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Review Article **Open Access**

Pathologic changes in patients infected with SARS-CoV-2: a review

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Abstract:

Severe acute respiratory syndrome–coronavirus-2 (SARS-CoV-2) enters cells using the angiotensin converting enzyme 2 (ACE2), which are expressed by the respiratory tract endothelium, epithelial cells of the stomach, duodenum, ileum, rectum, cholangiocytes, and hepatocytes. Pathological examinations of these organs are not feasible method of diagnosis but can explain pathological changes, pathogenesis of the disease, and the cause of death in COVID-19 cases. In this review, we performed a literature search for COVID-19-related pathological changes seen during post-mortem examinations in different organs of the body including the lungs, gastrointestinal tract, liver, kidney, skin, heart and blood. Our findings showed that SARS-CoV-2 has damaging effects on many organs, probably due to the host immune responses to the presence of the virus. It is recommended that both antiviral and immunomodulatory agents should be considered in the management of COVID-19 patients for better prognosis, and clinical outcome.

Keywords: COVID-19, SARS-CoV-2, ACE-2, pathology, autopsy findings

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Changements pathologiques chez les patients infectés par le SRAS-CoV-2: une revue

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Abstrait:

Le syndrome respiratoire aigu sévère-coronavirus-2 (SARS-CoV-2) pénètre dans les cellules à l'aide de l'enzyme de conversion de l'angiotensine 2 (ACE2), qui est exprimée par l'endothélium des voies respiratoires, les cellules épithéliales de l'estomac, du duodénum, de l'iléon, du rectum, des cholangiocytes, et les hépatocytes. Les examens pathologiques de ces organes ne sont pas une méthode de diagnostic réalisable, mais peuvent expliquer les changements pathologiques, la pathogenèse de la maladie et la cause du décès dans les cas de COVID-19. Dans cette revue, nous avons effectué une recherche bibliographique sur les changements pathologiques liés au COVID-19

observés lors d'examens post-mortem dans différents organes du corps, notamment les poumons, le tractus gastro-intestinal, le foie, les reins, la peau, le cœur et le sang. Nos résultats ont montré que le SRAS-CoV-2 a des effets néfastes sur de nombreux organes, probablement en raison des réponses immunitaires de l'hôte à la présence du virus. Il est recommandé que les agents antiviraux et immunomodulateurs soient pris en compte dans la prise en charge des patients COVID-19 pour un meilleur pronostic et des résultats cliniques.

Mots-clés: COVID-19, SARS-CoV-2, ACE-2, pathologie, résultats d'autopsie

Introduction:

In December 2019 an outbreak of a novel coronavirus disease was reported and subsequently declared a global pandemic (1). The World Health Organization (WHO) officially named the disease caused by the severe acute respiratory syndrome coronavirus - 2 (SARS-CoV-2) as coronavirus disease 2019 (COVID-19) (2). SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus belonging to the beta coronavirus family and is the seventh coronavirus that cause human infections (3). Among the other six coronaviruses that can cause diseases in humans are SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), which is associated with high mortality (4,5). SARS-CoV-2 is highly homologous to SARS-CoV and enters the cell via the angiotensin converting enzyme 2 (ACE-2).

COVID-19 notably present with symptoms of fever, dry cough, fatigue, muscle aches, shortness of breath, headache, diarrhea, and indigestion (6). It has been observed that from the onset of symptoms to death from the disease is between 6 and 41 days, and the average is 14 days (7). The aim of this review was to examine changes in various organs including the skin following infection by SARS-CoV-2. It is hoped that adequate knowledge of the pathology of the disease will aid early diagnosis and management of COVID-19, which can lead to reduction in mortality and length of hospital stay for the patients.

Methodology:

Online databases including the Web of Science, PubMed, Scopus, and Google Scholar were searched for relevant publications on the clinical features, pathogenesis, organ changes and complications in COVID-19 following the PRISMA guideline (8). We searched for pathological changes in terms of gross and microscopic morphology on autopsy, immuno-histochemistry, electron microscopy, fluorescence in-situ hybridization (FISH) and RT-PCR used to confirm SARS-COV-2 in these organs or tissues.

Search terms and phrases used include; "COVID-19 pathology", "COVID-19 autopsy findings", "COVID-19 diagnostic methods", "angiotensin-converting enzyme 2 (ACE2)", "SARS-CoV-2", "COVID-19", "2019-nCoV" and "organ changes in COVID-19". There was no restriction on the date, place, type of study, and inclusion/ exclusion criteria but publications not written in English were excluded. With greatest sensitivity search, we found 382 articles on external databases collected using Endnote Software. All the articles from the cited databases were then unified to avoid duplicates. Following review of the titles and abstracts, non-relevant articles were excluded, leaving a total of 60 eligible articles for the review (Fig 1).

Results and Discussion:

COVID-19 and the lungs

The lungs are the most affected organ in COVID-19 (9). However, severity of its involvement ranges from lack of symptoms or mild pneumonia to severe hypoxia, shock, respiratory failure, and multiorgan failure or death is associated with critical form of the disease (10). Grossly the lungs are heavy, often 3-5 times the normal size with evidence of congestion and haemorrhagic necrosis (11). In over 80% of cases, microscopic examination revealed various stages of diffuse alveolar damage, including the exudative phase with hyaline membrane formation, the proliferative phase with type 2 pneumocyte hyperplasia, and the early repair phase with interstitial spindle cell hyperplasia and/or intra-alveolar organization (12).

Other methods have been used to detect SARS-CoV-2 in the lung tissues including electron microscopy, immunohistochemistry to detect viral antigens, immunofluorescence viral nucleic acid detection by in-situ hybridization (FISH), and reverse transcriptase polymerase chain reaction (RT-PCR) (13). Effort has been made to detect SARS-CoV-2 on electron microscopy which reported "virus-like particles" (14).

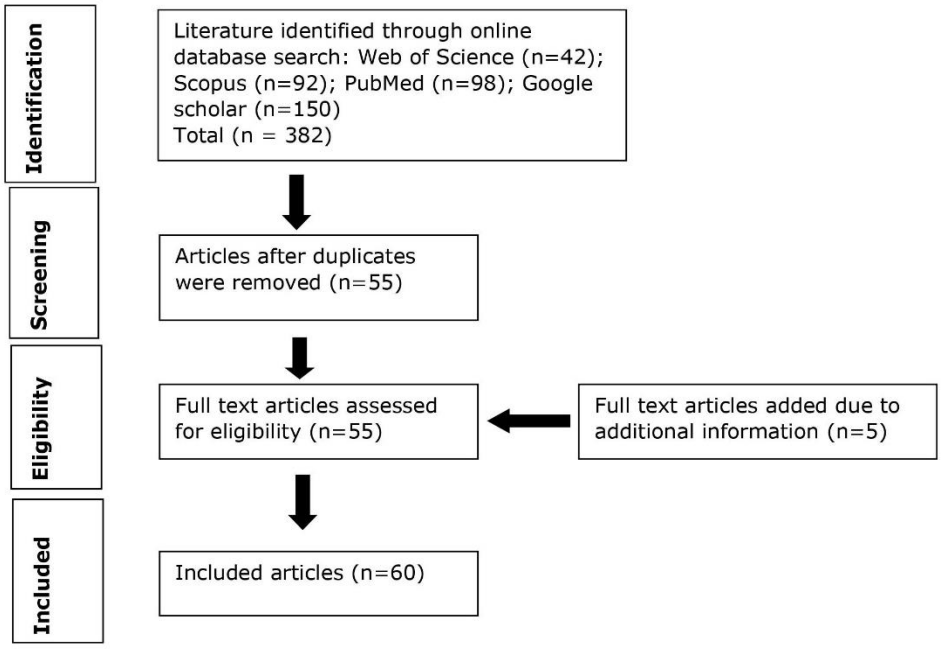

Fig. 1: Process of selection of publications (PRISMA guide) used for the review

In another study, it was reported that detection of SARS-CoV-2 by immuno-histochemistry was successful only in the lung, while no virus could be detected by this method in the heart, liver, kidney, small intestine, skin, adipose tissue, and bone marrow (15). Compared to immunohistochemistry, immunofluorescence has been used less frequently for the detection of SARS-CoV-2 proteins/antigens (16), and this could partly be due to stronger autofluorescence as a cofounding factor and potential infectivity of frozen tissues.

COVID-19 and the heart

Clinical features in COVID-19 patients suggest that SARS-CoV-2 has a major impact on the heart. Patients have features which suggest acute myocardial injury, including consistently elevated serum troponin level and ECG changes (17). The pathophysiology and the degree of myocardial injury, along with the short and long-term cardiovascular outcomes in COVID-19 survivors remain unclear. However, autopsy studies of the heart in these patients suggest that pre-existing heart diseases were dominant, particularly hypertensive heart disease (18). In other post-mortem studies, the findings showed endothelitis, as well as myocardial infiltration with lymphocytes, while direct injury of cardiomyocytes by the virus was not confirmed (19-21)

One autopsy case series study revealed severe right ventricular dilatation in patients, along with drop out myocyte necrosis and apoptosis. However there was no evidence of lymphocytic myocarditis suggesting that elevated troponin levels in these patients was due to extreme stress from acute pulmonary disease (22). Viruses with particular tropism for heart directly gain entrance to cardiomyocytes to cause their degeneration or to infect endothelial cells. These often lead to significant endothelial dysfunction, ischemia, cytokine release, and infiltration of myocardial tissue with immune cells (23). Consequently, innate and adaptive immune systems are activated, both being responsible for cytokine storm syndrome, as well as viral clearance.

Left ventricular systolic function impairment and cardiomyocytes dysfunction often lead to death (23). Of particular interest is the report of severe myocarditis and decreased systolic function after SARS-COV-2 infection, leaving us to wonder if the virus induces new cardiac pathologies or merely exacerbates underlying pathologies. It is obvious that as more studies are conducted and the disease evolves, more will be known about the long term effect of this virus on the heart (24).

COVID 19 and the kidney

Although, the first organs to be affected in SARS-COV-2 infection are the lungs, as initial clinical sign for the detection of COVID-19 is

pneumonia (25), many organ damages have been reported (6) and some cases of COVID-19 pneumonia present with kidney injury (26). Autopsy findings from patients who died of COVID-19 also revealed renal damage (27). Many studies have reported that SARS-CoV and SARS-CoV-2 use the ACE-2 to enter into target cells (28), and ACE-2 is well expressed on the surface of kidney tubular cells, which explains SARS-CoV-2 tropism for the kidney.

Many studies recognized the relevance of the inflammatory/immune-mediated reaction with the release of high levels of circulating harmful mediators such as IL-1, IL-6, TNF-α and chemokines capable of interacting with kidney-resident cells to cause endothelial dysfunction, microcirculatory derangement, and tubular injury (29). Acute kidney injury (AKI) developed on the average 9 days after admission together with secondary infections and acute cardiac damage (30). Many factors such as age, severity of illness, and the presence of diabetes mellitus contribute to AKI in patients with acute respiratory diseases (ARDS) (31).

The immune system responses to SARS-CoV-2 and direct cytotropic effect of the virus may be responsible for AKI in COVID-19 (32). Studies have shown that severe COVID-19 patients have reduced levels of $CD4^+$ (helper) and $CD8^+$ (cytotoxic) T lymphocytes, NK cells, and high levels of inflammatory cytokines. As soon as SARS-CoV-2 infiltrates into the renal cells, innate immune system and inflammatory responses might be triggered causing a cytokine storm syndrome, which is responsible for hypoxia, shock, rhabdomyolysis and acute kidney injury (33,34).

COVID 19 and gastrointestinal system

Similar to abundant expression of ACE-2 in the lungs, it has also been demonstrated on the epithelial cells of the stomach, duodenum, ileum, rectum, cholangiocytes, hepatocytes of the liver and esophageal mucosa (35). From physiological point of view, the kidney and the gut share a strong association or synergy during the maintenance of internal milieu known as the gut-kidney axis, which is further divided into metabolism-dependent and immune pathways (34). Gastrointestinal symptoms such as vomiting, diarrhea, loss of appetite and abdominal pain have been reported in SARS-CoV and COVID-19 patients (36-38).

Post-mortem changes in the gastrointestinal linings include vasculitis and increased inflammatory infiltrates. The spleen demonstrates increased neutrophil numbers, while the mesenteric lymph nodes show increased plamoblasts and congestion (39).

COVID-19 and the liver

Angiotensin converting enzyme-2 (ACE-2) is abundantly expressed in both the gastrointestinal epithelial cells and the liver, which explains a potential direct damage by SARS-CoV-2 on the liver (40). The liver enzymes, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, are elevated in COVID-19 patients, which indicate liver injury in these patients. AST elevation is more common than ALT, reflecting the contribution of AST from sources outside the liver. Hypoalbuminemia and slight increase in total bilirubin have been reported from several studies (41). Abnormal liver biochemistries are uncommon in children (42). Many drugs used in the treatment of COVID-19, such as antipyretic analgesics, antivirals, antibiotics and glucocorticoids, might have potential to cause drug-induced liver injury (43).

Autopsy findings from the first case of COVID-19 patient revealed that the liver tissue showed mild active inflammatory lesions in the hepatic lobular portal area, which suggest liver injury (44). *In vitro* studies have shown that SARS-CoV can cause direct liver injury (45). There is expression of moderate microvascular steatosis and mild lobular and portal activity, which indicate that liver injury could be caused by either SARS-CoV-2 infection or drug-induced liver injury (44).

COVID-19 and the skin

Viral illnesses are mostly associated with cutaneous manifestations, and may have diagnostic or prognostic value. With COVID-19, cutaneous manifestations range from rashes to eruptions.

Morbilliform rash

This is commonly seen with viral exanthemas. Studies from Italy reported that 78% of patients with COVID-19 had an erythematous/ morbilliform eruption (46).

Urticaria

A study from France reported that a patient developed an urticarial eruption along with odynophagia and diffuse arthralgia 48 hrs before onset of fever, chills and COVID-19 diagnosis (47). This unusual presentation of urticaria before the more well-known symptoms, signals the possibility that cutaneous eruptions can be a presenting symptom of COVID-19.

Vesicular eruptions

These resembles herpes vesicular eruptions and have been reported in COVID-19 patients (48). It was also observed that the median latency time from COVID-19 systemic symptoms to the rash was 3 days, and the median duration of skin manifestations was 8 days (49).

COVID toes

Research on cutaneous manifestations of coronavirus disease 2019 (COVID-19) are still going on. Acral cutaneous lesions also known as Covid toes have been reported in patients with COVID-19. the pattern of acral lesions is described as erythematous to purple, purpuric macules, papules and/or vesicles (50).

Livedoid eruptions

Many cases of Livedo reticularis-like eruptions have been reported in US patients with COVID-19 (51). It has been hypothesized that SARS-CoV-2 induces immune complexes formation with inflammation and vasculitis. This was further demonstrated on skin biopsies which showed small vessel thrombosis with no viral skin identification (52), demonstrating the possibility that tissue abnormalities are due to systemic toxicity triggered by a disproportionate immune response, rather than to direct viral spread. Another hypothesis is that the virus itself causes vascular damage, binding to ACE-2, which is widely expressed in endothelial cells (35). Early recognition of these cutaneous lesions may help to rapidly start treatment, since their worsening may be related to a severe systemic involvement**.**

COVID 19 and the neurologic system

Despite the fact that SARS-CoV-2 has been noted to principally affect the respiratory system, many studies have reported the involvement of neurological system. Neurological involvement in COVID-19 has been discussed in three sections; first is neurological features of viral infection, second is post-infective neurological complications, and third is infection in patients with neurological co-morbidity (53). Haematogenous spread and retrograde axonal transport have been described as routes for neuro-invasion by a coronavirus (54). Like other viruses, SARS-CoV-2, has been observed to directly invade the brain leading to clinical encephalitis (55). Other heterogeneous mechanisms such as cytokine storm and secondary hypercoagulability caused by the virus are thought to be involved.

Neurological manifestations in SARS-CoV-2 infection can be grouped into central nervous system (CNS) and peripheral nervous system (PNS). CNS features include headache, dizziness, ataxia, altered sensorium, encephalitis, stroke and seizures, while PNS features are seen as skeletal muscle injury and peripheral nerve involvement in the form of hyposmia and hypogeusia.

Post infective neurological complications including demyelinating conditions were previously reported (56). Guillain-Barré syndrome (GBS) is an inflammatory polyradiculoneuropathy associated with numerous viral infections. Recently, there have been many case reports describing the association between COVID-19 and GBS. However, despite numerous case reports of GBS associated with COVID-19, the prevalence remains unclear (57). In most of the cases reported, the patients were over 50 years of age, with male predominance (58). Coronavirus infection of the CNS has long provided a model for studying demyelinating diseases such as multiple sclerosis, vaccine design, and novel immunotherapeutic to limit virus spread (59). Even though the neurological manifestations in the majority of infected patients are mild, management of these patients should be a multidisciplinary approach.

The post-mortem nuclear magnetic resonance (NMR) findings of COVID-19 patients were parenchymal brain abnormalities such as subcortical macrobleeds and microbleeds, and edematous changes, which were suggestive of posterior reversible encephalopathy syndrome (PRES), and non-specific changes in the white matter (60).

Conclusion:

SARS-CoV-2 directly damage the lungs, heart, kidneys, liver, skin and brain. However, most of the injuries to these organs is caused by abnormal host immune responses to the virus. In the management of COVID-19 patients, it is recommended that both antiviral and immunomodulatory agents be applied for better prognosis and disease outcome.

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