

Non-Traumatic Fat Embolism Syndrome in Two HbSS Sickle Cell Disease Patients: A Case Series and Review

Mohammed Amouri Alzayer¹, Salah Abohelaika^{2,3}, Mousa Alhaddad⁴, Mazen Al Zayer⁵, Ahmed J Alali⁶, Abdullah Mohammad Al Abbas¹, Nabeel J Al Eid¹, Fatimah A Al Saeed¹, Hussain H Al Saeed¹

¹Hematology and Inherited Blood Disorders Center, Prince Mohammed bin Fahad Hospital of Inherited Blood Disorders, Qatif, 32654, Saudi Arabia; ²Research Department, Qatif Central Hospital, Qatif, 32654, Saudi Arabia; ³Pharmacy Department, Qatif Central Hospital, Qatif, 32654, Saudi Arabia; ⁴Adult Hematology and Stem Cell Transplantation Department, King Fahad Specialist Hospital, Dammam, 32253, Saudi Arabia; ⁵Adult Intensive Care Department, Qatif Central Hospital, Qatif, 32654, Saudi Arabia; ⁶Adult Intensive Care Department, Prince Mohammed bin Fahad Hospital of Inherited Blood Disorders, Qatif, 32654, Saudi Arabia

Correspondence: Mohammed Amouri Alzayer, Hematology and Inherited Blood Disorders Center, Prince Mohammed bin Fahad Hospital of Inherited Blood Disorders, Qatif, 32654, Saudi Arabia, Email Moaalzayer@moh.gov.sa; Salah Abohelaika, Research Department, Qatif Central Hospital, Qatif, 32654, Saudi Arabia, Email abohelaika@moh.gov.sa

Abstract: Non-traumatic fat embolism syndrome (FES) in sickle cell disease (SCD) is associated with high morbidity and mortality. This severe complication arises from bone marrow necrosis, which subsequently can lead to fat embolism syndrome and multi-organ failure. A key challenge in diagnosing and managing this syndrome lies in the absence of established diagnostic criteria and the variability of its clinical presentation. Instant red cell exchange transfusion could be lifesaving once the syndrome is suspected, and the use of therapeutic plasma exchange, as suggested in the literature, can improve outcomes. Here, we report two cases of SCD with FES that were managed successfully with blood transfusion and plasma exchange. Both of them rapidly deteriorated and required intensive care unit admission, where they received red cell exchange followed by plasma exchange. They both made a good recovery and were discharged from the hospital within two weeks.

Keywords: sickle cell disease, bone marrow necrosis, fat embolism syndrome, multiorgan failure, blood transfusion, plasma exchange

Introduction

One of the major and serious complications of sickle cell disease (SCD) is fat embolism syndrome (FES) which presents a diagnostic challenge due to its variable clinical manifestations, which can make the application of consensus criteria difficult.¹ Given the variability in clinical presentation and the frequent underrecognition of the syndrome, as well as the fact that fat embolism is sometimes confirmed during autopsy,^{2,3} a high level of clinical suspicion is essential. The first case of FES in SCD was reported in 1941 in a woman with SCD who deteriorated rapidly and died,⁴ and since then more other cases have been reported^{5–9} including some from Saudi Arabia.^{10,11} With current best practice, the mortality rate has been decreased from 66% to 33%.¹ Notably, patients with HbSS disease account for only 15% of all FES reported cases, while those with HbSC constitute around 75%.¹

In SCD, vaso-occlusion crises (VOC) in the bone marrow can lead to bone marrow necrosis. This process can result in the release of fat globules from the necrotic marrow into the circulation. It has been shown that the release of secretory phospholipase A2 (sPLA₂) levels is higher in SCD patients with VOC and acute chest syndrome (ACS).¹² sPLA₂ affects the metabolism of circulating phospholipids to arachidonic acid which leads to the formation of inflammatory cytokines. The release of these fat globules in VOC from the necrotic marrow could embolise the lung and other organs,¹³ whereas large amounts of fat droplets could be released in the circulation when bone marrow necrosis (BMN) is extensive which

could end up in multiorgan failure.¹⁴ The detrimental impact of fat embolism is the outcome of both mechanical obstruction by sickled cells, thrombogenicity and tissue toxicity via the cytokines inflammatory process.^{1,12,15,16}

Here, we present two cases of FES that were managed successfully through blood exchange and plasma exchange. The most commonly shared clinical and laboratory findings in patients with FES are discussed, while also emphasizing the timing of clinical deterioration and identifying the critical window for initiating plasma exchange which can significantly improve patient outcomes.

Case Presentation I

A 14-year-old Saudi boy with SCD (HbSS) who was non-compliant with hydroxyurea treatment presented to the emergency department at Prince Mohammed Bin Fahad Hospital of Inherited Blood Disorders (PMFH) in Eastern Province, Saudi Arabia with severe low back pain that did not improve with analgesia. His steady state Hb electrophoresis was HbS=75.8%, HbF 21.7%, and HbA2=2.5%. His past medical history was frequent admissions due to acute chest syndrome (ACS) that required intensive care unit (ICU) admission and exchange blood transfusion. No other complaints were found including fever, shortness of breath or neurological symptoms. On examination, he was vitally stable apart from tachycardia (110–120 beats per minute). Severe tenderness in both pelvic bones without signs of inflammation was reported.

Due to his unstable condition, the patient was immediately shifted to the ICU for pain management and close monitoring. He received multiple parenteral morphine doses, and then was placed on a fentanyl infusion with prophylactic enoxaparin. On day 2 of admission, he developed respiratory distress characterized by chest pain and shortness of breath, requiring 2 L/minute of supplemental oxygen. A chest radiograph showed no infiltration. A CT pulmonary angiogram confirmed the presence of a pulmonary embolism (PE) along with evidence of acute chest syndrome which was not detected by the initial chest X-ray. There was central filling defect noted within the posterior basal segment of the right lower lobe, denoting embolism and bi-basal air space opacities were noted with adjacent mild pleural effusion. The patient was placed on a therapeutic enoxaparin dose combined with antibiotics. The laboratory tests revealed a further drop in his Hb level with high lactate dehydrogenase (LDH) and creatine kinase (CK) along with a low reticulocytes index. The laboratory results are summarized in [Table 1](#).

As the patient was clinically deteriorating with evidence of multi-organs involvement in the form of respiratory, and muscle injuries, and in the context of bone marrow necrosis which was evident by high LDH, low reticulocyte and coagulopathy, the patient was presumed to have FES. An immediate automated red blood cell (RBC) exchange transfusion was initiated with three units of packed RBCs followed by one session of plasma exchange. For plasma exchange, it was performed using six units of fresh frozen plasma (FFP) along with another six units of 5% human albumin. The patient dramatically improved on days 3 and 4. His HbS level was 75.8% at steady state, and 38% post-exchange transfusion. He was discharged on day 9 in good condition after a period of observation.

Case Presentation 2

A 27-year-old Saudi male patient with SCD (HbSS) disease presented to the emergency department at PMFH with generalized body pain, mainly in his back. His steady state Hb electrophoresis was HbS=89.3%, HbF 7.2%, and HbA2=3.5%. He was on hydroxyurea, but with poor compliance. Although he had infrequent admissions, he had a severe SCD course, including a history of ICU admission for ACS, which required exchange blood transfusions.

His vital signs were notable for tachycardia of 140 beats per minute with an unremarkable general examination. His initial and subsequent laboratory findings are summarized in [Table 2](#). The patient's pain did not improve with parenteral morphine. Due to his unstable status, he was transferred to the ICU, and a fentanyl infusion was initiated. As his initial reticulocyte index on day 1 was suppressed with a presumed diagnosis of bone marrow necrosis, the patient received two units of simple packed RBC transfusion followed by 3 units of automated RBC exchange transfusion. His HbS level at his steady state, post-simple blood transfusion, and post-automated exchange transfusion was 89%, 52%, and 26%, respectively. Subsequently, he received on day 2 a plasma exchange session using 8 units of plasma protein fraction (PPF) (Human Plasma Protein Solution Octapharma 5%, Austria) and 8 units of FFP.

However, the patient continued to deteriorate, developing respiratory distress that required increasing the rate of supplemental oxygen. Despite increasing oxygen supplement, he continued to be hypoxic with oxygen saturation reaching down to

Table 1 Laboratory Results of the First Case

Lab Test	Normal Range	Day 0 (Admission)	Day 1	Day 2 (RCE and TPE)	Day 3	Day 9 (Discharge)
White Blood Cells (WBCs) [$\times 10^3/\mu\text{L}$]	4–10	4.4	5.8	6.3	6.9	6.3
Neutrophils [$\times 10^3/\mu\text{L}$]	2–7.5	3.8	4.7	5	5.1	3.5
Lymphocytes [$\times 10^3/\mu\text{L}$]	1.5–4	0.2	0.5	0.6	0.9	1.8
Hemoglobin [g/dL]	11.5–15.5	11.5	10	8.5	9.2	9.2
Platelets [$\times 10^9/\text{L}$]	150–450	162	148	152	204	459
Reticulocytes [%]	0.5–3	4.6	–	3.57	4.46	6.48
Total Bilirubin [mg/dl]	0–1	51	62	76	39	16
Direct Bilirubin [mg/dl]	0–0.2	26	34	26	22	8
Alkaline Phosphatase (ALP) [U/L]	50–137	241	432	358	322	246
Aspartate Transaminase (AST) [U/L]	15–60	80	49	51	27	29
Alanine transaminase (ALT) [U/L]	0–50	20	17	16	12	18
Gamma Glutamyl Transferase (GGT) [U/L]	5–85	25	30	27	15	14
C-Reactive Protein (CRP) [mg/dl]	0–0.99	27.30	–	–	–	–
Ferritin [$\mu\text{g/L}$]	30–322	> 1650	–	–	–	–
Creatine Kinase (CK) [U/L]	39–308	58	49	617	540	23
Lactic Dehydrogenase (LDH) [U/L]	81–230	621	1323	1774	590	434
Prothrombin Time (PT) [sec]	11.5–15.5	21.7	19.1	17	15.7	14.2
Prothrombin thrombin Time (PTT) [sec]	26.4–36	34.3	37.3	35.2	34	30.9
INR	0.85–1.15	1.67	1.45	1.19	1.28	1.05
Serum Creatinine [$\mu\text{mol/L}$]	53–114	28.5	41	37	28	32
eGFR mL/min/1.73m ²	> 90	372	245.1	275.9	380.6	326.3

Abbreviation: RCE=Red Cell Exchange, TPE=Therapeutic Plasma Exchange.

Table 2 Laboratory Results of the second Case

Characteristic	Normal Range	Day 0 A	Day 1 RCE	Day 2 TPE/I	Day 3 TPE	Day 4 TPE	Day 5	Day 6	Day 7 E	Day 8	Day 13 D
White Blood Cells (WBCs) [$\times 10^3/\mu\text{L}$]	4–10	16.8	14.5	14.5	12.5	13.2	12.	10	10	10.4	11
Neutrophils [$\times 10^3/\mu\text{L}$]	2–7.5	7.6	7.8	12.7	9.8	11.2	11.1	8.1	6.6	7.2	6.6
Lymphocytes [$\times 10^3/\mu\text{L}$]	1.5–4	8	5.5	0.7	2	0.9	1.3	1.4	2.9	2.9	3.5
Hemoglobin [g/dL]	11.5–15.5	7.7	6.7	9.9	7.5	8.4	7.5	7.7	7.7	8.1	6.9
Platelets [$\times 10^9/\text{L}$]	150–450	107	95	10	36	19	23	111	68	42	220
Reticulocytes [%]	0.5–3	7.05	2.32	1.63	–	–	6.94	7.9	8.11	–	18.06
Total Bilirubin [mg/dl]	0–1	92	126	248	–	93	89	64	63	97	41

(Continued)

Table 2 (Continued).

Characteristic	Normal Range	Day 0 A	Day 1 RCE	Day 2 TPE/I	Day 3 TPE	Day 4 TPE	Day 5	Day 6	Day 7 E	Day 8	Day 13 D
Direct Bilirubin [mg/dl]	0–0.2	27	44	142	–	48	36	29	35	49	20
Alkaline Phosphatase (ALP) [U/L]	50–137	91	414	495	–	251	254	258	223	279	204
Aspartate Transaminase (AST) [U/L]	15–60	77	302	227	–	139	122	87	68	85	59
Alanine transaminase (ALT) [U/L]	0–50	43	68	40	43	54	57	53	76	61	56
Gamma Glutamyl Transferase (GGT) [U/L]	5–85	79	65	91	99	160	191	173	188	194	190
C-Reactive Protein (CRP) [mg/dl]	0–0.99	–	9.98	–	–	–	–	–	–	–	–
Ferritin [ug/L]	30–322	–	> 3300	–	–	–	–	–	1193	–	–
Creatine Kinase (CK) [U/L]	39–308	54	157	1160	1262	540	985	489	259	299	59
Lactic Dehydrogenase (LDH) [U/L]	81–230	461	3415	3737	4443	2300	2276	2204	2141	1778	1602
Prothrombin Time (PT) [sec]	11.5–15.5	18.7	18	19.9	21	17.8	15.4	14.6	14.1	14.4	14.6
Prothrombin thrombin Time (PTT) [sec]	26.4–36	88	65	67	63	47	47	51	46	40	35
INR	0.85–1.15	1.65	1.59	1.8	1.9	1.53	1.6	1.52	1.37	1.25	1.29
Serum Creatinine [umol/L]	53–114	61	87	120	125	99	73	69	61	56	59
eGFR mL/min/1.73m ²	> 90	136.5	90.6	62.5	59.7	78.1	111	118.4	136.5	150.7	141.9

Abbreviations: A, Admission; E, Extubation; D, Discharge; I, Intubation; RCE, Red Cell Exchange; TPE, Therapeutic Plasma Exchange.

approximately 80% for which he was put on High Flow Nasal Cannula (HFNC) with high settings FiO₂ 85% / flow rate 60 LPM. A trial of Bi-level Positive Airway Pressure (BiPAP) was attempted as bedside lung ultrasound showed congested lungs with multiple B-lines and collapsed inferior vena cava, but the patient could not tolerate it as he started having large amounts of productive cough. Eventually, he was intubated on high ventilatory settings due to persistent hypoxia, respiratory distress and decreased level of consciousness on day 2. His blood pressure was elevated, and his chest radiograph showed bilateral infiltrations which were assessed initially to be possibly pulmonary edema from transfusion-associated circulatory overload (TACO). This was later assessed to be unlikely as the inferior vena cava collapsibility assessment was not suggestive of volume overload. The respiratory distress was deemed to be a part of a multi-organs failure that included hepatic, renal, muscle injuries along with coagulopathy with a final assessment of FES. Therefore, the patient continued to receive sequencing sessions of plasma exchange on days 3 and 4. After the third plasma session on day 4, the patient started to improve. The FiO₂ decreased gradually down to 30%, and he was eventually extubated on day 7 after fulfilling the extubation criteria. Although he continued to require some blood product support including packed RBCs, FFP and platelet transfusions following the plasma exchange, his abnormal laboratory results returned gradually to their baseline levels. Eventually, he was discharged in good condition on day 13.

Discussion

The exact incidence of FES in SCD patients is unknown with many cases occurring worldwide, but only a few have been reported. There are some common clinical and laboratory findings typically associated with FES that can aid in its diagnosis. Early recognition of these findings can improve outcomes by allowing prompt management. However, there are no clear and solid criteria to conform to the syndrome at the premortem level.

It is important to note that many of the FES occurrences were reported on those with double heterozygous state (HbSC) mild disease,^{1,5,7–9} and they tend to have poorer clinical outcomes. This infers HbSC might predominate in those geographical areas from which these reports came compared to other SCD genotypes. Among the Saudi population, HbSS is the most prevalent SCD genotype.¹⁷ Both of the two cases had HbSS severe disease course with a history of

ACS events and ICU admissions. They both presented with severe intractable pain (mainly in the back) that did not improve with aggressive parenteral morphine. Upon ICU transfer, a fentanyl infusion was promptly started, however, the two patients barely responded. Therefore, clinicians should have a very low threshold of suspicion of BMN and FES when SCD patients present with intractable pains with multiorgan involvement and start to deteriorate especially in those with infrequent hospitalizations and benign SCD courses.

Both patients clinically deteriorated within 48 hours of their presentation. In addition, both had respiratory symptoms, but they differed in the mechanisms of pulmonary involvement. The first patient had segmental PE which could possibly be a fat embolism, and he only required supplemental oxygen via a nasal cannula. In contrast, the second patient experienced more severe respiratory distress, requiring intubation. Pulmonary involvement in FES is very common and it is shared in almost all cases of FES.^{1,5,6}

We noticed that both patients initially had stable Hb levels with high LDH and low reticulocyte indices. Subsequently, on the following day of their presentations, both patients experienced a significant drop in Hb levels, with increasing LDH levels and a reduction in platelet count by almost 50% from baseline.^{1,5,6} Furthermore, one notable shared laboratory finding is the significant elevation in ferritin levels up to 100-fold in some cases,¹ whereas the ferritin increase in our two cases was up to 10-fold. This was accompanied by high CK levels. Parvovirus B19, which is well-known to trigger BMN in SCD patients and subsequently FES,^{1,5,7} was negative in both patients.

Both patients developed a fever 24 hours after presentation. Their C-reactive protein (CRP) levels were elevated, and blood cultures were negative, suggesting that the fever was likely related to cytokines and inflammatory processes rather than infection. Overall, both patients shared multiorgan damage with pulmonary and muscular involvement. In addition, the second patient had hepatic and renal injuries. Importantly, neither of the two patients experienced any clear symptoms of neurological involvement, nor a petechial rash was observed.

As there is no consensus on the criteria to define the syndrome in sickle cell disease, this case series highlights the importance of establishing clear diagnostic criteria. The traumatic FES is often results from large fat content with subsequent cytokines surge while the sickle cell bone marrow necrosis results in a microscopic and often soluble fat globule. The fibrosis of the blood alveolar membrane (BAM) in some sickle cell patients, resulting from previous subclinical or clinical acute chest syndrome (often leading to pulmonary hypertension), may serve as a protective factor. This fibrosis can impede the passage of fat through the BAM, potentially reducing the likelihood of fat emboli reaching the brain.

A septic workup is routinely performed in these cases. Blood cultures were negative in both cases. Each case presented with respiratory symptoms; however, the mechanisms underlying their pulmonary involvement differed. FES is considered as one of the etiologies underlying acute chest syndrome. While acute chest syndrome typically presents with pulmonary clinical features, FES is distinguished by its involvement of other organs, such as muscle, liver, kidney, and sometime the brain.

From our experience and what has been described in the literature, timely intervention is crucial to overcome the consequences and expected organ damage in FES. Prompt clinical judgement rather than waiting for adjuvant lab results may be lifesaving. Instead, the patients should immediately receive blood support through exchange transfusion immediately whenever FES is suspected.^{1,7,8} Delaying exchange transfusion significantly increases morbidity and mortality.⁷ It has been shown that blood exchange is preferred over simple packed RBC transfusion or no transfusion. The reported mortality rates for these three modes were 23%, 59%, and 92%, respectively.^{1,5,18}

In addition to its ability to lower the HbS to less than 30%, exchange transfusion carries other advantages over simple transfusion as it can remove white blood cells, cytokines, fat globules and platelets that potentially could reduce inflammation and hyperviscosity.^{19,20} However, it has a limited impact on reducing inflammatory cytokines and removing fat molecules.^{1,20} Therefore, FES patients might benefit from plasma exchange following RBC exchange.^{1,18,21–23} Based on local experience of many treated FES patients who were discharged in good condition, it might be preferred to proceed with plasma exchange using FFP as 50% of the required amounts with the remaining equivalent volume of 5% albumin or PPF.^{24,25} The aim of this is to minimize the risk of transfusion-related complications, such as acute lung injury (TRALI), a known complication of FFP use,²³ acute immune hemolytic reaction, blood-borne infections, and others.

SCD patients are prone to infectious complications which might be indistinguishable from FES since both share similar clinical manifestations (eg, fever and respiratory symptoms) and laboratory findings (eg, thrombocytopenia, coagulopathy and

elevated inflammatory markers). Therefore, it is crucial to initiate a broad spectrum antibiotic along with FES-directed interventions. The two presented patients were treated with piperacillin-tazobactam.

In cases of FES related to Parvovirus B19 infection, intravenous immunoglobulins might be helpful.^{26–28} However, it remains questionable whether to administer IVIG empirically when viral studies are not expected to be timely available. Relatedly, hydroxyurea use was shown to be protective against Parvovirus B19 infections,^{28,29} and it is not clear from the literature if this protective effect can offer preventative advantages in complaint SCD patients with hydroxyurea from developing FES. This can be rationalized by the positive impact of hydroxyurea on reducing bone marrow activity which is a precursor to Parvovirus B19 propagation.³⁰

Conclusion

FES in SCD patients is life-threatening complication. Early identification and management through RBC exchange transfusion and plasma exchange could be crucial to improve its outcomes. Fibrosis of the blood alveolar membrane in some sickle cell patients may reduce cerebral fat embolism risk by limiting fat passage, especially with the previous acute chest syndrome and hence no neurological symptoms involved. Future studies are required to standardize the diagnostic criteria and optimize the management approach for SCD patients presenting with BMN and FES.

Consent and Ethics Statement

The two patients have provided consent (by the parent of the 14-year-boy and for other patient by himself) for publication of this case report. The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Qatif Central Hospital, Eastern Province, Saudi Arabia (QCH-SREC057/2024, approved on 29 December 2024) for publication.

Acknowledgments

A special thanks goes out to all the medical staff from different specialties who were involved in the patients' care and management.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Tsitsikas DA, Vize J, Abukar J. Fat embolism syndrome in sickle cell disease. *J Clin Med*. 2020;9(11):3601. doi:10.3390/jcm9113601
2. Shrestha R, Gloth MK, Burke A, Shah NG. Fat embolism syndrome in sickle cell disease: from crisis to catastrophe. In: *A57. Critical Care Case Reports: Cardiovascular Disease II*. 2017:A1991–A1991.
3. Loupy A, Laissy JP, Klein I, et al. Fat emboli unleashed: an exceptional etiology of encephalitis in sickle cell disease. *Ann Hematol*. 2008;87(11):939–941. doi:10.1007/s00277-008-0491-y
4. Wade LJ, Stevenson LD. Necrosis of the bone marrow with fat embolism in sickle cell anemia. *Am J Pathol*. 1941;17(1):47–54.
5. Tsitsikas DA, Gallinella G, Patel S, Seligman H, Greaves P, Amos RJ. 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*. 2014;28(1):23–30. doi:10.1016/j.blre.2013.12.002
6. Gendreau S, Scholer M, Cecchini J, et al. Cerebral fat embolism in sickle cell disease. *Am J Hematol*. 2020;95(2):E41–E45. doi:10.1002/ajh.25686
7. Tsitsikas DA, May JE, Gangaraju R, Abukar J, Amos RJ, Marques MB. Revisiting fat embolism in sickle syndromes: diagnostic and emergency therapeutic measures. *Br J Haematol*. 2019;186(4):e112–e115. doi:10.1111/bjh.15941
8. Dang NC, Johnson C, Eslami-Farsani M, Haywood LJ. Bone marrow embolism in sickle cell disease: a review. *Am J Hematol*. 2005;79(1):61–67. doi:10.1002/ajh.20348
9. Rizvi S, Khakwani M, Pancham S, et al. Bone marrow necrosis and fat embolism syndrome in sickle cell disease during COVID-19 infection treated successfully with sequential red cell and plasma exchange. *EJHaem*. 2022;4(1):207–210. doi:10.1002/jha2.621
10. Almatar AM, Kawther K. Fat embolism in sickle-cell disease: a case report with literature review. *Caspian J Intern Med*. 2023;14(1):143–146. doi:10.22088/cjim.14.1.143
11. Alsaghir A, Alsaghir L, Alsaif J, Mobeireek A. Successful therapeutic plasma exchange for a patient with sickle cell disease and fat embolism syndrome after a failure of a response to red cell exchange transfusion. *Transfusion*. 2023;63(Suppl 1):S33–s36. doi:10.1111/trf.17220
12. Styles LA, Schalkwijk CG, Aarsman AJ, Vichinsky EP, Lubin BH, Kuypers FA. Phospholipase A2 levels in acute chest syndrome of sickle cell disease. *Blood*. 1996;87(6):2573–2578. doi:10.1182/blood.V87.6.2573.bloodjournal8762573
13. Vichinsky E, Williams R, Das M, et al. Pulmonary fat embolism: a distinct cause of severe acute chest syndrome in sickle cell anemia. *Blood*. 1994;83(11):3107–3112. doi:10.1182/blood.V83.11.3107.3107

14. Ataga KI, Orringer EP. Bone marrow necrosis in sickle cell disease: a description of three cases and a review of the literature. *Am J Med Sci.* 2000;320(5):342–347. doi:10.1097/00000441-200011000-00009
15. Almusalily RM. Early recognition of pulmonary complications of sickle cell disease. *Saudi Med J.* 2023;44(1):10–18. doi:10.15537/smj.2023.44.1.20220636
16. Targueta EP, Hirano ACG, de Campos FPF, Martinez J, Lovisolo SM, Felipe-Silva A. Bone marrow necrosis and fat embolism syndrome: a dreadful complication of hemoglobin sickle cell disease. *Autops Case Rep.* 2017;7(4):42–50. doi:10.4322/acr.2017.043
17. Al-Ali AK, Alsulaiman A, Alzahrani AJ, et al. Prevalence and diversity of haplotypes of sickle cell disease in the Eastern Province of Saudi Arabia. *Hemoglobin.* 2020;44(2):78–81. doi:10.1080/03630269.2020.1739068
18. Connelly-Smith L, Alquist CR, Aqui NA, et al. Guidelines on the use of therapeutic apheresis in clinical practice - evidence-based approach from the writing committee of the American Society for apheresis: the ninth special issue. *J Clin Apher.* 2023;38(2):77–278. doi:10.1002/jca.22043
19. Swerdlow PS. Red cell exchange in sickle cell disease. *Hematology.* 2006;2006(1):48–53. doi:10.1182/asheducation-2006.1.48
20. Liem RI, O’Gorman MR, Brown DL. Effect of red cell exchange transfusion on plasma levels of inflammatory mediators in sickle cell patients with acute chest syndrome. *Am J Hematol.* 2004;76(1):19–25. doi:10.1002/ajh.20054
21. Tsitsikas DA, Rowe S, Bosch A, et al. 5607225 Addition of therapeutic plasma exchange to red cell exchange improves outcomes of fat embolism syndrome in sickle cell disease. *HemaSphere.* 2023;7(S1):44–45. doi:10.1097/01.HS9.0000928476.36016.9a
22. Webb CB, Yates SG, Sarode R, Kim J. Plasma exchange-A useful adjunct therapy to red cell exchange in patients with sickle cell disease and multiorgan dysfunction. *Transfusion.* 2023;63(7):1384–1390. doi:10.1111/trf.17448
23. Zaidi GZ, Rosentsveyg JA, Fomani KF, Louie JP, Koenig SJ. Reversal of severe multiorgan failure associated with sickle cell crisis using plasma exchange: a case series. *J Intensive Care Med.* 2020;35(2):140–148. doi:10.1177/0885066619874041
24. O’Brien KL, Price TH, Howell C, Delaney M. The use of 50% albumin/plasma replacement fluid in therapeutic plasma exchange for thrombotic thrombocytopenic purpura. *J Clin Apher.* 2013;28(6):416–421. doi:10.1002/jca.21288
25. Louie J, Boctor F, Chiang J, Anwar Z, Wittenberg A, Gogas E. Efficacy of 5% Albumin and Fresh Frozen Plasma (AFFP) Versus Fresh Frozen Plasma (FFP) only as replacement fluid in plasma exchange for Thrombotic Thrombocytopenic Purpura (TTP). *Blood.* 2012;120(21):272. doi:10.1182/blood.V120.21.272.272
26. Modrof J, Berting A, Tille B, et al. Neutralization of human parvovirus B19 by plasma and intravenous immunoglobulins. *Transfusion.* 2008;48(1):178–186. doi:10.1111/j.1537-2995.2007.01503.x
27. Crabol Y, Terrier B, Rozenberg F, et al. Intravenous immunoglobulin therapy for pure red cell aplasia related to human parvovirus b19 infection: a retrospective study of 10 patients and review of the literature. *Clin Infect Dis.* 2013;56(7):968–977. doi:10.1093/cid/cis1046
28. Manaresi E, Gallinella G. Advances in the development of antiviral strategies against Parvovirus B19. *Viruses.* 2019;11(7):659. doi:10.3390/v11070659
29. Hankins JS, Penkert RR, Lavoie P, Tang L, Sun Y, Hurwitz JL. Original research: Parvovirus B19 infection in children with sickle cell disease in the hydroxyurea era. *Exp Biol Med.* 2016;241(7):749–754. doi:10.1177/1535370216636723
30. Brown KE, Young NS. Parvoviruses and bone marrow failure. *Stem Cells.* 1996;14(2):151–163. doi:10.1002/stem.140151

Journal of Blood Medicine

Publish your work in this journal

The Journal of Blood Medicine is an international, peer-reviewed, open access, online journal publishing laboratory, experimental and clinical aspects of all aspect pertaining to blood based medicine including but not limited to: Transfusion Medicine; Blood collection, Donor issues, Transmittable diseases, and Blood banking logistics; Immunohematology; Artificial and alternative blood based therapeutics; Hematology; Biotechnology/nanotechnology of blood related medicine; Legal aspects of blood medicine; Historical perspectives. The manuscript management system is completely online and includes a very quick and fair peer-review system. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <http://www.dovepress.com/journal-of-blood-medicine-journal>

Dovepress
Taylor & Francis Group