

# Gangrene of the digits of the right lower limb in a patient with homozygous sickle cell disease and ulcerative colitis

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that prevalence of ulcerative colitis (UC) among patients with sickle cell at that institution was greater than expected, with a rate of 3 per 1000 when compared to that in the United States of America 0.4 per 1000.<sup>2</sup>

Inflammatory bowel disease (IBD) is also associated with an increased incidence of thromboembolic disease. Hyperhomocysteinaemia (hyper-tHcy), a condition associated with the C677T variant of 5,10-methylenetetrahydrofolate reductase (*MTHFR*), is linked with an increased incidence of thromboembolic disease. Hyper-tHcy has been reported in patients with IBD.<sup>3</sup>

It is therefore important that the cases of patients with these conditions be highlighted in the medical literature so that clinicians may become more aware of this association.

## Case Report

A 16-year old girl, known to have homozygous sickle cell disease (HBSS) presented to the SCU after having vomited twice that day. This was non-bilious and there was no history of haematemesis. However she reported 5 episodes of watery stool, which was said to be *normal* in color but there was no associated abdominal pain. She also complained of frontal headache associated with nasal congestion with a bloody nasal discharge. She had experienced one episode of nosebleed and but there was no history of fever or cough. Of note, she had not yet attained menarche.

In her past medical history it was noted that she had defaulted from follow up at the Sickle Cell Clinic for 13 years and had only one visit the month prior to this presentation. She had been diagnosed at 21 months of age following an episode of dactylitis. There were no recorded admissions to the day hospital at the SCU, neither was there a history of serious life threatening complications such as acute chest syndrome and stroke. She reported no recent admissions to hospital the last being 15 years prior. However she experienced pain mainly to lower back and knees and ankles once every 4 months and had not had any episodes in the previous 4 months.

She was treated at the SCU with codeine 40 mg orally and maintained nil by mouth. She was started on intravenous fluids at 100 mL/hour, and then referred to the Accident and Emergency Unit of the University Hospital of the West Indies. While at the emergency room she reported having pain to the left shin. Of note this patient has had no previous history of thrombosis neither is there is a family history of thrombosis.

On physical examination she had a normal mental state. Her pulse was regular and apex was not displaced. A systolic murmur was auscultated at the apex. Her chest was clear with

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Key words: gangrene, homozygous sickle cell disease, ulcerative colitis, digital ischaemia, gangrene, thromboembolic disease.

Contributions: AER-M, getting the patient's consent, data acquisition, case report drafting and subsequent corrections and revisions, literature review, final approval of work and agreement to be accountable for all parts of the work; JMK-M, work design, drafts critical revision for important intellectual content, final approval of the version to be published, agreement for accountability for all aspects of this paper; MR, conception and design, drafts revision for intellectual important content, final approval of version to be published and agreement to be accountable for all aspects of the work; TSE, case report conception, drafts review and subsequent corrections and revisions, literature review, final approval of work and agreement to be accountable for all parts of the work.

Received for publication: 12 November 2013.  
Revision received: 19 February 2014.  
Accepted for publication: 25 February 2014.

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*Clinics and Practice* 2014; 4:610  
doi:10.4081/cp.2014.610

adequate air entry on auscultation. Abdominal examination revealed hepatomegaly with a liver span of 15 cm and the edge of the liver was smooth. Her left shin was found to be tender on palpation. She was assessed then as having acute gastroenteritis and HBSS with a vaso-occlusive crisis.

After being treated in accident and emergency with oral rehydration fluid, diclofenac 75 mg, ranitidine 50 mg and dimenhydrinate 50 mg, all given via the intramuscular route, she was allowed home on oral dimenhydrinate.

The patient returned to accident and emergency less than 24 h later complaining of sudden onset of pain to her right foot since early that morning. This was associated with swelling and discoloration of the first, second and third toes on her right foot. Examination revealed a swelling to the dorsum of her right foot; this was warm, tender and erythematous. The area was noted to be cold and there was decreased sensation to the area. However, all pulses to the limb were palpable and strong.

She was diagnosed with digital arterial occlusion and admitted for medical manage-

## Abstract

Thrombosis may play an important role in the pathophysiology of certain complications of sickle cell disease (SCD). While the association between SCD and ulcerative colitis (UC) is still debatable, inflammatory bowel disease is known to be associated with an increased incidence of thromboembolic disease. We report a case of a 16-year old girl known to have homozygous SCD and also diagnosed with UC who presented with digital ischemia of her right lower limb. This led to gangrene and subsequent amputation of the first, second and third digits of that limb. This case highlights that patients with both UC and SCD may have an increased risk of thromboembolism and raises the question as to whether patients with UC and SCD should be screened for thrombophilia.

## Introduction

It has been hypothesized that some patients with sickle cell disease (SCD) have an inherited hypercoagulable state. There is evidence of activation of both blood coagulation and platelets in plasma samples obtained from patients with sickle cell disease in the steady state and during painful crises. In 1998, Zimmerman and Ware examined the role of two commonly inherited thrombophilic mutations and found that the C677T mutation in the ethylene-tetrahydrofolate reductase gene was relatively common in patients with sickle cell disease.<sup>1</sup>

A study done at the Sickle Cell Unit (SCU), University of the West Indies in 1987 showed

ment which included heparin i.v. 3500 units given stat then i.v. heparin 700 U/h followed by warfarin for 3 months duration, with the aim to keep her international normalized ratio between 2-3. A referral was also made to surgery. The decision was however taken that there was no role for surgical embolectomy. Amputation of her right first and second toes was done approximately 4 months after her initial presentation. Her immediate post-operative period was complicated by a wound infection and anemia that required transfusion.

Approximately 9 months later the patient was investigated with colonoscopy due to a 4-month history of bloody diarrhea. She was found to have a pancolitis and was diagnosed with ulcerative colitis. Presently, she is maintained on sulfasalazine 1 gram orally twice daily, prednisone 40 mg once daily and pantoprazole 40 mg once daily.

It should be noted that relevant investigations were performed sequentially as her symptoms unfolded. Total evaluation took place over a one-year period. Regrettably an arterial Doppler was not done at the time of the ischaemic event. This was done 2 months later during follow up at the Sickle Cell clinic.

Results of laboratory tests and investigations are summarized in Tables 1 and 2.

## Discussion and Conclusions

The case illustrates some of the challenges of making a new diagnosis in a patient with a

chronic disease. Although her initial presentation included fairly prominent gastrointestinal symptoms, the link between these symptoms and the digital thrombosis was not immediately apparent. Earlier recognition may have prompted appropriate investigation and thus early initiation of treatment. This case report therefore highlights this link between SCD, UC and thromboembolism.

There are many cases of thromboembolic phenomena in patients with SCD, but most of these occur in the lungs. Arterial thrombosis involving the extremities is rare. Our search of the literature revealed only three case reports of ischemia and gangrene associated with sickle cell disease, two of which occurred with dactylitis or painful crisis. The first case is that of a 7 month African American boy with sickle cell disease and painful swelling of hands and feet. This was treated at home with emersion of his hands into cold water. Two days following this, the palm, thumb, third fourth and fifth digits of the right hand became cold and cyanotic. Coagulation studies revealed decreased protein S activity. In addition to having SCD, this infant's risk of clotting was influenced by excessive exposure to cold and a specific coagulopathy. Thrombosis complicating dactylitis was also reported once previously when a patient with sickle cell disease treated with sponge baths for fever, developed gangrene in all extremities.<sup>4</sup>

Reduced activity of naturally occurring anticoagulants protein C and protein S may contribute to vaso-occlusion in sickle cell disease.<sup>5</sup> Also, increased exposure of phosphatidylserine

in erythrocytes has been postulated to contribute to the pathophysiology of sickle cell disease because of its possible effects on blood coagulation, cell adhesion, and cell clearance.<sup>6</sup>

The third reported case is that of peripheral arterial lesions which were seen in a 14-year old boy with SCD. He presented to a surgical unit with gangrene of his right foot. The condition had been preceded a year earlier by ulceration to his right foot. His past medical history revealed a right-sided stroke at 8 years old but no identifiable risk factors for atherosclerosis. On examination there were no palpable pulses. Plain x-rays showed extensive calcifications of the brachial, femoral and popliteal arteries.<sup>7</sup>

Ulcerative colitis is also associated with hypercoagulability. However, peripheral thrombosis is also a rare complication with a reported incidence of less than 1 in 1000 with IBD. In a case report published in 2005, a patient with an exacerbation UC presented with thrombosis of the peripheral venous system, cerebral venous systems and peripheral arterial system all in the course of the same episode of illness.<sup>8</sup>

Miehsler *et al.* reported that the majority of patients with IBD do not have demonstrable specific coagulation defects although acquired deficiencies of antithrombin and protein S has been reported.<sup>9</sup> They therefore concluded that thromboembolism is a specific feature of IBD. In that study neither rheumatoid arthritis, nor coeliac both chronic inflammatory diseases had an increased risk of thromboembolism.<sup>9</sup>

The role of inherited DNA mutations contributing to thrombotic complications in persons with sickle cell disease and inflammatory

**Table 1. Initial investigations.**

Test	Date	Results
Complete blood count	10 Feb 2011	Hemoglobin 5.4 g/dL (fell to 4.5 g/dL on day 3); WBC 15; 10e9/L Neutrophils; 54% Lymph; 24% Monocytes 19%; Eosinophils 2%; Plat 719 (10e3/uL); MCV 75 fL
Blood film	13 Feb 2011	Target cells++ sickle cells++ polychromasia++, hypochromia with occasional microcytes
PT; PTT	12 Feb 2011	PT 12.5/12.3; PTT31.8/27.5
ESR	10 Feb 2011	128 mm/h
Urea and electrolytes	11 Feb 2011	*Na 138 (135-145 mmol/L); K 3.8 (3.5-5.0 mmol/L); Urea 1.5 (2.5-6.7 mmol/L); Creat 35 (9-124 Umol/L); Cl 111 (95-110 mmol/L); CO <sub>2</sub> 18 (20-28 mmol/L)
Liver function tests	12 Feb 2011	*Total proteins 78 g/L (68-84 g/L); Albumin 20 (38-52 g/L); Glob 58 (18-38 g/L); ALP 224 (30-120 U/L); GGT 40 (7-32 U/L); AST 101 (15-45 U/L); LDH 218 (105-200 U/L); Total bilirubin 29 Umol/L; Direct bilirubin 13 Umol/L
ANA	15 Feb 2011	Negative
dsDNA	15 Feb 2011	Not available
C3	15 Feb 2011	*115 (90-180 mg/dL)
Rh factor	15 Feb 2011	Negative
C-reactive protein	15 Feb 2011	*1.48 (<0.5)
Blood and urine cultures	11 Feb 2011	Negative
Urine analysis	10 Feb 2011	Trace urobilinogen only

WBC, white blood cell count; Lymph, lymphocytes; Plat, platelets; MCV, mean corpuscular volume; PT, prothrombin time; PTT, partial thromboplastin time; ESR, erythrocyte sedimentation rate; Na, sodium; K, potassium; Creat, creatinine; Cl, chloride; Glob, globulin; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; ANA, antinuclear antibodies.

\*References from local laboratory; °References from The Harriet Lane Handbook, 18<sup>th</sup> ed. (by Johns Hopkins Hospital). Mosby: Maryland Heights, MO; 2008.

Table 2. Further investigations.

Investigation	Date done	Results
Echocardiogram	12 Feb 2011	Mild to moderate RVH enlargement. No evidence of an intracardiac mass
Electrocardiogram	11 Feb 2011	Left ventricular hypertrophy with non-specific T-wave abnormalities
Abdominal ultrasound	18 Feb 2011	Features suggestive of early renal parenchymal disease
Arterial Doppler	10 Mar 2011	No occlusion of large or medium sized vessels. Peripheral small vessel occlusive disease is not entirely excluded
Histology (right great and second toes)		Ischemic necrosis (gangrene), intimal hyperplasia
Histology (colon)		All biopsies show similar features namely those of chronic active colitis. There is a polymorph infiltration with surface epithelial and crypt damage. No dysplastic changes are evident

disease has been explored. Zimmerman and Ware analysed the prevalence of the C677T mutation in the *MTHFR* gene and the C1565T mutation in the platelet glycoprotein 11a gene in 86 patients with SCD and a history stroke or avascular necrosis. It was found that the C677 *MTHFR* mutation is not an independent risk factor for the development of these thrombotic complications neither was the CT1565T GP111a mutation.<sup>1</sup> Arterial thrombosis of the digits in sickle cell disease is indeed rare. In two of the case reports mentioned exposure to cold was mentioned as an associated factor.

There is in fact an association between the thermolabile *MTHFR*C677T variant and IBD.<sup>3</sup> This accounts for the raised plasma homocysteine found in patients with IBD and may contribute to the increased incidence of thromboembolic complications.<sup>3</sup>

There are specific features of this case that require discussion. This patient was noted to have hepatomegaly and hepatic sequestration was suspected on day 3 when her hemoglobin fell to 4.5 g/dL and she required transfusion. However at that time there was evidence of over-anticoagulation and documented recurrent epistaxis. Chronic hepatomegaly is likely as a result of SCD. Hepatomegaly occurs in 40-80% of patients and seen in 80-100% of cases at autopsy. The anatomical basis of hepatomegaly is presumed to be chronic sinusoidal congestion.<sup>10</sup> It is noted that intrinsic disease results from recurrent ischaemia and bilirubin stones.<sup>11</sup> It was also noted that the liver function test was abnormal as indicated by hypoproteinaemia and the elevated aspartate aminotransferase. There was no indication of microalbuminaemia on urine microscopy. This could indicate gastrointestinal protein loss. A result for alanine aminotransferase was not available.

It is therefore likely that patients with both ulcerative colitis and sickle cell disease have an increased risk of thromboembolism. We are unable to say whether an arteritis may have been associated, as an antineutrophil cytoplasm antibody ANCA test was not done. The combined effect of SCD and IBD may have been summative in causing peripheral thromboembolism.

It is difficult to predict how each disease will impact an individual patient. This case however importantly demonstrates that rare complications occurring in a patient with a chronic disease should be extensively investigated. An important diagnosis may be missed if this is not done.

It seems plausible that patients who have one or more diagnosis known to be associated with a prothrombotic state should have thrombophilia testing. In some cases however a demonstrable disorder of coagulation may not be evident. So while thrombophilia screening is useful, it is our suggestion that patients with sickle cell disease, who are diagnosed with ulcerative colitis should be considered for anticoagulant prophylaxis during times when the risk increases for example during periods of immobilization or hospitalization.

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