BACKGROUND

Nontraumatic fat embolism syndrome (ntFES) is an under-recognized yet well-known complication of bone marrow infarction/necrosis (BMN) occurring in patients with sickle cell disease (SCD) with an estimated incidence of 0.3%-37%. Classic triad includes respiratory failure, neurological deficits, and a petechial rash. Fat embolism syndrome (FES) remains a clinical diagnosis. Its nonspecific manifestations require a heightened index of suspicion. Prompt recognition and treatment are vital to reduce mortality and limit disability.

OBJECTIVE

To report a case of ntFES manifested by multisystem organ failure in an elderly patient who attained neurologic recovery.
injury, bicytopenia, transaminitis, and lactic acidosis. She would later become febrile (up to 39.6°C), tachycardic, tachypneic, hypoxic, and hypertensive. Her symptoms progressed to unresponsiveness, respiratory distress, Cheyne-Stokes breathing, and eventually respiratory failure requiring urgent intubation. Initial head tomography and angiography were unrevealing. Chest imaging revealed small scattered focal infiltrates, mild pulmonary edema, and small-volume bilateral pleural effusions. She was started on broad-spectrum antibiotics for a presumed infection. Brain MRI showed extensive multiple microhemorrhages across the neuroparenchyma in a “starfield” pattern classic for cerebral FES (see Figure 1).

The combination of mental status changes, given MRI findings above, scattered pulmonary infiltrates on chest imaging, and leukoerythroblastic picture observed on peripheral smear, in a patient with HbSC disease, strongly supported the diagnosis of ntFES. The patient was transferred for urgent treatment via red blood cell exchange. Additional supportive measures were administered to limit the extent of morbidity including oxygenation/ventilation, volume resuscitation (with crystalloid and albumin—theoretically binds free fatty acids, FFAs, which are implicated in the pathophysiology of FES), blood products, and nutrition.2

Twenty-four hours after exchange transfusion, her GCS was 3/10T. She slowly and erratically recovered to GCS of 10/10T in 14 days. However, she remained profoundly parietic and required ventilation and assisted feeding via tracheostomy and gastrostomy, respectively. She was discharged to a specialty long-term acute care hospital (LTAC) after 18 days of treatment in the ICU. She remained in LTAC for an additional 45 days, and significant improvements were noted across all cognitive domains. She was weaned from the ventilator and decannulated on day 60. She was transferred to an acute rehabilitation facility (ARF) on day 66. Following treatment, she exhibited 4+/5 strength in all extremities, fluent speech, and ADL independence. She was discharged home 90 days following her initial presentation with ntFES.

4 | DISCUSSION

There exists a limited number of reports of cerebral FES in the setting of underlying SCD within the medical literature.3,4 Reports of successful treatment of cerebral FES in SCD are even rarer.3,5 This is an important clinical entity for healthcare personnel to recognize as (a) it can easily be misdiagnosed as other mimicking pathologies such as sepsis, vasculitis, hypoxic-ischemic encephalopathy, acute hemorrhagic leukoencephalitis, or thrombotic microangiopathies,6,7 and (b) early intervention reduces morbidity and mortality.

The first reported case of systemic/cerebral FES comes from Wade and Stevenson in 1941 where they share the story of a 49-year-old Mediterranean woman with SCD whose presentation is strikingly similar to our own patient.8 In many instances, significant localized or diffuse pain(s)/vaso-occlusive crises may be the initial presenting symptom. This can be associated with or escalate to systemic signs of illness. These include, but are not limited to, markedly elevated fevers, tachycardia, and tachypnea. One may also observe a rapid decrease in the patient’s level of consciousness.7 The hallmark clinical triad of respiratory failure, neurologic deficits/failure, and petechial rash are foreboding warning signs of pending clinical deterioration via “showering” of fat emboli within the microvasculature.8

The diagnosis of ntFES is clinical and should be made within the appropriate clinical setting. Though scoring systems exist to aid in its diagnosis, its nonspecific manifestations require a heightened index of suspicion. Clinical, laboratory, and imaging findings can further aid in the diagnosis of FES. Laboratory findings are consistent with systemic inflammation and signs of multisystem end-organ damage.3 There is often a leukoerythroblastic picture observed on peripheral smear.3 Chest radiography often shows diffuse bilateral infiltrates;29 Depending on the time course, susceptibility-weighted imaging may reveal diffuse micro-punctate hemorrhages in a “starfield pattern.” This finding is pathognomonic for acute cerebral microinfarcts and reflects microbleeds in the splenium and subcortical locations.6,6 This finding correlates with neurologic failure requiring urgent endotracheal intubation. It also reflects the underlying inflammatory response to circulating adipose tissue within the microcirculation.

The pathogenesis of FES, in SCD, is unknown.9 Several mechanical, biochemical, and immunological hypotheses have been suggested.2,3,9 One of them suggests that an unknown trigger (virus, immunologic reaction, or increased viscosity in HbSC patients due to higher hemoglobin) causes BMN which in turn causes fat embolism and hypoxia. Both mechanical and biochemical theories have been proposed to explain its pathophysiology—that is, mechanical obstruction by fat droplets within microvasculature, and degradation of embolized droplets into FFAs generating toxic metabolites with downstream pro-inflammatory effects.2 The resulting hypoxia perpetuates the cycle by increasing sickling, leading to further downstream vaso-occlusion/infarction ultimately increasing BMN.

When suspected, treatment is aimed toward the underlying cause as well as the pathophysiologic basis of FES. The time of onset for ntFES is usually 24-72 hours and manifests as central nervous system abnormalities, respiratory insufficiency, petechial rash, hemodynamic instability, and fever.8,8 Urgent hematology consultation should be obtained. Treatment is primarily supportive. In the 58 cases analyzed by Tsitsikas et al., patients receiving exchange transfusion, simple transfusion, and supportive care alone had mortality rates of 29%, 61%, and 91%, respectively, indicating decreased mortality with timely initiation of therapy.3
| Variable | Reference | Time after initial inpatient admission^a |
|----------|-----------|----------------------------------------|
|          | Range     | 0 h  | 18 h | 36 h | 2 d  | 2.5 d | 3 d  | 5 d  | 21 d | 66 d | 83 d |
| Leukocyte count, 10^3 cells/mm^3 | 3.6-10.6 | 12.1 | 14.3 | 20.8 | -    | 14.2  | 12.8 | 11.6 | 8.9  | 5.3  | 3.7  |
| Hemoglobin (Hgb), g/dL | 12-15 | 10.2 | 8.2  | 6.7  | -    | 5.9   | 6.1  | 9.7b | 7.9  | 8.6  | 9.3  |
| Platelet count, 10^3 cells/mm^3 | 150-450 | 180  | 55   | 29   | -    | 43    | 32   | 88   | 257  | 166  | 193  |
| Reticulocyte count Abs, 10^3 cells/mm^3 | 21-115 | 118.7 | -    | -    | 85.4  | -    | -    | -    | -    | -    | -    |
| Protime, seconds | 9-12 | -    | 11.6 | -    | 15.3  | -    | 14.8 | -    | -    | -    | -    |
| INR | 0.8-1.2 | -    | 1.2  | -    | 1.4   | -    | 1.35 | -    | -    | -    | -    |
| aPTT, s | 23.4-38.0 | -    | -    | 30.9 | -    | 31.0  | -    | -    | -    | -    | -    |
| Fibrinogen, mg/dL | 170-399 | -    | 460  | 442  | -    | 510   | -    | -    | -    | -    | -    |
| Arterial blood gas |          |      |      |      |      |      |      |      |      |      |      |
| pH | 7.35-7.45 | -    | 7.39 | 7.55 | 7.48 | -    | -    | -    | -    | -    | -    |
| pCO2, mmHg | 35-48 | -    | 47   | 25   | 29   | -    | -    | -    | -    | -    | -    |
| pO2, mmHg | 83-108 | -    | 40   | 55   | 229  | -    | -    | -    | -    | -    | -    |
| O2 saturation, % | 95-98 | -    | 96   | 102  | -    | -    | -    | -    | -    | -    | -    |
| Plasma values |          |      |      |      |      |      |      |      |      |      |      |
| Sodium level, mmol/L | 136-145 | 143  | 139  | 137  | 137  | 144  | 145  | 152 | 140  | 139  | 141  |
| Potassium level, mmol/L | 3.5-5.5 | 3.5  | 4.3  | 4.2  | 4.4  | 4.0  | 3.9  | 3.7  | 4.0  | 3.8  | 3.4  |
| Chloride level, mmol/L | 98-107 | 109  | 104  | 104  | 106  | 111  | 111  | 115  | 108  | 108  | 107  |
| Bicarb level, mmol/L | 21-32 | 25   | 25   | 25   | 15   | 24   | 24   | 24   | 24   | 25   | 24   |
| BUN level, mg/dL | 7-18 | 22   | 19   | 25   | 20   | 41   | 46   | 40   | 49   | 19   | 10   |
| Creatinine, mg/dL | 0.51-0.95 | 0.77  | 0.78 | 0.98 | 0.67 | 1.28 | 1.39 | 1.21 | 0.63 | 0.60 | 0.63 |
| Glucose, mg/dL | 74-106 | 132  | 125  | 127  | 106  | 140  | 129  | 140  | 101  | 83   | 86   |
| Calcium, mg/dL | 8.5-10.1 | 8.3  | 8.4  | 7.9  | 6.8  | 8.0  | 8.3  | 8.0  | 9.0  | 9.2  | 9.0  |
| Total protein, g/dL | 6.4-8.2 | -    | -    | 6.0  | 3.3  | 5.4  | -    | 5.6  | -    | -    | -    |
| Albumin, g/dL | 3.4-5.0 | -    | -    | 2.8  | 1.5  | 3.3  | -    | 3.2  | -    | -    | -    |
| Total bilirubin mg/dL | 0.2-1.0 | -    | -    | 1.0  | 0.7  | 0.9  | -    | 1.1  | -    | -    | -    |
| ALP, IU/L | 45-117 | -    | -    | 338  | 167  | 182  | -    | 124  | -    | -    | -    |
| AST, U/L | 15-37 | -    | -    | 188  | 104  | 88   | -    | 52   | -    | -    | -    |
| ALT, IU/L | 12-78 | -    | -    | 116  | 59   | 58   | -    | 41   | -    | -    | -    |
| Lactate, mmol/L | 0.4-2.0 | -    | -    | 2    | 11   | 2.7  | 1.3  | -    | -    | -    | -    |
| Troponin, ng/mL | 0.00-0.04 | <0.02 | -    | 1.88 | 1.18 | 1.23 | -    | -    | -    | -    | -    |
| D-dimer, mcg FEU/mL | 0.00-0.49 | -    | -    | -    | 35.20 | -    | -    | -    | -    | -    | -    |
| Ferritin, ng/mL | >292 | -    | -    | -    | -    | -    | -    | -    | -    | -    | -    |
| hs CRP, mg/dL | <0.30 | 0.56 | -    | -    | 13.7 | -    | -    | -    | -    | -    | -    |

(Continues)
SUMMARY

Sickle cell disease, particularly HbSC disease, has been implicated as a rare precipitant for FES—a potentially devastating syndrome resulting from BMN secondary to an inciting event (e.g., vaso-occlusion). Few cases of FES in HbSC disease have been published. Most present with pulmonary symptoms. While this eventually results in neurologic dysfunction, fat embolism in HbSC disease presenting as progressive nonresolving encephalopathy is rare. Cases presenting primarily with encephalopathy usually carry a worse long-term prognosis. Acute presentation with confounders such as encephalopathy, troponin elevation, and cytopenias can lead to time-consuming testing. Clinicians must have a high index of suspicion in patients with SCD who develop acute encephalopathy. Hematology consultation, RBC exchange, and supportive measures must be initiated promptly to limit morbidity and mortality, to preserve functionality, and to promote improved health outcomes and quality of life.

CONFLICT OF INTEREST
None declared.
AUTHOR CONTRIBUTION
AO and SU-A: prepared the manuscript. RK: reviewed the manuscript. All authors were involved in caring for the patient.

ORCID
Ayotunde Ositelu https://orcid.org/0000-0002-1187-6425
Samuel Urrutia-Argueta https://orcid.org/0000-0003-4634-2279
Rajat Kapoor https://orcid.org/0000-0003-0906-3924

REFERENCES
1. Alsafwani SA, Al-Saeed A, Bukhamsin R. Extensive bone marrow necrosis: initial presentation in sickle cell anemia—a case report and review of the literature. Case Rep Hematol. 2017;2017:7185604.
2. Saigal R, Mittal M, Kansal A, et al. Fat embolism syndrome. J Assoc Physicians India. 2008;56:245-249.
3. Tsitsikas DA, Gallinella G, Patel S, et al. 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.
4. Gendreau S, Scholer M, Cecchini J, et al. Cerebral fat embolism in sickle cell disease. Am J Hematol. 2020;95(2):E41-E45.
5. Greaves P, Mathew V, Peters C, et al. Successful outcome of three patients with sickle-cell disease and fat embolism syndrome treated with intensive exchange transfusion. Clin Case Rep. 2017;5(1):39–43.
6. Ramachandiran N, Raniga S, Al Kindi S, et al. Non-traumatic cerebral fat embolism in sickle cell disease (P3.234). Neurology. 2016;86(16 Suppl):P3.234.
7. Kammeyer R, Devnani R, Mehta R. Cerebral fat embolism syndrome mimicking thrombotic thrombocytopenic purpura in a patient with hemoglobin SC disease. Am J Hematol. 2016;91(5):539-542.
8. Wade L, Stevenson L. Necrosis of the bone marrow with fat embolism in sickle cell anemia. Am J Pathol. 1941;17(1):47-54.
9. Dang NC, Johnson C, Esalmi-Farsani M, et al. Bone marrow embolism in sickle cell disease: a review. Am J Hematol. 2005;79:61-67.
10. Shapiro MP, Hayes JA. Fat embolism in sickle cell disease: report of a case with brief review of the literature. Arch Intern Med. 1984;144(1):181-182.

How to cite this article: Ositelu A, Urrutia-Argueta S, Kapoor R. Neurologic recovery in systemic nontraumatic fat embolism syndrome in an elderly patient with hemoglobin SC disease: A case report. Clin Case Rep. 2020;8:1816–1820. https://doi.org/10.1002/ccr3.3023