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Trauma Case Reports

Case Report

Fat embolism syndrome with neurological involvement: A case report

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ABSTRACT

Background: Fat Embolism Syndrome (FES) occurs when the contents (or some component of) the bone marrow is released into the circulation, generally as the result of long bone fracture. It poses significant challenges in both diagnosis and treatment and, as such, is primarily a diagnosis of exclusion with no definitive treatment. We present a case where heightened awareness of the clinical team allowed for early identification and immediate initiation of supportive care, nitric oxide (NO) for potential mitigation of right heart failure, and pharmacological treatment with atorvastatin.
Patient: A 16-year-old male with multi-system trauma, including bilateral long-bone fractures, developed Fat Embolism Syndrome with neurological and respiratory symptoms within 24 h of admission.
Results: Within 24 h of initiation of high dose atorvastatin and inhaled Nitric Oxide our patient showed signs of improvement, including decreasing oxygen requirement's and normalization of mental status.
Conclusion: We postulate that the combined therapy of high-dose atorvastatin with Nitric Oxide may have played a role in our patients' full recovery in a shortened timeframe. Ideally, further prospective research is needed to determine a universally accepted treatment regimen for pediatric patients with FES.

Introduction

The diagnosis and management of Fat Embolism Syndrome (FES) is a disputable topic amongst researchers and clinicians. However, the correlation between long-bone fractures and the development of FES is universally accepted. From 1967 to 1974, the standard of care for orthopedic trauma and long-bone fractures transitioned from conservative management to early internal fixation resulting in a rapid decline in FES development [1]. In 1974, A. Gurd, with modification by R. Wilson, proposed the first clinical criteria for diagnosing FES that is still used as a reference today [1]. Clinical cases to date are rare, developing in approximately 1–11% of patients with long-bone fractures [2].

Here we report a case of FES with neurologic involvement that highlights both early diagnosis and interventions that minimized length of stay and maximized the best possible patient outcome, and areas that we identified as room for improvement.

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Case

A 16-year-old male, unrestrained driver was involved in a high speed, rollover, motor vehicle collision. Emergency medical services (EMS) report from the scene included an initial Glasgow Coma Score (GCS) of 14, significant deformities the femurs bilaterally, and stable vital signs. During transport, his vitals remained stable and on arrival to the Level 1 Pediatric Trauma Center he had a GCS of 15 with the aforementioned lower extremity findings. After resuscitation with primary and secondary surveys following ATLS guidelines he was transported to radiology to obtain CT head, CT abdomen & pelvis with IV contrast and additional extremity X-rays. Lower extremity imaging was significant for an acute displaced transverse mid diaphyseal fracture (Fig. 1a) with foreshortening of the left femur, an acute displaced fracture of the right proximal femur, as well as a right posterior acetabular fracture (Fig. 1b). The abdominal/pelvic CT scan identified mild bilateral pulmonary contusions (Fig. 2), grade 1 liver laceration (Fig. 3a), grade 1 spleen laceration, and a grade 3 right renal laceration with a perinephric hematoma (Fig. 3b). The head CT scan was normal. Initial trauma labs were significant for modestly elevated liver enzymes and total bilirubin and an elevated creatinine kinase at 2979. Complete blood count and renal function were normal. Urine toxicology screen was positive for tetrahydrocannabinol (THC). The patient was admitted to the Pediatric Intensive Care Unit (PICU) with ongoing stable neurologic exam and GCS of 15.

Regarding the management of his lower extremity fractures, he was placed into 10 lbs. of bilateral Buck's traction within 2 h of arrival to the trauma center and was taken to the operating room (OR) with orthopedic surgery 4 h after arrival. At operation, he underwent open reduction and internal fixation of bilateral femur fractures. The left femur was sequentially reamed to 13.5 mm over a guidewire and fixated with 12×420 mm antegrade locking nail. The right femur required a small fragment plate to hold the reduction and was then sequentially reamed to 13.5 mm over a guidewire. It was fixated with a 12×240 mm antegrade locking nail. Review of the anesthetic record revealed no physiologic abnormalities during fixation. The acetabular fracture was assessed and found to be stable. Bilateral Ropivicaine femoral nerve catheters were placed for post-operative pain control. He was extubated in the operating room and transferred directly to the PICU.

In the PICU, while emerging from anesthesia, he was found to be agitated and in pain. Despite attempts at managing these new symptoms with narcotics and clinician boluses of the femoral catheters, he continued to have intermittent episodes of altered mentation, which were associated with desaturations requiring increasing supplemental oxygen. A low dose of Naloxone infusion was unsuccessful in improving his mental status and was discontinued due to increasing agitation and concern for uncontrolled pain. His neurologic course continued to deteriorate with loss of ability to follow commands and ability to answer questions appropriately. At this time, the clinical team became concerned that he had suffered a FES event given the constellation of his exam and laboratory findings (neurologic decline, increased respiratory support, persistent anemia, and thrombocytopenia). The patient never developed a petechial rash. Over the next 12 h, he continued clinically decline, requiring 10 l of oxygen via mask and remained encephalopathic with a GCS 8–9 and extreme agitation, despite aggressive supportive therapy.

Given his ongoing neurologic decline he underwent magnetic resonance imaging (MRI) of the brain and neurology was consulted. The brain MRI was significant for numerous punctate foci of the parenchyma T2/DWI/SWI signal abnormality resembling the typical 'starfield pattern' seen with FES (Fig. 4). To further evaluate for FES a CT angiogram of the chest was performed which revealed scattered dependent consolidations with interstitial thickening and bilateral groundglass opacities concerning for pulmonary edema, contusion, or FES (Fig. 5). Given the cerebral findings on MRI a cardiac echo with bubble study was performed to evaluate for abnormal cardiac anatomy that could lead to right-to-left shunting or intra-cardiac thrombi. The echo showed normal systolic function
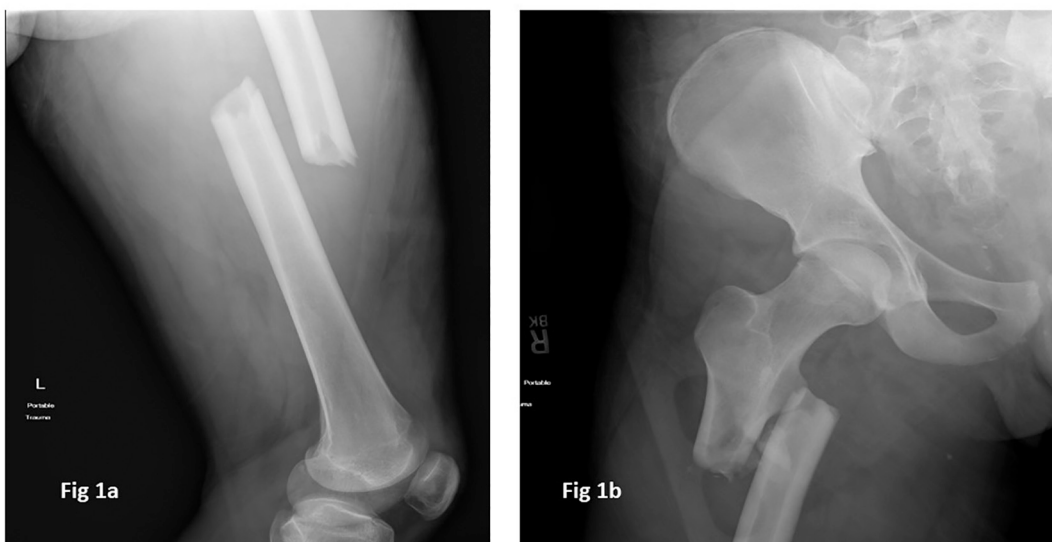

Fig. 1. These two lower extremity radiographs obtained in the trauma room revealed a left lower extremity displaced midshaft femur fracture (a) and right lower extremity displaced proximal femur fracture (b).
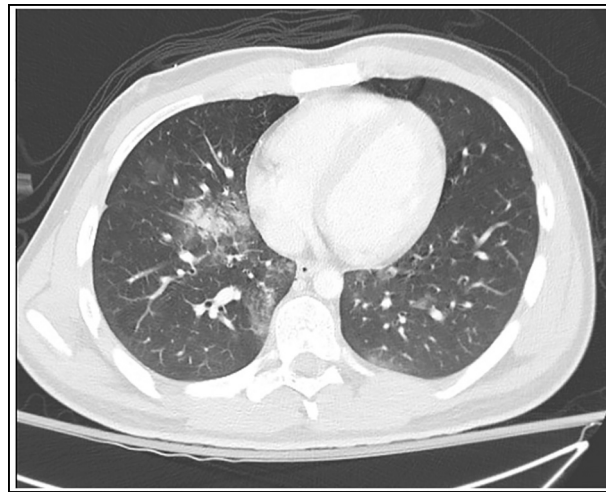
Fig. 2. The CT chest showing multiple pulmonary contusions.

Fig. 3. A grade 1 liver laceration (a) highlighted in the solid black circle and a grade 3 right renal laceration as indicated by the solid black arrow (b) were seen on the CT abdomen and pelvis.

with elevated right ventricular systolic pressure at least 55 mmHg plus mean right atrial pressure. His laboratory studies revealed persistent anemia and thrombocytopenia, despite multiple transfusions, and elevated CK level, which plateaued at 16,773, and an elevated creatinine. With the lack of significant impact from the ongoing clinical support, the team began researching treatment options.

A report by Whalen et al. reported the use of statins as a treatment option in FES. They described using a titrated dosing schedule for Rosuvastatin to treat FES with neurological involvement. A multidisciplinary care conference was held with our trauma team, ICU, pharmacy, neurology, and the patient's family to consider the risks and benefits. It was unanimously decided to proceed with statin therapy, which was initiated on post-injury day 2, approximately 12 h after the onset of his neurological symptoms. Because Rosuvastatin was not on available on our formulary, Atorvastatin was used and dosed at 40 mg on day 1, 60 mg on day 2, and 80 mg on days 3–6.

Concurrent to his neurologic deterioration, his respiratory status declined requiring escalation to bi-level positive airway pressure (BiPap). As we continued to research for additional therapies for FES, a separate study by Brotfain et al., was identified that described using nitric oxide (NO) in patients with FES to help mitigate right heart failure. Although our patient had a structurally normal echo, it did demonstrate elevated right ventricular systolic pressures. After a second multidisciplinary care conference, including cardiology, we initiated NO therapy at 20 ppm.

Shortly after the implementation of Atorvastatin and NO our patient began to stabilize. Within 24 h, his mental status showed signs
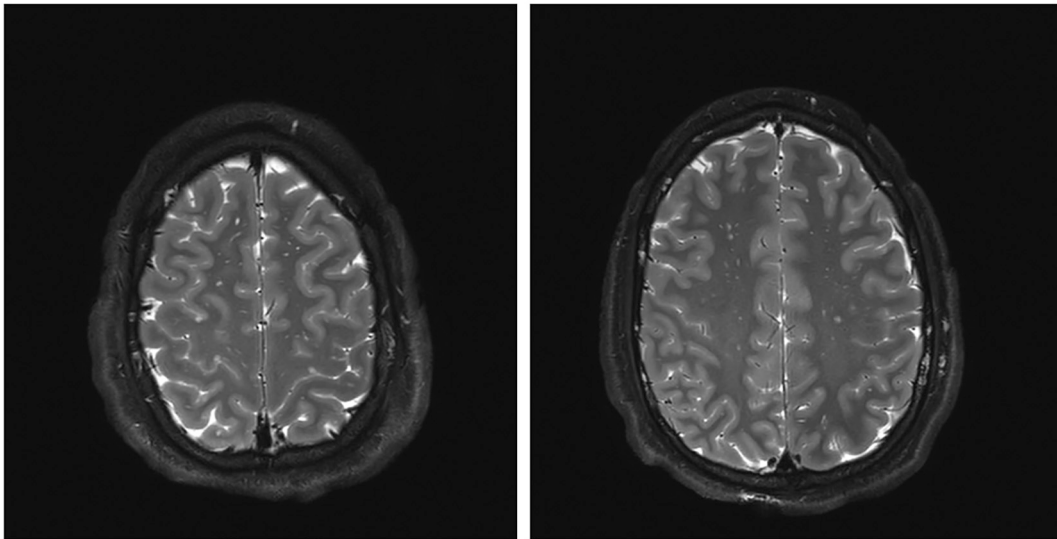
Fig. 4. These two images from the patients MRI head show numerous punctuate foci of parenchymal T2 signal abnormality resembling a "starfield pattern" which is classically seen in fat embolus syndrome.

Fig. 5. The CT angiogram of the chest revealed ground glass appearance concerning for pulmonary edema, contusion, or FES.

of improvement. His GCS increased to 11 and he was less agitated, answering questions intermittently and following some simple commands. Simultaneous to the improved neurological exam, there was an improvement in his respiratory status. A repeat cardiac echo showed resolution of his increased right ventricular systolic pressure at 23 mmHg. After approximately 48 h, NO and BiPAP were weaned to low flow nasal cannula.

At the recommendation of neurology, our patient also underwent daily Transcranial Doppler (TCD) to assess for thrombus and was evaluated by ophthalmology for retinal abnormalities. His daily TCDs remained normal, and his ophthalmology examination showed no evidence of disc edema or peripheral retinal changes. On post-injury day six, he was transferred out of the ICU to the general pediatric floor with no oxygen requirement and stable neurologic exams. He was transferred to inpatient rehabilitation on post-injury day 12, and discharged home on post-injury day 22. His ISS was calculated to be 27 with a TRISS of 97.4%.It should be noted that his course was complicated by a return to the OR for evacuation of a right thigh hematoma on hospital day seven and development a DVT secondary to a peripherally inserted central catheter (PICC) on hospital day eight. The patient is now 6 months post injury and has fully recovered with no neurologic or pulmonary sequelae.

Discussion

Two theories regarding the pathophysiology of FES have been proposed: the mechanical theory and the biochemical (or metabolic) theory. The mechanical theory associates the alterations in clinical presentation to an increase in intramedullary pressure, whether from operative fixation with intramedullary nailing or from a sudden and major manipulation of the fracture site. In both situations, the bone marrow contents are leaked into the vasculature. In order for FES to have neurologic affects, this theory initially suggested that an intracardiac shunt (patent foramen ovale) was required for the fat emboli to travel to the cerebral vasculature [1]. However, the most recent evidence points out that an intrapulmonary shunt or an arteriovenous shunt gives the fat particles access to the brain [2].

Gurd originally described the biochemical or metabolic theory as the induction of the body's inflammatory response related to the traumatic injury. This causes the bone marrow adipocytes to release free fatty acids into the venous system, where they are joined by chylomicrons and low-density lipoproteins to form the circulating fat emboli [1]. Current evidence suggests that the release of free fatty acids and chylomicrons results from of a hormonal change [2]. Regardless, the elevated free fatty acids lead to damaged capillary beds, increased permeability, pulmonary inflammation, and resultant hypoxemia. Arachidonic acid is one of the released free fatty acids that has been associated with cerebral edema [3]. Induced inflammatory mediators further damage the capillary beds and surrounding tissue. Interestingly, an increase in the inflammatory marker c-reactive protein (CRP) higher than the expected baseline elevation of CRP in trauma patients is specific to FES. A combination of the two theories when considering the entirety of the case from initial injury through operative fixation is also plausible. Regardless of which theory, the result is an increase in pulmonary artery pressure, impaired oxygen exchange secondary to ventilation-perfusion (VQ) mismatch, and an increase in vascular permeability and vasodilation secondary to the release of amines and neurotransmitters which can lead to systemic fat distribution [2].

A brief review of the origin of the "fat" in FES is warranted to understand the mechanism for potential benefit in using statins in FES. The bone marrow space inhabitants include low-density lipoproteins, chylomicrons, high-density lipoproteins, short-chain fatty acids, free fatty acids, adipocytes, and glucose [4]. The bone marrow fat cells also consist of free fatty acids and glycerol [4]. Lipid globules within the marrow adipocytes are identical to those found in peripheral adipocytes, susceptible to lipolysis when the body's energy demand increases, resulting in the release of free fatty acids and free glycerol [4]. Marrow adipocyte fatty acids are made up of saturated, monounsaturated, and polyunsaturated fat, with saturated fat comprising the largest percentage [5]. The most common saturated fatty acid released, palmitic acid, increases the production of mitochondrial reactive oxygen species, resulting in mitochondrial dysfunction stimulating apoptosis. The proportion of bone marrow adipocytes increases with age, dominating approximately 70% of the skeletal niche at its peak and males with a greater percentage than females [4]. Marrow adipocytes within long, axial bones reflect the most exaggerated increase in quantity at the peak of skeletal mass acquisition, which is noted during puberty [5]. According to the American Academy of Pediatrics, puberty in males starts at 9–14 years and lasts approximately four years. Of note, our patient was a 16-year-old male.

Membrane permeability and fluidity of marrow cells rely on the body's meticulous regulation of the cholesterol biosynthetic pathway to balance the cholesterol production with the homeostatic need. The primary mechanism of action of HMG-CoA reductase inhibitors, also known as "statins," is to prevent the rate-limiting step of cholesterol synthesis in the liver with subsequent upregulation of hepatic LDL receptors. This statin therapy impairs the pathway, resulting in a lipid-lowering effect [6]. Cholesterol embolization syndrome is a condition similar to FES with "showers of cholesterol microemboli" identified in the brain, renal system, gastrointestinal system, musculoskeletal system, and skin [7]. Statin therapy has been universally accepted as an efficacious treatment plan for this condition, making it more appealing when considering FES treatment.

Regarding use of statin therapy in the pediatric population, there have been numerous reports including from the American Academy of Pediatrics documenting its safety. Statin therapy is a universally accepted, cost-effective treatment for children due to the well-established lipid-lowering effect and short-term efficacy [8]. The American Academy of Pediatrics reports HMG-CoA reductase inhibitors' safety profile as mirroring statin therapy in adults and considering it a safe and effective pharmacological intervention for children identified as high risk [9]. According to the AHA Guidelines, statin therapy initiation for children as young as eight years old is recommended, for example, with familial hypercholesterolemia. It reports the side effect profile as one without cause for concerns that should discourage therapy [10].

Regardless, risk factors should always be considered before initiating any therapeutic regimen, as the therapy is only as beneficial as the side effects are negligible. Drugs that use the cytochrome 450 isoenzyme, CYP3A4, for metabolism are at risk of interacting if given simultaneously. A few statins that use this isoenzyme for partial metabolism, and therefore need to be considered when prescribing for a patient taking other medications [6]. Simvastatin, lovastatin, and atorvastatin are three HMG-CoA reductase inhibitors with this pharmacology [6]. Statins are also associated with teratogenicity. Precision medicine should be used to identify patient-specific risk factors, such as existing renal insufficiency, pregnancy, or other active medication management, that might affect the desired outcome [6].

One of FES's common effects is refractory hypoxemia, which developed in our patient approximately 24 h following his initial injury. Patients with FES can rapidly deteriorate with the onset of symptoms [3]. While this phenomenon's complete pathophysiology is not fully understood, the rapid deterioration often leads to complete respiratory collapse, ARDS, or mechanical obstruction of the pulmonary artery flow due to emboli resulting in pulmonary hypertension or cardiovascular collapse [11]. We opted to initiate NO therapy early given his continued respiratory deterioration, before the onset of significant pulmonary hypertension or right heart failure. As discussed, following the initiation of NO, his respiratory status rapidly improved, and his right heart function normalized, as evidenced by a repeat echocardiogram that demonstrated a right ventricular pressure decrease of 23 mmHg as compared to the pre-NO echo of 55 mmHg. NO therapy is safe with a relatively low risk profile of adverse effects and should be further evaluated in patients with FES to identify the specific benefits it may offer for treatment and prevention of worsening cardiovascular collapse.

With an array of potential signs, symptoms, and severity, FES is difficult to diagnose without a universally accepted diagnostic criteria. The added insult of multi-system trauma exponentially increases this clinical management dilemma. There have been multiple early studies describing the criteria for diagnosing FES. The first proposed diagnostic criteria by Alan Gurd in 1974 was based on a study of 100 FES cases. Based on the study results, he identified respiratory insufficiency, cerebral involvement, and petechial rash as "major features" and pyrexia, tachycardia, retinal changes, jaundice, and renal changes as "minor features." Anemia, thrombocytopenia, high erythrocyte sedimentation rate, and an abrupt change in fat macroglobulemia were the predominant hematology findings associated with FES. Gurd suggested a definitive diagnosis of FES if one major and four minor criteria plus an abrupt change in fat macroglobulemia were identified [1].

Other studies conducted around the same time as Gurd's continued to support the variability in clinical presentation. Allardyce et al. reported a minimal significance of arterial PO2, no significance in coagulation factors as thrombocytopenia was not a uniform finding, and there were no lipase abnormalities identified. Routine vital signs such as temperature, heart rate, and respiratory rate were reported as the most reliable indicators alerting the clinical team of possible FES [12]. Riska et al. proposed "snow-storm" infiltration on chest radiographs, cutaneous petechiae, altered mental status, progressive anemia without hemorrhage, pyrexia, tachypnea, hypoxemia evidenced by PaO2 < 60 mmHg, and thrombocytopenia as diagnostic criteria based on a study of 1095 patients [13]. Riska subsequently proposed a grading system based on the above criteria to determine severity and intervention requirement: Grade 1 is defined as fat embolization occurring immediately after the injury and presenting as petechiae and 1 or 2 other mild symptoms not requiring intervention. Grade 2 is defined as fat embolism syndrome with petechiae and other signs and symptoms from above but with no interventions necessary, and Grade 3 is clinical fat embolism syndrome with many of the suggested criteria presenting as severe and requiring, at a minimum, respiratory support [14]. The Schonfeld criteria is another proposed diagnostic approach using a cumulative score based on signs and symptoms. A petechial rash was given 5 points, diffuse infiltrates on radiographs equated to 4 points, hypoxemia equaled 3 points, and 1 point was given for each pyrexia, tachycardia, and altered mental status. A cumulative score greater than 5 points diagnosed FES [2].

Based on the Gurd criteria, our patient was diagnosed with clinical FES with 2 major criteria, respiratory insufficiency requiring escalation of support to BiPap and cerebral involvement evidenced by a change in GCS from 15 at admission to 8 in the post-operative period, and numerous minor criteria including pyrexia, tachycardia, mild jaundice, renal involvement, anemia, and thrombocytopenia. Per the Schonfeld criteria, he received 4 points for diffuse infiltrates on chest X-ray, 3 points for hypoxemia, and 1 point for each pyrexia, tachycardia, and altered mental status for a total cumulative score of 10 points meeting the diagnosis of clinical FES. According to the grading system proposed by Riska et al., he was a Grade 3 with multiple criteria met and requiring respiratory and other support. His brain MRI then revealed the classic "starfield pattern."

The clinical presentation of FES is dependent on a multitude of factors, including include sex of the patient, age, multiple fractures, closed fractures, long bone fractures vs. a single fracture, and amount of fat globules released [12,15]. Every manipulation of the fracture site starting with the initial injury, continuing with any movement, whether spontaneous by the patient or related to treatment by healthcare providers, and usually ending with the manipulation during internal fixation, results in fat showers. The more fat showers that occur, the more fat particles are released into the microcirculation and therefore increased likelihood of developing clinical FES [12]. Because the fat showers are systemic in nature, FES has been associated with an altered presentation in most body systems. Pulmonary, neurological, cardiac, retinal, and cutaneous have consistent and current evidence suggesting these are the most notable systems affected, with the degree of dysfunction also variable. In multi-system trauma cases that include a head injury, the altered mental status secondary to fat emboli invading the brain can be even more challenging to recognize as related to FES. This altered neurological presentation can also range from varying degrees of lethargy to varying degrees of restlessness, again highlighting the variability in presentation [1].

Respiratory distress from pulmonary fat emboli can be attributed to the broad range of other potential causes in trauma patients including, medication-induced, other distracting injuries such as pulmonary contusions, or bleeding resulting in hypovolemia and anemia. The severity is again variable, requiring a range of interventions depending on the severity of VQ mismatch. Some require a small amount of supplemental oxygen, while others will suffer a respiratory failure requiring intubation and mechanical ventilation. When fat emboli invade the pulmonary capillary beds, secondary alveolar edema distorts the gas transfer across membranes, resulting in carbon dioxide diffusing across the membranes faster than oxygen and veno-arterial shunting. A chest X-ray will usually reveal an ARDS-like presentation, including bilateral areas of patchy consolidation, congested hilar shadows, and dilation of the right heart [2] (Fig. 6).The petechial rash, despite being identified as a hallmark sign of FES, only presents during the very acute phase of FES and is often difficult to see with the naked eye. Without the acumen of the clinical team, by the time FES is identified as a differential, the petechial rash has likely subsided. Approximately half of known FES cases have associated retinal hemorrhages that have been reported as self-limited with resolution within a few weeks.

In addition to generic clinical signs and symptoms, diagnostic imaging and testing to date are also nonspecific for FES [2,3]. Magnetic Resonance Imaging (MRI) is the most sensitive to cerebral changes in FES [3]. If a patient suspected of having clinical FES with cerebral involvement, an MRI of the brain will demonstrate numerous punctate foci, usually high intensity, scattered throughout the white and deep gray matter with an arrangement described as a "starfield pattern" [2] (Fig. 3). Takahashi et al. differentiated between severity, based on lesions identified using a grading system, where grade 0 referred to a normal MRI, grade 1 had mild lesion involvement, grade 2 reflected moderate invasion by fat emboli, and grade 3 referring to severe lesion invasion [3]. However, this presentation is also associated with other diagnoses such as diffuse axonal injury with lesions similar in appearance on imaging and sickle cell crisis with secondary avascular necrosis [16]. Transcranial Doppler ultrasound can be used to look for microemboli in the middle cerebral artery [2]. Although infrequently considered due to its invasive and lengthy nature, bronchoalveolar lavage is a reliable option for detecting and measuring the presence of fat particles within macrophages [3].
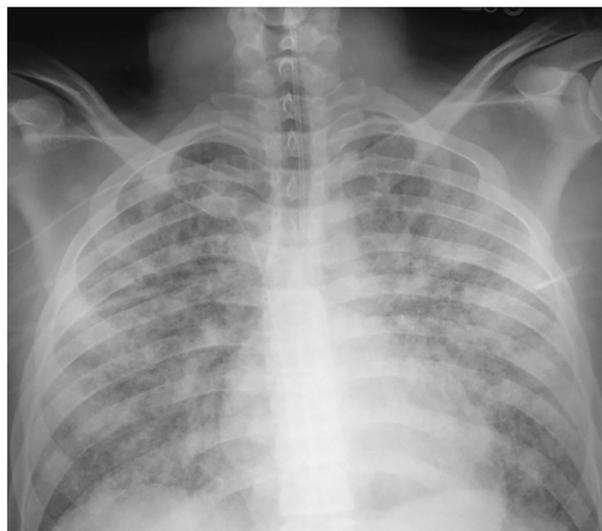
Fig. 6. During the evaluation of a patient with suspected fat embolus syndrome a CXR may show an ARDS like picture which could represent FES.

Without universally recognized diagnostic criteria to definitively diagnose FES, the argument for a standard treatment protocol is simply not possible. As of today, management and treatment are solely dependent on the clinicians caring for these patients. Current evidence describes most signs and symptoms of FES as self-limited and resolving without causing permanent deficits. Supportive care is recommended to manage the spectrum of potential effects. Most other suggested interventions remain controversial. The use of corticosteroids as prophylactic therapy in patients with long bone fractures was first studied in 1983. Membrane stabilization, limitation of free fatty acid concentrations, and preventing leukocyte accumulation related to compliment activation are a few of the potential benefits research has focused on when considering corticosteroid therapy for FES [17]. Schonfeld et al. determined that high-dose corticosteroid therapy, specifically in patients with isolated long bone fractures, is an effective intervention to prevent diffuse lung injury by minimizing the risk of developing FES. Although there may be evidence to suggest the use of corticosteroids for isolated long bone fractures, their use is not recommended in patients with multi-system trauma as the therapy may be ineffective or may be contraindicated for reasons not evident in the immediate acute care phase [17]. The recommended intervention for hypovolemia in patients identified as high risk for developing FES is albumin replacement due to its ability to bind free fatty acids while restoring intravascular volume [2].

Regarding our patient with bilateral long bone fractures, an alternative approach could have been to proceed with a damage control approach delaying IM nail fixation. However, regardless of the bilateral nature of his femur injuries, early operative fixation of long-bone fractures is advocated to reduce the incidence of FES.

Early management of FES has been reported widely and universally includes early operative intervention. In fact, one of the major quality indicators for the us News and World Reports is the time to operating room intervention for femoral shaft fractures within 18 h. Reported evidence also supports early intervention. The incidence of FES in patients with long-bone fractures that were treated conservatively with prolonged immobilization is reported as 22% [18]. The movement of fracture ends prior to operative fixation has been shown to result in transient showering of fat embolism [19]. Cytokines remain persistently elevated in patients undergoing conservative treatment and then return to normal after operative fixation [20].

The use of internal fixation devices for treatment of long bone fractures was accompanied by a reduction in the incidence of FES [21]. Several retrospective studies have also reported decreased incidence of FES with use of internal fixation devices [22–28].

Increased intramedullary pressure during fixation increases the amount of fat emboli entering the circulation [29]. While reaming may increase intramedullary pressure, reaming has not been shown to increase the incidence of FES. A randomized trial comparing pulmonary complications in patients undergoing fixation with reamed nailing and unreamed nailing found no difference between the two groups [30].

Numerous surgical techniques to reduce embolization have been utilized, including drilling holes in the cortex to reduce intramedullary pressure, lavaging bone marrow prior to fixation to reduce marrow for embolization, venting of the femur, use of a bone-vacuum, and use of tourniquets. None of these have clearly been shown to reduce FES [31].

Our patient was a male at the peak of puberty with multi-system trauma, including closed long bone fractures. He had no identified head injury. He likely experienced multiple fat showers related to the initial injury, both spontaneous and treatment-related movement in the acute care pre-op phases, and finally operative internal fixation with intramedullary nailing. We postulate that the combined therapy of high-dose atorvastatin with NO may have played a role in our patients' full recovery in a shortened timeframe. Ideally, further prospective research is needed to determine a universally accepted treatment regimen for pediatric patients with FES.

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