Journal of Veterinary Science and Public Health

J. Vet. Sc. Public Health, v. 7, n. 1, p. 054-061, 2020

MACROSCOPIC AND MICROSCOPIC INJURIES OF PATIENTS AFFECTED BY COVID-19

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DOI: 10.4025/rcvsp.v7i1.55500

ABSTRACT

After the first report of an outbreak of acute respiratory syndrome in China in December 2019, a new coronavirus, severe acute respiratory syndrome - coronavirus 2 (SARS-CoV-2) was identified. Despite to the high number of cases and deaths, limited information is available regarding the pathogenesis and injuries caused by the new coronavirus. This study aims to carry out a literature review concerning the macroscopic and microscopic aspects of the disease, since the progression of the disease is closely related to the viral action and the cellular and tissue response in the lesions caused by it. In conclusion COVID-19 is a disease that can affect all types of body tissues. The lesions affect mainly the pulmonary parenchyma and are usually macroscopically observed as consolidation areas, and histologically as plasmacytic lymphoid interstitial pneumonia and with neutrophil infiltration, already observed lesions outside the lung are mainly due to the inflammatory action of lymphocytes and histiocytes, and to the intense production of cytokines with systemic action.

Key words: necroscopy findings, histopathology, pneumonia.

INTRODUCTION

After the first report of an outbreak of acute respiratory syndrome in China in December 2019, a new coronavirus, severe acute respiratory syndrome - coronavirus 2 (SARS-CoV-2) was identified. Rockx et al. (2020). Despite to the high number of cases and deaths, limited information is available regarding the pathogenesis and injuries caused by the new coronavirus.

Li et al. (2020) reported that COVID-19 is a multisystemic disease, affecting patients with several concomitant illnesses, such as diseases of the nervous system, cerebrovascular and cardiovascular diseases, diseases of the respiratory system, diseases of the digestive system, diseases of the urinary system, diseases of the reproductive system and diseases of the endocrine system.

This study aims to carry out a literature review concerning the macroscopic and microscopic aspects of the disease, since the progression of the disease is closely related to the viral action and the cellular and tissue response in the lesions caused by it.

DEVELOPMENT

Once the pandemic is recent and current, studies are being carried out in the course of it. In the most severe form of the disease, there is the activation of an intense systemic inflammatory response, activating several cytokines, a process known as Macrophage Activation Syndrome (MAS, from the English "macrophage activation syndrome") and also as secondary hemophagocytic lymphohistocytosis. Hanley et al. (2020). Hemophagocytosis and acute consumption coagulopathy are key characteristics of MAS, which lead to disseminated intravascular coagulation, characteristics also observed in some patients with COVID-19. McGonagle et al. (2020).

Intense macrophages pulmonary infiltration that causes diffuse alveolar damage has been reported in pneumonia due to severe acute respiratory syndrome (SARS), with similar results in patients with SARS-CoV-2 pneumonia. here are distinctions between SARS and SARS-CoV-2, such as: The cytokines increasing that is often associated with the ferritin rise and that results in local cell activation, occurs in both, but this increasing in SARS is distinctly more pronounced. Nicholls et al. (2003).

All cellular mechanisms and their products are expressed in tissue damage. In a pulmonary autopsy examination using immunohistochemistry of 7 patients who died from SARS-CoV-2, the pattern found was diffuse alveolar damage and perivascular infiltration by T cells. Different vascular characteristics were also observed, consisting of severe endothelial injury associated with the presence of intracellular virus and ruptured cell membranes. Histological analysis showed thrombosis and widespread microangiopathy, with capillary microthrombi being 9 times more prevalent in COVID-19 than in H1N1 influenza. Ackermann et al. (2020).

Regarding the injuries found in people with SARS-CoV-2, there are reports of histological lung examinations, that detail to diffuse and bilateral alveolar damage, edema and hyaline membrane formation, and deposition of sinus cells in the alveoli lumen, characteristic of severe acute respiratory syndrome. Chen et al. (2020).

A Chinese study published in Lancet Respitarory Medicine investigated the pathological characteristics of a patient who died from severe infection with coronavirus 2 of severe acute respiratory syndrome (SARS-CoV-2). In a 50-year-old patient who died of COVID-19, whose microscopy data was not reported, microscopically was observed, diffuse alveolar damage with exudate, the infiltrate was predominantly lymphohistiocytic with the presence of multinucleated giant cells, presence of large and atypical penumocytes without viral inclusion. In the liver, microvesicular steatosis with mild inflammation was observed, but this finding was not possible to confirm whether it occurred due to the virus or iatrogenic causes. Xu et al. (2020).

A recent report describes the case of two patients who went to the surgery room for pulmonary adenocarcinoma and were later found to be infected at the time of the surgical procedure. Thus, tissue samples from these patients were collected, analyzed, and it was possible to observe non-specific lesions such as edema, pulmonary hyperplasia and multinucleated giant cells. Is important highlight that these patients were asymptomatic for COVID-19 and that, therefore, the lesions found must reflect this condition. Tian et al. (2020).

Other study conducted in the United States and published in July 2020 in The Lancet magazine selected 14 SARS CoV-2 positive cadavers, collected tissue material for processing and analysis in light microscopy, immunohistochemistry, and electron microscopy. The seven patients examined by autopsy showed edematous lungs, one of them had intracerebral hemorrhage and pulmonary consolidation were observed in another one. Pleural fluid volume was highly variable (from 0 ml to 450 ml per pleural space). Two

patients had evidence of central pulmonary embolism. Splenomegaly was observed in two patients, while splenic atrophy was observed in another one. Scattered dotted subarachnoid hemorrhages were observed in the brain of one of the patients. Additional routine findings showed abnormalities, including varying degrees of heart and atherosclerotic disease, hypertensive changes on the renal surface, and liver congestion in mostly of patients. Histopathological pulmonary examination revealed diffuse alveolar damage in 86 percent of cases, which was evidenced by the presence of intraalveolar fibrin, hyaline membranes, and connective tissue loss in the alveolar septum walls. 11 of the 12 patients who showed diffuse alveolar damage had an acute alveolar infiltrate (Bradley et al 2020). A study conducted in the Netherlands experimentally infected Cynomolgus monkeys (Macaca fascicularis) to compare the pathogenesis of SARS CoV-2 with previously emerging coronaviruses: SARS-CoV coronavirus and Middle East respiratory syndrome (MERS) –CoV. The study separated two groups of monkeys, one with young adults (from 4 to 5 years old) and the other with older adults (from 15 to 20 years old) and proceeded to inoculate intranasally and intratacheally a strain of SARS-CoV-2. No clinical signs were observed in any of the animals, except for a serous nasal discharge in one of the animals 14 days after inoculation. All animals produced antibodies. Using real-time PCR, it was possible to detect higher viral loads in olders animals than in young animals. Four of the animals were sacrificed 4 days after infection, at necropsy, in two of them it was possible to observe a pulmonary consolidation. These lung consolidations were well circumscribed, reddish-red in color, and less fluctuating than normal. There were no other notable changes in the other organs and tissues evaluated. In the histopathological evaluation of the consolidation regions, it was possible to detect the both bronchioles and alveoli lumen filled with a variable amount of protein-rich edema, fibrin and febrile cellular cells, alveolar macrophages and few neutrophils and lymphocytes. Both alveoli and bronchioles walls showed extensive necrosis. Hyaline membranes were observed in few injured alveoli. In areas with more advanced lesions, the alveoli walls were moderately thicker and covered by cuboidal epithelial cells (type II pneumocyte hyperplasia) and the alveolar lumen were empty. The alveolar and bronchiolar walls were thickened by edema, mononuclear cells, and neutrophils. There were lymphocyte aggregates around small lung vessels. Moderate numbers of lymphocytes and macrophages were present in both bronchial walls lamina propria and submucosa, and some neutrophils were detected in the bronchial epithelium. Epithelial regeneration was observed in some bronchioles, visible as an irregular layer of squamous to cuboidal epithelial cells with hyperchromatic nuclei. Occasionally, free multinucleated giant cells (syncytia) in both bronchioles and alveoli luminal and, according to the positive staining of pankeratin and negative staining of CD68, originate from epithelial cells. Rockx et al (2020).

A study carried out in the United States with Cynomolgus monkeys and published in Science, experimentally infected 9 rhesus monkeys with different concentrations of plaque-forming units through intranasal and intratracheal inoculation. Molecular and serological tests were performed on all animals and 4 of them underwent autopsy at different times, two animals two days after the challenge and two animals four days after the challenge. In animals subjected to autopsy on the second day, it was possible to observe multifocal regions of pneumonia and evidence of viral pneumonia, such as expansion of the alveolar septum with mononuclear cell infiltrate, consolidation, edema, and intense polymorphonuclear infiltrate, predominantly composed of neutrophils. The terminal bronchiolar epithelium was necrotic and scaled with diffuse reactive alveolar macrophages and epithelial cell blocks scattered in alveolar spaces. Hyaline membrane formation was occasionally found in the alveolar septa. Blocks of virus-infected cells were detected by immunohistochemistry and in situ hybridization in several lung parenchyma

regions. In animals necropsied four days after infection, a decrease in the degree of inflammation and viral pneumonia was observed, although the virus continued to be detected in the lung parenchyma and inflammatory cells. The data found in the study suggest that SARS-CoV-2 induces multifocal areas of acute inflammation and viral pneumonia involving pneumocytes, capillary epithelium cells and other cell types. Chandrashekar et al (2020).

The respiratory system is the most frequently affected by COVID-19. In the lungs, Inciard et al. (2020) reported that there is lung consolidation, pleural effusions without evidence of secondary bacterial infections, diffuse alveolar damage. Xiaohong et al. (2020) added that there is intense fibrous alveolar exudation, degeneration, diffuse pneumonia, fibrosis, and focal hemorrhage.

Hanley et al. (2020) emphasize pathological features and autopsy approach in suspected COVID-19 cases to assist coroners. According to Osborn et al. (2020) macroscopic aspects of COVID-19 are more likely to be found in the chest and may include pleurisy, pericarditis, both consolidation and pulmonary edema. The weight of the lung will be significantly increased. And may also be observed a secondary infection, which can overlap with a viral infection that can lead to the most typical purulent inflammation of bacterial infection. However, injuries to several other organs have been reported since COVID-19 pandemic beginning. Infection with SARS-CoV 2, in addition to respiratory involvement, can cause lesions in skin (RECALCATI et al., 2020), brain (POYIADJI et al., 2020), heart (BONOW et al., 2020; INCIARD et al ., 2020) liver (XU et al., 2020) kidneys (SU et al, 2020), gastrointestinal tract (CARVALHO et al., 2020; PAN et al., 2020) and eyes (CHEN et al., 2020).

On the skin, Recalcati (2020) reported that the manifestations are like the skin involvement that occurs during other viral infections. In an editorial letter, this author informed the prevalence of 20.4% of patients who presented a cutaneous manifestation related to COVID-19. The development was noticed both at the beginning of the clinical picture and later, when the patients were already hospitalized. The cutaneous manifestations were erythematous rash, generalized urticaria and chickenpox vesicles. The anatomical region of the trunk is the most frequently involved region. Itching is not common, and the lesions heal within a few days.

In the brain, Poyiadji et al. (2020) observed bilateral hemorrhagic lesions in the thalamus regions, the medial temporal lobes, and below the insula. Therefore, the lesions form an image of acute necrotizing hemorrhagic encephalopathy. These authors suggested that these lesions may be associated with intracranial cytokine storm, as occurs in other viral infections, being not necessary a viral invasion in the brain for arise the brain lesions. Still, there are not many studies that explain the degree of replication of SARS-CoV-2 in cells of the central nervous system, however, Baig et al. (2020) reported that predominantly isolated brain involvement can arise, and when this happen, the brain edema that results can lead to death long before systemic homeostatic dysregulation appears.

Cardiac involvement, according to Inciard et al. (2020) can arise without respiratory failure and in patients without heart disease history. They were able to visualize by transthoracic echocardiography and by resonance that the heart maintains normal dimensions, but there is an increase in the thickness of the wall of the ventricles. They also found marked biventricular edema and pericardial effusion, and these findings were associated with myocarditis. Ng et al (2014) reported that there may be pericardial effusion, however, without signs of cardiac tamponade.

In the liver, Inciard et al. (2020) reported hepatic steatosis and Jothimani et al. (2020) affirm that liver involvement in COVID-19 can have a multifactorial origin, either due to the direct cytopathic effect of the virus, uncontrolled immune reaction, sepsis, as secondary common respiratory infections, or due to injury induced by medications used in supportive treatment. These same authors suggested that cytokine storm is more important effect to hepatocytes when compared to direct virus damage. And when there is liver involvement, the disease is usually fatal. In a study by Tian et al (2020), liver injuries varied significantly between patients. These authors observed mild sinusoidal dilation, glycogenic degeneration, focal macrovesicular steatosis and infiltration of small lymphocytes in the portal tracts, regenerative nodules and thick fibrous bands, periportal and / or centrilobular necrosis were also observed. The great variation found in this study may be a consequence of pre-existing liver disease in patients or even the degree of liver involvement, which can vary between individuals.

In the kidneys, the lesions produced by COVID-19, according to Li et al. (2020), lead to a decrease in the size, inflammation and edema of the renal parenchyma and the condition characterizes acute renal failure. Urea and creatinine levels often increase, but also may increasing other renal laboratory parameters, such as uric acid, creatine kinase, and lactate dehydrogenase. Furthermore, proteinuria and hematuria suggest the presence of severe renal dysfunction both in patients with severe respiratory symptoms either without respiratory symptoms. According to Naicker et al (2020), the pathogenesis of kidney injury is still unclear, but the injuries may be a consequence of cytokine storm, sepsis, or also direct cell injury due to the presence of viruses in the kidneys. Su et al. (2020) identified by immunohistochemistry, the virus inside renal tubular cells, which makes clear that the kidney is also a target for virus replication.

In the study carried out by Ng et al (2014), during a necroscopic examination, notable changes were found: massive pleural effusion that reached 5 L, substantial pericardial effusion (150 ml), in addition to abdominal effusion; consolidated and edematous lungs, in addition to generalized vascular congestion throughout whole body. Such findings make clear the systemic effects of COVID-19.

CONCLUSIÓN

In conclusion COVID-19 is a disease that can affect all types of body tissues. The lesions affect mainly the pulmonary parenchyma and are usually macroscopically observed as consolidation areas, and histologically as plasmacytic lymphoid interstitial pneumonia and with neutrophil infiltration, already observed lesions outside the lung are mainly due to the inflammatory action of lymphocytes and histiocytes, and to the intense production of cytokines with systemic action.

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