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Short Communication

COVID-19: Brief check through the pathologist's eye (autopsy archive)

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ABSTRACT

During the COVID-19 pandemic, many deaths occurred especially among the old patients with cardiovascular comorbidities. Many questions have been asked and few simple answers have been given. The autopsy data are few and the aspects often observed are pulmonary diffuse alveolar damage (DAD), myocarditis, acute myocardial infarction (AMI), and disseminated intravascular coagulation (DIC); these aspects are not only in COVID-19 but also in other viral infections and in sepsis. It should be considered that coronavirus with its pathological organ changes have already been described in the years preceding the pandemic.

1. Introduction

A few but long months have passed since the "unknown" and "doubtful" beginning of the pandemic induced by novel SARS-CoV-2 coronavirus (Severe Acute Respiratory Syndrome Coronavirus), named CoV-19. Many things have been said about this RNA virus which is responsible of acute respiratory distress syndrome (ARDS), cardiovascular and multiple organ failure till death. The same has been said about the structure of the virus and its ability to interfere with ACE2 receptor, with the heme synthesis, and with the immune system [1–6].

During the pandemic many deaths have been caused, especially of patients with cardiovascular comorbidities and old age [7–9]. The research has developed quantitative and qualitative serological tests, but the only reliable test was the nasopharyngeal swab that detects the virus when it is in replication phase; various therapies have been tried without a unique protocol or vaccine [10–13]. Few autopsies were carried out for fear that the virulent agent could spread even more and for purely organizational reasons of the Italian autopsy rooms often not up to standard for infectious diseases. Many questions have been asked and few simple answers have been given. In this brief summary, I would like to induce the reader's reflection to the fact that coronavirus appears already before the pandemic in many texts of medical doctrine and that the pathological findings related to lung and multi-organ damage are described similar to those induced by other viral pathogens both from the same or different family. The autopsy pathologists can confirm that many deaths are due to complications from viral infections especially in subjects with comorbidities and they can also confirm that the aspects often observed are diffuse alveolar damage (DAD), cardiac damage from myocarditis or acute myocardial infarction (AMI), or even disseminated intra-vascular coagulation (DIC); these findings are also present in sepsis associated with various viral infections [14–20]. My observation wants to induce the reader to focus on the common histopathological findings that are present in various viral infections, through the clarification of some salient points.

2. Pathological characteristics of SARS-CoV-2

The SARS-CoV-2 is an RNA virus of the coronaviridiae family, that infect epithelial cells of the upper respiratory tract, pulmonary pneumocytes and different epithelial cells types, endothelial cells of arteries and veins, smooth muscle cells, and immune cells The main mechanisms of interaction between SARS-CoV-2 and host are represented by the binding with angiotensin-converting enzyme 2 receptors (ACE2), the inhibition of heme synthesis through competition for the binding of porphyrin to iron, the interference in the native immune response which trigger the expression and activation of anti-viral mediators, recruitment of inflammatory cells, and the dysregulation of host DNA replication with transcription anomalies with triggering of the apoptotic pathways. The dysregulation of major homeostatic cell systems is responsible for primary lung injury with interstitial pneumonia and DAD, and is responsible for secondary heart and multi-organ damage and hyperagulability occurring mainly in the comorbid population [1–6,18,21,22].

3. Lung findings in CoV-19 disease and in others viral infections

Lung histopathology in CoV-19 disease is characterized by interstitial pneumonia, DAD, oedema, haemorrhage, multinucleated cells,

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Table 1
DAD (acute lung injury with pathologic features and related agents).

Histology	Causes	Clinical features and complications
Exudative phase • Intra-alveololar proteinaceus edema • Inflammation • Possible intravascular thrombi • Haemorrhage • Multinucleated cells • Exfoliation • Possible or not viral inclusions	Viral Agents • Influenza virus • Parainfluenza virus • Adenovirus • Hanta virus • Herpers virus • Cytomegalovirus • Measles • MERS-CoV • Respiratory syncizial virus • SARS Coronavirus	• Dyspnea • Hypoxemia • Secondary heart failure • Secondary multi-organ failure • Death
Proliferative phases • Interstizial fibrosis • Epithelial hyperplasia • Enfisema • Remodelling	Others • Bacterial infection • Sepsis • Aspiration • Drug toxicity • Shock • Radiation • Interstizial pneumonia • Systemic disease • Etc.	

exfoliation associated with or without viral inclusions and associated with reactive aspect of rehash as alveolar epithelial hyperplasia, fibrosis and emphysema. These aspects are described in books as well as in scientific articles and are frequent autoptic findings from direct alveolar demage by viruses, atypical agents and associated with functional vascular and cardiac imbalance [17,19,20,23]. The microscopic observation provides a large spectrum of pathological findings that are not different or peculiar in many viral disease.

The Table 1 summarizes the pulmonary histology in SARS-CoV-2 infection and in other viral infections with the clinical manifestations. Dyspnea, hypoxemia, secondary heart and multi-organ failure up to death are clinical symptoms found in cases of SARS-CoV-2 infection and they are already been described but also for other viral infections both of the SARS-CoV family and for other viruses such as influenza virus and parainfluenza virus infections or more virulent infections such as MERS-CoV and Measles, and then in bacterial infection, sepsis and pneumonia caused by non-viral agents. Histologically, the exudative and the proliferative phases are the same. Direct and diffuse lung damage with the characteristic aspects called DAD are the first stage of respiratory failure with subsequent multiorgan failure, which is followed by the proliferative phase of fibrosis and remodelling responsible for restrictive insufficiency if death has not already occurred. It is understood that a differential diagnosis is not always simple except when the histology highlights inclusions or multinucleated giant cells that in reality may be present or not present in various infections (Table 1),(Fig. 1).

4. Cardiovascular findings (Myocarditis, IMA, DIC) in CoV-19 disease and in others viral infectios

In acute myocarditis which can be associated with SARS-CoV-2, histology is characterized by lymphomonocytic infiltrate, interstitial oedema, myocytolisys, as observed in myocarditis which is associated with other etiological agents according to Dallas Criteria [24]. It is cause of sudden cardiac death [18,25], (Fig. 2).

In AMI contraction band necrosis, areas of coagulative necrosis, edema and inflammatory infiltrate are the most characteristic aspect of hypoxia and of response within the timeframe from the beginning of the damage to the attempted resolution. Also, in this case the damage is common to many conditions including myocarditis by different viral agents and therefore not peculiar to the CoV-19 infection [26,27] (Fig. 2). Finally, platelet and fibrin aggregation with micro-thrombotic events and diffuse vascular occlusion are responsible of poor prognosis to death in DIC entity. As resumed in Table 2, many different viral and non-viral agents can be induce DIC [18,26,28,29], (Table 2) (Figs. 1, 3). Since other etiological agents may also be implicated in etiopathogenesis such as bacteria, it cannot be excluded that these pathologies may be determined by the superposition of the latter.

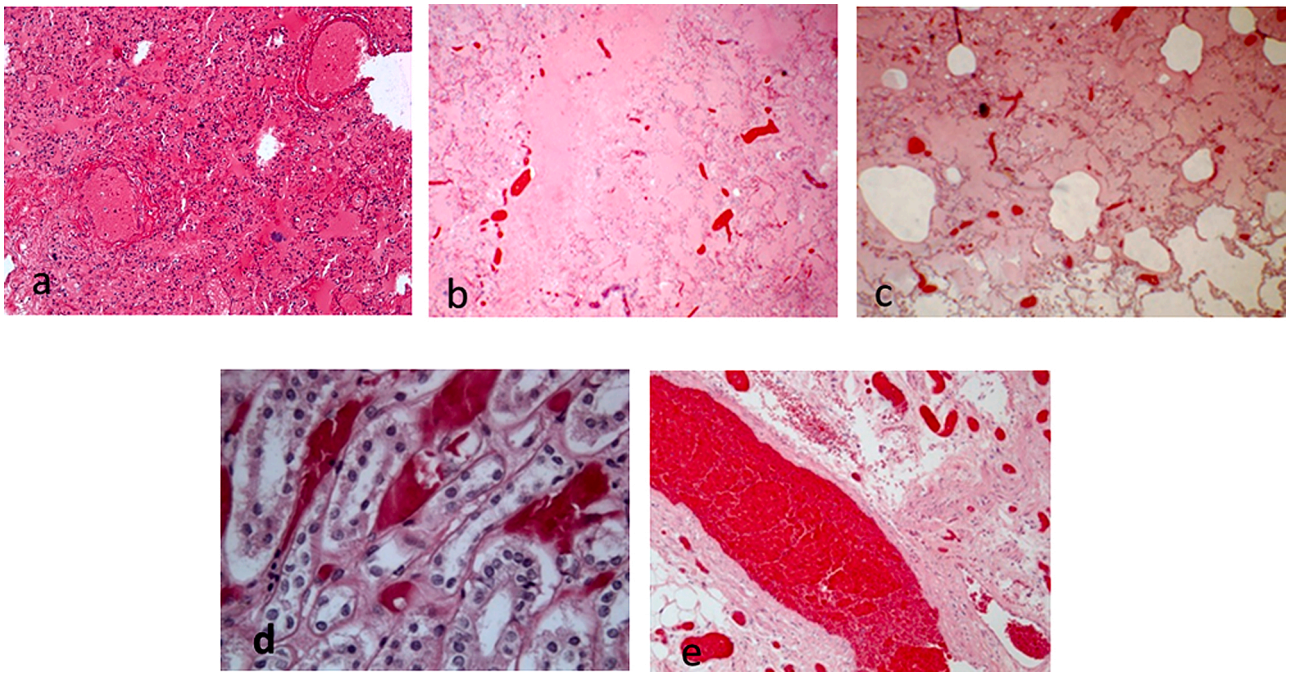

Fig. 1. Different phases of DAD. a. Cytomegalovirus. Proteinaceous edema, exfoliation, fibrin deposition, flogosis (H&E stain x20). b. Coronavirus. Proteinaceous edema with hyaline membranes, exfoliative aspects, vessels saffered by fibrinoid material as by intravasal coagulation (H&E stain x20). c. Influenza virus. Proteinaceous edema with hyaline membranes, exfoliative aspects, vessels saffered by fibrinoid material such as intravasal coagulation and emphysematous aspects (E&E x20). d.e. High resolution of intravascular coagulation in coronavirus infection(d. kidney, e. pulmonary vassells) (H&E x40).

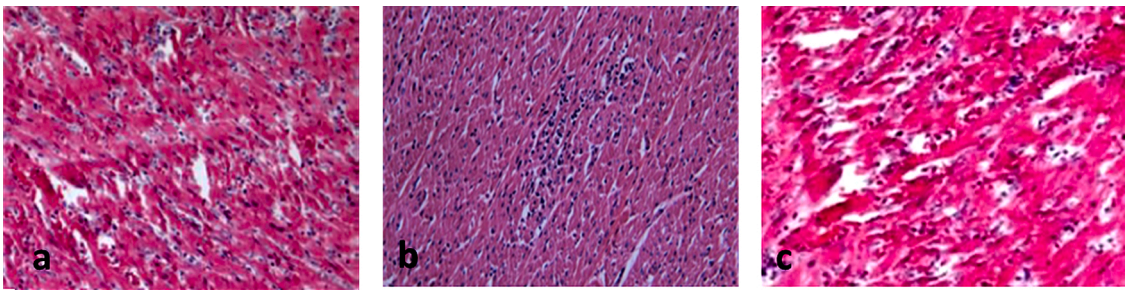

Fig. 2. Myocarditis. Mostly interstitial lymphomonocytic inflammatory infiltrate. a:. Enterovirus (H&E stain x10). b. Influenza virus (E&E stain x20). c. Coronavirus (H&E stain x20).

Table 2
Myocarditis, IMA, DIC (causes, histopathology and related clinical complications).

	Causes	Histopathology	Clinical features and compliacations
1.Acute Myocarditis	Virus agents • Coxackievirus • Polioviruses • Epsten-Barr virus • Cytomegalovirus • Herpes virus • HIV • Enterovirus • SARS coronavirus • Etc. Others • Bacteria • Fungi • Protozoans • Immune reactios • Drug toxicity • Systemic disease • Etc.	• Lymphomonocytic infiltrate according to Dallas Criteria* • Interstizial oedema • Myocytolisys • Others cell type (eosinoflis, giant cell, neutrophils)	• Aritmias • IMA • Heart failure • Death
2.IMA	• Acute myocarditis • Thromboembolism • DIC	• Contraction band necrosis • Oedema • Area of coagulative necrosis • Inflammatory infiltrate	• Aritmias • Heart failure • Thrombosis • Inflammatory • Death
3.DIC	• Virus agent at point 1 • Others agents at point 1	• Platelet aggregation • Fibrin deposition • Thrombotic occlusion	• Acute infarction • Heart failure • Multi-organ failure • Death

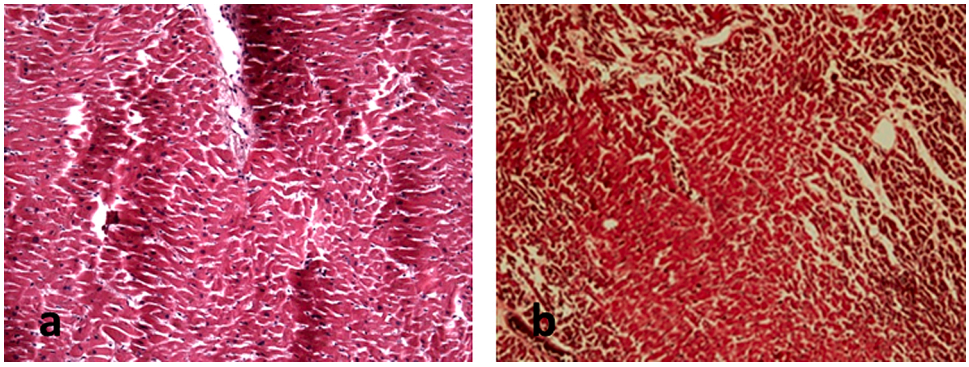

Fig. 3. IMA. Areas of coagulative necrosis of the myocardium as initial hypoxic damage. a. HIV (H&E stain x20). b. Coronavirus (H&E stain x20).

Also in this case the differential diagnosis with identification of the agent is not easy since there is often no evidence of the virus in the myocardium and the morphological changes are the indirect result of the damage caused which manifests itself as inflammatory infiltrate in myocarditis, with necrosis in IMA and with increased state of coagulability and thrombosis in DIC.

5. Current diagnosis and treatment in CoV-19 infection. Considerations

In cases with suspected clinical history and symptoms indicative of SARS-CoV-2 infection, the viral genome detection with PCR from the upper respiratory tract is currently the most valid diagnostic method. The test is primarily used to detect SARS-CoV-2 and to distinguish it

from other viral agents responsible for similar types of pneumonia. For a correct differential diagnosis, first instance laboratory investigations must be carried out to establish the patient's status as well as more specific investigations aimed at assessing the pre-existing status of the patient with the aim of excluding autoimmune disease, tumour lesions or cardiovascular diseases. Knowledge of the pre-existing clinical status is critical for the treatment of SARS-Cov-2 infection and complications in patients with comorbidities.

Regarding therapy, in fact, the respiratory support is considered for patients with hypoxemia; there is no evidence to support a specific drug treatment and the antiviral therapies against SARS-CoV-2 have a range of variability. However, the number of antivirals was reduced especially considering the side effects and drug interactions. There have been no changes in the use of corticosteroids, and the treatment plan only considers severe and critical cases. The immunotherapy is described as a therapeutic option. The prevention and treatment of complications in patients with comorbidities remain valid for a better prognosis [30,31].

It is clear that both in cases of exclusive pulmonary involvement and in cases with multi-organ dysfunction, treatment must aim at improving the symptoms especially in the population with comorbidities, while active prevention must aim at safeguarding populations especially with comorbidities with the aim of controlling the possible complications that are the real responsible for the deaths.

6. Conclusions

Only what is unknown is not understandable. Infections induced by viruses belonging to the SARS family have already been described although today we have called the new virus as SARS CoV-2 and a disease as COVID-19. In truth, for the first time we found ourselves in a pandemic and this scared us. The lack of autopsy findings did not allow us to evaluate with greater serenity what was happening and to understand that the specific pulmonary histological pictures and the secondary multiorgan damage in the patients with comorbidities were very similar to those already observed for other viral infections.

Early knowledge of the systemic changes resulting from the interaction between virus and host would have speeded up the therapeutic approach by targeting complications rather than the viral agent as such. Infact pulmonary pathology with systemic complication can currently be considered not very different from those caused by other viruses which can lead to systemic failure with worsening up to death. The deaths are currently reduced in subjects at risk due to early diagnosis and for the use of generic antiviral and symptomatic therapies non-specific directed towards SARS-CoV-2; the diagnoses have increased to the use of nasopharyngeal swabs that highlighted the presence of the virus even in younger asymptomatic subjects. This shows that although SARS-CoV-2 has high virulence, it behaves like other viruses, that in the population the symptoms occur in subjects often with comorbidities and that deaths are due to complications in the same way as it happens for other viral agents. Finally, the therapy for complications in the different cases has proved effective.

Statement

Not applicable. The images from the forensic autopsy archive of Mansueto Gelsomina MD, PhD.

Statement of ethics

Not applicable. The images from the forensic autopsy archive of doctor Mansueto.

CRediT authorship contribution statement

Gelsomina Mansueto: Writing - original draft.

Declaration of Competing Interest

The authors report no declarations of interest.

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