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JCIMCR OPEN ACCESS Journal of Clinical Images and Medical Case Reports

ISSN 2766-7820

Case Report

Open Access, Volume 4

Sickle cell disease - Impact of delayed diagnosis and non compliance to treatment

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Received: Feb 08, 2023
Accepted: Feb 24, 2023
Published: Mar 03, 2023
Archived: www.jcimcr.org

DOI: www.doi.org/10.52768/2766-7820/2310

Abstract

Sickle cell disease is an autosomal recessive hematological disorder resulting from a missense point mutation in the beta chain of the haemoglobin molecule. This article reports a case of homozygous sickle cell disease in an adult patient with long-standing history of non-healing ulcer. Subsequently, it calls for the need for detailed and careful investigation of inherited disorders in people of rural background and highlights the need for doctors to better convince people of low socio-economic status on compliance towards long term treatment.

Keywords: Sickle cell disease; Delayed diagnosis; Leg ulcer; Crizanlizumab.

Introduction

The sickle cell syndromes are autosomal recessive disorders caused by a mutation in the β-globin gene that changes the sixth amino acid from glutamic acid to valine. HbS (α2β2, 6Glu→Val) polymerizes reversibly when deoxygenated to form a gelatinous network of fibrous polymers that stiffen the RBC membrane, increase viscosity, and cause dehydration due to potassium leakage and calcium influx. These changes also produce the sickle shape. Sickled cells lose the pliability needed to traverse small capillaries. They possess altered "sticky" membranes that are abnormally adherent to the endothelium of small venules.

These abnormalities provoke unpredictable episodes of vaso-occlusion and premature RBC destruction (hemolytic anemia). The rigid adherent cells clog small capillaries and venules, causing tissue ischemia, acute pain, and gradual end-organ damage. This vaso-occlusive component usually dominates the clinical course.

Prominent manifestations include episodes of ischemic pain (i.e., painful crises) and ischemic malfunction or frank infarction in the spleen, central nervous system, bones, joints, liver, kidneys, and lungs. Several sickle syndromes occur as the result of inheritance of HbS from one parent and another hemoglobinopathy, such as β thalassemia or HbC (α2β2, 6Glu→Lys), from the other parent. The prototype disease, sickle cell anemia, is the homozygous state for HbS.

Homozygotes (SS) have Sickle-Cell Anaemia (HbSS), and Heterozygotes (HbAS) have sickle-cell trait, which causes no disability (and protects from falciparum malaria). Heterozygotes may still, however, experience symptomatic sickling in hypoxia, eg in unpressurized aircraft or anaesthesia.

Life expectancy is short in SCD, with studies reporting an average life expectancy of 42 and 48 years for males and females, respectively.

Case report

A 28 year old male of rural background presented with a non-healing ulcer on the lateral side of his left leg since 14 years with a history of frequent episodes of painful crisis and infections.

Patient was first admitted at the age of 7 years in 1999 with a history of joint swelling and pain in multiple joints involving

knee, inter-phalangeal, elbow and vertebral joints and blood reports showing hemoglobin levels of 6.6 gm/dl, ESR of 55 mm/hr, reticulocyte count of 5.4% and TLC was 19800/cu mm. He was treated with intravenous fluid, antibiotics, and blood transfusion and discharged after 15 days in hospital without a definitive diagnosis.

Patient then had multiple courses of admissions for complaints such as generalised body ache, pallor, joint swelling over the years across all of which low hemoglobin levels were found consistently but a peripheral blood smear was either not done or if done didn't show report sickle cells until in 2021, when the patient reported with the complaint of generalised body ache, thorough investigation was done and an HPLC reported findings consistent with sickle cell anemia [HBs = 82.1%, HbF = 15%, HbA2 = 2.9%, HbA = 0%] which indicated towards a diagnosis of sickle cell anemia, made at the age of 28 years with the diagnosis for that episode being of sickle cell crisis.

Additionally the patient also had low vitamin B12 levels [112.8 pg/ml], high serum ferritin levels [295.4 ng/ml], high SLDH [638 U/L], reticulocyte count was 7%, and anisopoikilocytosis and sickle cells in PBF.

USG findings showed shrunken spleen with coarse granular calcifications, mild hepatomegaly and small gall-bladder calculi. Changes suggestive of avascular necrosis of the head of femur were seen on X-Ray Pelvis. A cholecystectomy was advised to the patient for the gallstones which the patient did not undergo.

Family screening revealed that both the parents were sickle cell carrier and he had 3 siblings, one of which is elder to him and was found to have sickle cell trait on investigations done after the diagnosis of the reported patient. The other 2 siblings, both younger, died, one at 17 years and the other at the age of 14 years, the cause of which was not diagnosed then.

Patient was started on hydroxyurea at 20 mg/kg/day along with Crizanlizumab [Ryverna] at 5 mg/kg once every 2 weeks for 2 doses followed by 5 mg/kg once every 4 weeks thereafter and folic acid supplements on 28 July 2021 after which no episodes of vaso-occlusive crisis were reported and healing of the ulcer was noted in next three months but patient was non-compliant to the therapy in long term. The patient then reported to a tertiary care center on 31 August, 2022 with another episode of vaso-occlusive crisis and recurrence of the ulcer on same site.

Patient was then restarted on hydroxyurea and advised surgical debridement and cross-flap grafting for treatment of the non-healing ulcer but the patient hasn't underwent the surgery and continues to report symptoms of pain and discomfort with the ulcer.

Discussion

Sickle cell disease is an inherited blood disorder which is most common among people of African, Arabian and Indian origin. In India, the disease is still quite undocumented [5]. Though according to a study, it is widespread among the tribal population in India where about 1 in 86 births among tribes have SCD [7]. But still, there is an urgent need to upgrade the available statistics regarding SCD in India.

Clinical presentation of patients with Sickle Cell Disease (SCD) is quite variable. Some patients need intensive care while others need only routine check-ups.

Adolescent SCD patients present with complaints, including frequent pain crisis, gallstones, jaundice, pallor and avascular necrosis of hip while the common complications of adult sicklers include painful crisis, gallstones, osteonecrosis of hip and shoulder joints, leg ulcers, renal diseases, priapism, and retinopathy.

Median age at diagnosis of SCD is 2.0 years (2 months to 14.7 years) [2]. But the patient in this case study was diagnosed at the age of 28 years despite previous history of multiple vaso-occlusive crises and infections. Earlier diagnosis could have prevented the occurrence of complications seen in the patient such as recurrent VOCs, non-healing leg ulcer and avascular necrosis of head of femur.

Patient was started on hydroxyurea along with Crizanlizumab [Ryverna] which is a monoclonal antibody that binds to P-selectin. It is a drug used to reduce the frequency of vaso-occlusive crisis in people aged 16 years and older who have sickle cell anemia which was recently FDA approved in 2019. The patient did report complete relief in the occurences of vaso-occlusive crises when on the drug but became non-compliant in therapy later [6].

Leg ulcerations have been a long recognized complication of SCD. The prevalence of leg ulceration varies, being low before age 10 years. Leg ulcers occur in areas with less subcutaneous fat, thin skin, and with decreased blood flow. The commonest sites are the medial and lateral malleoli (ankles).

Treatment of leg ulcers includes wound care using wet to dry dressings. With regular and good localized treatment, many small ulcers may heal within a few months. Leg ulcers that persist beyond 6 months may require other modalities including blood transfusion, skin grafting, Unna boots, zinc sulphate, hyperbaric oxygen, arginine butyrate, etc.

Recent advances in the management of leg ulcers include topical applications of analgesics, including opioids for pain, topical application of a platelet-derived growth factor prepared either autologously (Procuren) or by recombinant technology (Regranex) and the use of cultured skin grafts [4].

Conclusion

High cost and long term nature of treatment for SCD in people with low financial security poses a challenge to proper patient care, especially in developing countries like India. Optimal management of SCD patients requires early diagnosis, proper patient education, persuading them to be compliant to treatment and regular follow ups. Proper genetic counselling should be done in such families with sickle cell carriers. Availability of newer drugs like crizanlizumab should be made easier and economical as far as possible to people with weak financial status.

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