Case Report

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Detect it Early! Fat Embolism Syndrome (FES)

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Abstract

Fat embolism syndrome (FES) is a rare but a serious clinical catastrophe occurring after traumatic injury to long bones. Cerebral involvement in the absence of pulmonary or dermatological manifestation on initial presentation may delay the diagnosis of cerebral fat embolism (CFE). Cerebral fat embolism typically occurs in patients with bony fractures (usually long bones of the lower limb). Fat embolism syndrome has an incidence of 1-3% following long bone fractures and 33% in patients with bilateral long bone fractures. We discuss a case series of CFE which posed a challenge in diagnosis. The clinical presentations of these patients did not satisfy the commonly used clinical criteria for aiding the diagnosis of FES. Early MRI brain (DWI and T2 weighted sequences) in patients with neurological symptoms after trauma even in the absence of pulmonary and dermatological findings should be the goal.

Keywords: Cerebral fat embolism; Fat embolism syndrome; Magnetic resonance imaging.

INTRODUCTION

Fat embolism is a rare clinical phenomenon frequently occurring following trauma and orthopedic procedures involving intramedullary region which releases fat globules, resulting in pulmonary and systemic signs typically manifesting after 24-72 hours. Fat embolism syndrome (FES) is classically identified as a triad of sudden pulmonary distress (*i.e.* dyspnea, hypoxemia and tachypnea), neurological symptoms and a petechial rash often involving the axilla, torso and sclera.[1] Furthermore, sudden circulatory collapse can occur in conditions with massive fat embolism. Diagnosis can be challenging relying primarily on early recognition of symptoms, and exclusion of other differential diagnosis.

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CASE REPORT

Case 1

A 23-year-old male with no past medical history presented to the emergency room with left midshaft femoral fracture following a road traffic accident. Initial neurological examination was normal however patient had facial injuries hence a computed tomography (CT) scan brain was performed which did not demonstrate any significant abnormality. Patient was admitted to the

orthopedic ward and planned for closed reduction with internal fixation (CRIF) with intramedullary nailing. The following day, the patient became increasingly drowsy with no response to verbal commands. On examination, patient appeared to be sweating with impaired breathing pattern. His examination demonstrated tachycardia (128 bpm), tachypnea (26/min), hypoxemia (sPO2- 89% on room air) and was febrile (T-101.4 F).

Patient was admitted to the Intensive care unit (ICU) with non-invasive ventilation for further diagnostics and treatment. Further examination revealed petechial rash over the chest. Fig. 1. A neurologist was consulted to exclude a neurological pathology. Neurological examination showed an impaired consciousness with a Glasgow coma scale (GCS) of 11 (E2V3M6), normal pupillary reaction, normotonic muscle state with intact deep

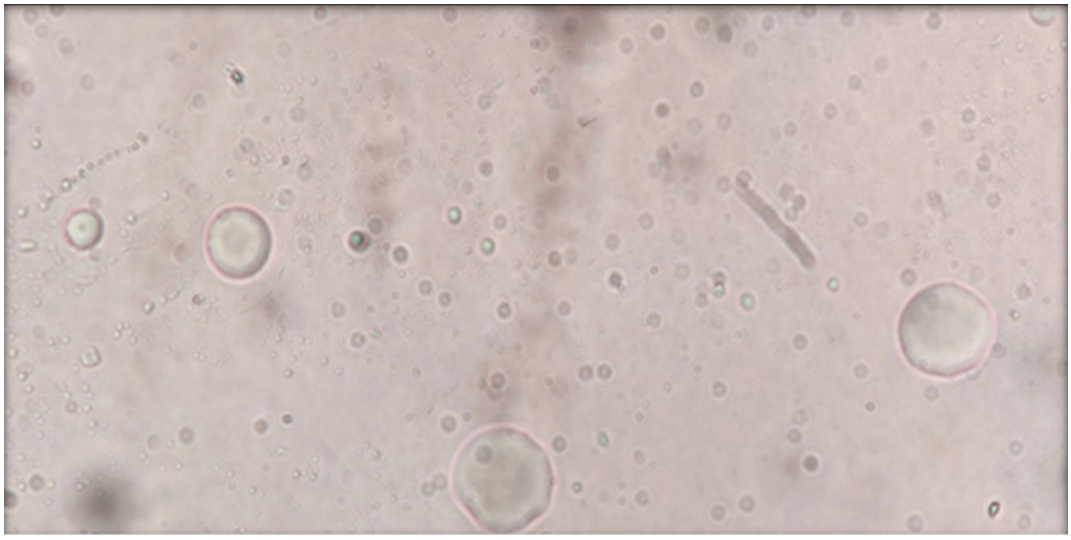

Fig. 1: Fat globules seen in Urine microscopy

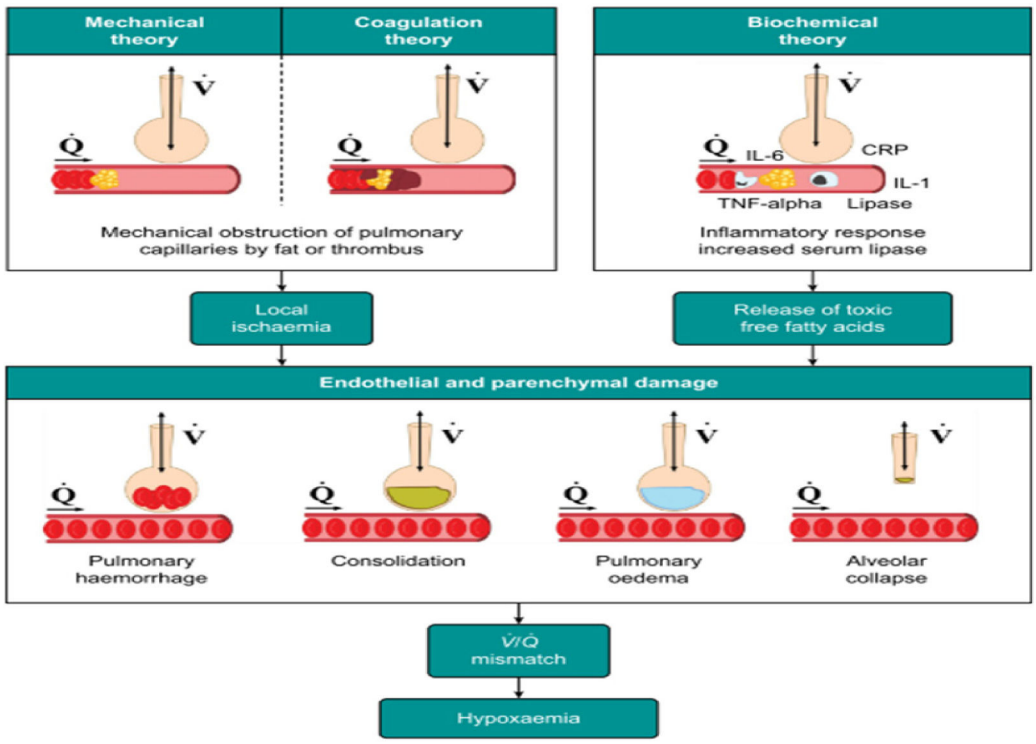

Fig. 2: Pathogenesis of fat embolism. Three thenries have been proposed: mechanical, coagulation, and biochemical. Fat embolisation causes local parenchymal damage after vascular occlusion (by fat or thrombus), an exaggerated inflammatory response, or both. Subsequently, pulmonary haemorrhage, consolidation, pulmonary oedema and/or alveolar collapse result in a ventilation (V)/ perfusion (Q) mismatch and hypoxaemia. CRP, C-reactive protein, IL-1, interleukin-1; IL-6, interleukin-6; TNF-alpha, tumour necrosis factor-alpha

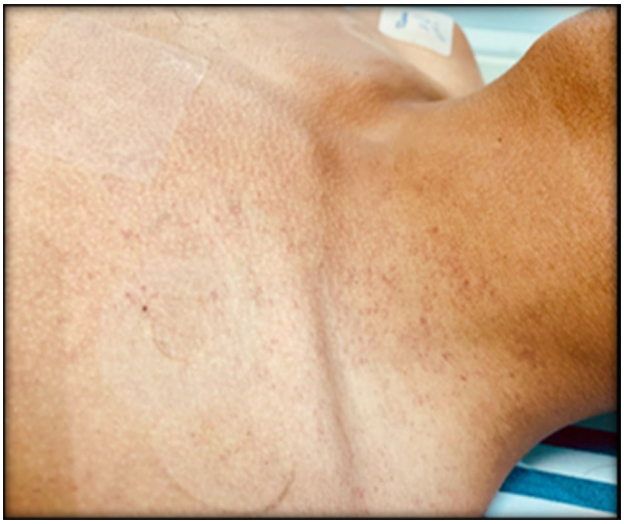

Fig. 3: Petechial rash seen over the chest and axilla

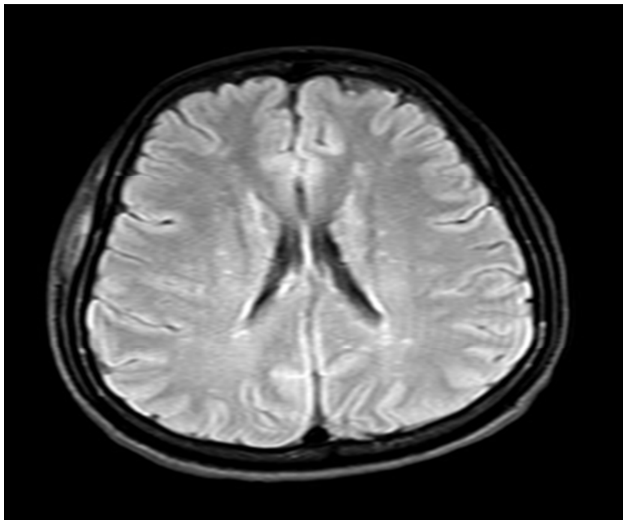

Fig. 4: Hyperintensities seen diffusely in bilateral cerebral hemispheres

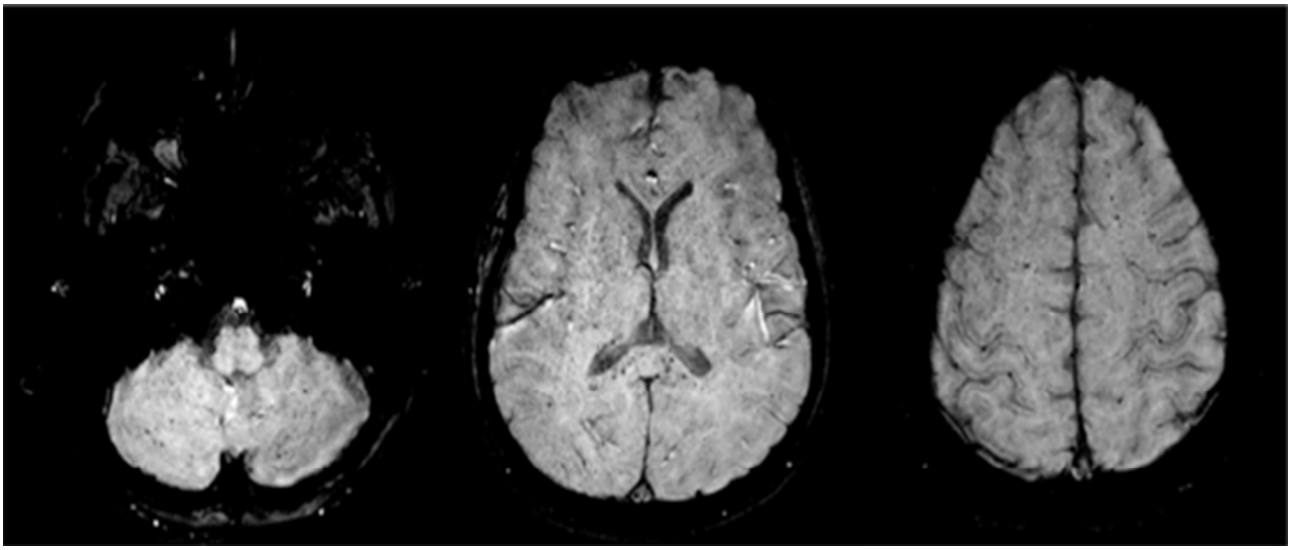

Fig. 5: Hyperintensities seen diffusely in bilateral cerebral hemispheres of diffusion susceptibility imaging

tendon reflexes. Routine labs demonstrated anemia, thrombocytopenia and elevated D-dimer levels. A screening echocardiography was done which did not demonstrate right ventricular (RV) dilation/ RV strain or any evidence of patient foramen ovale. A CT pulmonary angiography was performed due to suspected pulmonary embolism with a wells score of 6 demonstrating small wedge-shaped opacities in the posterior basal segment of both lower lobes with small pleural effusions and basal atelectasis. A magnetic resonance (MR) scan of brain with MR angiography was also performed which showed multiple tiny areas of restricted diffusion scattered in bilateral cerebral parenchyma and lentiform nucleus of thalami. These lesions have been described as a "starfield" pattern in literature. Fig. 2,3. MR scan was also suggestive of cytotoxic edema of corpus callosum with restricted diffusion seen in the splenium of corpus callosum. Urine for fat globules was sent which came back positive. Fig. 4. An ophthalmologic exam demonstrated bilateral subconjunctival hemorrhages however a fundus examination did not show any retinal changes secondary to embolism. Patient was started on therapeutic anticoagulation and remained hemodynamically stable without vasopressor support. Patient continued to be monitored and underwent CRIF with nailing following stabilization.

Case 2

A 17-year-old male with no past medical history presented to the emergency room with left distal end femoral and left midshaft tibia fracture following

a case of assault. Initial neurological examination was normal however patient had facial injuries hence a computed tomography (CT) scan brain was performed which did not demonstrate any significant abnormality. Patient was admitted to the orthopedic ward and planned for closed reduction with internal fixation (CRIF) with intramedullary nailing. The following day, the patient became increasingly drowsy with no response to verbal commands. On examination, patient appeared to be sweating with impaired breathing pattern. His examination demonstrated tachycardia (132 bpm), tachypnea (30/min), hypoxemia (SPO_2 - 86% on room air) and was febrile (T-102.4 F).

Patient had to be intubated in view of poor GCS to protect airway. Patient was admitted to the Intensive care unit (ICU) with non-invasive ventilation for further diagnostics and treatment. Routine labs demonstrated anemia, thrombocytopenia and elevated D-dimer levels. A screening echocardiography was done which did not demonstrate right ventricular (RV) dilation/ RV strain or any evidence of patient foramen ovale. A CT pulmonary angiography was performed due to suspected pulmonary embolism with a wells score of 7 demonstrating consolidatory changes in the posterior basal segment of both lower lobes and basal atelectasis. No evidence of pulmonary embolism was noted. A magnetic resonance (MR) scan of brain with MR angiography was also performed which showed multiple tiny areas of restricted diffusion scattered in bilateral cerebral parenchyma and lentiform nucleus of thalami. These lesions have been described as a "starfield" pattern in literature. Fig. 5. MR scan was also suggestive of cytotoxic edema of corpus callosum with restricted diffusion seen in the splenium of corpus callosum. Urine for fat globules was sent which came back negative. An ophthalmologic exam demonstrated bilateral subconjunctival hemorrhages however a fundus examination did not show any retinal changes secondary to embolism. Patient was started on therapeutic anticoagulation and remained hemodynamically stable without vasopressor support. Patient continued to be monitored and underwent CRIF with nailing following stabilization.

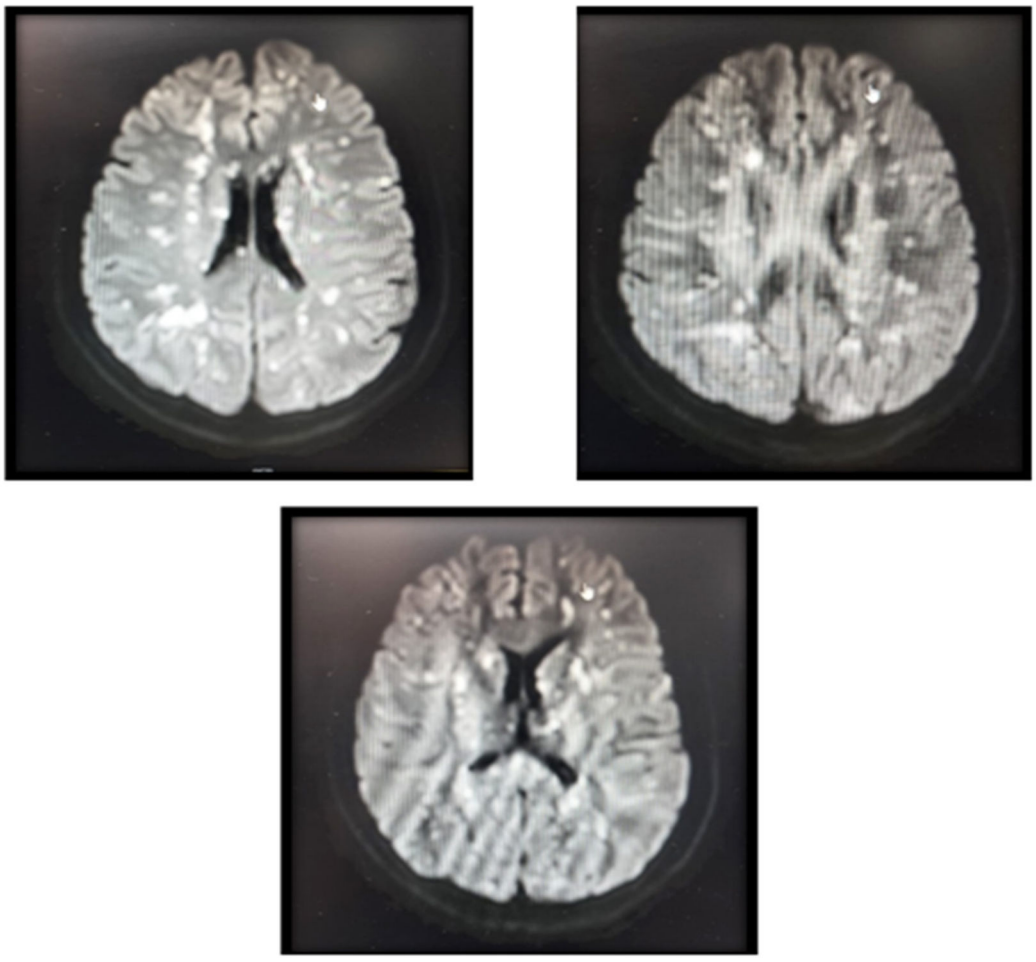

Fig. 6: Hyperintensities seen diffusely in bilateral cerebral hemispheres of diffusion susceptibility imaging

Table 1: Modified Gurds criteria

Modified Gurds criteria	
Major criteria	Minor criteria
Axillary or subconjunctival petechial rash*	Tachycardia*
Hypoxemia PaO2 <60mmHg*	Pyrexia <38.5 C*
Central nervous system depression disproportional to hypoxemia*	Emboli in retina on fundoscopic examination
Pulmonary edema	Fat present in urine*
	Sudden unexplained drop in hematocrit or platelet values*
	Increasing erythrocyte sedimentation rate
	Fat globules in the sputum
	Symptoms within 72 hour of skeletal trauma*
	Shortness of breath*
	Altered mental status*
	Occasional long tract signs or posturing
	Urinary incontinence

Table 2: Lindeque's criteria

Lindeque's criteria
Sustained PaO2 <8 kPa
Sustained PCO2 of >7.3 kPa or a pH <7.3
Sustained respiratory rate .35 breaths min despite sedation
Dyspnea, tachycardia, anxiety

Table 3: Schonfeld's criteria

Criteria	Score
Petechiae	5
Chest X-ray changes (diffuse alveolar infiltrates)	4
Hypoxemia (PaO2 <9.3 kPa)	3
Fever (>38°C)	1
Tachycardia (>120 bpm) Tachypnea (>30 bpm)	1
Confusion	1

DISCUSSION

FES is primarily related to traumatic fractures and rarely secondary to non-traumatic events like pancreatitis, sickle cell disease, lipid infusions and steroidal therapy.[2] The incidence of FES has been reported as 0.9% to 2.2% in patients with long bone fractures. Common risk factors include long bone fractures (mainly femoral and tibial intramedullary fractures), presence of multiple fractures and late surgical fixation of fractures.[3] FES is most diagnosed in males under 30 years of age due to high incidence of trauma in the age group.[4]

Symptoms of FES typically appear 24-72 hours after sustaining fracture and is characterized by major and minor findings, as defined by Gurd.[5] Three major and four minor changes marked as (*) in table, were manifested in our patient. Lindeque proposed a diagnostic criterion for FES based only on the respiratory status of the patient (table 2).[23] Respiratory symptoms like tachypnea and dyspnea are the most observed symptoms however pulmonary edema, acute respiratory distress syndrome (ARDS) and fulminant respiratory distress has also been reported. Massive fat embolism may even lead to obstructive shock progressing to acute RV failure. Neurological manifestations have been reported in more than 67% cases, and include confusion, altered mental status, seizures and focal neurological deficits.[6,7] More recently, Schonfeld proposed FE Index for diagnosing FES which is a quantitative measure comprised of seven clinical features, each one is given a particular score and a score of >5 is required for making the diagnosis of FES (table 3).[24] Depending upon the severity of cerebral emboli 'shower', refractory status epilepticus and sudden brain death has also been described in select cases. In addition to respiratory and neurological symptoms, a petechial rash mainly in the axilla, trunk and sclera is observed in 50% of patients. The rash tends to be transient lasting less than 24 hours.[8]

Pathophysiology involving FES is poorly understood with two leading theories (Fig 2). Gossling et al. described a mechanical theory which

suggests obstruction of the systemic vasculature by fat embolus occurs owing to elevated intramedullary mechanical pressure secondary to trauma leading to fat emboli release into open venous sinusoids leading to capillary bed occlusion. This further activates the clotting cascade in the pulmonary vasculature by thromboplastin leading to expansion of fat droplets, making it more likely for vessel occlusion.[4] Alternatively, the biochemical theory states tissue lipases induced by stress following trauma breakdown fat to free fatty acids (FFAs). FFAs cause systemic toxicity injuring the endothelium causing platelets aggregation and clotting.[9] This could potentially explain the delay between traumatic event and onset of symptoms.

Diagnosing FES is challenging as currently no diagnostic modality exists to establish a diagnosis. Laboratory tests and radiological tests are non-specific for FES with most common findings being anemia and thrombocytopenia.[6] An X-ray or CT scan may show no abnormalities or show non-specific findings like bilateral diffuse infiltration/ edema however are required to rule out more common etiologies for neurological dysfunction. MR scan is more sensitive and typically demonstrates a 'starfield' pattern consisting of bilateral diffusely spread hyperintense lesions in the cerebral white and grey matter, cerebellum and brainstem on T2-weighted or diffusion weighted images with fluid-attenuated inversion recovery (FLAIR) signals.[10,11]

Treatment primarily involves supportive care however anticoagulation with heparin is widely used. Heparin further stimulates lipase enzyme activity which lowers intravascular lipid concentrations reducing inflammation by FFAs. A meta-analysis conducted by Zuowen *et al* demonstrated a potentially protective effect of corticosteroid therapy.[12] Corticosteroids as a prophylactic measure has been studied as a prospective, randomized, double-blind study in patients with high risk for FES demonstrating the incidence of FES in patients treated with methylprednisolone vs placebo (0% vs 21%, p=<0.05) hence recommending corticosteroid use as a protective agent in patients with high risk for FES.[13] However, due to high risk for infection and conflicting results, current corticosteroid use is not recommended. Preventive measures include early fixation of fracture and lowering intramedullary pressure during surgery (*e.g.* Using reamer systems/ intramedullary cavity suctioning) however further studies to determine therapeutic benefit are limited.[14,15]

Cerebral Fat Embolism

CFE occurs after fat emboli enter the arterial circulation. Fat globules may enter the arterial circulation by 2 mechanisms. First, fat globules can enter the left atrium directly from the right heart through a shunt, such as a PFO (paradoxical embolism). Second, micro globules of fat may filter directly through the lung capillaries to reach the arterial system. These micro emboli are small and malleable and may not lead to significant pulmonary injury. There is direct evidence of passage of fat through a PFO, yet the absence of PFO in many patients with CFE supports the latter mechanism in some patients.[15,16] Therefore, PFO should be considered an additional risk factor for CFE but is not necessary for the syndrome.

The neurological findings in CFE vary greatly, ranging from mild confusion to coma, and rarely include seizures and focal findings.[15-17] These signs can occur in isolation but more often are associated with and occur after respiratory failure. They may occur as a consequence of hypoxemia or cerebral embolism.[17] The effects of CFE are often reversible and associated with a favourable outcome.[15,17] Mortality ranges between 5% and 15% with most deaths attributable to respiratory failure.[17] There are limited data on the cognitive outcomes of surviving patients with CFE; however, long-term studies of 2 young patients found a near-complete recovery at 4 months.[21]

CFE is a clinical diagnosis, but specific findings on neuroimaging studies can be strongly supportive. Computed tomographic scans are frequently normal in these patients. The characteristic MRI finding is the starfield pattern, demonstrating scattered foci of high-intensity restricted diffusion on diffusion-weighted imaging. This is most apparent in the acute phase, from 4 hours to the first few days from the time of injury. T2-weighted lesions may take several days to become apparent. These lesions are most commonly found in the deep white matter, including the basal ganglia, brain stem, and cerebellum.[20] Multiple scattered foci of hypointensity on susceptibility weighted imaging are indicative of cerebral microbleeds and can be useful in the acute setting.[21] Such widespread petechial hemorrhage and bland microinfarction have been demonstrated on autopsy.[22] Our patient presented to the hospital ≈1 week from the time of injury, and lesions on diffusion weighted imaging were not as apparent as with susceptibility weighted imaging. Takahashi et al correlated clinical findings with those on MRI and found that the number of

abnormal signals correlates with the Glasgow Coma Scale.[20] They also demonstrated that good outcome was associated with dissipation of lesions and that patients with poor outcome were more likely to have persistent multiple infarctions 2 months after presentation.[20]

There is no current treatment for FES or CFE other than supportive care to address both intrinsic lung pathology and airway protection in the setting of neurological impairment.[17] Corticosteroids have been extensively studied with variable results, and their use is controversial. Gupta et al. propose a regimen of methylprednisolone 1.5mg/kg IV every 8 hours for 6 doses in a select group of patients with long bone or pelvic fractures at high risk of developing FES and without significant contraindications.[17] Early fixation of fractures within 24 hours has been recommended to prevent further trauma at the injury site and thus decrease the incidence of FES.[15] Several studies, however, have failed to make an association between the incidence of FES among patients who had early fixation of fractures and those who did not.[18] Early surgical stabilization should be considered, though this intervention has not consistently been shown to decrease overall risk.[15,16]

In summary, clinical FES and CFE are relatively uncommon, whereas the true incidence of fat emboli, mostly asymptomatic, is high in the setting of long bone and pelvic fractures. The diagnosis should be investigated in patients who develop respiratory distress, new neurological symptoms, and petechial rash. Imaging studies are critical in the diagnosis of CFE, especially MRI. The classically described starfield pattern may only be present in the acute phase, and patients presenting later may instead demonstrate findings on susceptibility-weighted imaging consistent with diffuse, scattered micro haemorrhages. In patients presenting early, prophylactic corticosteroids may be considered. The mainstay of therapy remains supportive respiratory and neurological care. Although there are reports of excellent recovery in patients with CFE, some do not survive. Prognosis should be considered in the context of concomitant illness and premorbid functional status.

CONCLUSION

Most patients with FES recover fully without residual deficits. Mortality rate varies from 5% to 15% in various studies. However, patients with older age, numerous comorbid medical conditions, and diminished physiologic reserve have more terrible results. The fulminant form of FES displays as acute cor pulmonale, respiratory failure or embolism, and prompting to death of patient inside few hours of injury. Hence in short, a high index of suspicion is needed to diagnose FES and a combination of clinical criteria is needed to accurately diagnose it and early supportive therapy is the mainstay of treatment.

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