# Severe acute painful episode and hemolysis following systemic corticosteroid administration in a patient with sickle cell anemia

Nabeel Shamsan[1], Yahya El ficki[2], Safaa Allam[3], Abdulwahab Sultan Al Sultan[4], Mohammed Alabbasi[4], Abdullah Suleiman Babalghaith[4], Mohammed SalehDumyati[4], Hanadi Ali Alsadeq[4]

[1] Chairman internal medicine department and consultant Gastroenterology King Abdul Azziz Hospital Jeddah, KSA
[2] Vice Chairman and consultant Int Med, King Abdul Azziz Hospital, Jeddah, KSA
[3]Senior registrar Int Med, King Abdul Azziz Hospital Jeddah, KSA
[4] Research Assistant and Coordinator King Abdul Azziz Hospital, Jeddah, KSA
profelficki@yahoo.com

**Abstract:** Many cases have been reported with rebound pain and hospital readmissions after corticosteroid treatment for acute painful episode or acute chest syndrome in sickle cell disease (SCD), but there are only few case reports of severe pain episodes in SCD occurring shortly after initiating systemic steroids for other steroid-responsive conditions where steroids are mandatory line of treatment despite their well known rebound adverse outcome in sickle cell disease. We report another case of severe prolonged painful episode in a patient with SCD few days after starting systemic steroids for severe drug allergic reaction in the form of angio-edema, and intensely itching erythema marginatum lesions. Patient dramatic improvement and discharge from hospital was followed by readmission few days later with severe vasoocclusive crisis, andhence, continuous admission for observation should be considered for any sickle cell patient receiving systemic steroids**.**

**[**Nabeel Shamsan, Yahya El ficki, Safaa Allam, Abdulwahab Sultan AlSultan, Mohammed Alabbasi, Abdullahsulaiman Babalghaith, Mohammed Saleh Dumyati, Hanadi Ali Alsadeq. **Severe acute painful episode and hemolysis associated with systemic corticosteroid treatment in a patient with sickle cell anemia.** *J Am Sci* 2017;13(4):1-5]. ISSN 1545-1003 (print); ISSN 2375-7264 (online). http://www.jofamericanscience.org. 1. doi:10.7537/marsjas130417.01.

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## Introduction

Multiple studies have demonstrated that patients with SCD have chronically elevated levels of multiple inflammatory mediators. This suggested the utility of systemic corticosteroids as a treatment for vaso-occlusive events such as pain. However, the exact relationship between measures of pain and those of vaso-occlusion and sickle cell vasculopathy are still under study. Furthermore, recent retrospective data suggest a correlation between the use of corticosteroids for acute chest syndrome and complications such as rebound pain and stroke, raising the issue of both safety and efficacy of corticosteroids in this patient population(1). Few cases have been, also, reported acute sickle cell pain episode developing shortly after the initiation of systemic corticosteroid treatment for steroid-responsive conditions that are not related to SCD(2). We report another case of severe sickle cell pain episode that started shortly after initiating systemic steroid for acute severe AmoxicillinClavulanicAcid-related allergic drug reaction in the form of angio-edema and erythema marginatum in a patient with sickle cell anemia. The patient have had history of infrequent pain episodes, and had been leading normal or near-normal life with stable Hemoglobin level, and no requirement for blood transfusions prior to the reported steroid-related pain episode. The latest pain episode occurred 2 years prior to admission for this reported episode.

## Case Report

A 27-year-old female, known to have sickle cell anemia, presented to the Emergency Department (ED) of King Abdul-Aziz Hospital, Jeddah, KSA, by intensely itching erythema marginatum **(Figure1)**, fever, sore throat, headache, bony aches, and arthralgia involving the large joints (knees, elbows and shoulders). The condition started one week prior to presentation by fever, sore throat, bony aches for which she was prescribed Augmentin (Amoxicillin/Clavulanic acid) 625 mg PO TID, through an outpatient clinic for treatment of an Upper Respiratory Tract Infection. Two days later, she started to notice painless, pruritic rash of erythema marginatum over the legs which gradually spread to involve the upper limbs and the trunk when she came to our ED. Fever, bony aches, and arthralgia persisted till presentation to our ER. There was no history of previous similar attacks, history of allergy, nor past history of rheumatic fever. There was no past history, or family history of Connective Tissue Auto-immune Diseases. She had not been on any regular analgesics, infrequent episodes of pain, and infrequent blood

transfusions. Latest sickle pain episode was 2 years prior to presentation to our ED. Her regular medications, (other than Augmentin that was started one week prior to presentation), included Folic acid 1 mg PO daily and Hydroxy urea 500 mg PO BID. She was not on any regular analgesics or NSAIDs. On examination, she was febrile with a temperature of 37.8$^{o}$C. BP was 115 / 65 mmHg and HR was 102 B/m, regular. There was atypical pruritic, painless rash of erythema marginatum over both upper and lower limbs, and very mild puffiness of eyelids, that the patient ascribed to lack of sleep the preceding night. Throat examination showed mild congestion, and there were no clinical signs of arthritis. Chest, Heart and abdominal exam were unremarkable. Chest X-Ray was unremarkable with clear lung-fields, normal cardiac contour and normal cardio-thoracic ratio. ECG was normal, with no evidence of PR prolongation (PR: 160ms). CBC showed Hemoglobin (Hb) of 8.4 gm/dl, MCV: 86.3 fL, total and differential leucocytic count: (WBCs: 10.8 K/uL, Neutrophils 58.9%, Esinophils 7.7 %), and normal platelets (564 k/uL). ESR was 23, and CRP was 21.2 mg/L (Normal < 9). LDH was 299 U/L (Normal: 100 - 388), Total Bilirubin was 28.5 umol/L (Normal: 1 – 17), Direct Bilirubin was 4.8 umol/L (Normal: 0 – 3.4), AST was 65 U/L (Normal: 10 – 35), and ALT was 61 U/L (Normal: 14 – 45). Serum Albumin was 37 gm/L (Normal: 35 – 50), and total protein was 75.3 gm/L (Normal: 64 – 82). Urea, Creatinine, and Electrolytes were all within normal range. Urine dipstick was negative for proteins.

A throat swab was sent for culture and sensitivity, blood samples were taken for ANA, RF, Anti-dsDNA, and ASOT (Anti-Streptolysin O Titer), and blood Culture. She was scheduled for Echocardiography to be done the next day, and was admitted to the medical ward as a case of query Rheumatic fever, with the differential diagnosis of Connective Tissue Disease. She was started on Aspirin 1 gm PO QID, and Omeprazole 40 mg PO Daily. Folic acid, Augmentin, and Hydorxyurea were continued. Over the next few hours, edema of eye lids increased. Next morning, (nine hours after admission), she was found to have markedangio-edema involving the lips, nose, eyelids, and the whole face. Therewas no urticaria or wheals. Fever and arthralgia persisted, and she was very uncomfortable and anxious because of her facial swelling. ASOT was negative. Echocardiography done and showed normal findings, with nothing to suggest acute or chronic carditis. ANA, RF, and Anti-dsDNA were alsonegative. Blood Cultures were pending. With absence of the criteria required to diagnose Acute Rheumatic Fever ARF, the diagnosis was abandoned, and Aspirin was stopped. The contemporary occurrence of erythema marginatum, angio-edema, and peripheral blood esinophilia following starting Augmentin, gave us enough bases to diagnose the case as Allergic reaction to Augmentin, so Augmentin was stopped, and the patient started on Hydrocortisone 100 mg IV Q 6 hours, and Diphenhydramine 25 mg PO Q 8 hours. Blood samples taken for C1 Esterase Inhibitor level (C1-INH) and C4 level. The next day, (Day 2 after admission), the patient showed marked improvement regarding angio-edema which was almost resolved. The skin rash of erythema marginatum, also, started to fade. Fever subsided. Throat swab & Blood Culture were negative. Viral serology studies for Ebestien Barr Virus, Cytomegalovirus, and HIV were also negative. Hb and leucocytic count were stable. C1-INH & C4 levels came back normal. The patient was labeled as Allergic to Augmentin, and advised to avoid penicillins, and its related medications in the future. Hydrocortisone was changed to Prednisolone 30 mg PO daily. On Day 3 after admission, the patient remained afebrile, was doing perfectly fine asking for discharge. Angio-edema and erythema marginatum completely resolved. She was discharged, in a good condition, on Prednisolone 30 mg Po daily to be tapered gradually within 3 days of discharge, in addition to her usual medications (Folic acid and Hydroxy urea) were continued, and she was given appointment to follow up at our Out-patient Department within one month.

Three days after discharge, the patient came back to ED complaining of severe pain at the back, and thighs that started one day after discharge from our hospital. On examination, she was jaundiced and pale, afebrile and in severe pain. There were no signs suggestive of infection. Her hemoglobin dropped to 6.2gm/dl, MCV 84.8 fL, WBCs 9.02, esinophils 3%, Platelets 452 k/uL. Reticulocytes 6.2%. Total bilirubin was 41.9 umol/L, and direct bilirubin was 14.3 umol/L. LDH was 462 U/L. AST 49.7 U/L, ALT 84.7 U/L, and ALP 87 U/L. The patient was re-admitted as a case of acute painful Sickle episode and Hemolysis. Prednisolone was stopped. MRI requested to rule out femoral osteonecrosis. She was transfused one unit Packed RBCs, started on Acetaminophen 1 gm IV Q 6 hours, Ibuprofen 600 mg PO BID, Morphine 5 mg S.C Q 4 hours PRN, Omeprazole 40 mg PO daily, Sodium Docusate 100 mg PO BID, polyethylene Glycol 17 gm PO BID, Metoclopramide 10 mg IV Q 8 hours PRN, Folic acid 1 mg PO daily, and IVF. After transfusion, Hb picked up to 9.4 gm/dL. MRI was negative for osteonecrosis. The patient started to improve, and the requirement for Morphine gradually declined within 5 days of admission. She was discharged at day 7 of the second admission on Acetaminophen, and Ibuprofen PRN in addition to her usual medications (Folic acid & Hydorxyurea). Further routine follow up at outpatient clinic in the next 3 month were uneventful.

## Discussion

**First Hospital Admission: Diagnostic Difficulty** With the constellation of fever of 37.8 $^{o}$C, polyarthralgia, erythema marginatum, and precedent sore throat and upper respiratory tract infection, acute rheumatic fever (ARF) would be the most likely diagnosis. According to Revised Jones Criteria, diagnosis ARF requires evidence of preceding Group-A Streptococcal Infection plus either two major criteria, or one major, and two minor criteria [(3)]. Anti-streptolysin O Titer (AST) came back low and throat culture came back negative for group A Beta-Hemolytic Streptococci (GAS), and consequently, there was no evidence of GAS. So, the requirements for the diagnosis of ARF were not fulfilled, and the diagnosis was ruled out. Shortly after admission, the patient developed angioedema without urticaria. The development of angioedema, after erythema migratum, raised the possibility of either hereditary angioedema (HAE), or acquired angioedema (AAE). In around 25% of patients with HAE, erythema marginatum precedes the occurrence of edema [(4,5)]. Most cases of HAE present with their first episode before the age of 15[(6)]. However, HAE type-3 typically presents during the second decade of life or later [(7)]. Although there was no past history or family history of angioedema or allergy, still it could had been HAE. Although a family history is typically obtained in cases of HAE, spontaneous mutations may occur [(7,8)]. Our patient presented by Angioedema without urticaria, for the first time in her life, at the age of 27 which limits the possibilities to either type-3 HAE or AAE. Type-3 HAE is characterized by normal C1-INH level and function, and normal C4 level, but Factor 12 mutation may be present[(6,9)]. C1-INH & C4 levels were normal. C1q & Factor 12 mutation were delayed due to the observation of the dramatic response to steroids and antihistamines during the hospital course of management. So, the diagnosis was still either type-3 HAE, or AAE. Factor 12, would have differentiated between the two. HAE type-3 acute attacks are refractory to antihistamines and corticosteroids[(7)]. Corticosteroids and anti-histamines gave dramatic response, which would not happen if it was HAE, and consequently the diagnosis of non C1-INH AAE was made. Both Aspirin and Augmentin can cause erythema marginatum and non-C1-INHAAE[(1)]. On presentation to ED, before starting Aspirin, there was mild eyelid edema. That was erroneously attributed to lack of sleep, but, subsequently, progressed over few hours to the full-blown picture of AE. This leaves Augmentin as the culprit. So, the patient was diagnosed as having allergic drug reaction to Augmentin. The preceding sore throat, fever and arthralgia are due to Resolving Viral Upper Respiratory Tract Infection. The patient dramatically improved on corticosteroids and anti-histamines, after Augmentin cessation. She was discharged in good general condition.

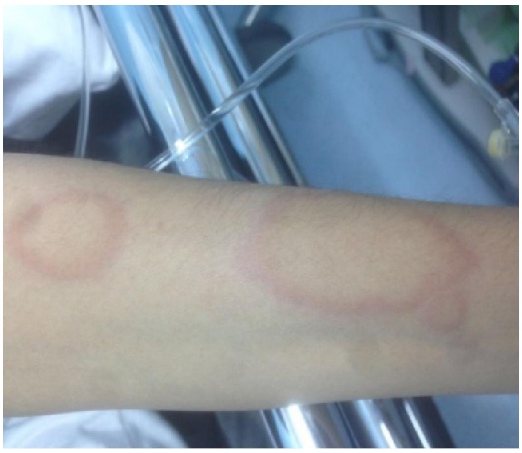

**Figure 1. T**ypical (non rheumatic) erythema marginatum lesions at first hospital admission

**Second Admission: Corticosteroid – Associated Pain Episode** The patient, we are reporting, was readmitted for severe sickle cell episode, within 72 hours after being discharged on prednisolone. The pain episode was severer than any previous pain episodes experienced throughout her entire life. Furthermore, before this admission, her pain episodes had been infrequent. The occurrence of the pain episode few days after initiation of corticosteroids, and the episode being more severe than previous episodes in a patient known to have very infrequent episodes; all point to the corticosteroid being triggering pain and hemolytic crisis's, or at least, being associated with them; not just co-incidence.

SCD has traditionally been considered a disorder of micro vascular vaso-occlusion secondary to mechanical obstruction by of deformed RBCs and subsequent tissue hypoxia. However, more recently a modified paradigm has emerged suggesting that the wide spectrum of clinical manifestations of SCA results from recurrent episodes of ischemia-reperfusion injury. Ischemia-reperfusion triggers a multifactorial cascade including inflammatory response characterized by increased leukocyte and sickle erythrocyte adhesion to vascular endothelium and activation of coagulation, platelets and neutrophils. The data suggest that acute lung vaso-occlusive injury causes an inflammatory response that triggers chemotaxis of leukocytes and secondary injury[(11)]. Multiple studies have demonstrated that patients with SCD have chronically elevated levels of multiple inflammatory mediators[(1)]. Due to the anti-inflammatory effects of corticosteroids, there has been

increasing interest in their role in treatment of different sickle cell crisis like pain episodes and ACS[1,11]. Several clinical studies using different preparations and doses of corticosteroids have held promising results. Griffin et al. used high dose methylprednisolone in vaso-occlusive crisis and reported significant reduction in the duration of analgesic therapy and hospitalization. Bernini et al investigated the efficacy of a lower dose of a longer acting glucocorticoid, dexamethasone in 43 children with mild to moderately severe ACS in a randomized, double-blind, placebo-controlled trial. They showed reduction in the length of hospitalization by about 40%, in the need for transfusion due to worsening anemia, in the duration of fever, and in need of oxygen requirement and pain treatment. Unfortunately, the successes associated with the use of corticosteroids in the setting of SCD have been accompanied by reports of complications ranging from recurrence of pain requiring readmission to the hospital, to episodes of severe vaso-occlusive crises, ACS, stroke, renal infarction and even coma and death. In the study by Griffin et al, 15% of the patients who were treated with corticosteroids had ‘‘rebound’’ pain crisis that required readmission within 6 days after discharge[12].. Similar results were reported by Bernini et al, although in their study the difference between those treated with corticosteroids was not statistically significant (27% vs 5%; P =.095). In a retrospective study, Strouse et al. reported that the odds ratio of readmission within 14 days following treatment with corticosteroids was 20-fold higher among those treated with corticosteroids [11,12].

The exact mechanism by underlying the rebound pain episodes and other sickle crisis events following corticosteroid treatment is not clear[12]. Hypothesized mechanisms include rebound up regulation of vascular adhesion molecule-1 (VCAM-1), delayed leukocytosis, rebound inflammation, and steroid-associated bone marrow necrosis and fat embolism [2,13].

In our case, and the 4 cases reported by Darbari et al[2], pain episodes and hemolysis occurred while the patients are on corticosteroid treatment, shortly after their initiation, not as rebound after their discontinuation or dose reduction, so rebound inflammation and upregulation of CAM-1 cannot explain the occurrence of the sickle crisis. Furthermore, in our case MRI did not show any evidence of bone marrow necrosis, and in 2 of the 4 cases reported by Darbari et al[2], there was no evidence, or at least no mentioning, of bone marrow necrosis, and consequently bone marrow necrosis does not fully explain the steroid-associated sickle crisis in these patients. We believe that further studies are needed to fully understand the mechanism(s) that underlie the effects of corticosteroids in SCD, and until then corticosteroids should be used with caution in SCD.

To minimize the adverse effects of corticosteroids in SCD, Darbari et al [2] proposed blood transfusion given with corticosteroid therapy, and aggressive clinical management of steroid-related adverse effects along with red-cell transfusion, and/or exchange transfusion.

**Conclusion:**

Acute painful episodes of vasoocclusive crisis as well as acute hemolytic crisis should be expected as an adverse outcome following corticosteroid therapy in sickle cell patients, and hence, extension of hospital stay for observation after corticosteroid withdrawal is recommended.

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