30.
11. **Maples BL,** Hagemann TM. Treatment of priapism in pediatric patients with sickle cell disease. *Am J Health Syst Pharm* 2004;**61**:355–63.
12. **Broderick GA**. Priapism and Sickle-Cell Anemia: Diagnosis and Nonsurgical Therapy. *J Sex Med* 2011 (In Press).
13. **Kheirandish P,** Chinegwundoh F, Kulkarni S. Treating stuttering priapism. *BJU Int* 2011;**108**:1068–72.
14. **Jesus LD,** Dekermacher S. Priapism in children: review of pathophysiology and treatment. *Jornal de Pediatria (Rio J)* 2009;**85**:194–200.
15. **Rachid-Filho D,** Cavalcanti AG, Favorito LA, *et al*. Treatment of recurrent priapism in sickle cell anemia with finasteride: a new approach. *Urology* 2009;**74**:1054–7.
16. **Armstrong T,** Barnette C, Bartoshesky L, *et al*. Sickle cell disease in children and adolescents: diagnosis, guidelines for comprehensive care, and protocols for management of acute and chronic complications. Mid-Atlantic Sickle Cell Disease Consortium (MASCC) Practice Guidelines Workgroup. *Children* 2001:61–4.
17. **Hendricks-Ferguson V,** Nelson MA. Treatment of cholelithiasis in children with sickle cell disease. *AORN J* 2003;**77**:1170–8, 1181–2.
18. **Bogue CO,** Murphy AJ, Gerstle JT, *et al*. Risk factors, complications, and outcomes of gallstones in children: a single-center review. *J Pediatr Gastroenterol Nutr* 2010;**50**:303–8.
19. **Gumiero AP,** Bellomo-Brandão MA, Costa-Pinto EA. Gallstones in children with sickle cell disease followed up at a Brazilian hematology center. *Arq Gastroenterol* 2008;**45**:313–8.
20. **Rosenberg JB,** Hutcheson KA. Pediatric sickle cell retinopathy: correlation with clinical factors. *J AAPOS* 2011;**15**:49–53.