SARS-CoV-2 Associated Pulmonary Pathology

Subjects: Virology

Contributor: George S. Stoyanov , Hristo Popov , Lilyana Petkova , Dimo Stoyanov , Martin Ivanov , Anton B. Tonchev

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel entry in the betacoronaviridae group of coronaviruses. This is the second member of this group, and the third of the family overall to emerge in the last 20 years, which has caused significant health concerns due to the clinical severity and spread of the disease it causes—coronavirus disease identified in 2019 (COVID-19). While initially emerging as a respiratory disease, and while most cases experience symptoms predominantly from this system, SARS-CoV-2 has emerged as a multisystem pathogen. From a pathomorphological point of view, the severity of changes in the respiratory system can be summed up as diffuse alveolar damage—desquamation of the alveolar epithelium with exudative and proliferative changes—pulmonary hyaline membranes, Clara cell hyperplasia, squamous cell metaplasia, and fibrosis. The second most prominent way the disease affects the lung is through endotheliitis—damage to the endothelial cells of the pulmonary vasculature, predominantly affecting the medium and large caliber blood vessels that cause the well-established clinical phenomenon of thrombosis/thromboembolism of the pulmonary vasculature. As the spread of the disease continues with the emergence of new variants and the number of cases continues to grow, including a large percentage of recurrent cases, it is essential to remember that the viral effects are not only acute but, due to the proliferative phenomena, can produce chronic sequelae. Therefore, in the background of dwindling publication interest, it is critical to focus on the histopathological aspects of the pulmonary disease, with the goal of better understanding the effects of the virus on the organism and identifying probable future complications after infection.

SARS-CoV-2 COVID-19 pathology autopsy diffuse alveolar damage pulmonary pathology virus-induced lung damage long COVID

The novel representative of coronaviruses (SARS-CoV-2) and the clinical disease it causes (COVID-19), which emerged at the end of 2019, have led to healthcare and social consequences not seen in the last 100 years [1][2][3][4][5][6]. The rapid spread of the infection, the severe organ damage to multiple systems, and the lack of effective prevention forced the World Health Organization (WHO) to officially declare a pandemic of the disease [7][8][9]. Given the new nature of the infectious agent and the many unknowns surrounding it, the WHO implemented protocols developed during the most closely related infectious agents—MERS and SARS-CoV, namely, social distance, personal protective equipment, quarantine of healthy disease carriers and contacts of the sick, and strict monitoring of the epidemiological process [10][11][12]. The severe health challenges including the unknowns surrounding the course of the disease and the epidemiological process, the large number of healthy infection spreaders, the severe clinical course with high and sometimes sudden mortality in some patients, the lack of healthcare personnel, and effective prevention and misinformation (at the beginning of the pandemic due to lack of

scientifically proven facts, and, in the later stages, for non-medical reasons) led to the mobilization of medical science in the study of SARS-CoV-2 not only towards the origin of the virus and the study of its clinical consequences and morphology, but also to the rapid development of effective vaccine prophylaxis, largely possible based on the experience gained in the previous two severe coronavirus diseases [9][13][14][15][16].

With the abatement of the pandemic in 2022 and given the mutational variants of the disease leading to a significantly milder clinical course and a decrease in overall mortality, as well as due to the availability of widespread effective vaccine prevention, not only the public but also the publication interest in the subject has gradually subsided [17][18][19]. The question remains open not only about the origin of the virus and, to a large extent, the characteristics regarding organ involvement, but above all about the chronic consequences of the illness, which the medical community has yet to face [20][21][22][23][24][25][26][27].

Historically, this is not the first time that medicine has encountered a similar situation; numerous pandemics, not only of viral origin but also of bacterial origin, have led to the permanent disability of those who have suffered, and subsequently to the development of new and, at first glance, unexpected long-term consequences [28]. A relatively recent example is the HIV-AIDS infection, which, in addition to immune deficiency, has been proven to lead to many severe consequences, including neoplasia and dementia [29][30][31][32]. In the history of medicine, there are many more such examples, such as von Economo's disease (lethargic encephalitis), often confused as a consequence of the Spanish flu; although, the epidemic process began several years before it and led to postencephalitic parkinsonism [33][34][35].

It is for these reasons that it is necessary to retain the interest of medical science in the matter of the detailed study of the acute and chronic effects of the virus that are yet to be encountered and that can be used in combating future pandemic variants of coronavirus infections [36][37][38][39].

Autopsies of patients with COVID-19 have revealed a myriad of gross and especially histological changes in multiple internal organs, namely, the lungs, where the changes lead to the dominating clinical symptom of hypoxia, but also the liver, heart, and other organs [40][41][42][43][44]. It is important, however, that autopsies reveal only the most severe effects of the disease in patients who had either a severe protracted clinical course or those who expired suddenly. It is highly likely that in cases with a moderate clinical course, either a significantly less diffuse and developed set of complications is present or it did not manifest at all.

Furthermore, it is likely that in patients with mild clinical disease, a whole new spectrum of changes can be present, with all of these further developing and evolving into chronic changes in the spectrum of post-COVID syndrome. Post-COVID syndrome, or long COVID or persistent COVID, are a direct result of the persistent damage caused by the viral infection. While mainly focusing on the diverse pulmonary pathology, which leads to chronic complications, this spectrum also includes sequelae from other systems and organs, such as the kidneys, cardiovascular, gastrointestinal, and especially the central nervous system [21][45][46][47][48].

Safety Precautions during Autopsy—Determining the Hazard Group

As the causative agent of the disease has been identified by the WHO as a pandemic entity, special precautions must be taken during the autopsy of suspected, probable, and identified cases [49]. Furthermore, as a general precautionary rule in the presence of diffusely spreading infectious pandemic entities, safety precautions should be taken in all cases, even if the autopsy case is not suspected or even has been ruled out to be a carrier of the disease.

For autopsy practice, especially for infectious disease entries, cases are separated into hazard groups (HG) based on the ability of the pathogens to infect new hosts, the severity of the disease it causes, and the presence of effective prevention, treatment, or the lack thereof [50]. HG1 refers to pathogens that are unlikely to cause human disease, cause minimal illness, or there is effective prevention and treatment; HG2 refers to pathogens that can lead to infection in the personnel but are unlikely to spread to the general population, and there is effective prevention and treatment; HG3 refers to pathogens that cause severe disease to the personnel and can spread to the community, but there is effective prevention and treatment; and HG4 refers to pathogens that cause severe diseases, can spread in the general population, and there is no effective prevention and treatment. It is essential to know that in many regions, based on their legislation, HG4 autopsies are counter-indicated, while in others, HG4 is mandated as it is viewed as a threat to national and regional security [49][51][52][53][54].

During the initial phases of the pandemic, there was a broad discussion regarding which HG COVID-19 should be placed in, with initial decisions putting it in HG4, and, hence, the number of autopsy cases was very low [49][51][55]. As data started to accumulate and there was a relatively low incidence of periautopsy infection, it was gradually moved down to HG3 and, in some areas after the introduction of vaccinations, even to HG2. Based, however, on the significant mutation frequency of the virus and the evasion of acquired immunity by the new variants, in the future, it would be sound to keep SARS-CoV-2 in HG3 to prevent the spreading of potentially deadly variants of the virus to healthcare personnel and the population in general [56].

References

1. Li, X.; Zai, J.; Zhao, Q.; Nie, Q.; Li, Y.; Foley, B.T.; Chaillon, A. Evolutionary history, potential intermediate animal host, and cross-species analyses of SARS-CoV-2. J. Med. Virol. 2020, 92, 602–611.
2. Andersen, K.G.; Rambaut, A.; Lipkin, W.I.; Holmes, E.C.; Garry, R.F. The proximal origin of SARS-CoV-2. Nat. Med. 2020, 26, 450–452.
3. Wu, Y.-C.; Chen, C.-S.; Chan, Y.-J. The outbreak of COVID-19: An overview. J. Chin. Med. Assoc. 2020, 83, 217–220.
4. Liu, Q.; Luo, D.; Haase, J.E.; Guo, Q.; Wang, X.Q.; Liu, S.; Xia, L.; Liu, Z.; Yang, J.; Yang, B.X. The experiences of health-care providers during the COVID-19 crisis in China: A qualitative study. Lancet Glob. Health 2020, 8, e790–e798.

5. Sun, N.; Wei, L.; Shi, S.; Jiao, D.; Song, R.; Ma, L.; Wang, H.; Wang, C.; Wang, Z.; You, Y.; et al. A qualitative study on the psychological experience of caregivers of COVID-19 patients. Am. J. Infect. Control 2020, 48, 592–598.
6. De Brier, N.; Stroobants, S.; Vandekerckhove, P.; De Buck, E. Factors affecting mental health of health care workers during coronavirus disease outbreaks (SARS, MERS & COVID-19): A rapid systematic review. PLoS ONE 2020, 15, e0244052.
7. Wang, C.; Horby, P.W.; Hayden, F.G.; Gao, G.F. A novel coronavirus outbreak of global health concern. Lancet 2020, 395, 470–473.
8. Hu, B.; Guo, H.; Zhou, P.; Shi, Z.-L. Characteristics of SARS-CoV-2 and COVID-19. Nat. Rev. Microbiol. 2021, 19, 141–154.
9. Baloch, S.; Baloch, M.A.; Zheng, T.; Pei, X. The Coronavirus Disease 2019 (COVID-19) Pandemic. Tohoku J. Exp. Med. 2020, 250, 271–278.
10. Guarner, J. Three Emerging Coronaviruses in Two Decades the Story of SARS, MERS, and Now COVID-19. Am. J. Clin. Pathol. 2020, 153, 420–421.
11. Peeri, N.C.; Shrestha, N.; Rahman, M.S.; Zaki, R.; Tan, Z.; Bibi, S.; Baghbanzadeh, M.; Aghamohammadi, N.; Zhang, W.; Haque, U. The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: What lessons have we learned? Int. J. Epidemiol. 2020, 49, 717–726.
12. Dagens, A.; Sigfrid, L.; Cai, E.; Lipworth, S.; Cheung, V.; Harris, E.; Bannister, P.; Rigby, I.; Horby, P. Scope, quality, and inclusivity of clinical guidelines produced early in the COVID-19 pandemic: Rapid review. BMJ 2020, 369, m1936.
13. Dzieciatkowski, T.; Szarpak, L.; Filipiak, K.J.; Jaguszewski, M.; Ladny, J.R.; Smereka, J. COVID-19 challenge for modern medicine. Cardiol. J. 2020, 27, 175–183.
14. Harris, C.; Carson, G.; Baillie, J.K.; Horby, P.; Nair, H. An evidence-based framework for priority clinical research questions for COVID-19. J. Glob. Health 2020, 10, 11001.
15. Khalifa, S.A.M.; Mohamed, B.S.; Elashal, M.H.; Du, M.; Guo, Z.; Zhao, C.; Musharraf, S.G.; Boskabady, M.H.; El-Seedi, H.H.R.; Efferth, T.; et al. Comprehensive Overview on Multiple Strategies Fighting COVID-19. Int. J. Environ. Res. Public Health 2020, 17, 5813.
16. Kuhn, S.A.K.; Lieb, R.; Freeman, D.; Andreou, C.; Zander-Schellenberg, T. Coronavirus conspiracy beliefs in the German-speaking general population: Endorsement rates and links to reasoning biases and paranoia. In Psychological Medicine; Cambridge University Press: Cambridge, UK, 2021; pp. 1–15.
17. Karim, S.S.A.; Karim, Q.A. Omicron SARS-CoV-2 variant: A new chapter in the COVID-19 pandemic. Lancet 2021, 398, 2126–2128.

18. Del Rio, C.; Omer, S.B.; Malani, P.N. Winter of Omicron—The Evolving COVID-19 Pandemic. JAMA 2022, 327, 319.
19. Hoffmann, M.; Krüger, N.; Schulz, S.; Cossmann, A.; Rocha, C.; Kempf, A.; Nehlmeier, I.; Graichen, L.; Moldenhauer, A.-S.; Winkler, M.S.; et al. The Omicron variant is highly resistant against antibody-mediated neutralization: Implications for control of the COVID-19 pandemic. Cell 2022, 185, 447–456.e11.
20. Phillips, N. The coronavirus is here to stay—here's what that means. Nature 2021, 590, 382–384.
21. Torres-Castro, R.; Vasconcello-Castillo, L.; Alsina-Restoy, X.; Solis-Navarro, L.; Burgos, F.; Puppo, H.; Vilaró, J. Respiratory function in patients post-infection by COVID-19: A systematic review and meta-analysis. Pulmonology 2021, 27, 328.
22. Shaw, B.; Daskareh, M.; Gholamrezanezhad, A. The lingering manifestations of COVID-19 during and after convalescence: Update on long-term pulmonary consequences of coronavirus disease 2019 (COVID-19). Radiol. Med. 2021, 126, 40–46.
23. Zhao, Y.-M.; Shang, Y.-M.; Song, W.-B.; Li, Q.-Q.; Xie, H.; Xu, Q.-F.; Jia, J.-L.; Li, L.-M.; Mao, H.-L.; Zhou, X.-M.; et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. eClinicalMedicine 2020, 25, 100463.
24. Castagnoli, R.; Votto, M.; Licari, A.; Brambilla, I.; Bruno, R.; Perlini, S.; Rovida, F.; Baldanti, F.; Marseglia, G.L. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents: A Systematic Review. JAMA Pediatr. 2020, 174, 882–889.
25. Dehingia, N.; Raj, A. Sex differences in COVID-19 case fatality: Do we know enough? Lancet Glob. Heal. 2021, 9, e14–e15.
26. Lazzerini, M.; Putoto, G. COVID-19 in Italy: Momentous decisions and many uncertainties. Lancet Glob. Health 2020, 8, e641–e642.
27. Levin, A.T.; Hanage, W.P.; Owusu-Boaitey, N.; Cochran, K.B.; Walsh, S.P.; Meyerowitz-Katz, G. Assessing the age specificity of infection fatality rates for COVID-19: Systematic review, meta-analysis, and public policy implications. Eur. J. Epidemiol. 2020, 35, 1123–1138.
28. Huremović, D. Brief History of Pandemics (Pandemics Throughout History). In Psychiatry of Pandemics; Springer: Cham, Switzerland, 2019; pp. 7–35.
29. Quinn, T.C. HIV epidemiology and the effects of antiviral therapy on long-term consequences. AIDS 2008, 22, S7–S12.
30. Clutton, G.; Xu, Y.; Baldoni, P.L.; Mollan, K.R.; Kirchherr, J.; Newhard, W.; Cox, K.; Kuruc, J.D.; Kashuba, A.; Barnard, R.; et al. The differential short- and long-term effects of HIV-1 latency-reversing agents on T cell function. Sci. Rep. 2016, 6, 30749.

31. Lake, J.E.; Currier, J.S. Metabolic disease in HIV infection. Lancet Infect. Dis. 2013, 13, 964–975.
32. Degano, B.; Yaïci, A.; Le Pavec, J.; Savale, L.; Jaïs, X.; Camara, B.; Humbert, M.; Simonneau, G.; Sitbon, O. Long-term effects of bosentan in patients with HIV-associated pulmonary arterial hypertension. Eur. Respir. J. 2009, 33, 92–98.
33. Dickman, M.S. von Economo Encephalitis. Arch. Neurol. 2001, 58, 1696–1698.
34. Reid, A.; McCall, S.; Henry, J.M.; Taubenberger, J.K. Experimenting on the Past: The Enigma of von Economo′s Encephalitis Lethargica. J. Neuropathol. Exp. Neurol. 2001, 60, 663–670.
35. Hoffman, L.A.; Vilensky, J.A. Encephalitis lethargica: 100 years after the epidemic. Brain 2017, 140, 2246–2251.
36. Assaad, R.; El-Adaway, I.H. Guidelines for Responding to COVID-19 Pandemic: Best Practices, Impacts, and Future Research Directions. J. Manag. Eng. 2021, 37, 6021001.
37. Khanna, R.C.; Cicinelli, M.V.; Gilbert, S.S.; Honavar, S.G.; Murthy, G.S.V. COVID-19 pandemic: Lessons learned and future directions. Indian J. Ophthalmol. 2020, 68, 703–710.
38. Saqr, M.; Wasson, B. COVID-19: Lost opportunities and lessons for the future. Int. J. Health Sci. 2020, 14, 4.
39. Lai, J.W.; Cheong, K.H. Superposition of COVID-19 waves, anticipating a sustained wave, and lessons for the future. BioEssays 2020, 42, e2000178.
40. Siripanthong, B.; Nazarian, S.; Muser, D.; Deo, R.; Santangeli, P.; Khanji, M.Y.; Cooper, L.T.; Chahal, C.A.A. Recognizing COVID-19–related myocarditis: The possible pathophysiology and proposed guideline for diagnosis and management. Hear. Rhythm 2020, 17, 1463–1471.
41. Buja, L.M.; Wolf, D.A.; Zhao, B.; Akkanti, B.; McDonald, M.; Lelenwa, L.; Reilly, N.; Ottaviani, G.; Elghetany, M.T.; Trujillo, D.O.; et al. The emerging spectrum of cardiopulmonary pathology of the coronavirus disease 2019 (COVID-19): Report of 3 autopsies from Houston, Texas, and review of autopsy findings from other United States cities. Cardiovasc. Pathol. 2020, 48, 107233.
42. Haider, A.; Siddiqa, A.; Ali, N.; Dhallu, M. COVID-19 and the Brain: Acute Encephalitis as a Clinical Manifestation. Cureus 2020, 12, e10784.
43. Menezes, R.G.; Rizwan, T.; Ali, S.S.; Hasan, W.; Khetpal, A.; Aqil, M.; Madadin, M.; Siddiqi, T.J.; Usman, M.S. Postmortem findings in COVID-19 fatalities: A systematic review of current evidence. Leg. Med. 2022, 54, 102001.
44. Montero-Fernandez, M.A.; Pardo-Garcia, R. Histopathology features of the lung in COVID-19 patients. Diagn. Histopathol. 2021, 27, 123–127.
45. Anaya, J.-M.; Rojas, M.; Salinas, M.L.; Rodríguez, Y.; Roa, G.; Lozano, M.; Rodríguez-Jiménez, M.; Montoya, N.; Zapata, E.; Monsalve, D.M.; et al. Post-COVID syndrome. A case series and

comprehensive review. Autoimmun. Rev. 2021, 20, 102947.

46. Ceban, F.; Ling, S.; Lui, L.M.; Lee, Y.; Gill, H.; Teopiz, K.M.; Rodrigues, N.B.; Subramaniapillai, M.; Di Vincenzo, J.D.; Cao, B.; et al. Fatigue and cognitive impairment in Post-COVID-19 Syndrome: A systematic review and meta-analysis. Brain Behav. Immun. 2022, 101, 93–135.
47. Oronsky, B.; Larson, C.; Hammond, T.C.; Oronsky, A.; Kesari, S.; Lybeck, M.; Reid, T.R. A Review of Persistent Post-COVID Syndrome (PPCS). Clin. Rev. Allergy Immunol. 2021, 1, 1–9.
48. Ayoubkhani, D.; Khunti, K.; Nafilyan, V.; Maddox, T.; Humberstone, B.; Diamond, I.; Banerjee, A. Post-covid syndrome in individuals admitted to hospital with COVID-19: Retrospective cohort study. BMJ 2021, 372, n693.
49. Kim, M.-Y.; Cheong, H.; Kim, H.-S. Medicine TWG for SAG for C-19 from TKS for L: Proposal of the Autopsy Guideline for Infectious Diseases: Preparation for the Post-COVID-19 Era (abridged translation). J. Korean Med. Sci. 2020, 35, e310.
50. Lee, J.A. Guidelines on autopsy practice. In The Royal College of Pathologists; The Royal College of Pathologists: London, UK, 2002.
51. Hanley, B.; Lucas, S.B.; Youd, E.; Swift, B.; Osborn, M. Autopsy in suspected COVID-19 cases. J. Clin. Pathol. 2020, 73, 239–242.
52. Schwartz, D.A.; Herman, C.J. Editorial Response: The Importance of the Autopsy in Emerging and Reemerging Infectious Dis-eases. Clin. Infect. Dis. 1996, 23, 248–254.
53. Buja, L.M.; Barth, R.F.; Krueger, G.R.; Brodsky, S.V.; Hunter, R.L. The Importance of the Autopsy in Medicine: Perspectives of Pathology Colleagues. Acad. Pathol. 2019, 6.
54. Nolte, K.B.; Muller, T.B.; Denmark, A.M.; Burstein, R.; Villalobos, Y.A. Design and Construction of a Biosafety Level 3 Autopsy Laboratory. Arch. Pathol. Lab. Med. 2021, 145, 407–414.
55. Barton, L.M.; Duval, E.J.; Stroberg, E.; Ghosh, S.; Mukhopadhyay, S. COVID-19 Autopsies, Oklahoma, USA. Am. J. Clin. Pathol. 2020, 153, 725–733.
56. Lacy, J.M.; Brooks, E.G.; Akers, J.; Armstrong, D.; Decker, L.; Gonzalez, A.; Humphrey, W.; Mayer, R.; Miller, M.; Perez, C.; et al. COVID-19: Postmortem Diagnostic and Biosafety Considerations. Am. J. Forensic Med. Pathol. 2020, 41, 143–151.