Successful outcome of three patients with sickle-cell disease and fat embolism syndrome treated with intensive exchange transfusion

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Key Clinical Message

Fat embolism syndrome (FES) is a rare complication of sickle-cell disease (SCD) associated with extremely high mortality rates. It affects predominantly non-SS patients and those with previously mild disease. Rapid institution of exchange transfusion with an aim to reduce HbS to very low levels as soon as FES is suspected can be life-saving.

Keywords

Bone marrow necrosis, fat embolism syndrome, parvovirus B19, sickle cell, transfusion.

Introduction

Fat embolism syndrome (FES) resulting from extensive bone marrow necrosis (BMN) is a rare but potentially underdiagnosed and probably the most devastating acute complication of sickle-cell disease (SCD). It is characterized by acute respiratory failure, neurological manifestations, thrombocytopenia, and involvement of various other organs and systems. The peripheral blood smear shows a leukoerythroblastic picture with a striking number of circulating nucleated red blood cells (NRBCs), whereas biochemical analysis shows extremely high levels of serum ferritin (SF) and lactic dehydrogenase (LDH) [1]. In the largest to date systematic review of the literature, 58 cases were identified. Only 19% of patients had sickle-cell anemia (HbSS) whereas the remainder had other genotypes, mostly HbSC and HbSβ+ that are usually associated with milder disease. In addition, lack of serious previous sickle-related complications and an overall milder phenotype were evident for the majority of cases with 33% having undiagnosed SCD until they developed FES. Mortality in the reported cases was 29, 61, and 91% for patients receiving exchange, top-up, or no transfusion, respectively. A possible association with human parvovirus B19 (HPVB19) was also identified [2]. Here, we present three consecutive cases of FES in SCD presenting over the course of 12 months treated successfully with intensive exchange transfusion. The diagnosis of FES was made according to the following published definitions: FES was defined as multi- or single organ histologically proven involvement by fat and/or necrotic marrow emboli or development of acute respiratory distress and neurological manifestations or multiorgan failure with evidence of BMN (pathological proof or laboratory evidence). BMN was defined as histologically proven (autopsy or biopsy) extensive BMN or a relevant clinicopathological picture in the context of FES; that is the rapid development of anemia and thrombocytopenia...
with a leukoerythroblastic peripheral smear with high numbers of circulating NRBCs [2].

Cases

We present here three cases of FES in SCD. All three patients provided their written consent. The first patient was a 29-year-old man with hitherto mild HbSC disease. He was known to have avascular necrosis (AVN) of the left shoulder but no other sickle-related complications and no history of hospitalization since childhood. He was admitted with lower limb pain of extreme and unusual severity and was treated with parenteral opiate analgesia and fluids. There were no obvious precipitating factors for his crisis, and he only gave a history of a “flu-like” illness while visiting Amsterdam 2 weeks before this presentation. His vital signs at presentation were stable, and his baseline hematological and biochemical investigations are summarized in Table 1. However, within the first 48 h of presentation, he deteriorated rapidly developing respiratory failure and bilateral pulmonary infiltrates on the chest radiograph. A diagnosis of acute chest syndrome (ACS) was made, and he was transferred to the intensive care unit (ICU) for noninvasive ventilation (NIV). He was commenced on broad spectrum antibacterials, and an emergency manual partial exchange transfusion was undertaken achieving a posttransfusion HbS level of 34%. A few hours later, he became suddenly comatose and required intubation. An urgent CT head was reported as normal. Antivirals were added to his treatment, and he was further exchanged to an HbS of 22%. In the following 72 h, he developed progressive pancytopenia with a leukoerythroblastic picture on the peripheral blood smear and a striking number of circulating nucleated red cells. No bacteria or viruses were detected in his blood, or cerebrospinal fluid except for HPVB19 that was detected by serology (IgM+/IgG-) and polymerase chain reaction (PCR). An MRI brain showed multiple widespread microhemorrhages consistent with cerebral fat emboli (Fig. 1), and based on the clinical, hematological, and radiological features, a unifying diagnosis of FES was made. He remained in ICU with reduced Glasgow coma scale for a month, but then started making a gradual but slow neurological recovery. He was discharged after prolonged inpatient neuro-rehabilitation, 1 year after the original admission, substantially improved, independently mobile but with some residual cognitive impairment. He was initially treated with regular automated red cell exchange transfusion (ARCET) for a year (until he declined it) but continues to take hydroxycarbamide.

The second patient, a 26-year-old man, with previously uncomplicated HbSC disease, and no previous hospital admissions presented with 24 h of severe abdominal pain.

Table 1. Evolution of hematological and biochemical parameters for patients 1, 2, and 3.

| Patient | Hb (g/L) | PLT (x10⁹/L) | Cr (umol/L) | Bili (umol/L) | ALP (u/L) | ALT (u/L) | LDH (u/L) | SF (ug/L) | N (d) |
|---------|---------|-------------|-----------|-------------|----------|---------|---------|---------|-------|
| 1 | 116 | 135 | 89 | 238 | 137 | 212 | 146 | 74 | 16 |
| 2 | 112 | 135 | 89 | 238 | 137 | 212 | 146 | 74 | 16 |
| 3 | 112 | 135 | 89 | 238 | 137 | 212 | 146 | 74 | 16 |

+ | *Cr (umol/L) | Bill (umol/L) | AIP | ALT (u/L) | LDH (u/L) | SF (ug/L) | N (d) |
|---|----------|---------|-----|---------|---------|---------|-----|
| | | | | | | | |

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that was felt to be referred pain from his lumbar spine and vomiting. He was afebrile, and his vital signs normal except for a tachycardia of 112 bpm. Chest X-ray on admission was normal. Initial laboratory investigations were unchanged from steady state except for mild renal impairment that corrected promptly with rehydration when retested 12 h later. However, the repeat test at 12 h showed new marked elevation in liver enzymes and a drop in Hb and platelets (Table 1). The peripheral blood smear showed a leukoerythroblastic picture with 42% nucleated red blood cells/100 circulating nucleated cells. 24 h later, he became pyrexial and developed acute type 1 respiratory failure. Chest radiography showed new bilateral pulmonary infiltrates. At the same time, he became drowsy but rousable and confused. He was admitted to ICU for NIV and antibiotics. Based on the multi-organ involvement and hematological picture, a diagnosis of multiorgan failure secondary to FES was made and he underwent ARCET to HbS&C of 8.9%. Bone marrow sampling was undertaken to further elucidate the diagnosis on d4 and showed necrosis on the aspirate and HPVB19 in erythroid precursors on the trephine. HPVB19-specific DNA was not detected in peripheral blood, and he was IgG+ but IgM-indicating infection weeks to months before the acute presentation. His renal function started deteriorating again on d3, and he eventually required hemofiltration (d6 Cr: 936 μmol/L). An abdominal ultrasound showed mild hepatomegaly and splenomegaly and normal color Doppler flow in both renal arteries but decreased color Doppler flow in the renal parenchyma bilaterally suggestive of decreased parenchymal perfusion. An MRI brain performed on d4 was normal; by that time, his previously altered mental status had returned to normal. After significant initial respiratory improvement, he deteriorated again suddenly on d9 with further X-ray changes, requiring intubation and mechanical ventilation, possibly resulting from a second “shower” of fat emboli. A second cycle of ARCET was undertaken to Hb S&C of 4.7%. His respiratory function started improving again and was extubated by d12 while by d17 his renal function started improving steadily. Liver enzymes normalized by d26; of interest, the ALP elevation was biphasic, with the delayed phase predominantly bone isoform, presumably arising from previous widespread bony necrosis. Over the following fortnight, he was weaned from organ support and has now made a complete recovery.

The third patient was a 40-year-old woman with HbSS and mild previous disease with very infrequent hospital visits and no evidence of other end organ damage except for severe AVN of hips and shoulders. She was admitted with a 3-day history of fever, rigors, and dysuria and few hours of severe lower back and upper and lower limb pain. On admission, her temperature was 37.8°C, her oxygen saturation (SaO2) 100% breathing room air, and her chest radiograph unremarkable. She was treated with parenteral opiate analgesia, broad spectrum antibacterials, and fluids. On d2 of admission, she deteriorated suddenly with development of type I respiratory failure with extensive bilateral infiltrates on chest radiograph, altered mental status, and pancytopenia (Table 1). The peripheral blood smear showed a leukoerythroblastic picture with 36% nucleated red cells/100 circulating nucleated cells. Given the clinical and hematological picture, a diagnosis

![Figure 1](image1.png)

**Figure 1.** T2* weighted gradient echo images through the head reveal numerous small hypointense lesions (arrows) throughout the brain due to susceptibility artifact from hemosiderin deposition. These lesions predominantly lie in the corpus callosum and periventricular and subcortical regions.

![Figure 2](image2.png)

**Figure 2.** Necrotic, faintly stained cells (arrowheads) mixed with some normal hemopoietic cells, and cellular debris (circle) on an amorphous background material (arrow).
of FES due to BMN was made. She was transferred to ICU and underwent emergency ARCET to an HbS of 6.9%. This led to significant improvement of her respiratory function and mental status, but her cytopenias as well as her liver function tests continued to deteriorate and she also developed renal impairment (creatinine 136 µmol/L). Bone marrow biopsy performed on d4 confirmed extensive bone marrow necrosis (Fig. 2). E.Coli was isolated from her blood, and urine. Testing for HPV B19 was not undertaken. Due to her deteriorating liver function, she was transferred to a specialist liver unit on d5. Without any further intervention there, her liver function gradually improved and was discharged 2 weeks after the transfer. She made a full recovery and is on no long-term treatment.

Discussion

FES is a rare and devastating complication of SCD. It is mostly associated with nonhomozygous SCD and disease of a previously milder clinical phenotype. Several hypotheses have been put forward to explain this association including the higher hematocrit in HbSC compared to HbSS patients and the resulting higher blood viscosity [3] and HPV B19 induced endothelitis resulting in increased vascular adhesion and infarction in patients with high baseline hemoglobin [4] whereas we have previously suggested an immune-mediated mechanism in these patients who unlike HbSS patients may retain some splenic function [2].

FES is potentially underdiagnosed: Its association with milder forms of SCD may lead to late diagnosis or under-recognition. Several reports have previously identified rates of unexplained or “sudden” death as high as 40% occurring in relatively healthy patients during a painful crisis [5–7] while an autopsy study showed that pulmonary fat emboli were present in one-third of cases of “sudden death” in SCD [8]. Moreover, some cases of “multiorgan failure syndrome” a well-recognized but poorly understood in its pathophysiology entity also affecting previously well patients presenting with a seemingly uncomplicated painful crisis and deteriorating rapidly [9] may indeed represent cases of FES.

Given the respiratory and neurological manifestations, the syndrome can be mistaken for isolated ACS or stroke whereas the combination of fever, neurological manifestations, and thrombocytopenia may suggest a diagnosis of thrombotic thrombocytopenic purpura [10] or even acute leukemia if the cytopenias are severe. Examination of the peripheral blood smear is essential, and our current practice is to also obtain a bone marrow sample.

Despite the rarity of the syndrome, three cases presented within 1 year; such experience has previously been reported where three patients with FES were identified and treated in a single institution within a seven-month period [10]. Such skewing of cases may reflect heightened physicians’ awareness after treating a case but may also be related to periodic epidemics of viruses such as HPVB19 that has been reported to be associated with FES [11, 12].

Two of the three patients we present had HbSC disease, and all three had a previous mild course of their illness. Their presentation highlights the importance of being highly vigilant when previously well patients present with unusually severe crises and their outcome illustrates the importance of prompt recognition of FES, adequate supportive care, and easy access to ICU and more importantly, the potential success of early intensive exchange transfusion targeting marked reduction in HbS levels. Given the relative safety of the procedure in the context of a life-threatening illness and its fulminant course, our policy is to institute ARCET as soon as FES is suspected. Despite rapid deterioration, multiple organ impairment and requirement for intensive care support, all patients survived, two without any residual deficit.

Conflict of Interest

The authors have no conflict of interest to disclose.

Authorship

PG designed the project and wrote the paper; VM collected data and coauthored the paper; CP, SR, and RJA critically reviewed the paper; and DAT designed the project, critically reviewed, and revised the paper.

References

1. Paydas, S., M. Ergin, F. Baslamisli, S. Yavuz, S. Zorludemir, B. Sahin, et al. 2002. Bone marrow necrosis: clinicopathologic analysis of 20 cases and review of the literature. Am. J. Hematol. 70:300–305.
2. Tsitsikas, D. A., G. Gallinella, S. Patel, H. Seligman, P. Greaves, and R. J. Amos. 2014. Bone marrow necrosis and fat embolism syndrome in sickle cell disease: increased susceptibility of patients with non-SS genotypes and a possible association with human parvovirus B19 infection. Blood Rev. 28:23–30.
3. Castro, O. 1996. Systemic fat embolism and pulmonary hypertension in sickle cell disease. Hematol. Oncol. Clin. North Am. 10:1289–1303.
4. Lowenthal, E. A., A. Wells, P. D. Emanuel, R. Player, and J. T. Prchal. 1996. Sickle cell acute chest syndrome associated with parvovirus B19 infection: case series and review. Am. J. Hematol. 51:207–213.
5. Manci, E. A., D. E. Culberson, Y. M. Yang, T. M. Gardner, R. Powell, J. Haynes Jr, et al. 2003. Causes of death in sickle cell disease: an autopsy study. Br. J. Haematol. 123:359–365.

6. Darbari, D. S., P. Kple-Faget, J. Kwagyan, S. Rana, V. R. Gordeuk, and O. Castro. 2006. Circumstances of death in adult sickle cell disease patients. Am. J. Hematol. 81:858–863.

7. Platt, O. S., D. J. Brambilla, W. F. Rosse, P. F. Milner, O. Castro, and M. H. Steinberg, et al. 1994. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N. Engl. J. Med. 330:1639–1644.

8. Graham, J. K., M. Mosunjac, R. L. Hanzlick, and M. Mosunjac. 2007. Sickle cell lung disease and sudden death: a retrospective/prospective study of 21 autopsy cases and literature review. Am. J. Forensic Med. Pathol. 28:168–172.

9. Hassell, K. L., J. R. Eckman, and P. A. Lane. 1994. Acute multiorgan failure syndrome: a potentially catastrophic complication of severe sickle cell pain episodes. Am. J. Med. 96:155–162.

10. Adamski, J., C. A. Hanna, V. B. Reddy, S. H. Litovsky, C. A. Evans, and M. B. Marques. 2012. Multiorgan failure and bone marrow necrosis in three adults with sickle cell-β+ -thalassemia. Am. J. Hematol. 87:621–624.

11. Eichhorn, R. F., E. J. Buurke, P. Blok, M. J. Berends, and C. L. Jansen. 1999. Sickle cell-like crisis and bone marrow necrosis associated with parvovirus B19 infection and heterozygosity for haemoglobins S and E. J. Intern. Med. 245:103–106.

12. Kolquist, K. A., C. L. Vnenck-Jones, L. Swift, D. L. Page, J. E. Johnson, and M. R. Denison. 1996. Fatal fat embolism syndrome in a child with undiagnosed hemoglobin S/beta+ thalassemia: a complication of acute parvovirus B19 infection. Pediatr. Pathol. Lab. Med. 16:71–82.