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Lungs of COVID-19 affected patients: an autoptic morphological profile

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Abstract

Current knowledge concerning the recently occurred Coronavirus disease 2019 (COVID-19) is largely based on human and laboratory reports, even if pathogenic mechanisms have been greatly elucidated by autoptic procedures. Consequently, the aim of this study is to describe macroscopic changes and histopathological findings documented in lung tissue of these patients. Moreover, the need of an optimised autopsy protocol and the application of ancillary techniques, such as immunohistochemistry (IlHC), in situ hybridization (ISH), PCR-based assay and electron microscopy, have to be recorded in order to assess the presence of COVID-19 virus-like particles in lung tissue, although the risk of autolytic changes as well the incorrect interpretation of artefacts should be cautiously considered.

Key Words: Coronavirus, autopsy, lung tissue, alveoli, endothelial cells, viral-like particles

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Introduction

Coronavirus disease 2019(CoVID-l9) has been firstly recognized in Wuhan (China) at the end of 2019, with occurrence in people attending animal markets (1,2). This current human pandemic has been realized by a potential animal contact, utilizing pangolins as vector (2,3).

Many studies have tried to better define the pathogenic mechanisms as well as the different grades of severity in clinics (4-7). Generally, the great majority of patients only presents a mild illness. while a percentage of them (15-20%) may exhibit a more severe form requiring oxygen therapy (7,8). Moreover, high risk factors as well as high mortality rate have been associated with older age and co-morbidities, such as diabetes mellitus, hypertension, chronic obstructive pulmonary disease, congestive heart failure and coronary disease, chronic renal failure collagenopathies and immune system dysfunction (5.8,9). Nevertheless, while literature about clinical manifestations has been diffusely provided, reports and findings concerning autoptic and histopathological examinations

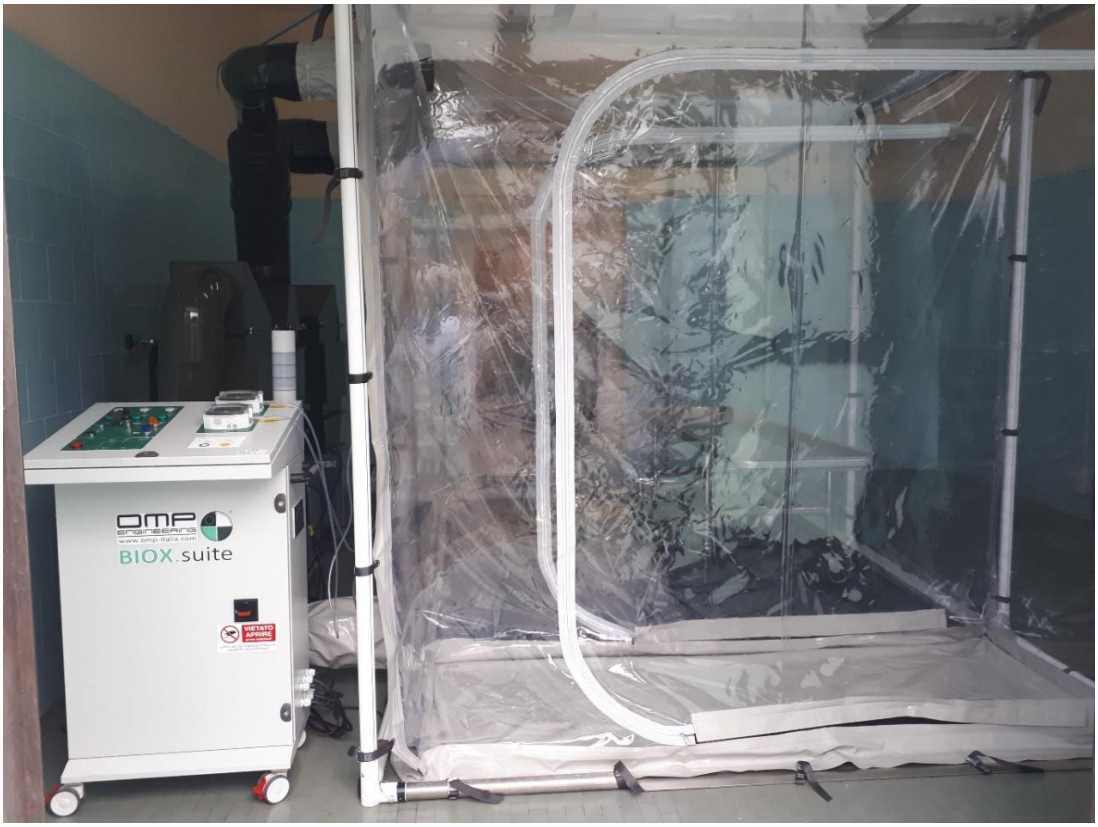
partially remain neglected and not largely commented, although such insights may help and orient the development of therapies against COVID-19.

The aim of the present paper is to report pathological findings documented from autopsy material in order to contribute to a significant increase to the knowledge of COVID-19 infection; in particular, we will be focusing the attention to the lung characteristics, also analyzing histopathological features.

Optimising COVID-19 Autopsy Protocol

In order to have an efficient precaution against COVID-19 infection, a specific autopsy protocol has been recommended and applied (9-12). In detail, it has been suggested that some hours prior to autopsy, a 4% diluted solution of neutral buffered formalin should be applied to oral cavity and nose of the dead body. Of course, the autopsy must be performed in a special pressure-negative room (Fig.1) with adequate airflow corresponding at least six air changes per hour of total room volume, similarly to that performed in Creutzfeld-Jakob disease (9,12). Moreover, the personal protective equipment is mandatory for pathologists and/or technicians and, therefore, surgical hat and scrubs, single use disposable gloves and cut-resistant under-gloves, boots, goggles, clear face visors and FP2/3 masks have to be available for the post-mortem examination of COVID-19 cases (9,12). In any case, a well detailed autopsy protocol has been recently published by pathologists of the Italian University of Padua (2020).

Figure 1: Autopsy safety cabinet present in our Department.

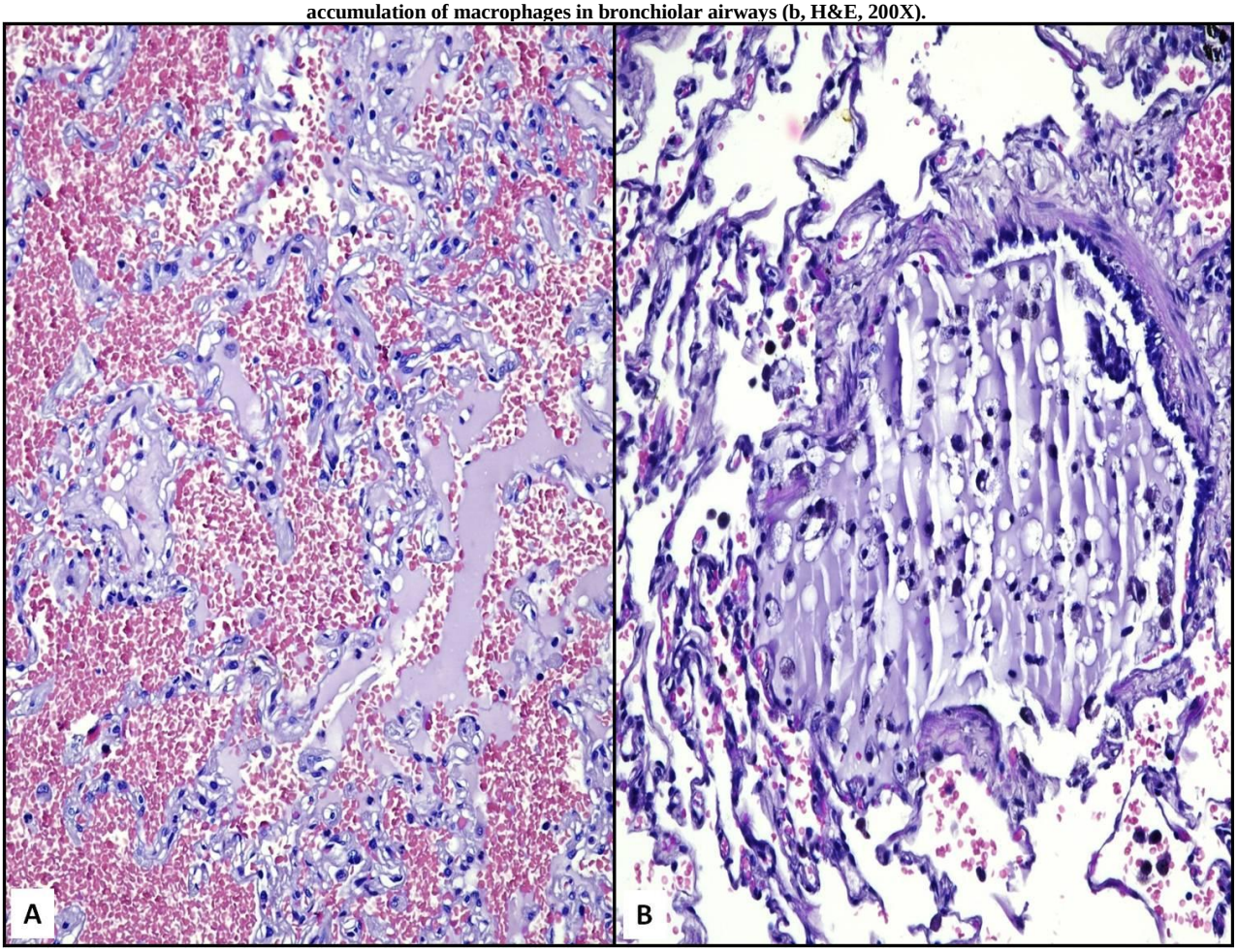


In some conditions such as widespread infections, a regional or minimally invasive post-mortem examination can be performed (12,13). In these cases, thoracic respiratory organs (lungs, trachea, larynx) were eviscerated intact, immediately perfused by formalin and immersed in it for 72 hours at room temperature before dissection. Tissue fragments of each pulmonary lobe and trachea were subsequently taken and routinely treated in order to obtain paraffin blocks. All kinds of histological, histochemical and immunohistochemical stainings may be applied if necessary.

Gross Findings in COVID-19 Affected Lungs

Gross findings of the lungs and upper airways revealed at autopsy in patients affected by COVID-19 are frequently lacking or not reported, while a great macroscopic heterogeneity has been signaled (4,9). Generally, lungs appeared heavy and firm, with a bluish-red colour and an extensive severe congestion; moreover, areas of consolidation, mucus plugs, diffuse edema, infarction as well as thrombi in pulmonary vessels, tracheo-bronchial hyperemia and suppurative bronchopneumonia have been diffusely reported in literature (4,9,14-22). Additional relevant pathological findings, such as aspiration pneumonia, lung carcinoma, pleural effusion, necrotizing granuloma, have been sporadically encountered at autopsy of COVID-19 affected patients (4,8,23).

Figure 2: Lung parenchyma exhibits hyaline membranes and hemorrhagic areas, sometimes in alveoli (a, H&E, 160X); accumulation of macrophages in bronchiolar airways (b, H&E, 200X).



Histopathological Pulmonary Findings in COVID-19 Cases

It is largely accepted that the relevant primary aspect associated with the cause of death of COVID-19 affected patients is represented by the respiratory failure due to diffuse alveolar damage (DAD) (8,9). Nevertheless DAD is often associated to other pathological findings, such as thickening of alveolar walls with interstitial fibroblasts, edema and proteinaceous exudates realizing hyaline membranes, hyperplasia and/or desquamation of alveolar epithelium, accumulation of mononuclear lymphoid inflammatory elements, macrophages and multinucleated giant cells (Fig. 2a,b) (4,8,9,24-26).

In some areas, incipient organizing changes were appreciable with interstitial plugs of proliferating fibroblasts and early collagen deposits within the alveolar cavity (8,9,24). Nevertheless, with the increasing number of performed autopsies, the vascular district and corresponding injuries have raised a consistent attention. In particular, microvascular changes appeared to be significant and characterized by a massive neutrophilic presence in capillaries as well as in medium-sized vessels (4,24); moreover, this acute vasculitis has been associated with the damage occurring in alveoli and trachea-bronchial airways (4,24). Successively, a thrombogenic vasculopathy was described in lungs of COVID-19 patients, with microthrombi present in alveolar capillaries, but also with evident peripheral and/or central pulmonary embolism and infarcts (9,23,24,27-30). This massive hypercoagulability has been attributed to an increase of D-dimer and fibrin products in patients (27,28) and it has been considered responsible for the high mortality for COVID-19 patients, mainly for those affected by myocardial damage or cardiovascular risks. However, the hypothesis that endotheliitis and microthrombi are strictly related to COVID-19 infection may have further support in the observations regarding other organs, such as heart, kidney, brain, in which endotheliitis could represent the sign of a viral direct infection in endothelial cells or, alternatively, a consequence of host inflammatory response (4,30). Finally, the multi-organ endothelial and tissue damage may be considered as the result of a pro-inflammatory cytokine storm (6,31,32).

Closing Remarks

It is important to emphasize that clinical autopsies have greatly promoted our knowledge about COVID-19 tissue damage, clarifying the pathogenesis as well as the cause of patient's death. Nevertheless, ancillary techniques such as immunohistochemistry (IHC), in situ hybridization (ISH), PCR-based assay and electron microscopy may be required to assess the presence of COVID-19 virus particles in lung tissue, although the risk of occurrence of autolytic changes in autopsy samples should be greatly considered to avoid incorrect interpretation of artifacts.

In the light of the above-mentioned considerations, the possibility to detect COVID-19 in lung tissue has been developed in order to demonstrate the link between viral etiology and pathological

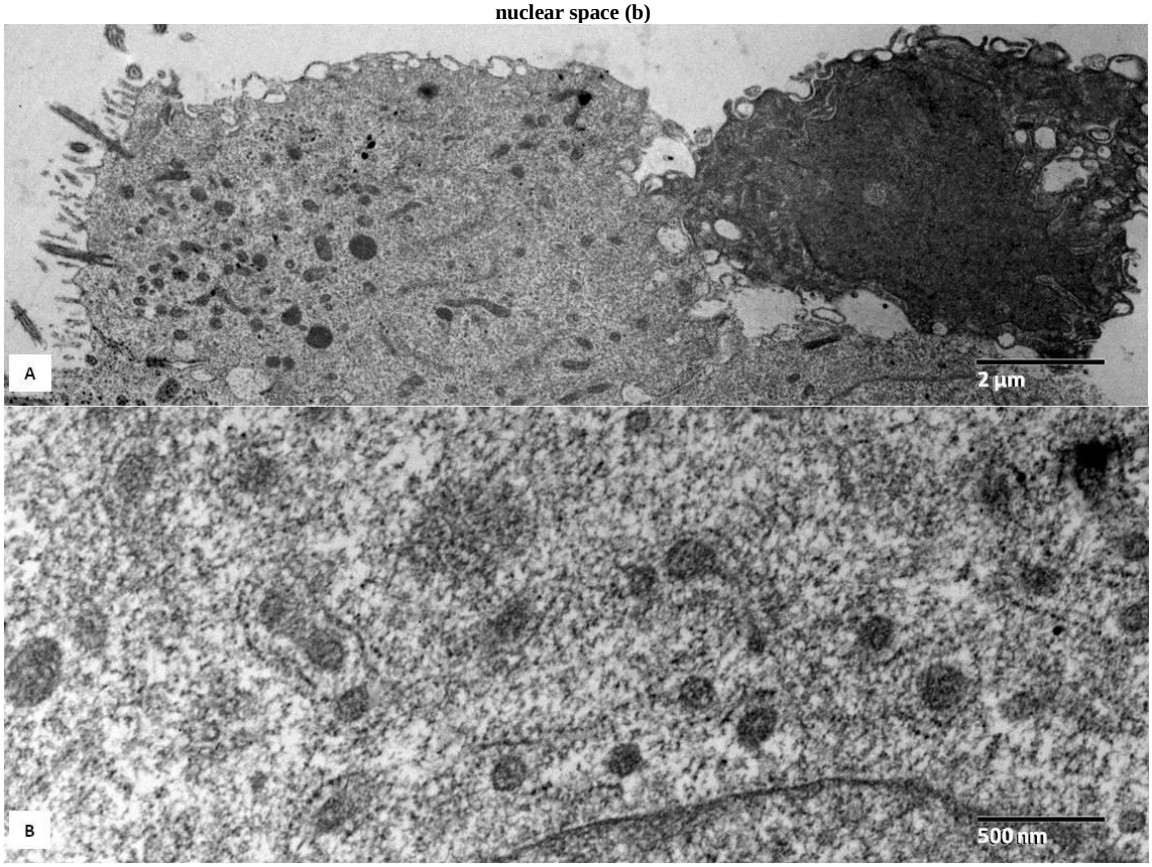
findings occurring in the lung. Therefore, IHC has been performed in formalin-fixed paraffin-embedded tissue blocks, utilizing either rabbit polyclonal anti-spike protein antibody either mouse monoclonal anti-nucleocapside protein antibody (32-35); results obtained were not always reproducible in post-mortem fragments, showing better immunostainings in cell-pelleted sections or in minimally invasive core needle biopsies (32). Moreover, conflicting reports have also regarded other tissue districts (33,34).

ISH to identify COVID-19 RNA has been developed using the S antisense probe (32,34), but this approach appears to be effective mainly in freshly fixed tissues, with a further need of validation in samples taken at autopsy.

Transmission electron microscopy (TEM) should be considered an important tool to identify COVID-19 viral particles in cells and in sub-cellular components. In particular, ultrastructural analysis has documented the presence of roundish virions (80-120 nm diameter) in cytoplasmic inclusion bodies observed in epithelial respiratory cells as well as in endothelial cells and macrophages (21,30,36-38).

On ultrathin sections, severe endothelial damage in lung small vessels is associated with widespread thrombosis (39); the respiratory epithelium showed loss of cilia, membrane fragmentation and a variable amount of intracytoplasmic viral particles (Fig.3a, b).

Figure 3: respiratory epithelium with loss of cilia and apoptosis (a); 100 nm viral particles were encountered in the peri-nuclear space (b)



COVID-19 particles were identified for their spherical shape, frequently surrounded by an envelope covered with faint projections, with intermediate electron-dense cores (Fig. 3b); sometimes, nucleocapsid inclusions were revealed as electron-dense granular material in different cells. Finally, in order to better define the nature of viral-like particles, the immunogold TEM labeling may provide definite answers.

Conflicts of interest: There is no potential conflict of interest and the Authors have nothing to disclose. The present work isn't supported by any grant.

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