

Unusual Cause of Death in a Patient with COVID-19

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This is a case presentation of a patient with confirmed coronavirus disease (COVID-19) who ended his life with suicide by hanging. We are presenting the history of the disease, a clinical feature, the onset of the psychiatric symptoms and finally the pathological feature. Aims are: to perceive, in which phase of the disease occurred the psychiatric symptoms and eventually their connection with some morphological feature of the brain; to evaluate the changes of the primary disease to internal organs and finally, the ethical aspect i.e. how are these patients protected by the health care system. Results: patient committed suicide on the 12th day of the disease and around the 21st day after the infection, looking by its serum antibodies. On lungs dominated the picture of acute restrictive pulmonary disease and ARDS (acute respiratory distress syndrome) with strong inflammatory answer. A psychiatric disorder occurred with the epilof of double suicide attempt, of which the second one was successful.

Key words: COVID-19, suicide, psychiatric disorder, ARDS

Introduction

Of imminent importance and the main aim of this report is to present, in which phase of the disease occurred the onset of the psychiatric symptoms, in a person with no previous history of psychiatric illness, and if there has been found some morphological feature of the brain, underlining these symptoms. A wide discussion exists between medical professionals about that, if COVID-19 is causing some neurological and psychiatric disturbances, which are actually connected with some morphological manifestation of the disease on the CNS (central nervous system) [8, 9].

The second aim of this paper comes out by the fact that, the patient didn't die due to COVID-19 itself, but died of a violent death, which in turn has been found as a

special challenge during the examination of the internal organs. We expected to see the typical pathological feature of a developed COVID-19 disease, often described before [3, 5, 8,14] with no feature characteristic for the terminally ill patients, which more or less can mask and mimic the feature of the primary disease.

Finally, one of the important aspects of this paper is the ethical one. Are COVID patients protected enough by the health care system, having in regard the pretty diverse and still very unknown, in fact not explored enough yet, clinical manifestation of this disease.

Material and Methods

Presentation of the case

By the order of the public prosecutor, a body of a 39 years old man has been admitted to the Institute of forensic medicine for forensic autopsy, because of the obviously violent death i.e. suicide by hanging. During the collection of the data before the autopsy, we realized that the deceased was confirmed COVID-19 patient, who was receiving medical treatment for the disease. In fact, as shown by the records, death by suicide occurred 12 days since the beginning of the illness.

History of the illness

Day 1 (12 days before death). The illness has started with mild to moderate symptoms: raised temperature to 38°C, feeling of exhaustion and muscle pain. After two to three days he was advised by his family doctor to make PCR COVID-test.

Day 5 Patient had problems to schedule for a PCR-test in his own city (he was living in the capital city), so he decided to make test in the city about 40 km far from the capital. He signed the statement that from the moment of giving material for testing, he is going to be in self-isolation.

Day 7 Still waiting for the result from the SARS CoV-2 molecular biology testing, the patient decided to visit the City hospital, one of the three centers for COVID-19 in the capital city. By that time, he developed respiratory symptoms, difficulty breathing, feeling of chest pressure and also loosing of the sense for smell and taste.

During his first admission to the City-hospital in the early hours of the day 7, patient has not been hospitalized, even the fact that he had positive radiological feature (bilateral pulmonary inhomogeneous consolidations in middle and basal parties, phrenic-costal sinuses free of liquid) and the CRP (C-reactive protein) of 97,5, the body temperature of 37,4°C and saturation O₂ of 96%. With the prescribed therapy (paracetamol, azythromycin, anticoagulants, vitamin C and probiotics) he was released for home treatment.

Meanwhile, he received positive result for SARS CoV-2, when, by the words of his wife, parallel to his breathing symptoms, he started to develop psychiatric symptoms like feeling very much scared, restless and with difficulty sleeping.

In the late hours on the day 7, the patient attempted his first suicide, by injecting himself subcutaneously a poison (some grass drying substance used in the agriculture), for what he has been admitted to the toxicology clinic, from where was readmitted to the COVID centre, and then was released home with an advice to consult the toxicology

clinic if symptoms of intoxication occur. This moment, by the records, saturation O₂ was 95%, body temperature was 38°C and blood pressure was 110/70.

Day 11 With the ambulance the patient has been urgently admitted to the COVID center because of developing symptoms of extreme psychomotor tension, anxiousness, sleeplessness and black thoughts. A psychiatric therapy has been prescribed (amp. Diazepam 10 mg for acute treatment and then: risperidone, escitalopram, biperidone and zolpidem) and the patient has been released at home again.

Day 12 In the early morning hours, several hours after his last visit to the hospital, the patient committed a suicide by hanging.

Results

Autopsy finding

On autopsy we found a body of a 39 years old male, with regular osteomuscular constitution.

During the external examination dominated a feature of an asphyxiation death: subconjunctival hemorrhages, cyanosis, and the hanging mark in the neck region.

During the examination of the internal organs, some specific signs of inflammation of the pharynx, larynx and trachea haven't been found except some petechial hemorrhages of the tracheal mucosa (**Fig. 1a**).

The lung finding was rich. Lungs have been voluminous, heavy and full of liquid, especially in the down and back parts and with compensatory hyperinflation in the upper parts. The lung tissue has been found as colorful, consolidated, and solid by its consistence. In the basal parts there have been zones of whitish color and like rubbery consistence and a lot of spot bleedings on the cut surface (**Fig. 1b, c**). Effusion of liquid hasn't been found in the pleural and pericardial cavity, but a fibrin adhesion has been found on the pleura of the left lung and on the epicardium.

No specific feature on the other internal organs, except the dark-colored kidneys and congestion of the internal organs as non-specific but typical signs of asphyxiation.

Hanging has been established as a cause of death.



Fig. 1a



Fig. 1b

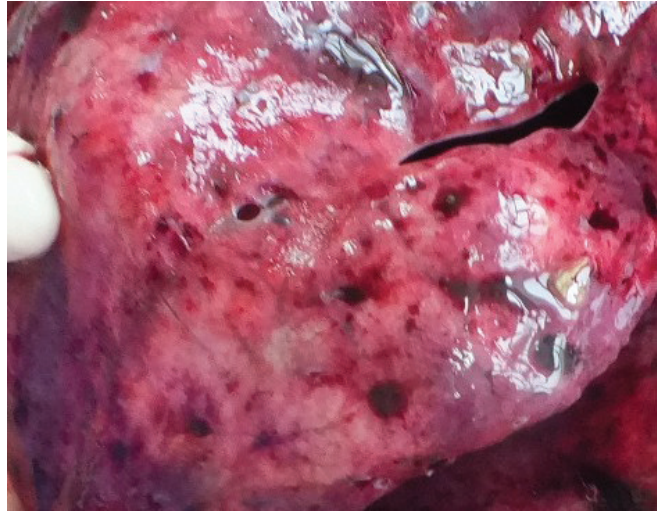


Fig. 1c

Fig. 1. Findings of the examination of internal organs: **a.** spot bleedings of the tracheal mucosa; **b.** the appearance of lungs (voluminous, heavy and full of liquid); **c.** on cut surface tissue was colorful, consolidated, and solid by its consistence, with zones of whitish color and a lot of spot bleedings between.

Histopathology

A significant pathohistological feature has been found on lungs presented as diffuse alveolar damage. There have been found zones of the consolidation of the lung tissue and next to them zones of hyperinflation, probably compensatory (**Fig. 2a**). It has been found the exudative phase of ARDS (acute respiratory distress syndrome), with diffuse alveolar damage, edema and cellular infiltration with leukocytes, lymphocytes and also desquamated pneumocytes (**Fig. 2b**). Also, the presence of the pulmonary micro

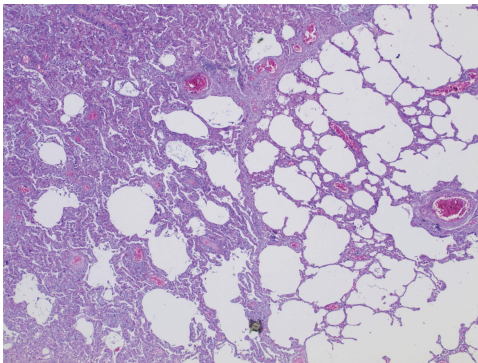


Fig. 2a

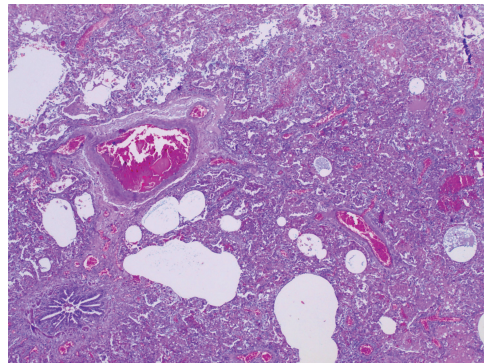


Fig. 2b

thrombi inside the blood vessels has been documented (**Fig. 2c**). Additionally, in some parts were seen signs of a transition to proliferative phase with the pneumocytes type 2 hyperplasia and zones of the organization (**Fig. 2d**).

No specific feature has been found to the other organs. Special attention has been paid to the brain tissue, where some signs of hypoxia have been found, but very unsure if they were result of the primary COVID disease or of the asphyxiation that has been found as the cause of death.

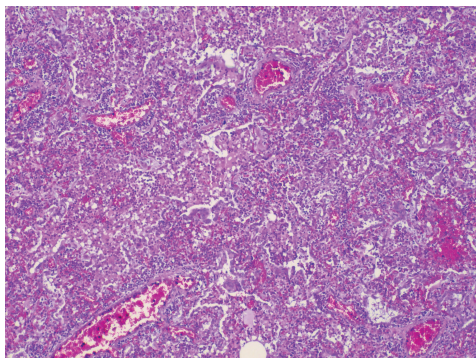


Fig. 2c

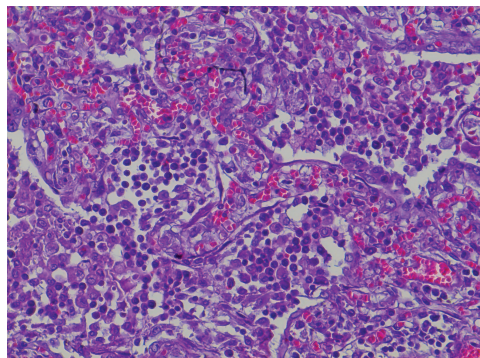


Fig. 2d

Fig. 2. Histopathology of lungs presented as diffuse alveolar damage: **a.** consolidation zones of the lung tissue and next to them zones of hyperinflation, probably compensatory; **b.** exudative phase of ARDS, with diffuse alveolar damage, edema and cellular infiltration with leukocytes, lymphocytes and also desquamated pneumocytes; **c.** the presence of the pulmonary microthrombi inside the blood vessels; **d.** in some parts were seen signs of a transition to proliferative phase with the pneumocytes type 2 hyperplasia and zones of the organization.

Laboratory findings

Intravital laboratory findings (received by medical records)

Day 7 laboratory results: CRP of 97,5; LDH (lactate dehydrogenase) of 267; CK (creatinase) of 246; ACT (aspartat transaminase) of 40; d-dimers of 21; mild leukocytosis of 12,8 with the domination of the granulocyte fraction.

Radiology finding: inhomogeneous bilateral consolidations in the middle and basal parts, phrenicocostal sinuses have been free of liquid.

Postmortem laboratory findings

By applying molecular diagnostics on the pharyngeal and tracheal swabs, a presence of SARS Cov2 has been confirmed.

Additionally, detection of the anti-COVID antibodies has been undertaken. A positive result has been received for IgM antibodies with value of 30 AU/ml (referent value <1.00 AU/ml), and the positive result for IgG antibodies, with the value of 47,5 AU/ml (referent value <1.00 AU/ml).

Detection of the antiCOVID IgM antibodies has been expected which has been proof of the developed and lasting COVID-19 disease, fully coinciding with the data received that the death occurred on the 12th day of the disease. The presence of the

antiCOVID IgG antibodies undoubtedly has shown that the infection existed at least a week longer than the onset of the symptoms.

Postmortem biochemical analyses have shown a moderately raised values of myoglobin and the serum troponin, as well as the enzymes Alkaline phosphatase, AST (aspartat aminotransferase), CK (creatin kinase), and more significantly raised values of the LDH (lactate dehydrogenase), GAMA (glutamyl transpeptidase) and ALT (alanine aminotransferase). Erythrocytes have been found $3,11 \times 10^{12}/L$, hemoglobin of $92g/L$; leukocytosis of $14,9 \times 10^9/L$ with the lymphocyte fraction of $6,3 \times 10^9/L$; as well as mildly raised thrombocytes of $594 \times 10^9/L$.

Toxicology analysis has shown benzodiazepines in the blood with therapeutically values.

Discussion

Coronavirus disease 2019 (COVID-19) first occurred in China by the end of 2019, but very fast has spread over the planet. The first confirmed case in USA has been on January 20, 2020 [3]. The first case in Republic of North Macedonia has been confirmed in the middle of February 2020. Until recently it has been a relatively new and unexplored disease with very diverse clinical picture. Some author concluded that severe COVID-19 form is a consequence of immune-mediated, rather than pathogen-mediated organ injury [2]. That is why, autopsies are essential to understand all the organ alterations in COVID-19 [2, 5, 14].

This disease is represented by two phases. For the first phase of the disease are typical symptoms very much like influenza syndrome: muscle pain, headache and fatigue. In mild cases the disease stops here. If condition continues more than 7 days, then a second pulmonary phase sets in. Careful medical records and autopsy reports published worldwide have shown that coronavirus 2 (SARS-CoV-2) is actually organotropic to many other organs than lungs [4, 8, 10], especially involving the thrombotic system and causing a kind of coagulopathy [1].

In the case presented here, a 39 years old man committed suicide by hanging on the 12th day of the COVID-19 disease, which is the second pulmonary phase of the disease and at least 21 days after the contact with the coronavirus 2 (SARS-CoV-2), as shown by the anti- SARS-CoV-2 antibodies found in his blood. The clinical course of the disease developed as typical acute restrictive lung disease i.e. a virus pneumonia, as in detail described in the classic pathology books [7] with strong inflammatory answer, as seen by the laboratory indicators (CRP, LDH, transaminaze enzymes, etc.)

Psychiatric symptoms first occurred on the seventh day of the disease and have been strongly related with the receiving of the positive PCR (polymerase chain reaction) molecular testing results. Actually, on that day the patient has been admitted to the hospital and there is a medical record that then he had oxygen saturation of 96%. Unfortunately, we don't have the exact recording of the oxygen saturation in the next 4 days (from the seventh to twelfth day, when he committed suicide), because the patient hasn't been hospitalized.

That is the reason why, our analysis has been directed toward the possible changes and conditions that eventually can be considered as a morphological substrate for the occurring of the psychiatric symptoms, and the hypoxia as the most probable among

them. A question arose: can the hypoxia of the brain be the pathological substrate for the onset of the psychiatric symptoms in COVID-19 patients?

During the 2020 there have been a lot of reports about the connection between COVID-19 and neurologic and also neuropsychiatric complications [9]: encephalopathy, meningo-encephalitis, ischemic stroke, acute necrotizing encephalopathy and Guillain-Barre syndrome (GBS).

Collecting the data from the 24 medical institutions in United Kingdom, in a study [8] has been described a wide range of the neurological complication in COVID-19 patients. A total of 43 patients have been analyzed where five major categories of neurological conditions have been described: 1. Encephalopathy (n = 10) with delirium/psychosis and no distinct MRI or CSF abnormalities; 2. Inflammatory CNS syndromes (n = 12) including encephalitis; 3. Ischemic strokes (n = 8) associated with a pro-thrombotic state; 4. Peripheral neurological disorders (n = 8), and five patients with miscellaneous neurological complication who did not fit these categories. As a possible mechanisms have been described: the direct viral neuronal injury; a secondary hyperinflammation syndrome; postinfectious inflammatory or immune-mediated disorders; and also the effects of a severe systemic disorder with the neurological consequences of sepsis, hyperpyrexia, hypoxia, hypercoagulability and critical illness. Those conditions occurred in the period from 6 days before and up to 27 days following the onset of the COVID-19 symptoms.

Upon that, the previous mentioned study shows that hypoxia of the brain can be found as a serious factor for the occurring of the neurological and the psychiatric disturbances. Examining the brain in the presented case some signs of hypoxia have been seen, but not clear if they are result of the primary disease or of the asphyxiation. The degree of the neurological disturbance often is not correlated with the severity of the primary COVID disease and also the neurological symptoms can be found as a first presentation of the COVID disease [6, 8]. Hence, it is a kind of challenge early recognizing and managing of the neurological and psychiatric disturbances in the COVID-19 disease.

Based of the aforementioned, if we look back to the medical history of the presented case, in fact the patient has asked for a psychiatric support twice: first time, indirectly by his first attempt for suicide, and second time, four days later he and his family directly asked for it. Unfortunately, the patient has been released home only with the prescribed antipsychotic therapy. This event shows that, regarding the COVID-19 patients, medical professionals must be aware about the neurological and psychiatric manifestation of the disease, as well as the possible consequences of it.

The second important aspect of this case report is to perceive the pathological feature of the lungs in a confirmed COVID-19 patient, who actually didn't die of the disease itself but of a violent death. The clinical data along with the pathological findings were pointing to the acute restrictive lung disease which started as an atypical viral pneumonia and then progressed to diffuse alveolar damage, known as ARDS (acute respiratory distress syndrome).

The concept of the primary atypical pneumonia has been presented since 1938 and described as non-productive pneumonia, with minimal physical and rich radiology findings, with predominantly good prognosis and bad outcome only in immunosuppressed organisms [7]. The bad outcome actually means the development toward the diffuse alveolar damage and ARDS.

Acute respiratory distress syndrome (ARDS) is a clinical syndrome defined in 1994 by the American-European Consensus Conference (AECC) which is characterized by: 1. acute respiratory distress, 2. decreased arterial oxygen pressure and 3. the development of diffuse pulmonary infiltrates on radiographs [7, 11, 12, 13]. By the Berlin Definition [11] there are proposed three categories of ARDS upon the severity: mild, moderate and severe, with strict parameters given. Diffuse alveolar damage is the morphologic counterpart of ARDS [7]. It is characterized by diffuse injury of the alveolar epithelial and capillary endothelial cells, accompanied with the pulmonary edema.

In the pathogenesis of ARDS, no matter of the initiating agent (chemical, physical or viral), there is a sequence of the events: 1. endothelial and epithelial damage; 2. the cellular reaction by neutrophils and macrophages; 3. releasing of the TNF-alpha (tumor necrotizing factor alpha) and activating of the complement with subsequent production and release of the cytokines, powerful mediators, proteases etc. which all further damage the endothelium and increase vascular permeability. These all cause the changes of the first or exudative phase of ARDS: interstitial and intraalveolar edema and hemorrhage, necrosis of the epithelial cells and forming of the typical hyaline membranes underlining the alveolar walls which sufficiently compromise the oxygenation. 72 hours after the process begins, a disseminated intravascular coagulation may become evident and complicate the clinical picture [7]. The next two phases in the morphology of ARDS are the proliferative phase characterized by the proliferation of the type II pneumocytes and fibroblasts, and finally the fibrotic phase with the progressive fibrosis involving the interstitial and alveolar spaces, leading to diffuse interstitial fibrosis (honeycomb lungs) [7].

In the presented case were found changes of the exudative and proliferative phase of ARDS. Having in regard that the mortality rate of ARDS nowadays is beneath 50% [13], comparing with the past when it was almost 100%, we can assume that if patient overcomes the exudative phase, there are good chances of survival. Implying that to the presented case, there are good chances that the person could have overcome the COVID-19 disease, but unfortunately he died of suicide. Here lies the obligation for the medical professionals to recognize the neurological and psychiatric disturbances as part of the diverse clinical picture of COVID-19, in order to provide a complete health care for the patient.

Conclusion

This case presentation shows that the psychiatric and neurological disturbances can be significant part of the clinical picture of the COVID-19 disease and they are not necessarily correlated with the severity of the primary disease. Medical professionals must be aware of these manifestations of the COVID-19 disease, because sometimes they can be more fatal than the lung disease itself. High degree of caution and care are important in these cases.

Having in regard the diverse and still not enough explored clinical manifestation of the COVID-19, besides treating the pneumonia and coagulopathy in these patients, attention to the psychiatric status of the patient must be paid, in order to enable him/her a complete health care protection.

References

1. **Campbell, C., R. Kahwash.** Microvascular thrombi in COVID-19. Expert Analysis. – *American College of Cardiology*. January 25th 2021. <https://www.acc.org/latest-in-cardiology/articles/2021/01/25/14/28/microvascular-thrombi-in-covid-19>
2. **Dorward, D. A., C. D. Russell, I. H. Um, M. Elshani, S. D. Armstrong, R. Penrice-Randal, T. Millar, C. E. B. Lerpiniere, G. Tagliavini, C. S. Hartley, N. P. Randle, N. N. Gachanja, P. Potey, A. M. Anderson, V.L. Campbell, A. J. D. BChir, W. Al. Qsous, R. BouHaidar, J. K. Baillie, K. Dhaliwai, W. A. Wallace, C. Bellamy, S. Prost, C. Smith, J. A. Hiscox, D. J. Harrison, C. D. Lucas.** Tissue specific immunopathology in fatal COVID-19. – *Am. J. Respir. Crit Care Med.*, **203**(2), 2021, 192-201.
3. **Fox, S. E., A. Akmatbekov, J. L. Harbert, G. Li, J. Q. Brown, R. S. V. Heide.** Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. – *Lancet Respir. Med.*, **8**, 2020, 681-686.
4. **Guo, T., F. Yongzhen, M. Chen, W. Xiaoyian, L. Zhang, J. Wan, X. Wang, Z. Lu.** Cardiovascular implications of fatal outcomes of patients with Coronavirus disease 2019 (COVID-19). – *JAMA Cardiol.*, **5**(7), 2020, 811-818.
5. **Hanley, B., S. B. Lucas, E. Youd, B. Swift, M. Osborn.** Autopsy in suspected COVID-19 cases. – *J. Clin. Pathol.*, **73**, 2020, 239-242.
6. **Helms, J., S. Kremer, H. Merdji, R. Clere-Jehl, M. Schenck, C. Kummerlen, O. Collange, C. Boulay, S. Fafi-Kremer, M. Ohana, M. Anheim.** Neurologic features in severe SARS-CoV-2 infection. – *N. Engl. J. Med.*, **382**, 2020, 2268-2270.
7. **Kumar, V., R. S. Cotran, S. L. Robbins.** Acute restrictive lung diseases. Chapter 13. – In: *Basic Pathology – Sixth edition*, W. B. Saunders company, USA, 1997, 405-407.
8. **Mushumba, H., C. Edler, A.S. Schroeder, A. Fitzek, A. Ron.** An autopsy study of SARS-CoV-2-related deaths examined at the Hamburg Institute of legal medicine between March 20th and August 15th 2020. *DGRM 2020 Congressbook*. Lucern.
9. **Paterson, W. R., L. R. Brown, L. Benjamin, R. Nortley, S. Wiethoff, T. Bharucha, D. L. Jayaseelan, G. Kumur, R. E. Raftopoulos, L. Zambreau, V. Vivekanandam, A. Khoo, R. Geraldles, K. Chinthapalli, E. Boyd, H. Tuzlali, G. Price, G. Christofi, J. Morrow, P. McNamara, B. McLoughlin, S. T. Lim, P. R. Mehta, V. Levee, S. Keddie, W. Yong, S. A. Trip, A. J. M. Foulkes, G. Hotton, T. D. Miller, A. D. Everitt, C. Carswell, N. W. S. Davies, M. Yoong, D. Atwell, J. Sreedharan, E. Silber, J. M. Schott, A. Chandratheva, R. J. Perry, R. Simister, A. Checkley, N. Longley, S. F. Farmer, F. Carletti, C. Houlihan, M. Thom, M. P. Lunn, J. Spillane, R. Howard, A. Vincent, D. J. Werring, C. Hoskote, H. R. Jager, H. Manji, M. S. Zandi.** The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. – *BRAIN*, **143**, 2020, 3104-3120.
10. **Puelles, V. G., M. Lütgehetmann, M. T. Lindenmeyer, J. P Sperhake, M. N. Wong, L. Allweiss, S. Chilla, A. Heinemann, N. Wanner, S. Liu, F. Braun, S. Lu, S. Pfefferle, A. S. Schröder, C. Edler, O. Gross, M. Glatzel, D. Wichmann, Th. Wiech, S. Kluge, K. Pueschel, M. Aepfelbacher, T. B. Huber.** Multiorgan and renal tropism of SARS-CoV-2. – *N. Engl. J. Med.*, **383**, 2020, 590-592.
11. **Ranieri, V. M., G. D. Rubenfeld, B. Taylor Thompson, N.D. Ferguson, E. Caldwell, E. Fan, L. Camporota, A. S. Slutsky.** Acute Respiratory Distress Syndrome: the Berlin definition. – *JAMA*, **307**(23), 2012, 3072542-3072544.
12. **Schmitt, W., E. Marchiori.** Covid-19: Round and oval areas of ground-glass opacity. - *Pulmonology*, 2020. doi: 10.1016/1.pulmoe.2020.04.001.
13. **Thompson, T., B. R. C. Chambers, K. D. Liu.** Acute Respiratory Distress Syndrome. – *N. Engl. J. Med.*, **377**-6, 2017, 562-572.
14. **Tzankov, A.** Lessons learned from autopsies of COVID-19: deadly disease courses due to (micro-) angiopathy and thrombosis. – *DGRM 2020 Congressbook*. Lucern.