

# Journal Pre-proof

The COVID-19 pandemic: pathologist's support to clinical infectious team

Antonio Ieni, Giovanni Tuccari



PII: S1201-9712(20)32593-5

DOI: <https://doi.org/10.1016/j.ijid.2020.12.069>

Reference: IJID 4987

To appear in: *International Journal of Infectious Diseases*

Received Date: 12 December 2020

Accepted Date: 23 December 2020

Please cite this article as: { doi: <https://doi.org/>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2020 Published by Elsevier.

## **The COVID-19 pandemic: pathologist's support to clinical infectious team**

**Antonio Ieni\* and Giovanni Tuccari**

Department of Human Pathology in Adult and Developmental Age "Gaetano Barresi", Section of Pathology, University of Messina, 98125 Messina, Italy.

Correspondence: Ieni A & Tuccari G, Department of Human Pathology in Adult and Developmental Age "Gaetano Barresi", Section of Pathology, University of Messina, Via Consolare Valeria 1, 98125 Messina, Italy (aieni@unime.it; tuccari@unime.it)

### **Abstract**

In the management of COVID-19 affected patients, the pathologist is involved in many diagnostic steps together with the clinical infectious team. In particular, cytological and histopathological procedures as well as autoptic findings may represent an useful tool to better understand the pathobiology of the disease as well as to correctly define causes of patient's death. Moreover, in COVID-19 pandemic, pathologists have been forced to reconsider the usual laboratory workflow and to introduce adequate guidelines against virus diffusion, requiring high biosafety level.

**Keywords.** COVID-19; SARS-CoV2; pathologist; cytopathology; histopathology; autopsy

## **Introduction**

The severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) virus produced a worldwide diffusive disease (COVID-19), defined by the World Health Organization as a pandemic on March 2020. Consequently, many governments have adopted a series of public health measures in order to promote the social distancing and to reduce the spread of COVID-19; therefore, cultural and political meetings have been cancelled, schools, universities and gyms have been closed, smart working from home has been recommended, frequency of bars and restaurants as well as discretionary travel among different countries have been considered to be avoided. However, analyzing the clinical course of COVID-19, the WHO considered 3% of cases as critical requiring intensive care, 15% as severe needing hospitalization and 82% as mild being sufficient quarantine and home therapy (Yang et al., 2020; Vetter et al., 2020)

## **Safety in pathology laboratory**

There is no doubt that in all health-care operators, pathologists have to be included, mainly because they are involved in many diagnostic steps, such as cytology and histopathology process, until the autopsy of COVID-19 affected cases in order to better understand the pathobiology of the disease as well as to correctly define causes of patient's death. Therefore, in the present pandemic, laboratories of pathology have to reconsider the usual workflow, introducing adequate guidelines against virus diffusion among staff personnel and also requiring typical biosafety level 2 (Barbareschi et al., 2020; Carpenito et al., 2020; Kaufer et., 2020; Pambuccian et al., 2020). Nevertheless, it should be reminded that in laboratory pathology the main fixatives utilized are represented by alcohol solutions >70% and formalin, both considered extremely effective to destroy COVID-19. Obviously, protective equipment and additional measures (hand-washing with sanitizers, wearing gloves...) have to be respected together with decontamination of all working surfaces (Centers for Disease Control and Prevention, 2020).

### **Cytology procedures**

The first impact for pathologists concerning COVID-19 patients has been represented by the cytological approach. In fact, sputum and broncho-alveolar lavage fluid (BAL) should represent the first relevant laboratory step, especially when nasopharyngeal/oropharyngeal swabs have been already performed with negative results. Nevertheless, cytological findings encountered in the above mentioned cytological samples are generally unspecific, reflecting the lung's injuries; therefore, the presence of macrophages, frequently in aggregates, with characteristic foamy cytoplasm and ground glass nuclei, together with a variable component of granulocytic neutrophils, multinucleated cells, damaged alveolar elements and squamous metaplastic bronchial epithelium, has been repeatedly reported (Damiani et al., 2020; Parada et al., 2020; Reusken et al., 2020; Vasquez-Bonilla et al., 2020). However, although the cytological features are inconclusive for the diagnosis of COVID-19 disease, it must be greatly stressed that some fixatives characterized by a weaker alcohol concentration utilized in thin preparations (PreservCyt, CytoLyT, SurePath,...) may probably not adequate to inactivate virus and then a great caution is mandatory to be applied in cytology laboratory (Pambuccian et al., 2020).

### **Histopathology approach**

It is well known that SARS-CoV-2 determines histologic changes in lungs, producing acute respiratory distress syndrome and presenting a diffuse alveolar damage (DAD) (Al Nemer, 2020; Damiani et al., 2020). In detail, DAD is associated with edema, vascular congestion, proteinaceous exudates constituting hyaline membranes as well as inflammatory infiltration of various entity, with the presence of fibrin thrombi and vascular injuries as well as a various degree of fibroblastic organized plugs (Konopka et al., 2020; Polak et al., 2020). Moreover, by electron microscopy, viral particles have been detected in type I and II pneumocytes, in tracheal biopsies and in bronchial mucus (Bradley et al., 2020; Prieto-Pérez et al., 2020). Additionally, other relevant pathologic

findings COVID-19 induced have documented outside of the respiratory tract, including some organs such as heart, liver, kidney and central nervous system; the characteristics of these lesions came from autoptic postmortem examinations (Damiani et al., 2020; Vasquez-Bonilla et al., 2020). Consequently again, the central role of the pathologist to ascertain this peculiar kind of diffusive pathology is furtherly stressed.

### **Autopsy information**

For suspected or affected COVID-19 patients a specific autopsy protocol should be applied taking into consideration measures provided by governments, ministry of health and local regional advices; in any case, the autopsy room as well as the procedures of internally manage biological samples needs a safety level 3, as designed by CDC (Centers for Disease Control and Prevention, 2020). In detail, the autopsy room need to be at a negative pressure, considering minimum of 6-12 air change for hour for existing or new structures, respectively, and having an efficient adequate particulate filter (Centers for Disease Control and Prevention, 2020). Although the details about technical execution of autopsy is out of scope of the present commentary, it may be signaled that any COVID-19 affected or suspected deceased patient should be preliminary investigated by a swab for molecular detection of SARS-CoV-2 by PCR (Carpenito et al., 2020; Centers for Disease Control and Prevention, 2020). Moreover, an early performed autopsy has been suggested, specifically before the routine 16 or more hours expected after death, in order to avoid postmortem phenomena and likewise to obtain biological samples of high quality to perform immunohistochemical, ultrastructural and biomolecular investigations (Carpenito et al., 2020).

Many series of autopsies concerning patients affected by COVID-19 coming from different countries have been reported and all of them have stressed the viral cytopathic effect not only in lungs, but also in different organs and parenchyma (Ackermann et al., 2020; Calabrese et al., 2020; Pesaresi et al., 2020). From many of these reports it can be argued that SARS-CoV-2 infection represents a multiorgan pathology, in which together with DAD some additional lesions have been encountered in heart (lymphocytic myocarditis, thrombotic vascular occlusion), brain (encephalitis,

ischemic or hemorrhagic infarcts, vasculitis), kidney (tubular injury, arterionephrosclerosis), liver (steatosis, lymphatic lobular infiltration), lymph nodes and bone marrow (histiocytosis, hemophagocytosis) (Calabrese et al., 2020; Damiani et al., 2020; Vasquez-Bonilla et al., 2020). Therefore, all the reported postmortem findings again suggested a central role for pathologists in order to better understand and explain the pathological impact of SARS-CoV-2 infection.

### **Conclusions**

The knowledge of pathological lesions in different organs as well as the analysis of their peculiar tissue characteristics may greatly contribute to critically examine the interactions between human host and virus, addressing a more accurate therapeutic approach against symptoms and complications during COVID-19 pandemic.

### **Declaration of interests**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### **Conflict of interest**

None declared.

### **Ethical Approval**

Not Applicable.

### **Funding**

None.

### **REFERENCES**

- Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *N Engl J Med* 2020; 383: 120-8. doi: 10.1056/NEJMoa2015432.
- Al Nemer A. Histopathologic and Autopsy Findings in Patients Diagnosed With Coronavirus Disease 2019 (COVID-19): What We Know So Far Based on Correlation With Clinical, Morphologic and Pathobiological Aspects. *Adv Anat Pathol* 2020; 27: 363-70. doi: 10.1097/PAP.0000000000000276.
- Barbareschi M, Facchetti F, Frassetto F, et al. What are the priorities of pathologists' activities during COVID-19 emergency? *Pathologica* 2020;112: 57-8. doi: 10.32074/1591-951X-15-20.
- Bradley BT, Maioli H, Johnston R, et al. Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington State: a case series. *Lancet* 2020; 396:320-32. doi: 10.1016/S0140-6736(20)31305-2.
- Calabrese F, Pezzuto F, Fortarezza F, et al. Pulmonary pathology and COVID-19: lessons from autopsy. The experience of European Pulmonary Pathologists. *Virchows Arch* 2020; 477: 359-72. doi: 10.1007/s00428-020-02886-6.
- Carpenito L, D'Ercole M, Porta F, et al. The autopsy at the time of SARS-CoV-2: Protocol and lessons. *Ann Diagn Pathol* 2020;48:151562. doi: 10.1016/j.anndiagpath.2020.151562.
- Centers for Disease Control and Prevention. Interim guidance for health care facilities: preparing for community transmission of COVID-19 in the United States. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/healthcare-facilities/guidance-hcf.html>. Accessed March 23, 2020.
- Damiani S, Fiorentino M, De Palma A, et al. Pathological post-mortem findings in lungs infected with SARS-CoV-2. *J Pathol* 2020. doi: 10.1002/path.5549.
- Kaufer AM, Theis T, Lau KA, et al. Laboratory biosafety measures involving SARS-CoV-2 and the classification as a Risk Group 3 biological agent. *Pathology* 2020;52:790-5. doi: 10.1016/j.pathol.2020.09.006.
- Konopka KE, Nguyen T, Jentzen JM, et al. Diffuse alveolar damage (DAD) resulting from coronavirus disease 2019 Infection is Morphologically Indistinguishable from Other Causes of DAD. *Histopathology* 2020;77:570-8. doi: 10.1111/his.14180.
- Pambuccian SE. The COVID-19 pandemic: implications for the cytology laboratory. *J Am Soc Cytopathol* 2020; 9:202-11. doi: 10.1016/j.jasc.2020.03.001
- Parada D, Peña KB, Gumà J, et al. Liquid-based cytological and immunohistochemical study of nasopharyngeal swab from persons under investigation for SARS-CoV-2 infection. *Histopathology* 2020;24:10.1111/his.14257. doi: 10.1111/his.14257
- Pesaresi M, Pirani F, Tagliabracci A, et al. SARS-CoV-2 identification in lungs, heart and kidney specimens by transmission and scanning electron microscopy. *Eur Rev Med Pharmacol Sci* 2020; 24: 5186-8. doi: 10.26355/eurrev\_202005\_21217.
- Polak SB, Van Gool IC, Cohen D, et al. A systematic review of pathological findings in COVID-19: a pathophysiological timeline and possible mechanisms of disease progression. *Mod Pathol* 2020;33:2128-38. doi: 10.1038/s41379-020-0603-3.
- Prieto-Pérez L, Fortes J, Soto C, et al. Histiocytic hyperplasia with hemophagocytosis and acute alveolar damage in COVID-19 infection. *Mod Pathol* 2020; 33:2139-46. doi: 10.1038/s41379-020-0613-1
- Reusken CB, Buiting A, Bleeker-Rovers C, et al. Rapid assessment of regional SARS-CoV-2 community transmission through a convenience sample of healthcare workers, the Netherlands, March 2020. *Euro Surveill* 2020;25:2000334. doi: 10.2807/1560-7917.ES.2020.25.12.2000334.
- Vasquez-Bonilla WO, Orozco R, Argueta V, et al. A review of the main histopathological findings in coronavirus disease 2019. *Hum Pathol* 2020; 105:74-83. doi: 10.1016/j.humpath.2020.07.023.
- Vetter P, Vu DL, L'Huillier AG, et al. Clinical features of covid-19. *BMJ* 2020; 369:m1470. doi: 10.1136/bmj.m1470.

Yang Y, Zhao Y, Zhang F, et al. COVID-19 in Elderly Adults: Clinical Features, Molecular Mechanisms, and Proposed Strategies. *Aging Dis* 2020;11:1481-95. doi: 10.14336/AD.2020.0903.

Journal Pre-proof