Acute respiratory distress syndrome secondary to fat embolism syndrome: A case report

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Summary

Fat embolism syndrome is a rare syndrome typically described after closed long bone fractures. Acute respiratory distress syndrome is a feared complication of fat embolism syndrome. We present a case of a 17-year-old teenager who developed acute respiratory distress syndrome with fat embolism due to traumatic fractures of the left femur and tibia after a traffic accident. This report has highlighted that acute respiratory distress syndrome is a life-threatening complication of fat embolism syndrome and the most common cause of morbidity or mortality. Supportive care for acute respiratory distress syndrome to minimize lung damage from fat embolism syndrome is vital.

Keywords: Fat embolism syndrome, acute respiratory distress syndrome, femur fractures.

I. BACKGROUND

Fat embolism (FE) is defined as the presence of fat globules in the pulmonary or peripheral circulation, and fat embolism syndrome (FES) refers to the clinical symptoms that follow an identifiable insult[1]. FES is a rare but serious medical condition that German pathologist Friedrich Albert von Zenker first described FES in 1861[2]. FES is most often associated with long bone fractures, particularly of the femur, and orthopedic surgery[1]. In one of the largest clinical studies, using Gurd criteria[3] 27 cases of FES were identified from 3,000 patients with long bone fractures with an incidence of 0.9%. Mortality rates are estimated to be between 5% and 20%[4]. The most common cause of morbidity or mortality includes acute respiratory distress syndrome (ARDS). We present a case of a 17-year-old teenager who developed ARDS with FES due to traumatic fractures of the left femur and tibia after a traffic accident.

***Received**: 18 January 2024, **Accepted**: 12 June 2024*

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II. CASE PRESENTATION

A 17-year-old male teenager with a normal past medical history presented to our Emergency Department of 108 Military Central Hospital in Vietnam after two hours in a traffic accident. On initial assessment, the patient was stable (temperature of 36.5°C, respiratory rate of 18bpm, saturation of peripheral oxygen (SpO_2) 98%, heart rate 106 beats/per/min, blood pressure 110/60mmHg. He had a normal neurologic examination without focal symptoms and an initial Glasgow coma scale of 15. There were no chest or abdominal upon initial imaging workup, and the head computed tomography (CT) scan was normal, chest X-ray was normal with no cardiomegaly and no broken ribs (Figure 1). X-ray of femur and tibia had a fracture of the upper third of the left femur and the middle third of the left tibia (Figure 3, 4). He had a white blood cell count of 26.46G/dL, neutrophils of 71.1%, red blood cell count of 5.02 (T/L), hemoglobin of 142 (g/l), platelet count of 368 (G/l). At 14th hours of admission, the patient presented with mild dyspnea, with an increase in

respiratory rate of 22bpm, cannula oxygen 5 liters/min, SpO_2 of 95%. At 18th hour of admission, he presented with serious respiratory failure with symptoms of dyspnea, tachypnea (respiratory rate of 35-40bpm), and SpO_2 of 92-93% (10 liters of oxygen) but the pulmonary examination revealed normal sounds. He developed a fever of 39°C, petechial rash in the chest, tachycardia with a rate of 130bpm, blood pressure of 130/70mmHg, and central venous pressure (CVP) of 10mmHg. The patient had no indication for blood transfusion, fluid intake was 1000ml/14h, urine 800ml/14h, fluid Bilan of 200ml/14h. Complete blood count: White blood cell count of 8.99 (G/dL), neutrophils of 80.4%, red blood cell count of 3.75 (T/L), hemoglobin of 102 (g/l), platelet count of 243 (G/l). Air blood gas test showed PaO2 of 59mmHg, $PaCO_2$ of 39mmHg, pH 7.41, HCO_3^- 24.07mmol/l, BE 0.1, lactate 0.8mmol/l. Procalcitonin level in blood of 0.05ng/ml (Table 1). Chest X-ray showed bilateral diffuse patchy infiltrates, no cardiomegaly, and no broken ribs (Figure 2). The patient's condition was severe, so we were unable to transport the patient to the imaging department for a chest CT scan. The patient was transferred to the Surgical and Transplant Intensive Care Unit due to acute respiratory failure and initial management for the aforementioned fractures included skeletal traction of the left femur and tibia. He was treated high-flow nasal cannula (HFNC) at a flow rate of 50 liters/minute, with a fraction of inspired oxygen (FiO_2) of 60%, but did not respond to HFNC and required endotracheal intubation. The initial diagnosis was moderate ARDS, possibly due to FES. We have not ruled out pneumonia, sepsis, pulmonary edema, pulmonary embolism, and COVID-19. However, results of blood culture, sputum culture, influenza virus A, B and SARS-CoV2 at the time of onset of fever and acute respiratory failure showed negative results. NT-proBNP and troponin T was normal. Cardiac echocardiography showed no intracardiac shunts, such as the patent foramen ovale or significant right ventricular dysfunction signs. The mitral valve, tricuspid valve, aortic valve, and pulmonary valve were normal. The chambers of the heart did not dilate and left ventricular function was normal. Lung ultrasound showed no pleural fluid and no B-line in both lungs. Two-point compression ultrasonography for lower extremity showed no deep venous thrombosis. Therefore, we excluded pneumonia, sepsis, pulmonary edema, pulmonary embolism, and COVID-19.

Table 1. Laboratory data

Test	Reference range	1st hour	14th hour	1st day	3rd day	5th day	7th day	12th day
WBC (G/l)	4-10	26.46	8.99	11.61	14.02	11.3	13.7	9.5
Neu (%)	40-74	71.1	80.4	82.3	84	73.7	68.3	65
Lym (%)	19-48	24	12.2	8.7	8	12.5	18	20
RBC (T/l)	4.2-6	5.02	3.75	3.66	2.87	3.04	3.38	4.01
Hb (g/l)	130-170	142	102	101	81	84	99	110
Hct	0.38-0.49	0.427	0.31	0.311	0.233	0.25	0.29	0.42
PLT (G/l)	140-350	368	243	178	221	259	401	420
PT (%)	70-140	91	75	73	-	-	85	-
APTT (s)	25-38	30.3	36.5	35.1	-	-	27.6	-
Fib (g/l)	2-4	3.51	5.0	5.17			6.19	
D-dimer (ng/ml)	<500	-	-	7831	-	-	-	-
Ure (mmol/l)	3.2-7.4	4.63	4.2	3.4	4.58	5.9	6.72	5.2

Test	Reference range	1st hour	14th hour	1st day	3rd day	5th day	7th day	12th day
Cre (mcmol/l)	64-110	101	90	84	65	44	45	50
AST (U/l)	5-34	452.9	320	164	121.8	97.7	82.5	60.4
ALT (U/l)	0-55	153	120	84	42.3	37.8	43.4	40.2
Troponin T (ng/L)	0-14		10	12	8			
NT-proBNP (pg/mL)	0-50	-	40	30	35	-	-	-
pH	7.35-7.45	7.42	7.41	7.42	7.42	7.46	7.51	
PaO_2 (mmHg)	83-108	123	59	64	134	122	133	-
P/F	>400	586	147.5	128	223	244	380	-
$PaCO_2$ (mmHg)	35-48	39	39	37	37	39	39	-
HCO_3^- (mmol/l)	18-23	25.3	24.7	24	23.6	27.5	31	-
BE (mmol/l)	-2: +3	0.8	0.1	-0.5	-1.3	3.6	8.1	-
Lactate (mmol/l)	0.5-2.2	0.7	0.7	0.8	1.2	1.3	1.1	-
PCT (ng/ml)		-	0.07	-	-	0.05	-	-
SARS-CoV2		-	Negative	-	-	-	-	-
Influ A, B		-	Negative	-	-	-	-	-
Blood culture		-	Negative	-	-	-	-	-
Sputum culture		-	Negative	-	-	-	-	-

WBC - White blood cell count (G/l); Neu - Neutrophils; Lym - Lymphocytes; RBC - Red blood cell count; Hb - Hemoglobin; Hct - Hematocrit; PLT - Platelet count; PT - Prothrombin; APTT - Activated partial thromboplastin time; Fib - Fibrinogen; Ure - Urea nitrogen; Cre - Creatinine; AST - Aspartate aminotransferase; ALT - Alanine phosphatase; NT-proBNP - B-type Natriuretic Peptide; PaO_2 - the partial pressure of oxygen; FiO_2 - fraction of inspired oxygen; P/F - PaO2 / FiO2; $PaCO_2$ - the partial pressure of CO_2; BE - base excess; PCT - Procalcitonin; SARS-CoV2 - severe acute respiratory syndrome corona virus 2; Influ A, B - influenza virus A, B.

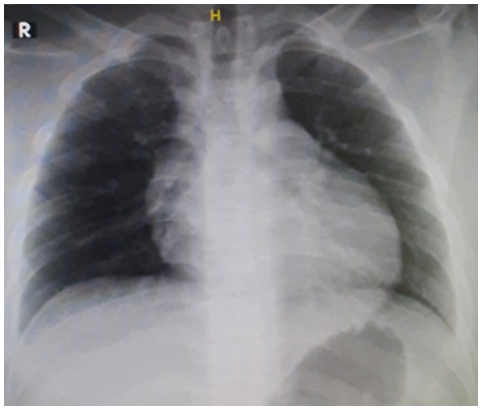

Figure 1. The chest X-ray of the patient at the time of admission was normal

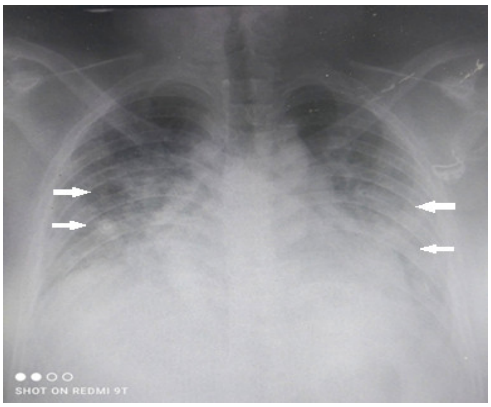

Figure 2. The Chest X-ray the patient at 14th hours of admission showed bilateral difuse pathchy infiltrates

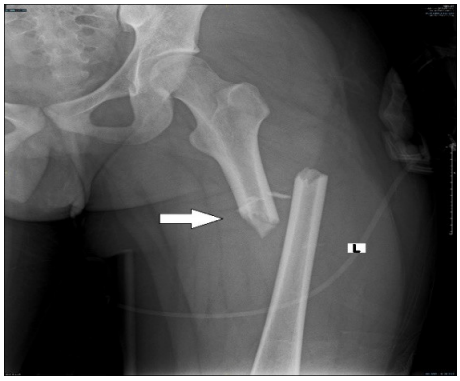

Figure 3. X-ray of the femur at the time of admission: Fracture of the upper third of the left femur

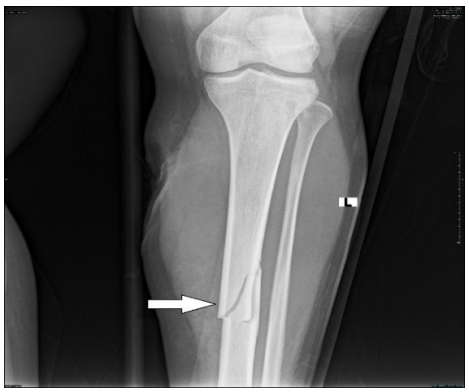

Figure 4. X-ray of two shin bones at the time of admission: Fracture of the left middle third of the tibia

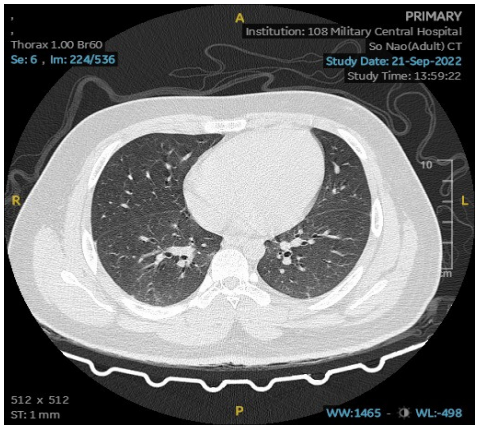

Figure 5. Chest computed tomography on 7th of admission, showed that two clean lungs

The patient was ventilated according to ARDS net guidelines. In addition, methylprednisolone at a dose of 80mg/day intravenously and enoxaparin 40UI/day subcutaneously were also used. He was treated skeletal traction of the left femur and tibia. On the 3rd day of hospitalization, he was fever-free. On the 7th day of hospitalization, his respiratory status improved, with a PaO_2/FiO_2 ratio > 300, chest CT showed two clean lungs (Figure 5), stable hemodynamics, and alert mental status. He was weaned off mechanical ventilation and extubated on the 8th day. On the 9th day, he underwent surgery to fix the left femur and tibia. After his surgery, his general condition was stable, he was discharged on the 12th day.

III. DISCUSSION

We have presented a case of a male teenager who developed early ARDS after a fracture of the femur and tibia following a traffic accident. It is a life-threatening complication of FES.

3.1. Clinical presentation

The classic triad of symptoms of FES is acute respiratory distress, neurologic changes, and a petechial rash. Pulmonary symptoms occur first, typically 24 to 72 hours after trauma; but symptoms have been reported as early as 12 hours[1]. Hypoxemia, dyspnea, and tachypnea are the most frequent early findings. In one series, hypoxemia was present in 96 percent of case[5]. Approximately one-half of patients with FES caused by long bone fractures develop severe hypoxemia and require mechanical ventilation. In particular, some cases develop into ARDS, which is a dangerous complication of FES that increases morbidity and mortality. The occurrence of ARDS associated with FES suggests that the lung is one of the target organs following intravasation of fat emboli. Neurological manifestations manifest in as many as 80% of patients, typically following, though not consistently, the onset of pulmonary symptoms[1]. These symptoms commence with a state of confusion and restlessness akin to delirium, and can advance to focal impairments like hemiplegia and aphasia, alongside occurrences of seizures and eventual coma. Only 20% to 50% of patients experience a petechial rash, which is usually distributed across the head, neck, thorax, axillae, subconjunctival space, and oral mucous membranes[7]. Less common manifestations of FES include the following: Fever, myocardial ischemia or infarction, cor pulmonale, hypotension, retinopathy, jaundice, oliguria or anuria, lipiduria, anemia, thrombocytopenia, coagulation abnormalities.

3.2. ARDS pathophysiology in FES

Two main theories try to explain the development of ARDS in fat embolism syndrome.

Mechanical theory: This theory proposes that fat from disrupted bone marrow or adipose tissue enters torn venules following trauma. It is supported by the observation that fractures of marrow-containing bone have the highest incidence of FES and cause the largest volume of fat emboli because the disrupted venules in the marrow are tethered open by their osseous attachments, allowing the marrow contents to easily enter the venous circulation. Fat embolism sufficiently explains the respiratory symptoms of FES since fat globules collect and obstruct pulmonary capillaries. In addition, it is thought that circulating fat cells may have prothrombotic potential and may trigger the aggregation of platelets and fibrin resulting in further obstruction of the pulmonary vascular bed, local inflammation, hemorrhage, and edema[9].

Biochemical theory: Baker et al. proposed this theory for the development of fat embolism syndrome. According to this theory, the precipitating event, whether traumatic or nontraumatic, triggers a hormonal change in the body system. This leads to release of free fatty acid (FFA) and chylomicrons. The presence of acute phase reactants, such as C-reactive protein, causes the chylomicron to coalesce and migrate. Baker et al. attribute the development of fat embolism syndrome to FFA. Pneumocyte hydrolysis of fat particles generates FFA which migrate to other organs, causing multiple organ dysfunction syndromes[9]. In a study for ARDS after FES by Kao et al[6] showed that histopathological micrographs demonstrated pathological alterations in the lung, kidney, and brain. Alveolar haemorrhagic edema with fat droplet accumulation and fibrin thrombi were evident through haematoxylin and eosin staining. Lung sections subjected to fat staining exhibited numerous fatty droplets. Immunohistochemical staining revealed significant inducible nitric oxide synthase (iNOS) levels within alveolar macrophages. Specific fat staining techniques involving Oil Red, Sudan Black, and Sudan III confirmed the existence of fat droplets within the lumen of pulmonary arterioles.

3.3. Diagnosis of fat embolism syndrome

One of the challenges in the study and recognition of FES is that there is no benchmark test[1]. Gurd was the pioneer in establishing diagnostic criteria through the examination of a group of 100 patients. He categorized his observations into major and minor criteria, proposing that a minimum of one major criterion and four minor criteria or two major criteria should be present to establish the diagnosis (Table 2)[3]. Our patient had 2 major criteria according to Gurd's diagnostic criteria, include respiratory insuffficiency and petechial rash. To facilitate the diagnosis of FES, a clinical scoring mechanism known as the Schonfeld criteria has been devised. The components of this scoring system are outlined in Table 3. Schonfeld introduced an additional set of criteria, emphasizing the most crucial attributes according to his perspective. He assigned varying weights to these findings depending on their demonstrated specificity, using a threshold of 5 or higher to establish the presence of FES[8].

Table 2. Gurd criteria for the diagnosis of fat embolism syndrome

Criteria	Findings	
Gurd criteria	Major	
	Respiratory insufficiency Cerebral involvement Petechial rash	
	Minor	
	Fever Tachycardia Retinal changes Jaundice Renal changes	• Anemia • Thrombocytopenia • Elevated ESR • Fat macroglobulinemia
ESR = erythrocyte sedimentation rate. Gurd criteria: Two major criteria or at least 1 major feature and 4 minor features are needed for diagnosis.		

Table 3. Schonfeld criteria for the diagnosis of fat embolism syndrome

	Findings	Points
Schonfeld criteria	Petechia	5
	Chest radiograph changes	4
	Hypoxemia (PaO_2 < 9.3kPa)	3
	Fever (> 38◦C)	1
	Tachycardia (> 120bpm)	1
	Tachypnea (> 30bpm)	1
Schonfeld criteria: Cumulative score > 5 required for diagnosis.		

3.4. Differential diagnosis of fat embolism syndrome

The differential diagnosis of FES are related to each system that this system disease affects.

Respiratory: FES should be distinguished from pulmonary contusion, pulmonary edema, apiration pneumonia, pulmonary thromboembolism. CT of the chest can aid in distinguishing FES from other pathologies of the lung. Pulmonary contusion typically develops after about 6 to 10 hours of a chest injury, on CT of the chest, there is a localized ground glass opacification on the lung. In pulmonary edema, there is symmetrical vascular engorgement with pleural effusion and ground-glass opacification. Thromboembolism: The gold standard for diagnosis is CT angiogram of the chest where classically a filling defect will be present[9].

Central nervous system: Clinical conditions affecting the central nervous system that should be factored in the differential diagnosis: Meningitis, encephalitis, brain tumor, epidural, subdural, subarachnoid bleed. CAT scan of the brain can help delineate a bleed or tumor. Meningitis and encephalitis can be ruled out with a lumbar puncture and cerebrospinal fluid analysis[9].

Skin rash: The following conditions can present with petechial skin rashes Idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, leukemia. All of these blood disorders should be considered in the presence of skin rash and other associated clinical signs and symptoms[9].

3.5. Management

There is no specific treatment for fat embolism or fat embolism syndrome.the primary treatment approach remains focused on providing supportive care[1]. This care is primarily aimed at ensuring sufficient oxygen supply to the body's vital organs. The objectives of supportive care encompass ensuring proper oxygenation and ventilation, sustaining stable hemodynamics, administering packed red blood cell transfusions when necessary to enhance oxygen transportation, utilizing sequential compression devices to prevent deep venous thrombosis, and maintaining appropriate nutritional and hydration levels[9].

3.6. Hypoxaemia and acute respiratory failure

When ARDS occurs as a consequence of FES, the management approach strives to ensure effective gas exchange while reducing the risk of ventilator-associated lung injury[10]. Some of the supportive therapies employed to achieve this include promoting natural breathing and coughing, initiating early mobilization, applying positive end-expiratory pressure, and decreasing the use of sedation and neuromuscular blockade. Prone positioning and extracorporeal membrane oxygenation may be beneficial in more severe cases.

3.7. Pharmacological management

The administration of systemic corticosteroids is controversial. Silva DF et al conducted a meta-analysis, the results revealed a nearly 77% decrease

in the likelihood of fat embolism syndrome occurrence in patients with long bone fracture, but no distinctions in terms of mortality, infection, or avascular necrosis were observed between the group receiving treatment and the control group[11]. In exceptional instances, where patients are grappling with life-threatening FES, a short-term trial of systemic corticosteroids, such as hydrocortisone at a dosage of 100mg thrice daily or methylprednisolone at a range of 1 to 1.5mg/kg/day, could be considered suitable. Heparin enhances the activity of the lipase enzyme, aiding in the clearance of lipemic plasma. However, this action might lead to elevated concentrations of free fatty acids, potentially speeding up local tissue damage, so the routine administration of heparin is not advised[12].

3.8. Surgical management

The release of fat emboli into the circulatory system from a fracture in a long bone is most likely to occur during three specific stages of injury: Immediately after the initial trauma, during later stages of closed manipulation and splinting, and finally during the process of definitive surgical fixation[12]. Minimising physical movement at the fracture site during and between these episodes, and expediting definitive fixation as early as practical, may reduce FE and therefore the risk of subsequent FES.

IV. CONCLUSION

This report has highlighted that acute respiratory distress syndrome that develops several hours after traumatic long bone fracture may be due to fat embolism. Acute respiratory distress syndrome is a life-threatening complication of fat embolism syndrome and the most common cause of morbidity or mortality. Supportive care for acute respiratory distress syndrome to minimize lung damage from fat embolism syndrome is vital.

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