**Co-existing sickle cell anaemia and inflammatory bowel disease: case report and review of the literature**

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ABSTRACT

Sickle cell anaemia (SCA) is a chronic haemolytic anaemia associated with vaso-occlusive painful crises which may affect several systems including the gastro-intestinal system, resulting in abdominal pain. The concurrence of inflammatory bowel disease and a haemoglobinopathy is rare. No previously reported concurrent cases of both SCA and ulcerative colitis (UC) in sub-Saharan Africa were found in the literature. A 16-year-old girl with concurrent SCA and UC is presented. She was admitted to University College Hospital, Ibadan with a 1-year history of recurrent peri-umbilical pain and bloody stools. These symptoms were mainly attributed to SCA at the referring hospital, and she was managed for chronic tropical diarrhoea without a remarkable clinical response. This case illustrates the concurrent presentation of SCA and ulcerative colitis which led to the missed and delayed diagnosis of ulcerative colitis.

**Keywords**: Sickle cell anaemia; ulcerative colitis; concurrence; colonoscopy; abdominal pain and bloody stools.

**Abbreviations**: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CKD, chronic kidney disease; GGT, γ-glutamyltransferase; Hb, haemoglobin; HbSS, haemoglobin S homozygous gene; H&E, haematoxylin and eosin; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; PUCAI, paediatric ulcerative colitis activity index; SCA, sickle cell anaemia; UC, ulcerative colitis; UCH, University College Hospital; WBC, white blood cells; WHO, World Health Organisation

**Introduction**

Sickle cell anaemia (SCA) occurs in 2–3% of the Nigerian population [1-4] and each year 150,000 Nigerian neonates are born with the disorder [1]. In hypoxic states, red blood cells sickle, resulting in vaso-occlusion, ischaemia and pain. Abdominal pain owing to vaso-occlusive SCA crises is often a diagnostic challenge and may be indistinguishable from ischaemic colitis, infectious colitis, appendicitis and inflammatory bowel disease (IBD) [5]. Until recently, only 17 children with IBD had been reported from Nigeria [6-10]. The concurrence of SCA and IBD in children is extremely rare. A systematic search of public databases, namely PubMed and Google Scholar, from inception to June 2020 yielded only five case reports from Jamaica, the West Indies, Saudi Arabia (two cases) and Nigeria [11–15] (Table 1). The search was confined to articles in English using the terms ‘inflammatory bowel disease’, ‘sickle cell anaemia’ and ‘sub-Saharan Africa’ as well as equivalent MeSH terms. This is probably the first report of a child with both SCA and ulcerative colitis (UC) in sub-Saharan Africa. In children with SCA, the possibility of missing a diagnosis of UC can have serious effects on the management and outcome.

**Case report**

A 16-year-old girl was diagnosed at the age of 7 years with homozygous SCA (HbSS) using the haemoglobin electrophoresis with cellulose acetate method [11]. She presented initially to the Children’s Outpatient Department, University College Hospital (UCH), Ibadan with a 1-year history of up to four episodes a day of loose and occasionally bloody stools. During that time, she had mild intermittent peri-umbilical colicky abdominal pain associated with poor appetite and poor weight gain. There was no previous history of abdominal distension, recurrent fever, joint swelling or pain, skin rash or mouth ulcers. She had been admitted three times to different private hospitals (non-Government public health facilities) for vaso-occlusive crises including abdominal pain and had received two blood transfusions. The first admission and blood transfusion were in a private facility at around 7 years of age when the diagnosis of HbSS was confirmed, and the second blood transfusion was at 16 years of age when she was admitted for a few days to a different health facility and then discharged. Approximately a month later, she presented to the Children’s Outpatient Department, UCH. No record of previous regular hospital follow-up or immunisations was available, and she had not had a transcranial ultrasound scan which is available only at UCH in that part of Nigeria. The patient and her mother stated that she was not sufficiently unwell to necessitate attending the hospital. Compliance with routine medication (folic acid and Paludrine) and clinic visits including to UCH had been poor over the years. At the time of this admission, her steady-state haemoglobin concentration was 6–9 g/dL.

The family of four children is of a low socio-economic class. Another member of the family, a 22-year-old female who is a twin, is being followed up in another hospital for HbSS and is said to have had only mild and infrequent vaso-occlusive crises. There was no family history of IBD or any other gastro-intestinal disorder.

Physical examination demonstrated a pale, slightly icteric adolescent girl with sickle cell habitus including gnathopathy and long, thin limbs with no finger clubbing. Weight at presentation was 43.5 kg (<9th centile), height 168.5 cm (81st centile) and BMI 15.6 kg/m2 (0.5 centile) (WHO AnthroPlus®) [12]. Temperature was 36.7°C, pulse 90/minute and of normal volume, blood pressure 100/60 mmHg and heart sounds were normal, and no murmur was detected. There was abdominal tenderness in the peri-umbilical, suprapubic and left iliac fossa areas. The liver was not enlarged, but a liver ultrasound was not undertaken. There were no oral lesions, peri-anal skin tags or fistulae. The remainder of the physical examination was normal.

*Investigations*. Haemoglobin (Hb) was 5.8 g/dL, white blood cell count (WBC) 24×109/L (neutrophils 56%, lymphocytes 32% and monocytes 12%) and platelets 593×109/L (Table 1). Total serum protein was 7.6 g/L (6.0–8.0), serum albumin 4.2 g/L (3.5–5.0) and liver enzymes were mildly raised. Stool microscopy and culture were negative for ova, cysts and trophozoites of parasites but red blood cells and pus cells were detected. The serology test for HIV was negative. After obtaining consent from the patient and her mother, colonoscopy was undertaken. It demonstrated marked distortion of the anatomy of the colon; the haustral markings and mucosal pattern were disrupted with widespread mucosal oedema and erosions (Figure 1). The ileum was not intubated and oesophagogastroduodenoscopy and imaging of the small bowel was not undertaken owing to financial constraints.

**[t]TABLES 1&2[/t]**

**[f]FIGURE 1[/f]**

Histology of the colonic biopsies demonstrated widely spaced glands with intense lymphoplasmacytic and eosinophilic infiltrations between the branched and distorted glands and crypts, as well as crypt inflammation. There was a regenerated gland lining with no goblet cells (Figure2). Figure 3 shows intense lymphoplasmacytic infiltrate of the lamina propria of the mucosa and sickle erythrocytes in the microvasculature. The clinicopathological features were in keeping with UC.

**[f]FIGURES 2A–D and 3[f]**

The patient was managed with daily oral prednisolone 40 mg for the first 2 weeks, tapered by 5 mg weekly over the next 8 weeks. After 1 week of prednisolone, she started to show clinical signs of remission, the abdominal pain and diarrhoea subsided and her energy level improved. After 2 weeks of prednisolone, she was commenced on sulfasalazine 500 mg four times daily. She remained in remission with no diarrhoea or abdominal pain and her appetite had been better for about 12 months following the diagnosis and while she was on regular sulfasalazine. The paediatric ulcerative colitis activity index (PUCAI) score [13] was zero during follow-up clinic visits and her weight was 50 kg (50th centile). (The PUCAI is a six-item score ranging from 0 to 85).

Three years after her first visit and after being lost to follow-up for 2 years, the patient presented again to the UCH outpatient clinic at the age of 19 years. Her symptoms had relapsed when she stopped taking sulfasalazine regularly owing to the cost. The PUCAI score was now 60. On review at relapse, she weighed 55 kg (25–50th centile) with a height of 172 cm (85th centile) and BMI 18.6 kg/m2 (12th centile) Results of investigations were as follows: Hb was 7.4 g/dL, WBC 19.0×109/L and platelets 363×109/L. C–reactive protein was 111.0 mg/L (10.0–50.0). Other investigations including liver enzymes, electrolytes and urea are shown in Table 1. The urinary albumin/creatinine ratio was 19.5 mg/mmol (0–1 mg/mmol) and the estimated glomerular filtration rate was 80 ml/min/1.73 m2 (≥90–130/140ml/min/1.73 m2), leading to the diagnosis of stage II chronic kidney disease (CKD).

A repeat colonoscopy was not possible because of the cost. After intestinal infection was excluded, she was re-commenced on prednisolone 40 mg daily for 2 weeks with a plan to commence azathioprine; unfortunately, however, she was again lost to follow-up. During her follow-up in hospital, she was also being reviewed by the paediatric haematologist for her SCA.

**Discussion**

In Nigeria, SCA is a significant burden on patients and imposes a socio-economic impact on the family. Although infrequently reported in Nigerian children [6-10, 14], emerging epidemiological data suggest that the incidence of IBD is increasing in low- and middle-income countries [15]. In both SCA [16] and IBD [6, 17], abdominal pain is a common presentation. Therefore, when a patient with SCA has abdominal pain, the possibility of IBD should be considered in the differential diagnosis. In some of the earliest reports of IBD in Nigerian children over an 8-year period in Lagos State University Hospital, five cases of IBD were reported, three of whom presented with recurrent abdominal pain [10]. In a report of eight cases of IBD who presented to Lagos University Teaching Hospital, four had chronic symptoms of abdominal pain, three of whom had bloody diarrhoea [6]. In the present case, the patient presented with the rare combination of SCA and UC, confirmed by colonoscopy and histology. It is probably the first case of UC associated with SCA in sub-Saharan Africa.

A review of the literature found only five case reports of SCA and IBD (and this single case from Nigeria makes it six). In patients with SCA, there were three cases of UC [18-20], one case of indeterminate IBD and a case of Crohn’s disease [21] (Table 2). The age of one of the patients on presentation was 2 years and, in the remainder, it ranged from 9 to 16 years [17, 19, 22]. The duration of the symptoms of IBD before presentation in this case (about 1 year) is similar to that in other children with IBD and underlying SCA (4 months to 3 years).

In SCA the differential diagnosis of abdominal pain and bloody diarrhoea includes infectious colitis and ischaemic colitis [5, 23]. No organism was isolated in the index patient, despite culture and examination of stools on two occasions. Although ischaemic colitis is uncommon in those with SCA and only a few cases have been reported [24], it should be considered in patients with persistent abdominal pain which does not improve with conservative management. The index patient presented with a longstanding history of diarrhoea which is unusual in ischaemic colitis and the prompt clinical response to anti-inflammatory therapy was consistent with UC. Furthermore, the colonoscopic findings did not support a diagnosis of ischaemic colitis which is usually associated with segmental distribution of disease, abrupt transition between injured and uninjured mucosa, and rectal sparing. Typically, the histology of ischaemic colitis demonstrates pseudo membranes on the mucosal surface, submucosal and lamina propria hyalinisation, and sometimes thrombi in the micro vasculature [25, 26], all of which were absent from the histology of the index case. Although sickled cells are found in the intestinal vasculature in ischaemic colitis in SCA, it is unlikely in this case that they signified ischaemic colitis.

In the index patient, the PUCAI score varied over the years which reflected the activity of the UC during therapy with sulfasalazine and prednisolone which resulted in a score of zero (remission <10). Unfortunately, the patient defaulted for 2 years and her PUCAI score on re-attendance was up to 60, suggesting moderate disease (moderate disease is 35–64 and severe disease is ≥65–85). The PUCAI score is used to monitor the UC [13]. The score is based on stool consistency, frequency per 24 hours, nocturnal stools, rectal bleeding and degree of limitation of activity which ranges from none to severe.

Several studies have documented that the gut microbiota is altered in IBD [27, 28] and there is growing evidence that patients with SCA may have an abnormal intestinal microbiota which could contribute to the development of ischaemia and consequently vaso-occlusive crises [16, 29]. A mouse model of SCA suggests that the intestinal microbiota may play a role in the regulation of systemic neutrophils and vaso-occlusive crises [16, 29]. However, a systematic review did not support the use of probiotics in the initial treatment of UC [30], and presently there is no evidence of the value of probiotics in the treatment of SCA.

The patient in this report posed a management challenge, particularly because of the failure of follow-up. Corticosteroids, anti-inflammatory drugs and immunomodulators are the standard first- and second-line treatments for UC, while, in SCA, steroids are commenced only when there is associated systemic and/or auto-immune disease [31]. However, the use of steroids for SCA is controversial, especially given the risk of severe vaso-occlusive episodes and haemorrhagic stroke [31]. The patient was initially on prednisolone for 10 weeks and no side-effects were reported.

Stage II chronic kidney disease (CKD) was diagnosed following micro-albuminuria and an estimated GFR of 80 ml/min/1.73m2. The observed CKD may be attributable to individual or synergistic contributions of SCA, UC and sulfasalazine [32-35]. There are reports of patients with UC and SCA developing acute kidney injury and CKD [36-38]. This patient had stage II CKD which, without intervention, has the potential to progress to end-stage kidney disease. The micro-albuminuria recorded in this patient is an acute phase reactant and a marker of endothelial damage in the kidneys which has been shown to correlate strongly with the severity of IBD [39-41] and of SCA [37, 38]. It is uncertain whether the micro-albuminuria and the stage II CKD in this patient was owing to the UC or caused by the medication administered. Whatever the cause of the micro-albuminuria, screening for early markers of kidney disease such as the cystatin-C and neutrophil gelatinase-associated lipocalin [42] should be encouraged to enable early intervention in the management of micro-albuminuria.

Although very rare, UC should be considered in patients with SCA and abdominal pain and diarrhoea, especially bloody diarrhoea, to minimise the risk of a delayed and often missed diagnosis of IBD. An appropriate gastro-intestinal investigation facility will be required, especially the routine (free-of-charge) availability of endoscopy which is essential for the prompt diagnosis of IBD in children. When this is available, more cases of IBD and SCA might be recognised.

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**Table 1**. Investigations

|  |  |  |  |
| --- | --- | --- | --- |
| Type of test | Date of test | Result | Normal range |
| Full blood count | 21/11/201621/08/2019 | Hb 5.8 g/dL WBC 240×109/L Neutrophils 56%Platelets 593×109/LHb 7.4 g/dL WBC 19.0×109 /LNeutrophils 52%Platelets 363×109/L  | 12.0–16.0 g/dL4.0–11.0×109 /L150–450×109/L12.0–16.0 g/dL 4.0–11.0×109/L150–450×109/L |
| Haematocrit | 21/11/201613/6/20175/12/2019 | 19%25%21% | 35–48% |
| Urinalysis | 8/12/2016 | Protein: positive + |  |
| Liver function tests | 4/9/201921/08/2019 | Total bilirubin 2.6 mg/dLDirect bilirubin 1.0 mg/dLALT 10 IU/LGGT 56 IU/LAST 52 IU/LALP 134 IU/LTotal protein 7.4 g/LAlbumin 3.5 g/LLactate dehydrogenase 1150 U/L | 0.2–1.0 mg/dL0–0.4 mg/dL0–37 IU/L7–50 IU/L0–40 IU/L187–400 IU/L6.0–8.0 g/L3.5–5.0 g/L0–247 U/L |
| Electrolytes, urea and creatinine | 15/12/201602/10/2019 | Urea 16 mmol/LCreatinine 80 umol/LUrea 10 mmol/LCreatinine 97 umol/L | 2.9–8.2 mmol/L39–91 umol/L2.9–8.2 mmol/L39–91 µmol/L |
| C-reactive protein | 04/09/2019 | 111 mg/L | 10.0–50.0 mg/L |
| Serum creatinine | 21/08/2019 | 102 µmol/L | 39–91 µmol/L |
| Urinary albumin/creatinine ratio | 21/08/2019 | 19.5 mg/mmol | 0–1 mg/mmol |

**Table 2**. Case reports of inflammatory bowel disease in 5 children with sickle cell disease.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Authors and country | Age at diagnosis, y | M/F | Duration of symptoms | Major clinical symptoms | Colonoscopy findings | Histology and diagnosis |
| 1 | Terry et al., 1987 [15]Jamaica | 9 | M | 3 y | Rectal bleeding | Diffuse, severe erythema, marked oedema | Patchy ulceration of the epithelium with crypt injury owing to polymorph infiltration. Congested capillaries with sickled erythrocytes, lymphocytes and increased plasma cells in the lamina propria. **Ulcerative colitis** |
| 2 | Rankine-Mullings et al., 2014 [13]West Indies | 16 | F | 4 m | Bloody diarrhoea | Pancolitis | Chronic active colitis, polymorph infiltration with surface epithelial and crypt damage.**Ulcerative colitis** |
| 3 | Alqoaer et al., 2014 [14]Saudi Arabia | 11 | F | >1 y | Colicky abdominal pain, bloody stools | Pancolitis with friable and oedematous mucosa, diffuse erythema and decreased vascular markings | Scattered hyperplastic lymphoid follicles. Lamina propria contains focally branched and distorted glands and heavy infiltration by lymphocytes and plasma cells.Muscularis mucosa, thickened and inflamed.**Indeterminate colitis** |
| 4 | Al-Johar et al., 2017 [15] Saudi Arabia | 2 | M | Not stated | Colicky abdominal pain and bloody diarrhoea | Inflamed mucosa of the entire colon with a lack of vascularity, oedema, pallor and distorted caecum | Moderately to markedly increased architectural distortion of lamina propria owing to neutrophilic infiltration of the lamina propria and crypt epithelium. Crypt abscess formation and foci of goblet cell depletion. **Ulcerative colitis** |
| 5 | Azar et al., 2014 [16]USA | 13 | M | Not stated | Abdominal pain and occasional blood-streaked stools | Patchy chronic active pancolitis | **Crohn’s disease** |
| 6 | Present caseNigeria | 16 | F | 1 y | Colicky abdominal pain and diarrhoea | Marked distortion of colonic anatomy, haustral marking and disrupted mucosa, oedema and erosions in rectum and parts of the colon. | Widely spaced glands, lymphoplasmacytic and eosinophilic infiltration in the branched and distorted glands and crypts, crypt inflammation, regenerated gland lining with no goblet cells present. **Ulcerative colitis** |

**Legends to Figures**

Figure 1. Endoscopy of the colon demonstrating marked distortion of the anatomy; the haustral markings and mucosal pattern are disrupted with widespread mucosal oedema and erosions.

Figure 2 A-B. Photomicrograph of the colonic biopsies demonstrating widely spaced glands with intense lymphoplasmacytic and eosinophilic infiltration between the branched and distorted glands and crypts, and crypt inflammation (arrow).

Figure 2 C-D. Shows a regenerated gland lining with no goblet cells (arrow) (Figure 2C, ×400) crypt inflammation (Figure 2D, ×100).

Figure 3. (×400) shows intense lymphoplasmacytic infiltrate of the lamina propria of the mucosa and sickle erythrocytes in the microvasculature (arrow)