21-Year-Old Man With Chest Pain, Respiratory Distress, and Altered Mental Status

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A 21-year-old male, unrestrained driver presented to our institution after being involved in a head-on collision with a semitrailer at 55 mph. On examination by first responders, he had stable vital signs but had a traumatic deformity of the right thigh. The patient had no remarkable medical history and was not taking any prescription medications. His social history was remarkable for methamphetamine abuse.

On presentation to the emergency department, his vital signs were as follows: blood pressure, 140/90 mm Hg; pulse, 80 beats/min; arterial oxygen saturation, 100% with a face mask; and respiratory rate, 18 breaths/min. Physical examination revealed symmetrically round and reactive pupils and no evidence of head or facial trauma. Findings on respiratory, cardiac, and abdominal evaluation were unremarkable. Right lower extremity examination revealed 2 small lacerations over the patella and generalized swelling of the thigh. Neurovascular examination findings were unremarkable, except for weak active hip flexion and knee extension.

Laboratory analyses were remarkable for a negative serum alcohol level but a positive urine amphetamine screen. Findings on computed tomography (CT) of the head, chest, abdomen/pelvis, and full spine were normal. Plain radiography demonstrated a right femoral shaft fracture and open patellar fracture. Given the extent of the injury, the patient underwent irrigation and débridement of the open patellar fracture and placement of a proximal tibia traction pin. Internal fixation was not performed because of extensive hematoma at the site of fracture. The patient had minimal blood loss without any complications intraoperatively and was subsequently admitted to the hospital in stable condition on patient-controlled analgesia with intravenous morphine.

Approximately 4 hours postoperatively, the patient reported sudden onset of chest pain. He developed tachycardia (pulse rate, >120 beats/min), hypoxia (oxygen saturation, <70%), hypotension (systolic blood pressure, 80 mm Hg), and fever (core temperature, 38.7°C). Physical examination revealed a patient with tachypnea in acute distress. He had no rashes or bruising on skin examination and his right lower extremity was unremarkable for any changes. He had tachycardia without extra heart sounds on cardiac auscultation, and he had bibasilar pulmonary crackles. Complete blood cell counts and a basic metabolic panel were normal.

1. Which one of the following is the most helpful test to evaluate the cause of respiratory and cardiac distress in our patient?

a. *Computed tomographic pulmonary angiography*
b. *Conventional pulmonary angiography*
c. *Echocardiography*
d. *Chest radiography*
e. *Electrocardiography*

Given the high risk of pulmonary embolism in orthopedic trauma patients, high-resolution CT pulmonary angiography is a useful initial imaging strategy in patients exhibiting respiratory distress postoperatively. It carries a high sensitivity and specificity, often obviating the need for pulmonary angiography (considered the gold standard for diagnosis), thereby avoiding the risks and cost of this invasive procedure. Echocardiography is useful in evaluating the extent of right-sided heart strain in patients with massive pulmonary embolism but is not very sensitive and therefore would be suboptimal to exclude pulmonary embolism. Similarly, chest radiography and electrocardiography would not help us exclude pulmonary embolism because of their low sensitivity.

The patient underwent emergent intubation and fluid resuscitation. Computed tomography of the chest was negative for pulmonary embolism. His oxygenation continued to worsen, requiring increased mechanical ventilator support.

2. Which one of the following is the most likely diagnosis for this patient?

a. *Acute myocardial infarction*
b. *Acute pulmonary embolism*
c. *Fat embolism syndrome (FES)*
d. *Sepsis*
e. *Amphetamine withdrawal*

Although the presenting symptoms of chest pain, hypotension, tachypnea, and hypoxia are consistent with

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See end of article for correct answers to questions.

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acute myocardial infarction and acute pulmonary embolism, FES would be the most likely diagnosis in our young patient without any known cardiac disease and negative findings on CT pulmonary angiography. Our patient had several risk factors associated with increased risk of FES, including temporal proximity to a long bone fracture, sex, age, and intramedullary nailing. Sepsis similarly presents with a systemic inflammatory response syndrome and can complicate orthopedic injury but is a less likely differential diagnosis at this stage with no clear evidence of infection and a normal leukocyte count. Amphetamine withdrawal symptoms, including excessive fatigue, irritability, hypersomnia, and psychosis, were absent in this case.

On the following day, the patient developed neurologic deterioration with extensor posturing, bilateral up-going plantar reflexes, and tonic-clonic activity. He remained unresponsive to noxious stimuli, but neurologic examination confirmed intact brainstem reflexes.

3. Which one of the following is the most sensitive diagnostic modality to evaluate neurologic compromise in our patient with suspected FES?

a. *Computed tomography of the head*
b. *Magnetic resonance imaging (MRI) of the brain*
c. *Magnetic resonance imaging of the brain with diffusion and susceptibility-weighted imaging*
d. *Magnetic resonance angiography*
e. *Electroencephalography*

Computed tomography of the head is the test of choice to rule out intracranial hemorrhage or other acute pathology. However, MRI has better anatomic resolution for evaluating neurologic injury due to cerebral fat embolism (CFE), the more likely cause of neurologic deterioration in our patient. The sensitivity of MRI is supplemented with diffusion- and susceptibility-weighted imaging, which would be the diagnostic test of choice. Magnetic resonance perfusion imaging with gadolinium can further anatomically correlate the diffusion abnormalities with cerebral perfusion; however, magnetic resonance angiography is not indicated in a work-up of CFE unless evaluation for vascular events is being pursued. Electroencephalography is a reasonable test in a patient with seizure activity; however, it does not offer diagnostic structural information in a patient at risk of CFE.

Findings on noncontrast CT of the head were unremarkable. Diffusion-weighted MRI of the brain showed innumerable foci of restricted diffusion in the infratentorial and supratentorial regions, predominantly within the subcortical and deep white matter. Similarly, susceptibility-weighted imaging showed multiple punctate hyperintense areas. Magnetic resonance perfusion imaging revealed microperfusion defects in the corresponding regions. These findings are compatible with a diagnosis of CFE.

4. Which one of the following is the most appropriate initial therapy in our patient?

a. *Hypertonic saline*
b. *Aspirin*
c. *Sildenafil*
d. *High-dose intravenous corticosteroids*
e. *Supportive care only*

Hypertonic saline, aspirin, sildenafil, and high-dose intravenous corticosteroids have been evaluated for a role in prevention of FES in high-risk patients undergoing orthopedic procedures. The results have been largely disappointing, and none of these approaches are recommended in routine practice at this time; however, high-dose intravenous corticosteroids can be considered in very high-risk patients. Currently, no approved therapy is available for treatment of FES, and management consists of supportive care measures only.

On the following day, our patient underwent closed reduction and external fixation of the femur shaft fracture, which was uneventful. He was closely monitored in the critical care setting and remained comatose despite discontinuation of all sedatives. He developed a faint petechial rash over his upper anterior thorax, upper back, and neck. On hospital day 5, he was noted to have intermittent episodes of tachycardia, diaphoresis, hyperthermia, and extensor posturing of the extremities. Electroencephalography performed during these episodes showed no seizure activity. He was diagnosed as having paroxysmal sympathetic storms related to the central nervous system injury.

5. Which one of the clinical features is associated with the highest mortality risk in a patient with FES?

a. *Hypoxemic respiratory failure*
b. *Right ventricular strain*
c. *Seizures*
d. *Coma*
e. *Paroxysmal sympathetic storms*

Most of the mortality that occurs secondary to FES is attributable to hypoxemic respiratory failure and acute respiratory distress syndrome. Pulmonary hypertension and right ventricular strain are usually transient and rarely of any clinically relevant severity. Severe cerebral involvement imparts a poorer prognosis in patients with FES, but neurologic manifestations, including seizures, altered mental status, and paroxysmal sympathetic storms, are reversible, and patients with even the most severe central nervous system deficits have been reported to make almost complete neurologic recovery.

Despite the initial severe neurologic dysfunction and prolonged coma, our patient made considerable neurologic recovery during the hospital course. The episodes of paroxysmal sympathetic storms gradually subsided with concurrent improvement in consciousness, alertness, and orientation. During the course of a month, the patient made remarkable progress and was dismissed to a rehabilitation facility for further physical therapy.

DISCUSSION

Patients sustaining trauma and undergoing orthopedic surgery are at a risk of several complications, including myocardial infarction, venous thromboembolism, pneumonia, sepsis, as well as FES, which is a less common but potentially catastrophic complication. A fat embolism forms when fat droplets from the bone marrow form an embolus that becomes entrapped in the pulmonary, cerebral, dermal, or other systemic microcirculation. A fat embolism that causes clinical manifestations is termed *FES*.[1-4]

Fat embolisms were first described by Zenker in 1862 and their source identified as bone marrow after fractures by Wagner in 1865. The first clinical diagnosis of FES was reported by Von Bergmann in 1873. Further work to study the pathophysiology of FES was done by Peltier et al, Sevitt, and others.[1]

The incidence of FES after orthopedic procedures varies with the procedure and is higher after traumatic injury, and the assessment of incidence is impaired by the lack of specific clinical features and diagnostic criteria. The overall reported incidence ranges from 0.25% to 35.0%. Factors that increase the risk of FES include male sex (4-fold higher), younger age (0.37% in age ≤40 years vs 0.05% in age >40 years), long bone (especially femoral shaft) and pelvis fractures, multiple fractures, closed fractures, external fixation, and longer time between injury and surgery.[1-4]

The pathologic basis of FES is still not completely defined. Increased intramedullary pressure from trauma or surgery is thought to cause medullary fat to extravasate through the torn venules into the pulmonary circulation and further into the systemic circulation aided by increased pulmonary pressures and shunting. The mechanical obstruction theory hypothesizes tissue damage through microcirculatory obstruction and downstream ischemia. The biochemical theory[5] implicates release of toxic free fatty acids from degradation of fat locally in the tissues.[1-3]

Usually presenting within 24 to 72 hours after orthopedic trauma, FES is classically characterized by the triad of progressive respiratory failure, neurologic deterioration, and a petechial rash. Respiratory distress with hypoxemia similar to acute respiratory distress syndrome is usually the initial manifestation and develops in most patients with FES. Neurologic symptoms, including an initial acute confusional state and altered consciousness, usually occur later and can evolve into seizures, focal neurologic deficits, stupor, and coma. Patients who are awake usually display nonspecific symptoms, such as lethargy, anxiety, and restlessness, that mimic diffuse encephalopathy. A pathognomonic transient petechial rash preferentially involving the head, neck, anterior thorax, subconjunctiva, and axillae occurs in less than half of cases and usually presents later. Other features of FES can include fever, tachypnea, tachycardia, retinal changes and scotomas, jaundice, anuria/oliguria, thrombocytopenia, coagulation abnormalities, and fat macroglobulinemia.[1,3,4]

The clinical presentation of FES is variable and nonspecific and often presents a diagnostic challenge. Cerebral fat embolism is easily confused with delirium, adverse effects of medication, and metabolic derangements. Because FES is a diagnosis of exclusion, it should be considered in the differential diagnoses of cardiorespiratory and neurologic deterioration after trauma and long bone fractures.

Presence of fat globules in sputum, in urine, or via wedged pulmonary artery catheter is common in trauma patients without clinical FES, and thus these tests are nonspecific and not indicated. Alveolar macrophages with fat droplets as assessed by bronchoalveolar lavage might have some diagnostic utility.[6] Findings on chest radiography can be unremarkable or show diffuse or patchy pulmonary consolidation. Computed tomography of the chest shows focal ground glass changes and interlobar septal thickening. Ventilation-perfusion scanning shows subsegmental perfusion defects in a mottled pattern.[7] The most sensitive test for CFE is MRI of the brain, which shows diffuse scattered hyperintense lesions on T2 and diffusion-weighted images, representing acute cerebral infarcts that preferentially involve cerebral and cerebellar white matter along with the splenium of the corpus callosum. Susceptibility-weighted imaging shows punctate hypointense foci (consistent with cerebral microhemorrhages) that are considered to be the hallmark of CFE. Diffuse axonal injury after head trauma can reveal similar findings; however, the cerebral gray-white matter junction, splenium of the corpus callosum, and dorsolateral brainstem are preferentially involved. Also, diffuse axonal injury presents immediately after trauma,[8,9] unlike CFE, which has a delayed presentation.

No definitive treatment is available for FES other than supportive care, including mechanical ventilation, optimization of oxygenation, and cerebral perfusion pressure. Nevertheless, several measures to decrease the incidence and mitigate the severity of FES have been evaluated. These include early stabilization and internal fixation of fractures and surgical techniques to maintain intraoperative negative intramedullary pressures. However, results of

pharmacological modalities have been disappointing. Prophylactic aspirin, hypertonic saline, and low-molecular-weight dextran have not been proven to be beneficial. Preoperative sildenafil has been shown to reduce pulmonary complications in sheep, but its clinical utility in humans has not been assessed.[10] A recent meta-analysis of small, poor-quality randomized trials suggested that prophylactic corticosteroid administration reduced FES and hypoxemia without increasing the rate of infection but did not improve mortality.[11] Thus, routine administration of prophylactic intravenous corticosteroids for orthopedic cases is not recommended but can be considered in selected high-risk cases (eg, methylprednisolone, 1.5 mg/kg intravenously every 8 hours for 6 doses).

Much of the morbidity associated with FES is related to pulmonary dysfunction. Acute respiratory distress syndrome develops in up to 10% of cases.[1] Although development of neurologic compromise carries a poorer prognosis, several studies have demonstrated complete neurologic reversibility even in the severest cases of CFE.[12] Overall mortality due to FES with good supportive care is less than 10%.[1]

In conclusion, FES is a complication of orthopedic trauma and surgery related to systemic embolization of intramedullary fat. Classic presenting symptoms are respiratory compromise, neurologic manifestations, and a petechial rash. Diagnosis is made by a high index of suspicion and exclusion of other causes. No definitive treatment has been established, but most patients make a complete recovery with intensive supportive measures.

REFERENCES

1. Akhtar S. Fat embolism. *Anesthesiol Clin*. 2009;27:533-550.

2. Gossling HR, Donohue TA. The fat embolism syndrome. *JAMA*. 1979;241:2740-2742.

3. Stein PD, Yaekoub AY, Matta F, Kleerekoper M. Fat embolism syndrome. *Am J Med Sci*. 2008;336:472-477.

4. Taviloglu K, Yanar H. Fat embolism syndrome. *Surg Today*. 2007;37:5-8.

5. Nixon JR, Brock-Utne JG. Free fatty acid and arterial oxygen changes following major injury: a correlation between hypoxemia and increased free fatty acid levels. *J Trauma*. 1978;18:23-26.

6. Chastre J, Fagon JY, Soler P, et al. Bronchoalveolar lavage for rapid diagnosis of the fat embolism syndrome in trauma patients. *Ann Intern Med*. 1990;113:583-588.

7. Park HM, Ducret RP, Brindley DC. Pulmonary imaging in fat embolism syndrome. *Clin Nucl Med*. 1986;11:521-522.

8. Butteriss DJ, Mahad D, Soh C, Walls T, Weir D, Birchall D. Reversible cytotoxic cerebral edema in cerebral fat embolism. *AJNR Am J Neuroradiol*. 2006;27:620-623.

9. Zaitsu Y, Terae S, Kudo K, et al. Susceptibility-weighted imaging of cerebral fat embolism. *J Comput Assist Tomogr*. 2010;34:107-112.

10. Krebs J, Ferguson SJ, Nuss K, et al. Sildenafil prevents cardiovascular changes after bone marrow fat embolization in sheep. *Anesthesiology*. 2007;107:75-81.

11. Bederman SS, Bhandari M, McKee MD, Schemitsch EH. Do corticosteroids reduce the risk of fat embolism syndrome in patients with long-bone fractures? A meta-analysis. *Can J Surg*. 2009;52:386-393.

12. Gregorakos L, Sakayianni K, Hroni D, et al. Prolonged coma due to cerebral fat embolism: report of two cases. *J Accid Emerg Med*. 2000;17:144-146.

Correct answers: 1. *a*, 2. *c*, 3. *c*, 4. *e*, 5. *a*