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

Angela E. Rankine-Mullings,1 Jennifer M. Knight-Madden,1 Marvin Reid,2 Trevor S. Ferguson3

1Sickle Cell Unit, Tropical Medicine Research Institute (TMRI), University of the West Indies, Kingston; 2Tropical Metabolism Research Unit, Tropical Medicine Research Institute (TMRI), University of the West Indies, Kingston; 3Epidemiology Research Unit, Tropical Medicine Research Institute (TMRI), University of the West Indies, Mona, Jamaica

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 is 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.1

A study done at the Sickle Cell Unit (SCU), University of the West Indies in 1987 showed 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 1000.2 Inflammatory bowel disease (IBD) is also associated with an increased incidence of thromboembolic disease. Hyperhomocysteinemia (hyper-Hcy), a condition associated with the C677T variant of 5,10-methylenetetrahydrofolate reductase (MTHFR), is linked with an increased incidence of thromboembolic disease. Hyper-Hcy has been reported in patients with IBD.3

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 nausea 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 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 vital signs. Her chest was clear with 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-
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±2.3; PTT 31.8±27.5                                               |
| ESR                         | 10 Feb 2011| 135 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 mmol/L); Cl 111 (95-110 mmol/L); CO2 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 (38-120 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, 18th ed. (by Johns Hopkins Hospital). Mosby: Maryland Heights, MO, 2008.
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.

There 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.

References

1. Zimmerman SA, Ware RE. Inherited DNA mutations contributing to thrombotic complications in patients with sickle cell disease. Am J Hematol 1998;59:267-72.
2. Terry SI, Rajendran A, Hanchard B, Serjeant GR. Ulcerative colitis in sickle cell disease. J Clin Gastroenterol 1987;9:55-7.
3. Mahmud N, Molloy A, McPartlin J, et al. Increased prevalence of methylenetetrahydrofolate reductase C677T variant in patients with inflammatory bowel disease, and its clinical implications. Gut 1999;45:389-94.
4. Michaels LA, Maraventano MF, Drachman RA. Thrombosis and gangrene in a patient with sickle cell disease and dactylitis. J Pediatrics 2003;142:449.
5. Schnog JB, Mac Gillavy MR, van Zanten AP, et al. Protein C and S and inflammation in sickle cell disease. Am J Hematol 2004;76:26-32.
6. Wood BL, Gibson DF, Tait JF. Increased erythrocyte phosphatidylserine exposure in sickle cell disease: flow-cytometric measurement and clinical associations. Blood 1996;88:1873-80.
7. Elsharawy MA, Moghazy KM. Peripheral arterial lesions in patient with sickle cell disease. Eur J Vasc Endovasc Surg 2007;34:492.
8. Jain S, Bhatt P, Muralikrishna GK, et al. Extensive arterial and venous thrombosis in a patient with ulcerative colitis – a case report. Medscape General Med 2005;7:10.
9. Miehsler W, Reinisch W, Valic E, et al. Is inflammatory bowel disease an independent and disease specific risk factor for thromboembolism? Gut 2004;53:542-8.
10. Ali SB, Cumming V, King L, et al. Sickle cell disease: the clinical care guidelines of the Sickle Cell Unit. Mona, Kingston: Tropical Metabolism Research Institute University of the West Indies; 2008.
11. Dallas SK, Kesen MR, Goldberg MF, et al. Beyond the definitions of the phenotypic complications of sickle cell disease: an update on management. Sci World J 2012;2012:949535.