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Frequency and Intensity of Fat Particles in Multiple Organs in Lethal Fat Embolism

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Abstract: The case of fat embolism is frequently encountered in forensic practice. Fat embolus enters into the bloodstream and blocks the circulation of multiple organs, and leads to death in severe cases. However, the relationship between the degree of fat embolism and its lethality remains unclear under microscopic examination in forensic pathology. In addition, the main lesion site of fat embolism is controversial. In this study, we retrospectively examined cases of death by fat embolism, and quantified the degree of fat emboli in the lung, cerebrum and kidney with Sudan III stain. Our quantified data further refined the examination of fat embolism in forensic pathology by comparing it with previous morphological descriptions. Our results also indicate that pulmonary fat embolism is the most common in forensic examinations in the majority of the death cases of fat embolism within 48 hours after injury. However, cerebral fat embolism may play an important role in the death case of multiple organs over 48 hours after injury.

1. Introduction

Fat embolism is common in forensic and clinical medicine that is pathologically characterized by fat embolism in multiple organs [1]. Pulmonary fat embolism (PFE) is a notable complication of blunt force trauma. It describes the fat embolism into the circulation and lodges in the lung, which causes respiratory and circulatory dysfunction that can lead to death. Of course, the fat globe is also blocked into other organs, like cerebrum and kidney.

The fat embolism syndrome (FES) was first recognized by Zenker in the 19th century [2]. Accumulating causes have shown that fractures, soft tissue trauma, burns, liposuction, and alcoholic fatty liver disease, can be seen in fat embolism cases [3]. The fat embolism syndrome refers to clinical life-threatening symptoms, followed by a diagnosis with respiratory insufficiency, neurological symptoms, and a petechial rash. It is generally that the pathophysiology has two theories to explain the FES: the mechanical hypothesis and biochemical hypothesis [4]. The mechanical hypothesis is considered that the fat droplets originate from long bone and soft tissue entry into the vessels after the fracture and trauma, blocking the pulmonary artery [5]. The biochemical hypothesis postulates that trauma and intense stimulation occurs when blood lipid

stability is decreased, resulting in the release of a fat droplet, initiating an inflammatory response [6].

Fat embolism has previously been reported rates up to 100%, following trauma [7]. However, clinically, while only a small percentage develop FES. Even so, we should attach great importance to FES because of its high mortality rate [8].

Although Falzi has graded fat embolism [9-10], in the present study, we further quantified the lipid droplet of pathological tissue with fat staining in fatal fat embolism cases, analyzed the relationship of the cerebrum, lung, and kidney fat embolism grading. We assessed the number of lipid droplets in the fatal fat embolism cases. The purpose is to better apply it to forensic pathology case.

2. Method and Materials

2.1 Case

We retrospectively selected 16 cases of death from a fat embolism, which analyzed the autopsy protocols and pathological sections. The antecedent cause of these cases is a bone fracture and tissue injury due to a blow, surgery or traffic accident.

2.2 Samples Collection

To examine the grade of fat embolism, each lobe of the bilateral lungs was fixed in 4% paraformaldehyde. At the same time, we also collected the cortex of the kidney, parietal lobe, frontal lobe, temporal lobe, and occipital lobe of the cerebrum, which were fixed in paraformaldehyde. We used the fixed tissue for the staining experiments of the Sudan III method. Experiments were performed in accordance with the Declaration of Helsinki. The study was approved by Institute of Forensic Science, Criminal Investigation Police University of China. Informed consent was obtained from legal guardians of all subjects.

2.3 Sudan III Stain

Sudan III stain was performed on 4% formalin-fixed and frozen OCT-embedded tissue sections. Then, 10-μm-thick sections were cut and stained with Sudan III protocol for fat staining.

2.4 Morphometric Analysis

In the section of the lung, five field images were randomly taken without overlap under 200× magnification with a Leica microscope (DMi8). The number of fat liquids was counted, and the ratio between fat liquid and parenchymal and mesenchymal tissue was measured in each field. At the same time, this method was performed on the cortex of the kidney and each cerebral lobe. For the quantification analysis, images and data acquisition were made randomly.

2.5 Statistical Analysis

All results were analyzed by GraphPad Prism and are presented as the mean±standard error. P values were calculated by the t-test. $P<0.05$ was considered to be statistically significant.

3. Result

Fifteen cases presented fracture and soft tissue injury in death from 16 fat embolism cases, on the

other hand, only 1 case presented soft tissue injury without fracture. 11 cases had a survival time less than of 48 h, and the other 5 cases had a short survival time of over 48 h. Traffic accidents, account for 75% (12 cases), was the most common primary cause of death from a fat embolism, and of 16 cases, sport, surgery and high fall only accounted for 25% (4 cases). The incidence of fat embolism was higher in males, but there was no significant difference in age. The results were shown in Table 1.

Table 1: Overview of sex, survival time, injury, and cause of injury in the 16 cases.

Factors		Number
Age	20-40 years	8
	>40 years	8
Sex	M	10
	F	6
Survival time	<48 h	11
	>48 h	5
Injury	Tissue injury	1
	Fracture and tissue injury	15
Cause of injury	Traffic accident	12
	Sport	1
	Surgery	1
	High fall	2

The pulmonary fat embolism was only observed in the lung in 11 cases. The fat embolism was observed in the lung and kidney in 3 cases. 2 cases presented the fat embolism in the lung, kidney, and cerebrum. Notably, in the 11 cases of survival time of less than 48 h, the fat emboli were found in the lung, without kidney and cerebrum. However, in the 5 cases of survival time of more than 48 h, the fat emboli were observed in the lung, kidney, or cerebrum, and of these, 3 cases displayed in the lung and kidney and 2 cases presented in the lung, kidney, and cerebrum. In traffic accidents, there were 3 cases of fat emboli located in the lung and kidney. The results were shown in Table 2.

Table 2: Number of cases of fat embolism involving organs

Factors		Lung	Lung and kidney	Lung, kidney and cerebrum
Survival time	<48 h	11	-	-
	>48 h	-	3	2
Cause of injury	Traffic accident	9	3	-
	Sport	-	-	1
	Surgery	-	-	1
	High fall	2	-	-

To better compare fat embolism in different organs, we divided them into 3 groups as shown in Table 2. Only pulmonary fat embolism was termed L group, while pulmonary fat embolism and glomerular fat embolism appeared together in a case was termed LK group, and pulmonary fat embolism, glomerular fat embolism and cerebral fat embolism appeared together was called LKB group. Orange globular fat emboli were found in the pulmonary capillary lumen in each group, and they were located in some glomeruli between LK and LKB group. In the LKB, a small number of fat particles were embolized in the tiny vessels of the brain (Fig. 1A). The area ratio of fat embolism of the lung was greater in group L and group LK than in group LKB (Fig. 1B). The area ratio of glomerular fat embolism was higher in group LK than in group LKB (Fig. 1B).

In the 16 cases, the area ratio of pulmonary, glomerular, and cerebral fat embolism, suggested the values can be used as reference data for deaths due to fat embolism (Table 3).

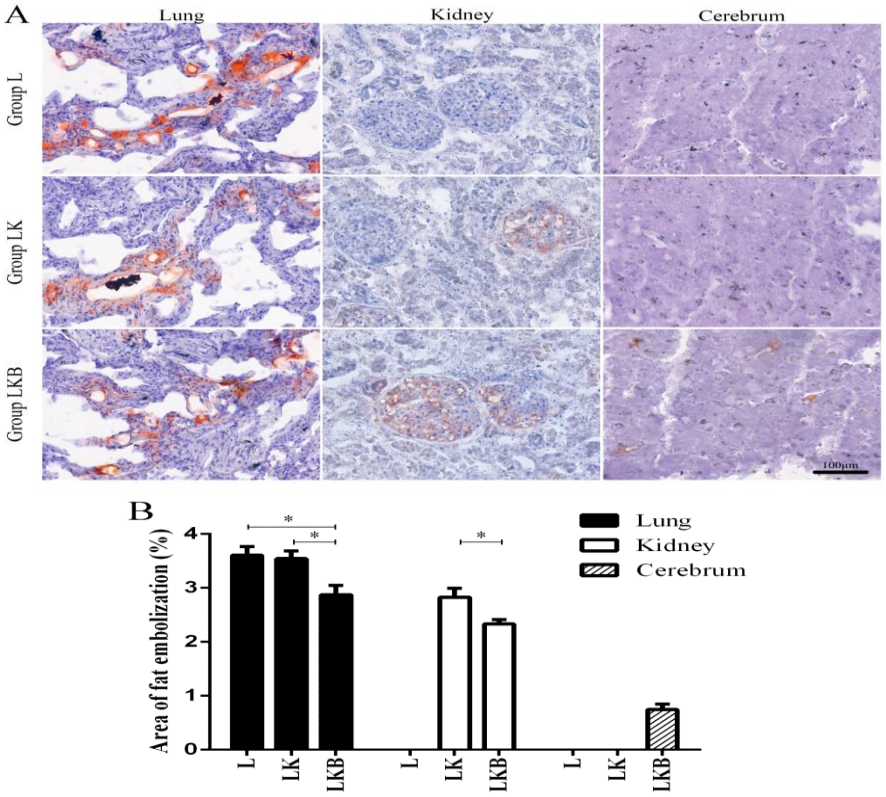

Figure 1: Histological analysis of lung, kidney, and cerebrum (Sudan-III stain 200×).

A, Multiple fat particles were present in the pulmonary capillary in group L, group LK, and group LKB. Far droplets were embolized glomeruli in the group LK and group LKB, while not detected in the group L. Fat droplets were only found in the tiny vessels in the group LKB cerebrum.

B, the area ratio between pulmonary fat embolism and the alveolar wall was significantly different from group L and group LKB, group LK and group LKB (*P < 0.05), but there was no difference between group L and group LK. The area ratio of glomerular fat embolism was significantly different between group LK and group LKB (*P < 0.05). Data is represented as means ±SEM.

Table 3: Area ratio between pulmonary, glomerular, cerebral fat embolism and soft tissue

Organ	Area
Lung	3.34±0.12
Kidney	2.58±0.12
Cerebrum	0.75±0.10

Data is represented as means ±SEM.

4. Discussion

Fat embolism syndrome (FES) refers to a series of clinical symptoms caused by fat particles entering into the circulation to lodge in the systemic organs, particularly the lung, kidney, cerebrum, and so on [3]. Fat particles occurred fairly frequently in the peripheral circulation, particularly in the lung, after blunt trauma [11]. At autopsy, fat was found in the pulmonary vessels in most patients with skeletal trauma and presented in pulmonary artery blood of most patients with long bone and

pelvic fractures [12, 13]. However, not all patients with FE present clinically relevant FES2. In the present study, we also found the main cause of fat embolism was traffic accidents, most of which are accompanied by fractures. This is consistent with previous studies. Indeed, FES is more frequent in closed fractures, rather than open fractures, but the incidence of FES is unknown because mild cases were not noticed [14]. However, we found that open fractures in the traffic accidents were the main cause of FES (Data was not shown), which may due to our cases being from severe deaths in forensic autopsy, not mild.

FES is a triad of symptoms of serious manifestation that involves respiratory distress, neurologic change and petechial rash, respiratory insufficiency usually occur first within 24-72 h after trauma [4]; but symptoms have occurred within 24 h of injury [15]. In the present study, we also found fracture was the main injury form of FES, and most of the deaths occurred within 48 h after trauma. Notably, the fat emboli were only detected in the lung with Sudan of the deaths within 48 h; but fat emboli can also be found in the kidney and cerebrum more than 48 h after injury. Of course, we do not deny that there will be glomerular fat embolism and cerebral fat embolism within 48 h after trauma [16, 17]. It indicated that pulmonary fat embolism was the main mechanism of death within 48 h after injury. Glomerular fat embolism and cerebral fat embolism were involved in the mechanism of death over 48 h after injury, especially cerebral fat embolism. This suggests that we should strengthen the examination of kidney and cerebrum with Sudan III in forensic practice, especially over 48 h after trauma, when death from fat embolism was suspected. At the same time, it can also provide a reference for the clinic.

Forensic pathology was concerned with fat embolisms which, once detected, was able to establish a causal link between incurred trauma and death. But most importantly, the degree of fat embolism was closely related to death, so the intensity of fat embolism must be cleared. Falzi developed a scoring system of pulmonary fat embolism, which was modified from Janssen and Dettmeyer (Table 4) [3, 9, 10]. To my knowledge, there was no detailed data on glomerular and cerebral fat embolism, except for some studies showing that just positive or negative in the kidney and cerebrum with Sudan III staining. Here, similar to Falzi et al. studies, we found multiple fat emboli with antler-like configuration or sausage-shaped, disseminated in every or all microscopic field of vision (Falzi Grade 2 or 3, at 100× magnification). We also found the fat particles were located in the glomerular and cerebrum. More importantly, we quantified the ratio of fat particles in the lung, kidney, and cerebrum in the death of fat embolism. Collectively, these data not only supported the morphological manifestations of pulmonary, glomerular, and cerebral fat embolism in the death cases, but also showed the ratio of fat emboli in the lung, kidney, and cerebrum firstly. These results can provide some basis for the practice of fat embolism cases in forensic pathology.

Table 4: Falzi et al. classification of pulmonary fat embolism

Grade	Emboli present and localization
0	No fat embolism, punctiform when present, very rare fat emboli
1	Mild fat embolism, teardrop-like, scattered fat emboli
2	Distinct fat embolism, rounded or sausage-shaped, multiple fat emboli
3	Massive fat embolism,antler-like configuration, a huge number in all regions

It is controversial whether the main lesion site of fat embolism was in the lung or cerebrum. Data from Sevitt [18] proved that the main lesion was in the brain, while Peltier [19] suggested that the main lesion was in the lung. Our data also suggested that fat embolism was more common in the lung than the cerebrum. Although there is overwhelming evidence that the main lesion of fat embolism was in the lung, cerebral fat embolism was regarded as the main factor of death. This belief was also supported by evidence that chylomicron metabolism may be disordered and small

chylomicrons entered into the circulation system, leading to cerebral fat embolism [20]. Indeed, it was interesting that the content of fat emboli in the lung was lower in the death cases of PFE accompanied by a cerebral fat embolism (CFE), compared with the death cases of PFE without CFE. However, in the absence of CFE, there was no difference in the number of fat emboli in the lung whether the presence of glomerular fat embolism or not. Based on our data, we speculated that although both PFE and CFE were leading to death, the CFE played an important role in the death cases of PFE accompanied by CFE.

Urinary fat bodies were detected from the patient of FES [21]. The glomerular fat embolism was examined in group LK and LKB. In general, we do not believe that glomerular fat embolism will lead to death in the short term. However, the number of glomerular fat embolism was lower in the group LKB than LK. We speculated that cerebral fat embolism accelerated the death process, and the kidney did not have enough time to accumulate lots of fat embolu in the LKB group. To some extent, it also suggested that the CFE played an important role in the death cases of multiple organ fat embolisms.

In the present study, there are some limitations. Since samples of non-dead individuals were not available, we only used samples of death cases. In addition, we only retrospective analyzed autopsy data, although it would be better to use the animal model for further complementary study.

5. Conclusions

In summary, we reviewed and analyzed autopsy data, and again quantified the pulmonary fat embolism. This is more suitable for forensic medical practice. At the same time, we also quantified the degree of glomerular and cerebral fat embolism, suggesting that pulmonary fat embolism was the most common in forensic examinations in the majority of the death cases of fat embolism. However, cerebral fat embolism may play a crucial role in the death case of multiple organs.

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