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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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**Running Title** Paradoxical Cerebral Fat Embolism in Adolescent PLHA

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## ABSTRACT

Fat embolism syndrome (FES) is a life-threatening complication following long bone fractures, primarily affecting the pulmonary circulation. However, cerebral fat embolism (CFE) is a rare yet severe variant that can occur when fat emboli bypass the lungs through a right-to-left cardiac shunt, such as an atrial septal defect (ASD).

In individuals with HIV on antiretroviral therapy (ART), persistent endothelial dysfunction and ART-induced hypercoagulability predispose them to an exaggerated thrombo-inflammatory state, amplifying the risk of paradoxical embolism.

We describe a 14-year-old male with perinatally acquired HIV on ART who presented after a high-impact road traffic accident. The patient sustained comminuted fractures of the right femoral shaft, tibia, and femoral condyle. Initially neurologically intact (Glasgow Coma Scale [GCS] 15), he experienced rapid neurological deterioration (GCS dropped to 8), alongside respiratory distress and acute respiratory distress syndrome (ARDS)-like symptoms.

Urgent evaluation with a 2D echocardiogram revealed an ASD with a right-to-left shunt, strongly supporting the diagnosis of paradoxical cerebral fat embolism.

This case illustrates how trauma, combined with HIV-related endothelial dysfunction, ART-induced hypercoagulability, and a congenital cardiac anomaly, can converge to precipitate severe neurological decline through paradoxical embolism.

## Introduction

Fat embolism syndrome (FES) is a multisystem disorder that arises as a complication of long bone fractures, most frequently affecting the pulmonary, neurological, hematological, and dermatological systems. The earliest description of FES dates back to 1861 when Zenker observed the phenomenon in a railroad worker with a thoracolumbar crush injury. It was subsequently clinically characterized by Ernst von Bergmann in 1873 in a patient with a distal femur fracture [1]. Among its diverse clinical manifestations, cerebral fat embolism (CFE) is particularly rare yet carries the risk of severe neurological impairment and an unfavorable prognosis [2].

Traditionally, FES has been attributed to mechanical

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and biochemical mechanisms. However, emerging evidence supports the role of hypercoagulability, endothelial dysfunction, and systemic inflammation in its pathogenesis. In HIV-positive individuals, these pathological processes are further intensified by chronic immune activation and endothelial injury. This is compounded by antiretroviral therapy (ART) especially protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs) which are linked to increased platelet activation, dyslipidemia, and vascular dysfunction, thereby promoting micro-vascular thrombosis and embolic complications [3].

Under normal physiological conditions, fat emboli are entrapped within the pulmonary capillary network, precluding systemic embolization. In contrast, in individuals harboring a right-to-left cardiac shunt, such as an atrial septal defect (ASD), fat emboli may bypass the pulmonary filter and directly enter the systemic arterial circulation a process termed paradoxical embolism [4]. This aberrant pathway permits fat emboli to reach the cerebral vasculature, potentially resulting in neurological dysfunction, seizures, or coma. This mechanism is especially pertinent for patients with congenital heart disease (CHD), where an unrecognized intracardiac shunt may facilitate systemic embolization [5].

The diagnosis of FES is inherently challenging due to its variable presentation, which can range from mild respiratory compromise to severe neurological deficits and multisystem organ dysfunction (MODS). In HIV-positive patients on ART, the synergistic effects of trauma, hypercoagulability, endothelial dysfunction, and congenital cardiac anomalies accelerate disease progression, thereby increasing the risk of paradoxical embolism and extensive neurological involvement. Given the absence of a definitive diagnostic test, a multimodal approach encompassing clinical criteria, neuroimaging (such as magnetic resonance imaging [MRI] with the characteristic “Starfield pattern”), echocardiography for the detection of cardiac shunts, and biomarker analysis is essential for timely diagnosis and management [6].

Management of FES remains primarily supportive, emphasizing early stabilization of fractures, prompt identification of cardiac anomalies, and meticulous monitoring of coagulation parameters to mitigate complications [7]. Furthermore, this case provides novel radiological insights into cerebral fat embolism syndrome (CFES). Diffusion-weighted MRI (DWI) demonstrated the classic “Starfield pattern,” indicative of multifocal cytotoxic edema [8]. In addition, susceptibility-weighted imaging (SWI) revealed microhemorrhages in the corpus callosum and subcortical white matter—an emerging marker of severe microvascular injury in fat embolism that has rarely been documented in the literature [8].

## Case Presentation

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 collision between a two-wheeler and a truck. Arriving within one hour of the incident, he reported severe limb pain that had progressively worsened into an intense, sharp stabbing sensation. Unable to bear weight on the affected limb, his initial Glasgow Coma Scale (GCS) was documented as 15, indicating preserved neurological function at presentation.

Clinical and radiological assessments revealed multiple long bone fractures, including a displaced comminuted fracture of the right femoral shaft, a transverse fracture of the right tibia, and a medial condylar fracture [Figures 1 & 2]. Prompt orthopedic stabilization was achieved with the application of a Thomas splint within an hour, and the patient was admitted for further monitoring.

A few hours after admission, the patient developed worsening pain, muscle cramps, and progressive drowsiness, with his GCS declining rapidly from 15 to 8. In light of his acute neurological deterioration, an urgent consultation with general medicine was obtained, and he was transferred to the intensive care unit (ICU) for further evaluation and management.

Given the patient’s HIV status and the known ART-induced hypercoagulability, an embolic event was highly suspected. Initial laboratory investigations demonstrated a markedly elevated D-dimer (3.820 µg/mL), raising concerns for pulmonary embolism (PE). However, CT pulmonary angiography (CTPA) excluded PE and instead revealed bilateral patchy consolidations with a diffuse crazy-paving pattern findings more consistent with an infective etiology or acute respiratory distress syndrome (ARDS) rather than a thromboembolic event.

With neurological deterioration persisting, an urgent non-contrast CT (NCCT) of the head was performed, showing subtle confluent hypodensities interspersed with tiny hyperdense foci in the subcortical white matter. These findings raised the differential diagnosis of diffuse axonal injury (DAI) versus cerebral fat embolism (CFE). A contrast-enhanced MRI of the

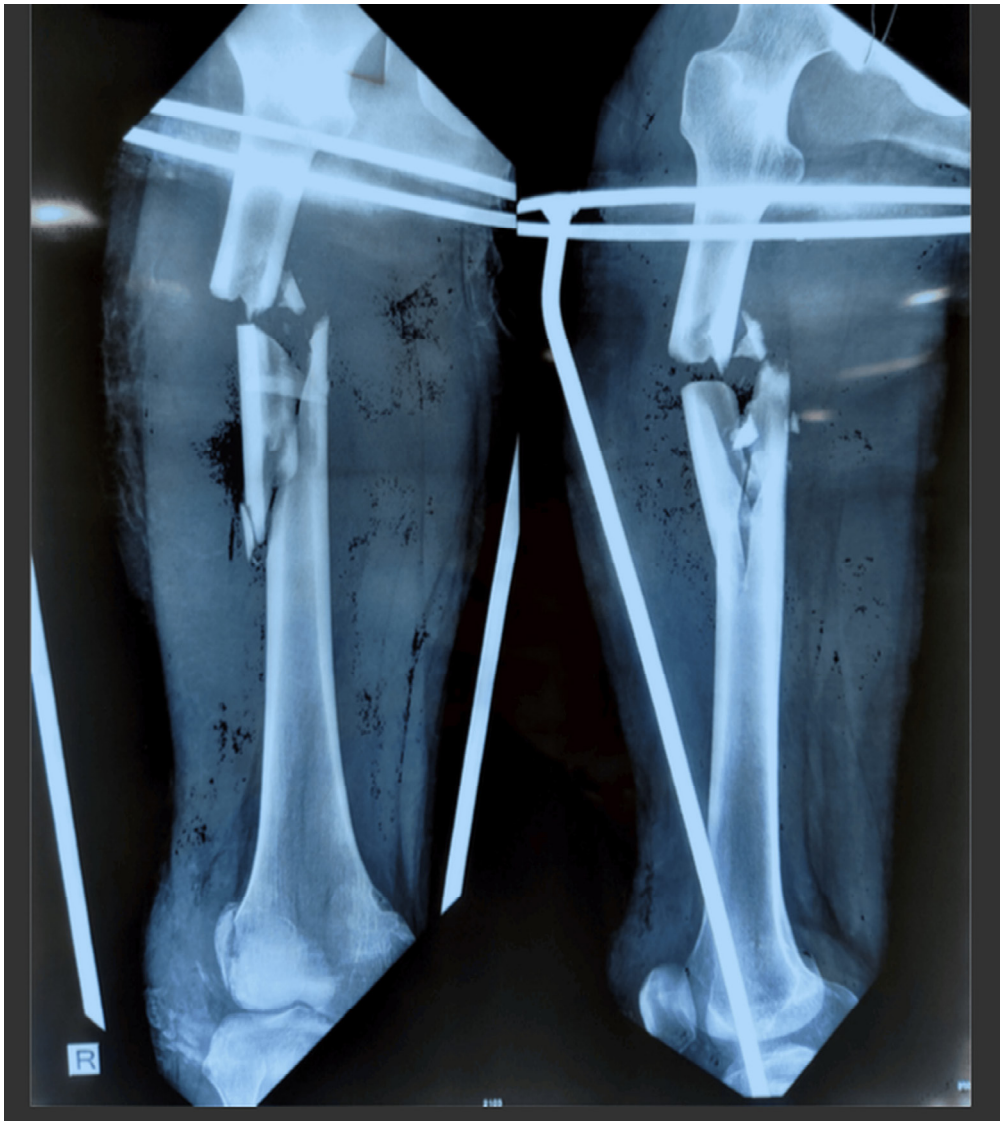

**Fig. 1.** X-ray Showing Comminuted Femur Fractures – A High-Risk Factor for Fat Embolism Syndrome (FES)

brain subsequently confirmed the diagnosis of CFE by demonstrating:

- Bilateral symmetrical T2-FLAIR hyperintensities in the subcortical and deep white matter of both cerebral hemispheres, the corpus callosum, and the cerebellum [Figure 3].

- Restricted diffusion on DWI with corresponding ADC defects, consistent with cytotoxic edema [Figure 4].

- Multiple small foci of blooming on SWI in the bilateral cerebral hemispheres, corpus callosum, capsulo-ganglionic region, and cerebellum [Figure 5].

Additionally, the presence of conjunctival petechiae noted on physical examination further supported the diagnosis based on Gurd's criteria—highlighting neurological impairment, respiratory dysfunction, and a petechial rash.

Further investigations revealed:

- Acute anemia (Hb 6.0 g/dL) with a low hematocrit (17.8%), despite minimal external blood loss, suggesting microvascular hemorrhage or coagulopathy.

- Thrombocytopenia (80 × $10^3$/$mm^3$), neutrophilia (91%), and lymphopenia (6%), indicating a systemic inflammatory state.

- Elevated ESR (105 mm/hr) and increased procalcitonin levels, suggestive of underlying sepsis.

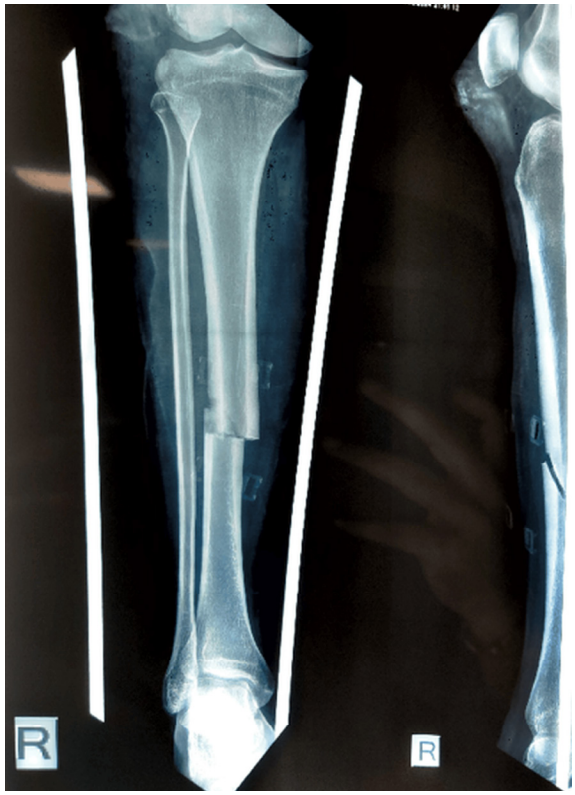


**Fig. 2.** X-ray Showing Comminuted Tibia Fracture – A Potential Trigger for Fat Embolism Syndrome (FES) Bubble Contrast Echocardiography Showing Right-to-Left Shunting Subconjunctival Hemorrhage in a Patient with Fat Embolism Syndrome (FES) – Confirmatory for Gurd and Wilson's Criteria

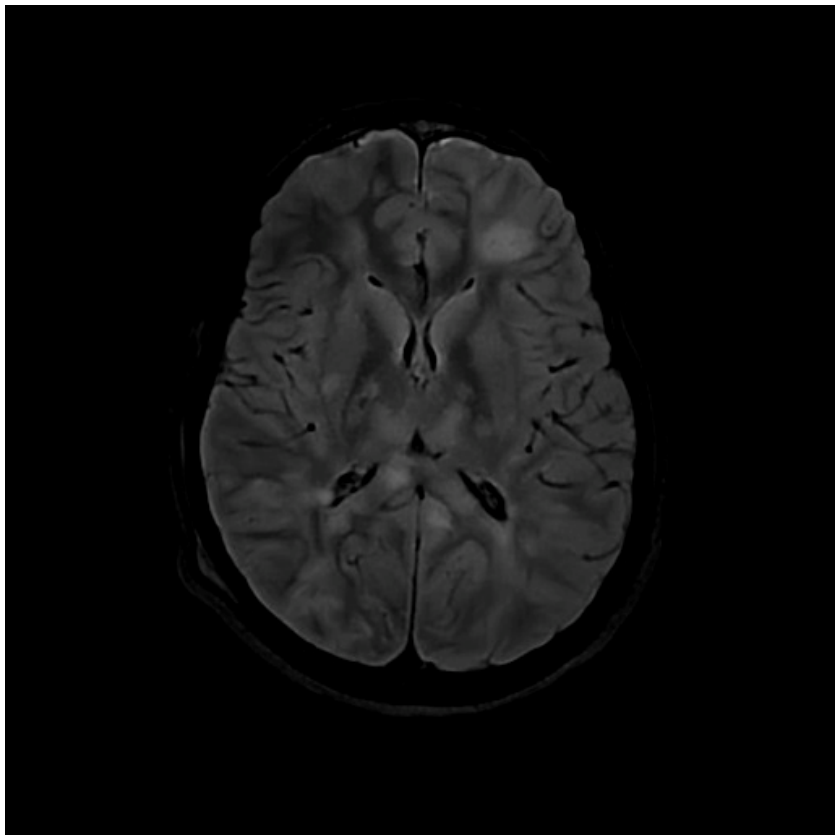

**Fig. 3.** Multiple white Matter T2 flair hyperintensity noted

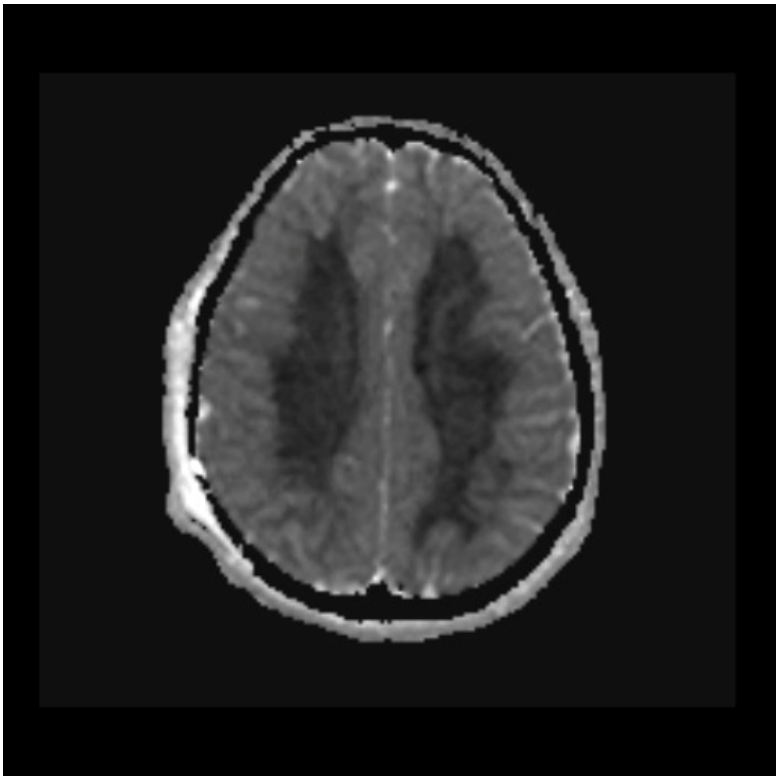

**Fig. 4.** Confluent White Matter Diffusion restriction noted Corresponding reversal of defect on ADC

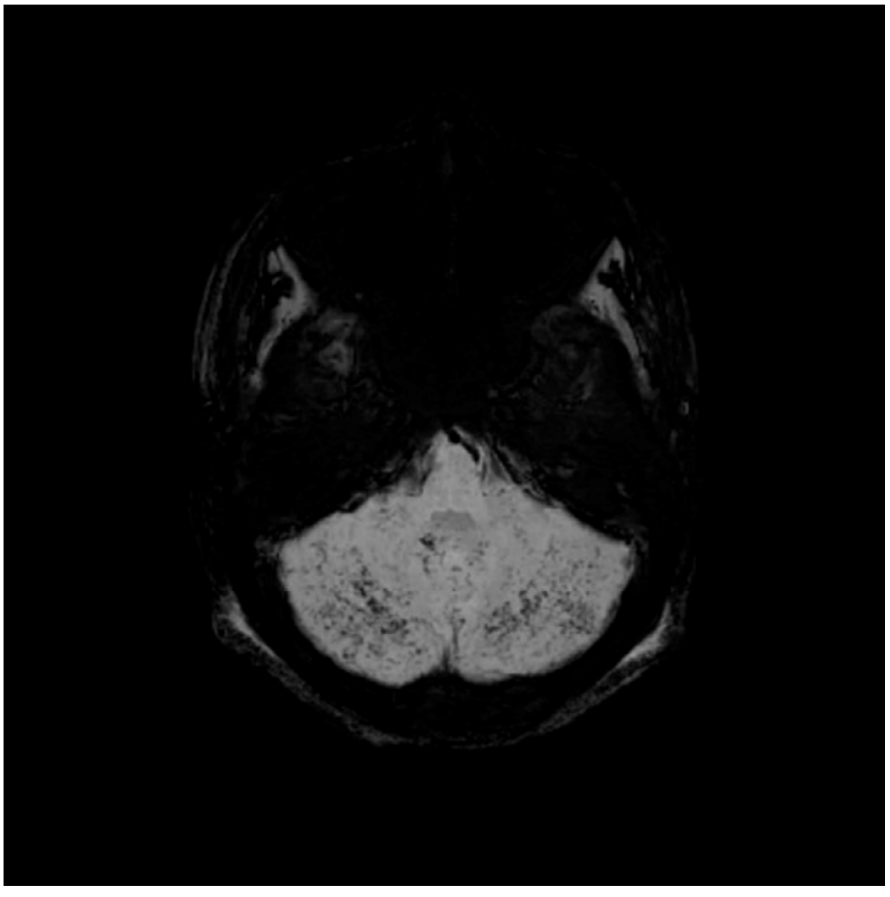

**Fig. 5.** Multiple foci of swi blooming noted in bilateral cerebellar hemisphere, called “Starry Sky Appearance”

- Blood cultures positive for *Acinetobacter lwoffii*, necessitating targeted antibiotic therapy.

Although fat embolism syndrome is typically confined to the pulmonary circulation, the patient's predominantly neurological presentation raised suspicion for paradoxical embolism. A 2D echocardiogram subsequently revealed a previously undiagnosed atrial septal defect (ASD) with a right-to-left shunt, validating the pulmonary bypass hypothesis. This structural defect allowed fat emboli to evade the pulmonary capillary filtration system and enter the systemic circulation, ultimately leading to cerebral embolization. This mechanism was further underscored by the presence of systemic inflammatory response syndrome (SIRS), multisystem organ dysfunction syndrome (MODS), and ARDS-like symptoms.

A comprehensive treatment approach was promptly implemented, incorporating the following key interventions:

**1. Admission to the ICU** for intensive supportive care and continuous monitoring.

**2. Initiation of mechanical ventilation** to manage respiratory distress and ARDS-like features.

**3. Administration of intravenous methylprednisolone** to reduce inflammation, mitigate endothelial dysfunction, and control cerebral edema.

**4. Withholding anticoagulation** due to the risk of hemorrhagic transformation associated with cerebral fat embolism.

**5. Initiation of targeted antibiotic therapy (Meropenem)** based on culture sensitivity for treating *Acinetobacter lwoffii*.

**6. Meticulous hemodynamic and coagulation monitoring**, with supportive blood transfusions as required to address anemia and thrombocytopenia.

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

## Discussion

This case underscores an exceptionally rare presentation of cerebral fat embolism syndrome (CFES) following trauma—a presentation further complicated by an unrecognized atrial septal defect (ASD), HIV-associated endothelial dysfunction, and hypercoagulability induced by antiretroviral therapy (ART) [1–4,11]. Although fat embolism syndrome (FES) is a well-known sequela of long bone fractures, its neurological manifestation via paradoxical embolization is exceedingly uncommon, especially in patients predisposed by HIV or congenital cardiac anomalies [3–6].

In classic FES, fat emboli are normally captured by the pulmonary capillaries—resulting in hypoxemia and ARDS-like symptoms. In contrast, this patient's undiagnosed ASD created a right-to-left shunt, allowing fat emboli to bypass the pulmonary filter and lodge in the cerebral circulation. This unusual pathway of paradoxical embolism is infrequently described in the literature, making this case a significant contribution to current medical understanding.

The convergence of several risk factors—including severe orthopedic trauma (long bone fractures), a cardiac anomaly (ASD), HIV-associated endothelial dysfunction, and ART-induced hypercoagulability—likely intensified the systemic inflammatory response, culminating in profound neurological impairment and widespread systemic complications. The established roles of HIV and ART in promoting platelet activation, dyslipidemia, and microvascular thrombosis may have further heightened the severity of CFES in this patient [7–10].

Conventionally, FES presents initially with respiratory distress, followed by neurological deterioration. However, in this case, neurological deficits emerged as the earliest and most prominent signs—likely due to immediate cerebral embolization via the ASD. This atypical sequence challenges established diagnostic paradigms and underscores the need for early, rigorous neurological evaluation in trauma patients with unexplained alterations in mental status.

In standard fat embolism syndrome (FES), fat emboli are confined to the pulmonary circulation, leading to hypoxemia and triggering acute respiratory distress syndrome (ARDS). In this instance, an unsuspected atrial septal defect (ASD) permitted right-to-left shunting, allowing fat emboli to bypass pulmonary filtration and enter the systemic circulation directly. This paradoxical embolization significantly influenced the clinical course by precipitating early and severe neurological dysfunction.

Furthermore, HIV-induced endothelial damage and antiretroviral therapy (ART)-associated coagulopathy likely potentiated microvascular thrombosis and the inflammatory cascade, exacerbating cerebral ischemia. Notably, components of ART, such as

protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs), have been linked to increased platelet aggregation, dyslipidemia, and endothelial dysfunction—conditions that predispose patients to systemic embolic events [12].

Establishing the diagnosis of cerebral fat embolism syndrome (CFES) is challenging due to its nonspecific presentation and overlap with post-traumatic neurological injuries (e.g., diffuse axonal injury [DAI] and traumatic brain injury [TBI]). The absence of definitive laboratory markers necessitates a comprehensive diagnostic approach combining clinical criteria, neuroimaging, and echocardiography.

In this case, several key diagnostic features were pivotal:

- **Gurd's Criteria:** The patient fulfilled three major criteria—neurological impairment, respiratory dysfunction, and petechiae—strongly supporting an FES diagnosis.

- **Magnetic Resonance Imaging (MRI) – "Starfield Pattern":** MRI demonstrated diffuse, punctate T2-FLAIR hyperintensities along with susceptibility-weighted imaging (SWI) blooming—hallmark features of microvascular injury due to fat embolism.

- **CT Pulmonary Angiography (CTPA):** CTPA ruled out pulmonary thromboembolism while revealing a crazy-paving pattern, suggestive of an inflammatory and embolic process rather than a primary thromboembolic event.

- **Echocardiography:** The detection of an ASD on 2D echocardiography provided direct evidence for the paradoxical embolism mechanism.

- **Hematological and Inflammatory Markers:** Acute anemia (Hb 6.0 g/dL), thrombocytopenia (80 × $10^3$/$mm^3$), elevated D-dimer (3.820 µg/mL), high ESR (105 mm/hr), neutrophilia (91%), and lymphopenia (6%) confirmed an intense thrombo-inflammatory state. Positive blood cultures for *Acinetobacter lwoffii* indicated secondary bacterial sepsis.

This case provides vital insights for the diagnostic and management strategies applicable to high-risk trauma patients:

- **Routine Cardiac Screening in Trauma:** Unrecognized cardiac anomalies such as ASDs or patent foramen ovale (PFO) can serve as conduits for paradoxical embolism. Incorporating transthoracic or transesophageal echocardiography into the evaluation of trauma patients with unexplained neurological changes is advisable [13].

- **Heightened Vigilance in HIV-Positive Patients:** Given that HIV-associated endothelial dysfunction and ART-induced hypercoagulability significantly increase the risk of systemic embolism, proactive monitoring of coagulation and inflammatory markers is essential in these individuals.

- **Broadening the Diagnostic Approach to FES:** Neurological symptoms preceding respiratory distress should prompt consideration of paradoxical embolism. Early utilization of MRI with diffusion-weighted imaging (DWI) and echocardiography is crucial for accurately diagnosing cerebral involvement.

## Conclusion

Fat embolism syndrome (FES) is a complex and often overlooked complication of long bone fractures, typically presenting with acute respiratory and neurological symptoms. Early detection and intervention are crucial to prevent outcomes ranging from mild hypoxia to severe multisystem failure.

This case is unusual due to cerebral fat embolism (CFE) triggered by an undiagnosed atrial septal defect (ASD), which allowed fat emboli to bypass the lungs and directly reach the brain, causing early neurological symptoms rather than the usual respiratory manifestations. Advanced MRI revealed the classic "starfield pattern" and microhemorrhages, highlighting severe microvascular injury.

Since there is no definitive laboratory test for FES, a combination of clinical criteria and neuroimaging is essential for diagnosis and management. This case underscores the importance of cardiac evaluation and a multidisciplinary approach in trauma patients with unexplained neurological deficits.

## Ethical Considerations

### Compliance with ethical guidelines

There were no ethical considerations to be considered in this article.

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## Conflict of Interests

The authors have no conflict of interest to declare.

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