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Paradoxical cerebral fat embolism in an adolescent PLHA: A convergence of trauma, art induced hypercoagulability, and septal heart defect

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Introduction

Fat Embolism Syndrome (FES) is a multisystem disorder that occurs as a complication of long bone fractures, most commonly involving the pulmonary, neurological, hematological, and dermatological systems. The earliest description of FES dates back to Zenker in 1861, who reported it in a railroad worker with a thoracolumbar crush injury, and it was later clinically diagnosed by Ernst von Bergmann in 1873 in a patient with a distal femur fracture [1,2]. Among the varied manifestations of FES, Cerebral Fat Embolism (CFE) is particularly rare but can lead to severe neurological impairment and poor prognosis [3]. Traditionally, FES has been explained through mechanical and biochemical theories. However, recent insights suggest that hypercoagulability, endothelial dysfunction, and systemic inflammation play a critical role in its pathogenesis [4]. In HIV-positive individuals, these mechanisms are further exacerbated due to chronic immune activation and endothelial injury, predisposing them to a prothrombotic state. This risk is amplified by AntiRetroviral Therapy (ART), particularly protease inhibitors (PIs) and Nucleoside Reverse Transcriptase Inhibitors (NRTIs), which have been associated with increased platelet activation, dyslipidemia, and vascular dysfunction, further contributing to microvascular thrombosis and embolic complications [5,6]. Under normal physiological conditions, fat emboli are trapped within the pulmonary capillary network, preventing systemic embolization. However, in individuals with a right-to-left cardiac shunt, such as an Atrial Septal Defect (ASD), emboli can bypass the pulmonary circulation and directly enter the systemic arterial system, a phenomenon known as paradoxical embolism [7,8]. This allows fat emboli to reach the cerebral vasculature, leading to neurological dysfunction, seizures, or even coma. This mechanism is particularly significant in patients with Congenital Heart Disease (CHD), where an undiagnosed intracardiac shunt can serve as a direct pathway for systemic embolization [9,10]. FES poses a significant diagnostic challenge due to its highly variable presentation, which ranges from mild respiratory distress to severe neurological compromise and Multisystem Organ Dysfunction (MODS) [11]. In HIV-positive patients on ART, the interplay of trauma, hypercoagulability, endothelial dysfunction, and congenital cardiac anomalies substantially alters disease progression, increasing the likelihood of paradoxical embolism and extensive neurological involvement [12]. Since no single diagnostic test exists, a multimodal approach utilizing clinical criteria, neuroimaging (such as MRI with the characteristic "Starfield pattern"), echocardiography to detect cardiac shunts, and biomarker evaluation is essential for timely diagnosis and management [13,14]. Management of FES remains predominantly supportive, with a focus on early fracture stabilization,

identification of cardiac anomalies, and vigilant monitoring of coagulation abnormalities to mitigate complications. This case highlights the critical importance of recognizing paradoxical embolism as a potential mechanism for cerebral fat embolism, particularly in patients with HIV, ART-related coagulopathy, and congenital heart defects [15,16]. Moreover, this case introduces novel radiological insights that enhance the diagnostic approach to Cerebral Fat Embolism Syndrome (CFES). Diffusion-weighted MRI (DWI) revealed the "Starfield pattern," a hallmark of multifocal cytotoxic edema associated with CFES [17]. Additionally, Susceptibility-Weighted Imaging (SWI) demonstrated microhemorrhages in the corpus callosum and subcortical white matter, which is an emerging marker of severe microvascular injury in fat embolism—a finding that has not been widely reported in the literature [18].

Case presentation

Patient presentation and initial assessment: A 14-year-old male with perinatally acquired HIV on conventional Antiretroviral Therapy (ART) presented to the emergency department of Chhatrapati Shivaji Subharti Hospital following a high-impact Road Traffic Accident (RTA) involving a two-wheeler collision with a truck. He arrived within an hour of trauma, complaining of severe limb pain that progressively worsened into an intense, sharp stabbing sensation. The patient was unable to bear weight on the affected limb. His initial Glasgow Coma Scale (GCS) score was 15, indicating preserved neurological function at presentation. Orthopedic Injuries and Early Management: Clinical and radiological evaluation revealed multiple long bone fractures, including a displaced comminuted fracture of the right femoral shaft, a transverse right tibial fracture, and a medial condylar fracture (Figures 1 & 2). Immediate orthopedic stabilization with a Thomas splint was performed within an hour, and the patient was admitted for further monitoring.

Neurological deterioration and ICU admission: A few hours after admission, the patient developed worsening pain, muscle cramps, and progressive drowsiness, accompanied by a rapid decline in GCS from 15 to 8. Given his acute neurological deterioration, an urgent general medicine consultation was obtained, and he was transferred to the Intensive Care Unit (ICU) for further evaluation and management.

Differential diagnosis and initial investigations: Considering the patient's HIV status and ART-induced hypercoagulability, an embolism-related event was suspected. Laboratory investigations revealed:

- Markedly elevated D-dimer (3.820 µg/mL), raising suspicion for pulmonary embolism (PE).
- CT pulmonary Angiography (CTPA) ruled out PE, instead demonstrating bilateral patchy consolidations with a diffuse crazy-paving pattern, suggestive of infective etiology or Acute Respiratory Distress Syndrome (ARDS) rather than a thromboembolic event.

Diagnosis of Cerebral Fat Embolism Syndrome (CFES): As neurological deterioration persisted, an urgent Non-Contrast CT (NCCT) of the head was performed, which revealed subtle confluent hypodensities with tiny hyperdense foci in the subcortical white matter, raising suspicion for Diffuse Axonal Injury (DAI) or Cerebral Fat Embolism (CFE).

A contrast-enhanced MRI of the brain confirmed **CFE**, showing:

- Bilateral symmetrical T2-FLAIR hyperintensities in the subcortical and deep white matter of both cerebral hemispheres, corpus callosum, and cerebellum (Figure 5).
- Restricted diffusion on DWI with corresponding ADC defects, consistent with cytotoxic edema (Figures 7 & 8).
- Multiple small foci of SWI blooming in the bilateral cerebral hemispheres, corpus callosum, capsulo-ganglionic region, and cerebellum (Figure 6).

On physical examination, conjunctival petechiae were observed (Figure 4) further supporting the diagnosis of cerebral fat embolism syndrome (CFES) based on Gurd's criteria, which include:

1. Neurological impairment (progressive encephalopathy, GCS decline).
2. Respiratory dysfunction (ARDS-like presentation).
3. Petechial rash (conjunctival involvement).

Laboratory findings and systemic involvement: Additional laboratory investigations revealed:

- Acute anemia (Hb 6.0 g/dL) and low hematocrit (17.8%), despite minimal external blood loss, suggesting microvascular hemorrhage or coagulopathy.
- Thrombocytopenia ($80\times10^3/mm^3$), neutrophilia (91%), and lymphopenia (6%), indicating systemic inflammation.
- Elevated ESR (105 mm/hr) and procalcitonin levels, suggestive of underlying sepsis.
- Positive blood cultures for Acinetobacter lwoffii, requiring targeted antibiotic therapy.

Role of Atrial Septal Defect (ASD) in paradoxical embolism: While FES is typically restricted to the pulmonary circulation, the predominantly neurological presentation raised suspicion for paradoxical embolism. A 2D echocardiogram confirmed a previously undiagnosed Atrial Septal Defect (ASD) with a right-to-left shunt (Figures 9 & 10), validating the pulmonary bypass hypothesis. This structural anomaly allowed fat emboli to bypass the pulmonary capillary filtration system and directly enter the systemic arterial circulation, leading to cerebral embolization. This pathophysiological mechanism explains the rapid onset of neurological impairment, which was out of proportion to respiratory symptoms, distinguishing this case from typical FES presentations. The presence of Systemic Inflammatory Response Syndrome (SIRS), Multisystem Organ Dysfunction Syndrome (MODS), and ARDS-like symptoms further emphasized the severity of systemic involvement.

Management and therapeutic approach: A multidisciplinary treatment approach was implemented, focusing on stabilizing the patient while addressing the complications of paradoxical embolism, ART-induced hypercoagulability, and congenital heart disease.

1. ICU admission for intensive supportive care and close monitoring.

2. Mechanical ventilation for respiratory distress and ARDS-like symptoms.

3. Intravenous methylprednisolone to reduce inflammation, endothelial dysfunction, and cerebral edema.

4. Withholding anticoagulation due to the risk of hemorrhagic transformation in cerebral fat embolism.

5. Targeted antibiotic therapy (Meropenem) for secondary bacterial infection (Acinetobacter lwoffii), guided by culture sensitivity.

6. Hemodynamic and coagulation monitoring, with blood transfusions as needed to correct anemia and thrombocytopenia.

7. Early mobilization and continued orthopedic stabilization to minimize further fat embolization and prevent immobility-related complications.

Discussion

This case highlights a rare presentation of Cerebral Fat Embolism Syndrome (CFES) secondary to trauma, further complicated by a previously undiagnosed Atrial Septal Defect (ASD), HIV-associated endothelial dysfunction, and Antiretroviral Therapy (ART)-induced hypercoagulability. While Fat Embolism Syndrome (FES) is a recognized sequela of long bone fractures, its neurological manifestation via paradoxical embolization remains exceedingly rare, particularly in patients with predisposing factors such as HIV and congenital cardiac anomalies.

Unique aspects of this case

Paradoxical fat embolism through an undiagnosed atrial septal defect: In typical cases of FES, fat emboli are filtered by the pulmonary capillaries, leading to hypoxia and Acute Respiratory Distress Syndrome (ARDS)-like symptoms. However, in this patient, the presence of a right-to-left cardiac shunt (ASD) facilitated pulmonary bypass, allowing fat emboli to enter the systemic arterial circulation and lodge in the cerebral vasculature. This pathophysiological mechanism of paradoxical embolism is rarely reported in the literature, making this case a valuable addition to current medical knowledge.

Interplay of trauma, congenital heart disease, and HIV: The coexistence of multiple risk factors, including severe orthopedic trauma (long bone fractures), a cardiac anomaly (ASD), HIV-associated endothelial dysfunction, and ART-induced hypercoagulability, likely exacerbated the Systemic Inflammatory Response Syndrome (SIRS), leading to worsened neurological impairment and systemic complications. HIV and ART-related endothelial dysfunction are well-documented contributors to increased platelet activation, dyslipidemia, and microvascular thrombosis, all of which may have intensified the severity of CFES in this patient.

Atypical clinical presentation: Neurological symptoms preceding respiratory distress: In classic FES, respiratory distress is typically the first clinical manifestation, followed by neurological deterioration. However, in this patient, neurological symptoms were the earliest and most prominent features, likely due to immediate cerebral embolization through the ASD. This atypical presentation challenges conventional diagnostic paradigms, highlighting the importance of early neurological assessment in trauma patients presenting with unexplained encephalopathy.

Pathophysiology and mechanism of embolization: Fat embolism in classic FES is confined to the pulmonary circulation, where it causes hypoxemia, ARDS, and respiratory distress. However, in this case, the previously undiagnosed ASD permitted right-to-left shunting, bypassing pulmonary filtration mechanisms and allowing fat emboli direct access to the systemic circulation. This paradoxical embolization pathway significantly altered the clinical course, leading to early and severe neurological dysfunction. Furthermore, HIV-induced endothelial dysfunction and ART-associated coagulopathy likely amplified the microvascular thrombosis and inflammatory cascade, exacerbating cerebral ischemia and neurological deterioration. Protease inhibitors and Nucleoside Reverse Transcriptase Inhibitors (NRTIs), key components of ART regimens, have been associated with increased platelet aggregation, dyslipidemia, and endothelial dysfunction, further predisposing this patient to systemic embolic events.

Diagnostic challenges and imaging utility: Diagnosing CFES remains challenging due to its nonspecific clinical presentation and overlap with post-traumatic neurological conditions, such as Diffuse Axonal Injury (DAI) and Traumatic Brain Injury (TBI). The absence of definitive laboratory markers necessitates a multimodal diagnostic approach, integrating clinical criteria, neuroimaging, and echocardiography.

Key diagnostic features in this case

Gurd's criteria: The patient met three major criteria (neurological impairment, respiratory dysfunction, petechiae), strongly supporting a diagnosis of FES.

Magnetic Resonance Imaging (MRI)–"Starfield pattern": MRI findings were consistent with CFES, demonstrating diffuse, punctate T2-FLAIR hyperintensities with Susceptibility-Weighted Imaging (SWI) blooming, a hallmark of microvascular injury due to fat embolism.

CT Pulmonary Angiography (CTPA): CTPA excluded pulmonary thromboembolism (PTE) but revealed a crazy-paving pattern, supporting an inflammatory and embolic pathogenesis rather than a primary thromboembolic event.

Echocardiography: The identification of an ASD on 2D echocardiography provided direct evidence of paradoxical embolism, confirming the pathophysiological mechanism underlying cerebral involvement.

Hematological and inflammatory markers –Indicators of disease severity:

- Acute anemia (Hb 6.0 g/dL) and thrombocytopenia (80 × 10^3/mm^3), suggesting microvascular hemorrhage or Disseminated Intravascular Coagulation (DIC).
- Elevated D-dimer (3.820 µg/mL) and erythrocyte sedimentation rate (ESR) (105 mm/hr), indicative of ongoing thrombo-inflammatory activity.
- Neutrophilia (91%) and lymphopenia (6%), reflecting HIV-associated immune dysregulation.
- Positive blood cultures for Acinetobacter lwoffii, indicating secondary bacterial sepsis.

Clinical implications and future considerations: This case provides critical insights into the diagnostic and management considerations for high-risk trauma patients.

1. Routine screening for cardiac anomalies in trauma patients

- Undiagnosed ASDs and Patent Foramen Ovale (PFO) can serve as conduits for paradoxical embolism.

- Transthoracic or transesophageal echocardiography should be considered in trauma patients with unexplained neurological symptoms.

2. Heightened vigilance in HIV-Positive trauma patients

- HIV-associated endothelial dysfunction and ART-induced hypercoagulability increase the risk of systemic embolism.

- Coagulation and inflammatory markers should be proactively monitored in these patients.

3. Expanding the diagnostic approach to fat embolism syndrome

- Neurological symptoms preceding respiratory distress should raise suspicion for paradoxical embolism.

- MRI with diffusion-weighted imaging (DWI) should be prioritized in trauma patients with unexplained neurological decline.

- Echocardiography should be included in cases of suspected paradoxical embolism.

Conclusion

Fat Embolism Syndrome (FES) is a complex and often underdiagnosed complication of long bone fractures, requiring a high index of suspicion in patients presenting with acute respiratory distress and neurological deterioration. Given its variable clinical spectrum, ranging from mild hypoxia to severe multisystem failure, early recognition and timely intervention are crucial for improving patient outcomes. This case is unique due to the presence of an undiagnosed Atrial Septal Defect (ASD), which facilitated paradoxical embolization by allowing fat emboli to bypass the pulmonary circulation and enter the systemic arterial system, resulting in Cerebral Fat Embolism (CFE). In typical FES, fat emboli are trapped within the pulmonary microcirculation, leading to hypoxia and ARDS-like symptoms. However, in this patient, the right-to-left shunt created by the ASD enabled fat emboli to bypass pulmonary filtration, leading to direct cerebral embolization. This rare embolic pathway resulted in early-onset neurological symptoms, challenging the traditional diagnostic paradigm of FES, where respiratory symptoms usually precede neurological involvement.

This case also presents novel radiological findings that enhance the diagnostic approach to Cerebral Fat Embolism Syndrome (CFES). Diffusion-weighted MRI (DWI) revealed the characteristic "Starfield pattern," indicative of multifocal cytotoxic edema, a hallmark of CFES. Additionally, Susceptibility-Weighted Imaging (SWI) demonstrated microhemorrhages in the corpus callosum and subcortical white matter, an emerging marker of severe microvascular injury in fat embolism-a finding not widely documented in existing literature. As there is no definitive laboratory test for FES, diagnosis relies on a combination of clinical criteria and advanced neuroimaging. This case underscores the critical role of MRI in detecting subtle yet clinically significant cerebral involvement, even in patients without overt neurological deficits. Furthermore, the presence of atypical hemorrhagic lesions in CFES suggests a pathophysiological overlap with other embolic encephalopathies, warranting further investigation into its implications for prognosis and management. The identification of an ASD and its role in pulmonary bypass expands our understanding of alternative embolic pathways, reinforcing the need for routine cardiac evaluation in trauma patients presenting with unexplained neurological decline. This case highlights the importance of a multidisciplinary approach in managing complex embolic phenomena, emphasizing the role of cardiac screening, neuroimaging, and early intervention in improving patient outcomes.

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