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CASE REPORT

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Neurologic recovery in systemic nontraumatic fat embolism syndrome in an elderly patient with hemoglobin SC disease: A case report

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Abstract

Cerebral fat embolism syndrome is an under-recognized yet well-known complication of bone marrow necrosis occurring in patients with sickle cell disease. We highlight a case manifested by multisystem organ failure in an elderly patient who attained neurologic recovery with prompt initiation of hematology consultation, RBC exchange, and supportive measures.

KEYWORDS

bone marrow necrosis, cerebral fat embolism syndrome, fat embolism, neurologic recovery, sickle cell disease

1 | 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%.[1] 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.

2 | OBJECTIVE

To report a case of ntFES manifested by multisystem organ failure in an elderly patient who attained neurologic recovery.

3 | CASE REPORT

A 75-year-old woman with HbSC disease, right hip avascular necrosis postreplacement, Chiari I malformation, and essential hypertension initially presented with one day of "deep" bilateral thigh pain progressing to diffuse body pain and chest pain. She has a history of infrequent sickle cell pain crises, last occurring several years ago. She had no history of recent travel and was born in the United States.

The patient was hospitalized for suspected vaso-occlusive crisis. On initial examination, she was communicative yet uncomfortable and distressed, afebrile, and hemodynamically stable. She exhibited significant bilateral thigh pain, severely restricting the range of motion. Admission laboratories (see Table 1) were largely unremarkable except for mild leukocytosis.

Within 36 hours of admission, she rapidly declined with multi-organ dysfunction, as evidenced by progressive encephalopathy, respiratory failure, troponinemia, acute kidney

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 paretic 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.[2,9] 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.[4,6] 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.[4,8] 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]

TABLE 1 Laboratory values obtained during the acute phase of illness and treatment

	Reference	Time after initial inpatient admission[a]									
Variable	**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**	9.7[b]	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	-	-	-	-	-	-
pCO_2, mmHg	35-48	-	47	25	29	-	-	-	-	-	-
pO_2, mmHg	83-108	-	40[c]	55	229	-	-	-	-	-	-
O_2 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	19	10	5
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	8.3	8.0	9.0	9.2
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**		-	-	-	-	-
, ng/dL	<292	-	-	-	-	**13 292**	**12 060**	**25 703**	**5280**	-	-
Ferritin, ng/mL	10-291	-	-	-	**>16 500**	-	-	-	-	-	-
, ng/mL	10-106	-	-	-	-	**25 110**	-	-	-	-	-
hs CRP, mg/dL	<0.30	0.56	-	-	**13.7**	-	-	-	-	-	-

(Continues)

TABLE 1 (Continued)

Variable	Reference Range	Time after initial inpatient admission[a] 0 h	18 h	36 h	2 d	2.5 d	3 d	5 d	21 d	66 d	83 d
Sed Rate, mm/h	0-30	-	-	9	23	-	-	-	-	-	-
Ammonia	11-32	-	-	12	-	-	-	-	-	-	-
Prolactin	2.8-29.2	-	-	9.7	-	-	-	-	-	-	-
Creatine Kinase, U/L	26-192	46	-	-	-	-	-	-	-	-	-
LDH, Units/L	84-246	-	-	-	**1707**	**2615**	-	**1530**	-	-	-
Haptoglobin, mg/dL	30-200	-	-	-	**14**	44	-	-	-	-	-
TSH, mcU/mL	0.400-4.200	-	-	-	-	-	-	1.142	-	-	-
Glasgow Coma Scale score		-	-	-	-	3/10T	-	-	10/10T	15/15	15/15

Note: Notable time points: 0 h = Admission, 36 h = Significant clinical deterioration, 2 d = Intubation for airway protection, transferred to tertiary institution, 2.5 d = RBC exchange transfusion initiated, 21 d = Transfer to LTAC, 66 d = Transfer to ARF, 83 d = Prior to discharge.

Significant abnormal laboratory values are depicted in **bold**. Laboratory testing revealed precipitous drops in hemoglobin (from baseline of 10 g/dL to nadir 5.4 g/dL, not shown) and platelets and increases in troponin (peak of 1.94 ng/mL not shown), lactate (12 mmol/L not shown), D-dimer, fibrinogen, ferritin, LDH, C-reactive protein, and A-a gradient. Initial acid-base analysis revealed triple acid-base disorder with respiratory alkalosis, anion-gap metabolic acidosis due to elevated lactate, and non-anion-gap metabolic acidosis. Prolactin was obtained during patient's workup for unresponsiveness and consideration for seizure. Of note, peripheral smear was consistent with a leukoerythroblastic picture, showing marked anemia with microcytosis, numerous target cells, frequent nucleated RBCs and few schistocytes, and mature WBC morphology with leukocytosis and neutrophilia, further supporting diagnosis of fat embolism syndrome.

Hemoglobin Electrophoresis Studies (not shown): *Historical, Patient's Baseline* (2014): Relative percentages of HgbA, HgbA2, HgbC, HgbF, and HgbS were 0%, 0%, 48%, 0%, and 52%, respectively. For this case, no electrophoresis studies were done prior to first exchange. *Following initial RBC Exchange transfusion*: Relative corresponding values were 28.8%, 3.6%, 28.4%, 5.1%, and 34.1%, respectively. Post-initial transfusion, corresponding values were 91.4%, 2.4%, 2.7%, 0.4%, and 3.1%, respectively. Two weeks after initiation of multiple transfusions, corresponding values were 76.3%, 3.2%, 9.3%, 0.4%, and 10.8%, respectively. Reference values: HgbA: 94.0%-98.5%, HgbA2: 1.5%-3.5%, HgbC: nil, HgbF: 0.0%-2.0%, HgbS: nil.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; d, days; FEU, fibrinogen-equivalent units; h, hours; Hgb, hemoglobin; hs CRP, high-sensitivity C-reactive protein; INR, international normalized ratio; LDH, lactate dehydrogenase; TSH, thyroid-stimulating hormone.

[a]For ease of reference, the time points listed are near approximations.

[b]After exchange transfusion.

[c]This partial pressure measurement is from venous blood gas.

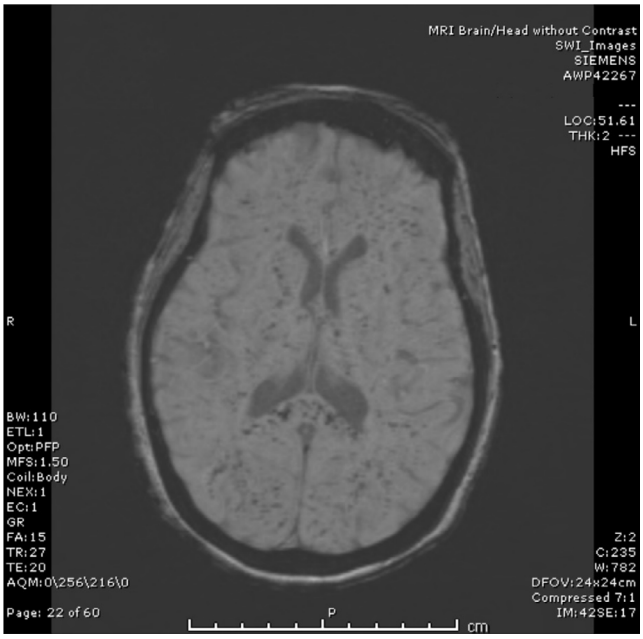

FIGURE 1 Susceptibility-weighted imaging which reveals diffuse punctate microhemorrhages throughout the neuroparenchyma in the "starfield" pattern consistent with cerebral fat embolism

5 | 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).[4,10] Few cases of FES in HbSC disease have been published.[1,3-5,7,9,10] 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.[10]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.[3]

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.

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