PATHOLOGICAL FEATURES OF THE NOVEL HUMAN CORONAVIRUS DISEASE (COVID-19) : A REVIEW
ASPECTS ANATOMO-PATHOLOGIQUES DE L'INFECTION PAR LE NOUVEAU CORONAVIRUS (COVID-19) : REVUE DE LA LITTERATURE

M. TRIKI[1, 2,*] ; S. CHARFI[1, 2] ; L. BOUZIDI[1,2] ; S. MAKNI[1,2] ;R. KALLEL[1,2] ET T. BOUDAWARA[1,2]

1: Department of pathology, Habib Bourguiba Univeristy Hospital, Sfax, Tunisia
2: Faculty of medicine, University of Sfax, Tunisia
*** E- mail of corresponding author :** *meriamtriki@yahoo.fr*

Abstract

To investigate the pathological characteristics of novel coronavirus (SARS-CoV-2) disease (termed by the world health organization as corona virus disease 2019, COVID-19), we tried to collect all autopsy studies and cases reports published in the literature. Then we assemble all pathological features by organ in order to facilitate understanding mechanisms underlying pathological changes. While SARS-CoV-2 affects mainly lungs, the infection also causes damages of heart, liver, kidney and other organs. Organ damages are caused either directly by the virus via the angiotensin converting enzyme 2 receptor or indirectly by the cytokine storm that induces an immune system dysregulation with an activation of the coagulation cascade responsible for disseminated intravascular coagulation and thus multiple organ failure. Further studies are warranted to further understand the pathogenesis of COVID-19.

Key words: SARS-CoV-19 ; COVID-19 ; Histopathology ; Pathogenesis.

Résumé

Afin d'étudier les caractéristiques anatomo-pathologiques de l'infection par le nouveau coronavirus (SARS-CoV-2) (nommée par l'Organisation mondiale de la santé maladie à coronavirus 2019, COVID-19), nous avons revu les études d'autopsie et les cas rapportés publiés dans la littérature. Ensuite, nous avons rassemblé ces données anatomo-pathologiques par organe afin de faciliter la compréhension des mécanismes physiologiques sous-jacents. Bien que le SARS-CoV-2 affecte principalement les poumons, l'infection cause également des altérations du cœur, foie, reins et d'autres organes. Ces dommages sont causés soit directement par le virus via le récepteur de l'enzyme de conversion de l'angiotensine 2, soit indirectement par la tempête de cytokines qui induit une dysrégulation du système immunitaire et une activation de la cascade de coagulation responsable de la coagulation intravasculaire disséminée et d'une de défaillance multiviscérale. D'autres études sont nécessaires pour mieux comprendre la pathogenèse du COVID-19.

Mots clés : SARS-CoV-2 ; COVID-19 ; Anatomo-pathologie ; Pathogenèse.

ملخص

من أجل دراسة الخصائص التشريحية المرضية للعدوى بالفيروس التاجي الجديد (SARS-CoV-2) (الذي أطلقت عليه منظمة الصحة العالمية لفيروس التاجي 2019 إسم COVID-19)، استعرضنا دراسات تشريح للجثث والحالات المبلغ عنها المنشورة في الأدبيات. ثم جمعنا هذه البيانات التشريحية المرضية من الأعضاء التي وقع أخذها من أجل تسهيل فهم الآليات الفسيولوجية الكامنة.

على الرغم من أن السارس - CoV-2يؤثر بشكل رئيسي على الرئتين، فإن العدوى تسبب أيضًا تلفًا للقلب والكبد والكليتين والأعضاء الأخرى. يحدث هذا الضرر إما مباشرة عن طريق الفيروس عن طريق مستقبلات الإنزيم المحول للأنجيوتنسين 2 ، أو بشكل غير مباشر من خلال عاصفة السيتوكين التي تؤدي إلى خلل في الجهاز المناعي وتفعيل سلسلة التخثر المسؤولة عن التخثر داخل الأوعية الدموية و نشر فشل الأعضاء المتعدد. هناك حاجة إلى مزيد من الدراسات لفهم أفضل لمسببات COVID-19.

الكلمات المفاتيح: SARS-CoV-2 ; COVID-19 ; علم الأمراض التشريحي ; طريقة تطور المرض.

1. INTRODUCTION

Since late December 2019, the outbreak of a novel coronavirus disease (COVID-19) which was caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) started in Wuhan (Hubei Province), China and spread rapidly around the word including Tunisia [1]. COVID-19 presentations can range from asymptomatic infection, self-limited influenza-type symptoms to severe respiratory failure [2]. According to the daily report of the world health organization, the COVID-19 pandemic has caused 3.175.207 laboratory confirmed cases and 224.172 death worldwide as well as 994 confirmed cases and 41 deaths in Tunisia by the 1st may 2020. The fatality rate of SARS-CoV-2 was around 3.7% [3]. The SARS-CoV-2 pathogen shares similarities with SARS-CoV in its genome sequence, biological behavior, and clinical manifestations. It has four major structural proteins including the spike surface glycoprotein which binds to host receptors via the receptor-binding domains of angiotensin converting enzyme 2 (ACE2) [4]. The ACE2 protein has been identified in various human organs including lungs, bone marrow, liver, gastrointestinal tract, spleen, kidney, thymus, brain and lymph nodes [5]. The respiratory, immune, and coagulation systems are the major targets of this disease [2]. Although clinical features and radiologic findings have been well described in the literature [2, 6-11]; few studies attempting to investigate pathological findings have been published and they are mostly cases reports [12-18]. The main reason of this limited pathological data is the high rate of transmission which makes autopsy or biopsy barely accessible and not a clinical priority. Without knowing the detailed mechanisms of SARS-CoV-2 infection, specific management is lacking. In this review we collected all pathological findings of COVID-19 reported in the literature in order to provide a better understanding of this pandemic disease's pathogenesis.

2. PATHOLOGICAL FINDINGS IN THE LUNGS

2.1 Macroscopic features:

Luo. W *et al* [19] described macroscopic features of a whole lung from a 60-year-old patient with severe COVID-19 infection. Grossly the surface of the lung was rufous, and showed diffuse congestive appearance with punctate hemorrhage and partly haemorrhagic necrosis. Mucinous and haemorrhagic exudation covered the bronchi. The cut surfaces displayed severe congestive and haemorrhagic changes. Other authors reported that lung weight in COVID-19 may be increased above normal due to pulmonary edema. Lung consolidation and pleurisy may be also seen. A secondary infection may be superimposed on the viral one and can lead to purulent inflammation more typical of bacterial infection [20].

2.2 Microscopic features

Histologically, the main findings of COVID-19 lesions are in the lungs. Tian. S *et al* [13] reported the early histopathological findings of COVID-19 in two patients operated for a lung adenocarcinomas at the time when the SARS-CoV-2 infection was not yet recognized. These findings were not specific and included edema, prominent proteinaceous exsudates, vascular congestion and inflammatory clusters with fibrinoïd material and multinucleated giant cells. Some signs of early organization were also noted including reactive epithelial hyperplasia and fibroblastic proliferation. Histopathologic examination of postmortem lung biopsies taken from patients who died from severe COVID-19 infection showed signs consistent with diffuse alveolar damage (DAD). They included exsudates, evident desquamation of pneumocytes, hyaline membranes formation and an interstitial monocellular inflammation predominantly lymphocytic with multinucleated giant cells and enlarged atypical pneumocytes in the intra alveolar spaces [12]. These findings were also reported in other pathological studies through post-mortem core biopsies and sections with signs of organizing pneumonia [15, 18, 20, 21]. The organizing pneumonia included large areas of intra-alveolar hemorrhages and intra-alveolar fibrin cluster, loose fibrous plugs and organizing fibrin as well as increased stromal cells with fibrin in the alveolar walls leading to interstitial thickening [15, 18, 21]. On the other hand, the preliminary autopsy results in the study of Dolhnikoff. M *et al* [22] found fibrinous thrombi in small pulmonary arterioles and endothelial tumefaction with a large number of pulmonary megakaryocytes in the pulmonary capillaries indicative of the activation of the coagulation cascade. Another study found similar changes with evidence of extensive microvascular damage and thrombotic occlusion as the predominant pattern of injury [23]. The fibrinoid necrosis and hyaline thrombi in microvessels were

described as well in other studies [15, 18]. Another finding reported is abundant intra-alveolar neutrophilic infiltration consistent with bronchopneumonia of a superimposed bacterial infection [15, 20]. No viral cytopathic-like changes or typical viral inclusions were observed in the study of Xu. Z *et al* [12] however Dolhnikoff. M *et al* [22] demonstrated intense epithelial viral cytopathic effects involving alveolar and small airway epithelium. Special stains including masson stain, sirius red staining and reticular fibers staining indicated massive pulmonary interstitial fibrosis [19]. Immunohistochemical staining showed that most of infiltrated lymphocytes were CD4-positive T lymphocytes. No CD8 positive or CD20 positive lymphocytes were observed in the study of Yao. XH *et al* [18] however they were present in other studies [19, 20]. Staining for SARS-CoV-2 antigen (SARS-CoV-2 spike S1, SARS-CoV-2 nucleocapside and Rp3 NP protein of SARS-CoV-2) revealed prominent expression in the alveolar epithelial cells including damaged desquamated cells and macrophages [18, 21].

2.3 Ultrastructural findings

On electron microscopy examination, type Ⅱ alveolar epithelial cells had large nuclei, abundant cytoplasm, and mitochondrial swelling. There were more lamellar bodies, Golgi complex, rough and smooth endoplasmic reticulum. Some coronavirus particles were seen in the ciliated columnar epithelial cells of the bronchiolar mucosa [18].

2.4 Clinical and physiopathological implications

Lung damages can be caused either directly by the SARS-CoV-2 via the ACE2 receptor or indirectly by cytokine storm which is linked to an excessively exaggerated and uncontrolled immune response [24, 25]. In fact, ACE2 protein is expressed in alveolar cells, bronchial epithelium and vascular endothelium. Therefore SARS-CoV-2 protein binds to ACE2 would result in acute lung injury and pulmonary edema. Microthrombosis formation also might explain the severe hypoxaemia and respiratory failure that severely ill patients develop. Vascular wall thickening, lumen stenosis and occlusion might explain pulmonary hypertension in later stage of critical patients. Diffuse pulmonary interstitial fibrosis is suggestive of changes in late-stage disease.

3. PATHOLOGICAL FINDINGS IN THE HEART

Some authors found no significant pathological changes in the heart of patients deceased from COVID-19 infection [20]. Tian. S *et al* [15] revealed no inflammatory cellular infiltration in the endocardium and myocardium of their four patients. However, they found irregularly shaped myocardial cells with darkened cytoplasm. The pathological changes were not sufficient for interpretation as acute myocardial injury. They found, as well, various degrees of focal edema, interstitial fibrosis, and myocardial hypertrophy but they were attributed to the patients' underlying diseases. Xu. Z *et al* [12] revealed that the only susbtential pathological change in the heart was the presence of few interstitial mononuclear inflammatory infiltrate. On the contrary, all three cases in the study of Yao. XH *et al* [18] showed hypertrophy, degeneration and necrosis of some myocardial cells, mild interstitial hyperemia, edema, infiltration of a small number of lymphocytes, monocytes and neutrophils. This study performed also immunohistochemical staining, electron microscopy examination and RT-PCR detection of the SARS-CoV-2 in all three heart tissue samples. They showed that the inflammatory cells infiltrating the myocardium were mainly macrophages and a small number were of CD4-positive T lymphocytes. No CD8-positive T lymphocytes or CD20-positive B lymphocyts were seen. Ultrastructural study showed myocardial fibers swelling and dissolution. Immunohistochemical staining and PCR detection did not identify SARS-CoV-2 component in myocardial tissue [18].

Clinical and physiopathological implications:

Clinically many patients with COVID-19 showed biochemical parameters consistent with myocardial injury. However pathological finding are controversial and varies from few interstitial monocellular infiltrate to myocardial cells degeneration and necrosis. Some authors suspected that acute tissue injuries related to lowered blood oxygen saturation are too mild to cause visible morphologic changes [15]. Others suggested that acute myocardial injury and small blood vessel injury may be caused by the cytokine storm induced by the viral infection especially IL-6 and IL-10 [18]. More studies are needed to say whether or not there are viral-induced pathologic changes to the myocardium.

4. PATHOLOGICAL FINDINGS IN THE LIVER

To our knowledge, the description of the liver's gross findings was not reported. However some authors described microscopic changes in post mortem biopsies of patients who died from severe COVID-19 infection. It was not clear if these microscopic changes were caused by the viral infection or the drug-induced liver injury. The pathological findings included moderate microvesicular and macrovesicular steatosis, mild lobular and portal activity, sinusoidal dilatation, mild increase in sinusoidal lymphocytes and patchy hepatic necrosis in the periportal and centrilobular areas [12, 15, 18]. Only one study was able to demonstrate direct evidence of the viral sequence in the liver in one of three cases tested by RT-PCR [15]. Authors suggested that this result may be caused by either limited test sensitivity or sampling problem. Yao. XH *et al* [18] did not identify positive signal for SARS-CoV-2 in the liver.

Clinical and physiopathological implications

It was reported that patients with COVID-19 had abnormal levels of alanine aminotransferase and aspartate aminotransferase during disease progression. Moreover liver injury is more prevalent in severe cases than in mild cases of COVID-19 [16]. Limited histological hepatic abnormalities are reported in the literature. Since it has been shown that bile duct epithelium expresses higher density of ACE2, the mild lobular lymphocytic infiltration is probably linked to the viral infection itself [15].

5. PATHOLOGICAL FINDINGS IN THE KIDNEY

In an autopsy study of 26 postmortem kidney biopsies, pathological findings included acute proximal tubular injury with loss of brush border and non isometric vacuolation, frank necrosis, occasional hemosiderin granules and pigmented casts as well as prominent erythrocyte aggregates obstructing the lumen of capillaries without platelet or fibrinoid material. There was no evidence of vasculitis, interstitial inflammation or hemorrhage [14]. Yao. XH *et al* [18] revealed also swelling of the glomerular endothelial cells, protein exudate, formation of hyaline thrombus in small vessels and deposition of protein and pigment in the lumen ducts. Immunohistochemical staining for various inflammatory cells did not reveal any specific accumulation of these cells, with expected mix of T and B lymphocytes in areas of nonspecific scarring. Direct immunofluorescent staining showed nonspecific IgM and C3 trapping and positive granular staining in tubular epithelium of SARS-CoV nucleoprotein [14]. Ultrastructural studies showed clusters of coronavirus particles with distinctive spikes in the tubular epithelium and podocytes [14]. However the detection of SARS-CoV-2 by PCR was reported to be negative in the study of Yao. XH *et al* [18].

Clinical and physiopathological implications:

Clinically, acute kidney injury and proteinuria are reported in COVID-19. Diffuse acute proximal tubular injury with loss of brush border and nonisometric vacuolation may be partially caused by the direct virulence of SARS-CoV-2. In fact, ACE2 is expressed in the apical brush borders of the proximal tubules as well as the podocytes in less intensity. Virus particles were observed in these sites of known ACE2 expression.

6. CLINICOPATHOLOGICAL FINDINGS IN THE SKIN

Yao. XH *et al* [18] analyzed postmortem skin biopsies of three adults (mean age 70 years). The structure of the skin and annexes was normal except the presence of few lymphocytes infiltrate around the superficial small blood vessels of the dermis. The three patients had no skin lesions. Cutaneous manifestations, such as erythematous rash and localized or widespread urticaria, seem to be the most common manifestations in severe COVID-19 cases, however, it is difficult to distinguish whether the underlying cause is the viral infection or a new medication prescribed. Estébanez. A *et al* [26] described a case of women with mild COVID-19 infection that developed pruritic and confluent erythematous-yellowish papules on both heels. Despite corticosteroid treatment, lesions persisted and became erythematous plaques that were both hardened and pruritic. Unfortunately in this case no biopsy was done. Zengarini. C *et al* [27] reported a case of a moderately itching erythematous confluent rash, with undefined margins, mostly located at the neck, trunk, back, and proximal portions of upper and lower limbs. Skin biopsy showed superficial perivascular lymphocytic infiltrate, extremely dilated vessel in the papillary and mid dermis. Gianotti. R *et al* [28] studied the cutaneous histopathological features of eight COVID-19

patients. Two of them had sudden diffuse maculopapular eruption involving the trunk, clinically suggestive for Grover disease.
Histological examination showed dyskeratotic cells, ballooning multinucleated cells and sparse necrotic keratinocytes with lymphocytic satellitosis. One patient developed at the early stage of the disease an exanthema involving the trunk and limbs. The skin biopsy demonstrated nests of Langerhans cells within the epidermis. Another patient had papular erythematous exanthema involving the trunk with edematous dermis and a lymphocytic vasculitis at histological examination. A hospitalized patient in intensive care unit had a severe macular haemorrhagic eruption, which corresponded to intravascular microthrombi in the small dermal vessels. The last cutaneous manifestation reported was a purpuric maculo-papulovesicular rash. Skin biopsy showed perivascular spongiotic dermatitis with exocytosis along with large nest of Langerhans cells and a dense perivascular lymphocytic infiltration around the swollen blood vessels with extravasated erythrocytes. Recalcati. S *et al* [17] examined 14 children and young adults at the time of the COVID-19 pandemic with acral eruption of erythemato-violaceous papules and macules, with possible bullous evolution, or digital swelling. Skin biopsies showed a diffuse dense lymphoid infiltrate of the superficial and deep dermis, as well as hypodermis, with a prevalent perivascular pattern, and signs of endothelial activation. Despite negative SARS-CoV-2 testing, authors hypothesized that these cutaneous manifestations represent late manifestations of the COVID-19 infection in young healthy subjects with an immunologic response targeting the cutaneous vessels.

Physiopathological implications

All these different clinical features of skin eruption in patients with COVID-19 infection probably reflect a full spectrum of viral interaction with the skin. In fact the exanthema may indicate a hematogenous spreading of the virus through the cutaneous vascular system. The activation of the immune system with mobilization of lymphocytes and Langerhans cells can be the second step of the viral infection. The creation of immune complexes, the production of cytokines by CD4+ T helper lymphocytes and the recruitment of eosinophils, cytotoxic T cells, B cells and natural killer cells will lead to a lymphocytic thrombophilic vasculitis [28]. The occurrence of a sepsis or severe viral infections may lead to the activation of the cytokine cascade and thus a disseminated intravascular coagulation phenomenon [29].

7. PATHOLOGICAL FINDINGS IN GASTROINTESTINAL TRACT

Yao. XH *et al* [18] reported some pathological changes in the gastrointestinal system including partial epithelial degeneration and necrosis, dilatation and congestion of lamina propria and submucosal small blood vessels with infiltration of lymphocytes, monocytes, and plasma cells. Xiao. F *et al* [30] found no significant damage in the epithelium lining the mucosa of esophagus, stomach, duodenum, and rectum. They observed also an infiltrate of occasional lymphocytes in esophageal squamous epithelium as well as numerous infiltrating plasma cells and lymphocytes with interstitial edema in lamina propria of the stomach, duodenum, and rectum. The viral nucleocapsid protein was visualized in the cytoplasm of gastric, duodenal, and rectum glandular epithelial cell by immunofluorescent staining, but not in esophageal epithelium.

Clinical and physiopathological implications

It is now well known that gastrointestinal symptoms including diarrhea, nausea, vomiting and abdominal pain can occur in the setting of COVID-19 infection [31]. Recent studies reported that SARS-CoV-2 RNA was detected in a stool specimen. Since ACE2 is highly expressed in the gastrointestinal tract, especially in the small and large intestines, these findings support the viral gastrointestinal infection and the fecal-oral transmission route [30].

8. PATHOLOGICAL FINDINGS IN OTHER ORGANS

Little is known about the pathological changes in other organs including pancreas, spleen, thyroid, lymph node and bone marrow. Some authors reported no histological changes in thyroid follicles, exocrine and endocrine pancreas cells; however they reported a significantly reduced number of splenic lymphocytes with degeneration and necrosis and a reduction in bone marrow three-lineage cells at variable degrees [18]. Further and larger autopsy series are necessary to understand the exact significance of these pathological findings.

9. CONCLUSION

In this review we tried to report all pathological findings of COVID-19 organ by organ. The main pathological changes are in lungs which show DAD at early phases then DAD with pulmonary organization and fibrosis at later phases. Heart, liver, kidney, skin and gastrointestinal tract are less involved; however they play an essential role in the pathogenesis of SAR-CoV-2 infection either directly via the ACE2 receptor or indirectly by the cytokine storm that induces a dysregulation of the immune system. Another interesting finding is the presence of hyaline thrombus in multiple organs and small vessels suggesting that severely ill patients developed disseminated intravascular coagulation during COVID-19 infection and thus multiple organ failure. To better understand the pathogenesis of COVID-19, further PCR investigations as well as studies of proper animal models mimicking the infection and the pattern of disease progression in humans are need.

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