Fat embolism and COVID-19 infection: autopsy and post-mortem laboratory findings in SARS-CoV-2 positive patients

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Introduction. The article is one of the very first autopsy reports worldwide, which associates COVID-19 infection and pulmonary fat embolism.
Aims. To point to a crucial connection between a severe acute respiratory syndrome caused by coronavirus 2 (SARS-CoV-2) infection and pulmonary fat embolism as one of the possible major mechanisms of severe COVID-19 symptoms.
Methods. Lung, brain and kidney tissues examination of 16 full human autopsy cases. All deceased suffered from COVID-19 infection, none of them was admitted to hospital prior to death, immediate causes of death vary. Autopsies accompanied by microbiological examination and histological examination using Oil Red O staining were performed. Consequently, we have implemented a control cohort consisting of 16 deceased with no presence of pulmonary infection and various immediate causes of death.
Results. Of the 16 autopsy cases, 11 (68.8%) were males and 5 (31.3%) females, with overall mean age 68.1 (39–86) years. Causes of death of studied subjects were natural, mostly from respiratory failure (in 12 cases, 75%). Cardiopulmonary resuscitation was performed in 7 cases (43.8%). None of dissected persons had larger signs of body trauma. Pulmonary fat embolism was found in 11 cases (68.8%), which generalised to kidneys in 8 patients (50% of all cases, 72.3% of cases with pulmonary fat embolism) and to brain tissue in 1 case.
Conclusion. We demonstrated a reasonable relation between a COVID-19 disease and a variously severe fat embolism, severity of which does not directly correlate with body weight. Further investigation or even change of medical treatment needs to be considered in patients with COVID-19.

Key words: COVID-19, coronavirus, autopsy, post-mortem, fat embolism, FES

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INTRODUCTION

In December 2019, the world was facing a novel coronavirus disease (COVID-19) pandemic, caused by acute respiratory syndrome coronavirus 2 (SARS-CoV-2). During the "second wave" of the global novel coronavirus disease, specifically on October 2020, the Czech Republic was reported as the most-affected European country with 451.2 COVID-19 cases per 100,000 inhabitants over a 14-day period, according to the European Centre for Disease Control and Prevention statistics. As of 17 December 2023, over 772 million confirmed cases and nearly seven million deaths were reported globally[1]. The majority of patients (approx. 80.9%) with COVID-19 usually experience mild symptoms such as fever, cough and dyspnea[2]. Severe symptoms include pneumonia and acute respiratory distress syndrome (ARDS) with a wide spectrum of other complications. Recent studies suggest obesity and complications associated with the metabolic syndrome as a risk factor for development of severe COVID-19 symptoms[3]. Despite a large number of recent new studies, little is known about the COVID-19 pathophysiology and its pathologic manifestations.

MATERIALS AND METHODS

The authors are reporting the history, autopsy, microbiological and pathohistological changes of 16 deceased, post-mortem tested positively for novel coronavirus from the 21st of October to the 10th of November 2020. These autopsies were performed by the forensic pathologists of the Department of Forensic Medicine and Medical Law in Olomouc, Czech Republic on the deceased, where the clinical autopsy by the examining doctor was ordered. This department provides clinical and forensic autopsies from the Olomouc and part of the Zlín region with an approximate number of 1400 autopsies of natural and traumatic deaths per year. During the COVID-19 pandemic, hundreds of SARS-CoV-2 positive deceased were dissected by this forensic department.

Patients with a positive history of various respiratory manifestation, or with signs of respiratory disease found during the autopsy or microscopic examination, such as stiff, non-aerish pulmonary tissue, were post – mortem tested for SARS-CoV-2 presence in the tracheobronchial sputum, left lung tissue, right lung tissue and tracheal wall using RT-PCT tests.

The major share of the COVID-19 positive patients chosen for the study of fat embolism presence did not undergo cardiopulmonary resuscitation, or the CPR was started at a relatively long interval after the time of death. This was determined by the history of patient in relation to the autopsy findings, based on the absence of significant haemorrhage surrounding the rib fractures caused by mechanical CPR.

Samples of both lungs, right cerebral frontal lobe and right kidney in these COVID suspected deceased were collected properly with a clean knife during the autopsy. Immediately after the main autopsy, the fresh tissues were frozen. When they obtained the results about COVID-19 positivity, these tissues were stained by Oil Red O and analyzed independently by two experienced forensic pathologists for the presence of pulmonary and systemic fat embolism. 128 histological samples in total in order to detect fat embolism were collected from deceased bodies. Histological grading of these samples was performed using a widely used classification[4] (introduced by Mason) providing a five-grade scoring system for pulmonary fat embolism. (Table 1)

Additionally, the authors collected 128 histological samples in total, taken during the autopsies of 16 deceased from various immediate causes of death, such as cardiovascular diseases, suffocation by hanging, isolated craniocerebral trauma and liver dysfunction. The samples were taken from both lungs, right cerebral frontal lobe and right kidney. These tissues were stained by Oil Red O and analyzed independently by two experienced forensic pathologists for the presence of pulmonary and systemic fat embolism.

Table 1. Grading of pulmonary fat embolism sec. Mason.

Grade	Description
0 = no PFE	No emboli seen
I	Emboli found after some search
II	Emboli easily found
III	Emboli present in large number
IV	Emboli present in fatal concentration

Table 2. Presence of pulmonary fat embolism in accordance to Mason's criteria.

Grade of emboli	Number (n = 16)	%
0 = no PFE	5	31.3
I	3	18.8
II	5	31.3
III	3	18.8
IV	0	0

CASES AND RESULTS

As seen in Table 3, age of studied cases ranged between 39 to 86 years (mean 68.1 years). All of the 16 dissected persons during the presented interval died with COVID-19 without previous hospitalization, mostly at home. In 12 cases (75%), acute respiratory failure in the terrain of interstitial pneumonia was reported as the cause of death. None of the cases reported larger signs of skeletal or soft tissue trauma, except of the fractures caused by cardiopulmonary resuscitation in 7 cases. In the cases which got through resuscitation, minimally vital or non-vital rib or sternum fractures were seen. The evaluation of fractures' vitality was based on the presence of haemorrhage of soft tissues surrounding the fracture lines, as mentioned above. One of the deceased was of normal weight, three of them were overweight and the rest suffered from 1st to 3rd grade obesity. The interval between the reported time of death and the autopsy varied from five hours to 12 days. The majority of those analysed were not tested pre-mortem for COVID-19. The tissue samples stained with Red Oil O were variably positive for fat embolism, independently of BMI. Most severe pulmonary and systemic fat embolism developed in an 82-years-old woman with moderate overweight, with no body trauma, and she was not resuscitated.

The pulmonary fat embolism was found in 11 patients, from whom systemic generalization was found in 8 patients, mostly to the kidneys. (Table 2 and Fig. 1) No macroscopic, or microscopic signs of thrombembolism were found.

In the control group, 25% of the deceased were positive for pulmonary fat embolisation. The control cohort consisted of 16 deceased, whereas 4 of them showed a pulmonary fat embolism grade 1–2, without systemic generalization to brain or kidney. Of these 4 cases, 2 underwent CPR with the findings of vital signs, such as heamorrhage surrounding the rib fractures, and in 2 cases, the fractures were evaluated as non-vital. The only deceased person with 2nd grade pulmonary FE had numerous vital rib fractures from CPR with major soft tissue haemorrhage surrounding the fractures. One of the 1st grade pulmonary FE

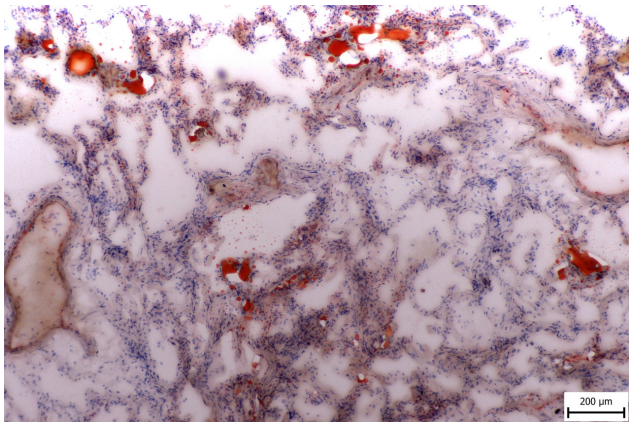

Fig. 1. Microphotograph showing fat emboli in pulmonary vessels (250x) Grade III.

patients died from liver insufficiency due to liver cirrhosis, with no vital signs of trauma.

DISCUSSION

One of the very first hypotheses interpreting the severe clinical outcome in persons positive for COVID-19 relating to destruction of adipose tissue was published in June 2020 by Cinti et al.[3].

According to his hypothesis, SARS-CoV-2 fat infiltration could worsen adipose inflammatory status in the expanded adipose tissues of obese patients. In addition, the SARS-CoV-2-infected adipocytes could massively undergo necrotic death, as shown in other cell types[5], exacerbating lipid remnant accumulation in the adipose interstitium, with free lipid droplets that, in turn, could predispose COVID-19 patients with obesity to the fat embolism syndrome (FES).

Another medical case report published by Kong et al. in 2023 described the sudden death of a female patient infected by SARS-CoV-2, who developed a pulmonary fat embolism in the small interstitial pulmonary vessels, which was confirmed by phosphotungstic acid haematoxylin staining and Oil Red O staining. In this paper, the weight of the woman's body is not further specified according to her height[6].

Our study showed 16 patients, of whom 15 suffered from obesity of various grades, or were overweight. However, we found no correlation between severity of pulmonary fat embolism and obesity grade.

The most substantial FES with systemic generalization was seen in a mildly overweight, 82 y. o. woman with a BMI of 25.82 without any resuscitation or other trauma pre-mortally.

The control cohort consisting of the same number of deceased with no signs of pneumonia confirmed that in patients dying from natural, mostly cardiovascular caused death, or from suffocation, with no signs of vital trauma, pulmonary FE does not develop. One case with signs of 1st grade pulmonary fat embolism was admitted to autopsy in a slightly decomposed status. One person with signs of 1st grade pulmonary fat embolism suffered from liver cirrhosis and died from liver insufficiency, which can lead to FES itself[7].

We are comparing the clinical features and imaging findings in COVID-19 patients and those suffering from fat embolism syndrome:

COVID-19

Infection with SARS-CoV-2 in humans is associated with a wide spectrum of clinical respiratory syndromes, ranging from mild upper airway symptoms to progressive viral pneumonia. Most patients are asymptomatic or overcome moderate symptoms, including fever, dry cough, and shortness of breath. However, some individuals deteriorate rapidly and develop acute respiratory distress syndrome (ARDS) (ref.[8]).

According to the European Centre for Disease Prevention and Control, the latest International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) reported most frequent clinical manifestations on 25 849 hospitalised patients of COVID-19. The five most common symptoms at admission were fever, shortness of breath, cough, fatigue/malaise, and confusion[9]. According to an analysis of Zhang JJY et al. on 4203 patients, the most common clinical symptoms were identified as fever, cough and dyspnoea (80.5%, 58.3% and 23.8%), and hypertension, cardiovascular disease and diabetes (16.4%, 12.1% and 9.8%, respectively) as most common comorbidities[10]. Obesity was identified as a further significant comorbidity[11].

Correlations of abnormal coagulation parameters with poor prognosis have been also observed. Non-survivors have shown significantly higher levels of plasma D-dimers and fibrin degradation products, elevated prothrombin times and activated partial thromboplastin times compared to survivors[12]. D-dimer elevation > 1 ug/L was stated for the strongest independent predictor of mortality[13].

As for the imaging, the chest radiograph (CXR) and computed tomography (CT) in COVID-19 positive patient is a supportive tool for reporting the severity of pulmonary manifestation. CXR usually shows patchy or diffuse asymmetric airspace opacities, similar to other viral pneumonias. The most common initial CT findings of COVID-19 pneumonia are bilateral, subpleural ground-glass opacity, ill-defined margins, and a slight right lower lobe predilection. However, the initial imaging findings are not specific[14].

Fat embolism syndrome (FES)

Fat embolism syndrome is a well-known medical condition among traumatologists, orthopaedists, anaesthesiologists and forensic pathologists. Fat embolisation is a serious complication usually associated with a skeletal trauma, extensive soft tissue damage, less often also with various non-traumatic conditions, such as acute and chronic pancreatitis, shock, fatty liver disease etc. It usually embodies within 72 hours of initial insult[15]. Nonetheless, the fat embolization infrequently results in a clinically evident, possibly fatal fat embolism syndrome.

FES is characterized by both pulmonary and systemic fat embolism, which results in triad of respiratory distress (95%), altered mental status (60%) and petechial rash (33%) (ref.[16,17]).

- Pulmonary signs are often the first clinical manifestation to present. Dyspnoea, tachypnoea and hypoxaemia are the most common early findings. The severity of these symptoms varies but they may progress to respiratory failure due to acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).
- CNS manifestations resulting from cerebral embolism are usually present in the early stages and often occur after the development of respiratory distress. The neurological changes exceed from mild confusion to severe seizures. An acute confusional state is a common appearance but focal signs such as hemiplegia, aphasia, apraxia, visual field disturbances and anisocoria have been described. Almost all neurological deficits are fully reversible[18].

Table 3. Findings in COVID-19 positive patients.

Patient, age	Fat embolism			BMI	CPR (length, fractures)	Other traumatic changes	Symptoms	Cause of death	Approx. interval between a time of death and autopsy	Other conditions	Other biochemical markers (post mortem samples)
	lungs	kidneys	brain								
Male, 39	negat.	neg.	neg.	35.37 2nd grade obesity	no resuscitation	no signs of trauma	fever	respiratory failure, interstitial pneumonia	36 hours	sclerosis of coronary arteries	–
Male, 50	3rd grade	posit.	neg.	32.55 1st grade obesity	BLS + ALS 1 hour, non-vital sternum fracture	no signs of trauma	fever, dyspnoe, cough, weakness	respiratory failure, interstitial pneumonia	38 hours	hypertension, myocardial hypertrophy,	CRP 74.1 mg/L
Male, 60	neg.	neg.	neg.	33.96 1st grade obesity	no resuscitation	no signs of trauma	unknown	acute failure of chronically insufficient coronary arteries	72 hours	hypertension, severe stenosis of RIA, myocardial myofibroses, myocardial hypertrophy	–
Male, 62	neg.	neg.	neg.	41.06 3rd grade obesity	no resuscitation	small healing haematoma on abdomen	fever, progreding dyspnoe, cough, deliria	respiratory failure, interstitial pneumonia	15 hours	bronchial asthma, diabetes mellitus, hypertension	CRP 83.7 mg/L PCT 0.03 µg/L
Male, 63	1st grade	posit.	neg.	29.7 overweight	no resuscitation	no signs of trauma	unknown	acute failure of coronary arteries, atherosclerosis	12 days severe decomposition	severe stenosis of RIA, myocardial hypertrophy	–
Female, 64	2nd grade	posit.	neg.	40.09 3rd grade obesity	no resuscitation	no signs of trauma	unknown	respiratory failure, interstitial pneumonia	27 hours	diabetes mellitus, hypertension	–
Male, 66	1st grade	posit.	neg.	43.57 3rd grade obesity	ALS 40 min, non-vital ribs and sternum fractures	no signs of other trauma	dyspnoe, fever, cough	respiratory failure, interstitial pneumonia	5 hours	diabetes mellitus, hypertension, severe stenosis of RIA, myocardial hypertrophy	–
Male, 68	2nd grade	neg.	neg.	31.31 1st grade obesity	BLS + ALS 30 min, non-vital ribs fractures	no signs of other trauma	dyspnoe, fever	respiratory failure, interstitial pneumonia	3 days	hypertension	–
Male, 71	2nd grade	posit.	neg.	30.3 1st grade obesity	ALS 35 min, ribs and sternum fractures, minimal haemorrhage	no signs of other trauma	dyspnoe, fever, cough, diarrhea	respiratory failure, interstitial pneumonia	19 hours	hypertension, hypercholesterolaemia, severe stenosis of RIA, myocardial hypertrophy	–
Female, 73	3rd grade	neg.	neg.	46.61 3rd grade obesity	BLS + ALS 40 min., ribs and sternum fractures, minimal haemorrhage	no signs of other trauma	fever, vomiting, chills	heart failure	72 hours	hypertension, diabetes mellitus, hyperaldosteronism, chronic renal failure, atherosclerosis	–

Table 3. *(Continued)*

Patient, age	Fat embolism			BMI	CPR (length, fractures)	Other traumatic changes	Symptoms	Cause of death	Approx. interval between a time of death and autopsy	Other conditions	Other biochemical markers (post mortem samples)
	lungs	kidneys	brain								
Male, 74	neg.	neg.	neg.	28.41 overweight	no resuscitation	no signs of trauma	unknown	bronchopneumonia, fungal superinfection	132 hours	hypertension, diabetes mellitus, myocardial hypertrophy	–
Female, 74	neg-	neg.	neg.	20.93 normal weight	no resuscitation	no signs of trauma	dyspnoe, fever	respiratory failure, interstitial pneumonia	33 hours	hypertension, diabetes mellitus, right ventricle dilatation, hyperlipidaemia, hypothyreosis, severe atherosclerosis	–
Female, 74	2nd grade	posit.	neg.	27.08 overweight	BLS + ALS 25 min., non-vital ribs and sternum fractures	no signs of other trauma	dyspnoe	respiratory failure, interstitial pneumonia	92 hours	myocardial hypertrophy	–
Female, 82	3rd grade	posit.	posit.	25.82 overweight	no resuscitation	no signs of trauma	dyspnoe, fever, cough, weakness	respiratory failure, interstitial pneumonia	45 hours	hypertension, diabetes mellitus, ischaemic heart disease	–
Male, 84	1st grade	neg.	neg.	25.78 overweight	no resuscitation	small haematomas on knees	fever, cough, weakness, stool incontinence	respiratory failure, interstitial pneumonia	64 hours	hypertension, arthralgia, septic spleen activation, severe atherosclerosis, BPH, chronic hepatic venostasis	
Male, 86	2nd grade	posit.	neg.	31.24 1st grade obesity	BLS + ALS 30 min non-vital ribs and sternum fractures	small haematoma on hand	unknown	respiratory failure, interstitial pneumonia	16 hours	hypertension, unspecified cardial condition	

CPR, Cardiopulmonary resuscitation; BLS, basic life support; ALS, advanced life support; CRP, C-reactive protein; PCT, procalcitonin; RIA, anterior interventricular branch of left coronary artery; BPH, benign prostate hyperplasia.

- Petechial rash can symbolize the last component of the triad to develop. It occurs in around 60% of cases, results from occlusion of dermal capillaries by fat and increased capillary fragility is leading to extravasation of erythrocytes. This manifests as suffusions in the conjunctiva, oral mucous membrane and skin folds of the upper body especially the neck and axilla[19]. This is considered to be the only pathognomic feature of fat embolism syndrome and usually appears within the first 36 hours.

Systemic fever is a very common early sign, which may increase up to 39° C in FES (ref.[20]). Cardiovascular system involvement includes early persistent tachycardia, which is almost invariably present in all patients with fat embolism. The fulminant form presents as acute cor pulmonale, respiratory failure and/or embolic phenomena and it usually means very poor prognosis.

PRE-MORTEM DIAGNOSIS

Diagnosis of fat embolism syndrome is based primarily on clinical signs. This is usually difficult as the symptoms are non-specific and may resemble other conditions, therefore the definitive diagnosis is stated *per exclusionem*[3].

FES is often under-diagnosed in general, since the classical signs of pulmonary, central nervous system, and cutaneous manifestations may not occur at all[18]. Furthermore, while there are published criteria to aid in diagnosis, these are not standardized. Various clinical diagnostic guideline systems are being used[21]. Specific biochemical markers have not been identified yet for the diagnosis of FES. However, according to several studies, in the majority of patients with FES, coagulopathy with elevated d-dimers also develops[22].

The chest X-ray in FES is initially usually normal, but in some patients, fluffy shadows may develop. A minority has diffused or patchy air space consolidation due to oedema or alveolar haemorrhage; this is most prominent in the periphery and bases. The classical chest X-ray of FES shows multiple flocculent shadows ("snowstorm appearance"). The radiological signs may remain for up to three weeks. On chest CT, focal areas of ground glass opacification with interlobular septal thickening are usually seen in FES and subpleural nodules representing alveolar oedema, micro-haemorrhage and inflammatory response may be seen[18].

THERAPY

For patients with pulmonary FES or systemic fat embolism, there is no therapeutic regimen for treatment apart from nonspecific supportive care[23], which often requires intensive care facilities.

PROGNOSIS

A severe presentation with fulminant onset (within 12 hours) is accompanied by a poor prognosis, as mentioned above. The onset may also be progressive (over 24–72 hours), with a broad range of unspecific presentations including subclinical.

CONCLUSION

We presented 16 autopsy cases of SARS-CoV-2 positive deceased, focusing on fat emboli present in vascular system. A significant similarity between the symptoms, laboratory and other clinical findings in FES and COVID-19 are crucial and surprising.

Recent studies put obesity, COVID-19 and thrombi formation in context[24]. However, the patomechanism of coagulopathy and microthrombotisation is not well explained so far. The formation of microthrombi in lung vessels are explainable by previous fat embolisation, due to fat droplets adhering to vascular wall representing a mechanical obstruction for the blood flow.

The findings of this modest study need to be discussed among clinicians, as well as autopsy providing specialists. The fact that fat embolism syndrome can occur in any COVID-19 positive patients could modify treatment procedures in COVID-19 positive patients, which should take account of the presence of fat emboli in circulation. Moreover, authors also revealed that the decomposition of the body is not a limiting factor for testing sputum and tissues for the presence of SARS-CoV-2 virus.

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