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COVID -19, Pathophysiology and Histopathology: A Review

AJAZ AHMED WANI*, IMTEYAZ AHMED, MUNEESH KUMAR, FAISUL FAROOQ AND SUKLA SKIDA

Department of Zoology, Govt. Degree College, Doda, University of Jammu, Jammu-180001, India
***Corresponding author's e-mail: dr.ajazwani@rediffmail.com**
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ABSTRACT

The emergence of the viral disease during the last 20th century which includes the Severe Acute Respiratory Syndrome (SARS-CoV) in 2002 to 2003,H1N1influenza in 2009,Middle East Respiratory Syndrome(MERS-CoV) *etc.* and now the COVID-19 which emerged in Wahun city of China and within no time became pandemic. The objective of the present article is to summarize the knowldge about the pathophysiology and histopathology and to understand the mechanism of tissue damage by this virus which takes lakes of lives and millions of infection throughout the world.

Keywords: *Severe Acute Respiratory Syndrome, Middle East Respiratory Syndrome, COVID-19, Pathophysiology and Histopathology*.

INTRODUCTION

The present viral pandemic of COVID-19, a relentlessly emerging serious threat, is expanding its tentacles over whole of the globe. Human history has witnessed various viral challenges. The data revealed that in the last twentieth century, several viral epidemics emerged such as Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in 2002 to 2003, H1N1 Influenza in 2009 and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in 2012. Present COVID-19 epidemic out broke in Wuhan, the largest metropolitan area in China, in December 2019. The published literature reveals that symptomatic individuals appeared first in December 2019, but Chinese didn't know the causative agent. So the first cases were classified as "Pneumonia of unknown etiology". The Chinese Centre for Disease Control and Prevention (CDC) and local CDCs organized an intensive outbreak investigation programme. Consequently the etiology of this pneumonia like disease now attributed to a very contagious novel virus belonging to the Coronavirus family. On the 30th January, 2020, International Health Regulation (IHR) and the outbreak was declared by WHO a Public Health Emergency of International Concern (PHEIC). At that time it had spread to 18 countries with four countries reporting human to human transmission. The exponential spread of this virus across the globe led WHO to declare it as pandemic on March, 11 2020.

Initially the new virus was called 2019-nCOV. Later on, the experts of the International Committee on Taxonomy of Viruses (ICTV) termed it as SARS-CoV-2 because of its similarity to that of SARS CoV virus. The CoVs have become the major pathogen of emerging respiratory disease outbreaks. They are a large family of single-stranded RNA Viruses (ssRNA) that can be isolated in different animal species (Perlman *et al*., 2009). At the moment the therapeutic strategies to deal with the pandemic are only supportive, preventive and just aimed at reducing transmission at the community level. This being the only way to

control the infection. Throughout the world incredible efforts are being made by political, health and scientist to contain the shock of this pandemic that is severely testing the health systems.

The aim of this review article is to collect information and scientific evidences and to provide an overview of the topic that needs regular updation.

MATERIALS AND METHODS

The current article is a narrative review of the existing literature on histopathology and physiopathology of COVID-19. A search of PuMed electronic database was undertaken using the search "COVID-19 pathophysiology and histopathology". A total of tewelve related citations were retrieved by this method, three were found to be in Chinese language whereas nine were related with the topic.

Pathophysiology:

CoVs are enveloped positive stranded RNA Viruses with nucleocapsid having spike named S-Proteins and E-Proteins of envelope. To understand the pathogenetic mechanism of SARS-CoV-2 its viral structure and genome must be considered. The genomic structure of coronavirus is ssRNA of approximately 30 kb in length, the largest known RNA viruses with a 5'cap structure and 3' poly A tail. The synthesis of poly protein 1a/1ab (pp1a/pp1ab) in the host is realised. The transcription works through the Replication Transcription Complex (RCT) organized in double membrane vesicle and via the synthesis of sub genomic RNAs (sg RNAs) sequence. The transcription termination occurs at the transcription regulatory sequence, located between the so called open reading frames (ORFs) that work as a template for the production of sub genomic mRNAs. In a typical CoV genome atleast six ORFs can be present. Among these a frameshift between ORF1a and ORF1b guides the production of both pp1a and pp1ab polypeptides that are processed by viral encoded chymotrypsin like proteases (3CL Pro) and main protease (MPro), as well as one or two papain like proteases for producing 16 non structural proteins (nsps). Apart from ORF1a and ORF1b other ORFs encoded for structural proteins including spikes, membrane, envelope and nucleocapsid proteins (Perlman and Netland, 2009) and accessory protein chains.

Pathophsiology and virulence mechanism of CoVs and therefore also SARS COV-2 have links to the function of nsps and structural proteins. For instance research underlined that nsps is able to block the host innate immune response (Lei *et al*., 2018). Among the functions of structural proteins the envelope has a crucial role in virus pathogenecity as it promotes viral assembly and release. Among the structural elements of COVs, there are the spike glycoproteins composed of two subunits (S1 and S2). Homotrimers of S Protein compose the spikes on the viral surface, guiding the links to the host receptors (Song *et al*., 2018). Of note in SARS-CoV-2 the S2 subunit, containing a fusion peptide, a trans membrane domain and cytoplasmic domain, being highly conserved. Thus it could be a target of antiviral (anti S2) compounds. On the contrary the spike receptor binding domains presents only a 40 % amino acid identity within other SARS- CoVs. Other structural elements on which research must necessarily focus are ORF3b that has no homology with that of SARS-CoVs and a secreted protein (encoded by ORF8) which is structurally different from those SARS-CoV because of role of nsps and nsp3 in pathogenecity (Angeletti *et al*., 2020). The pathogenic mechanism that produce pneumonia seem to be particularly complex. Clinical and preclinical research will have to explain many aspects that underline the

particular clinical presentations of the disease. The data so far available indicates that the viral infection is capable of producing an excessive immune reaction in the host. This reaction in whole is labelled as "Cytokine Storm". The effect is extensive tissue damage. The protagonist of this storm is Interleukin-6 (IL-6). This IL-6 is produced by activated leucocytes and acts on large number of cells and tissues. It is able to promote the differentiation of B lymphocytes, promote the growth of some category of cells and inhibits the growth of others. It also stimulates the production of acute phase proteins and plays an important role in thermoregulation in bone maintenance and in the functioning of central nervous system. Although the main role played by IL-6 is pro inflammatory, it can also have anti-inflammatory effect. In turn, IL-6 increases during inflammatory, infections, autoimmune disorders, cardiovascular diseases and some types of cancers. It is also implicated into the pathogenesis of Cytokine Release Syndrome (CRS), that is an acute systemic inflammatory syndrome characterized by fever and multiple organ dysfunction.

Histopathology:

Tian *et al.*,(2020) and others reported histopathological data obtained on lungs of two patients who underwent lung lobectomies for adenocarcinoma and retrospectively found to have had infection at the time of surgery. Apart from the tumours, the lungs of both accidental cases showed oedema and important proteinaceous exudates as large protein globules. They also reported vascular congestion combined with inflammatory clusters of fibrinoid material and multinucleated giant cells and hyperplasia of pneumocytes.

Steven J.Mentzer from Brigham and Women's Hospital in the US (Express Pharma 23 May 2020) have described the clinical features of those who died due to COVID-19, findings shed more light on the course of novel coronavirus infection and may help discover new drugs against disease. These findings were published in the New England Journal of Medicine, examined seven lungs obtained during autopsy from patients who died of COVID-19. They compared seven autopsied lungs of those who died due to influenza A H1N1 virus infection and also compared findings with 10 aged matched uninfected control lungs.

According to the study, both SARS-COV-2 and H1N1 are the same category of viruses and both infect the respiratory tract. The lungs of both groups shared some common features. However there were distinctive features related to blood vessels seen in the lungs of those who died due to COVID-19. Severe injury is caused to the endothelial cells that line blood vessels in the lungs along with widespread blood clotting as well as new vessel growth. They also noted signs of disinfective pattern of lung related blood vessel disease in some cases of COVID-19 compared to that of equally severe influenza virus infection. The damage to lungs was 2.7 times higher than the patients of influenza. The demaged blood vessels may also underlie other peculiar symptoms seen in some patients such as purple blue discolouration of fingers and toes called "COVID Toes" and vascular inflammation seen in children called "Kawasaki Syndrome".

RESULTS AND DISCUSSION

The study of SARS-COV showed that virus infected lung epithelial cells produce IL-8 in addition to IL-6 (Yoshikawa *et al*., 2009).Infiltration of a large no.of inflammatory cells were observed in the lungs from severe covid -19 patients (Tian *et al*., 2019) and these cells presumbly consist of constellation of innate immune cells and adoptive immune cells and majority of to be neutrophils , and the neutrophils can induce lung injury (Liu *et al*., 2016).

The majority of the observed infiltrating adoptive immune cells were likely T cells considering that the significant reduction in circulating T cells were reported. In addition of respiratory system, thrombosis and pulmonary embolism have been observed in severe disease. This is in line with the findings that elevated d- dimers and fibrinogen level were observed in severe disease. The function of endothelium include promotion of vasodilation, fibrinolysis and an anti-aggregation (Wang *et al*., 2018).

CONCLUSION

The primary cause of death was respiratory failure with exudative diffuse alveolar damage with massive capillary congestion often accompanied by microthrombi despite anticoagulation. But more investigation is required to ascertain that which other organs are also infested by this disease. As there is urgent need to develop targeted therapies and this could be possible only by understanding the path of infection and target organ.

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