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Chen Chen[1] · Yiwu Zhou[2] · Dao Wen Wang[1]

[1] Division of Cardiology, Department of Internal Medicine, and Hubei Key Laboratory of Genetics and Molecular Mechanisms of Cardiological Disorders, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

[2] Department of Forensic Medicine, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

SARS-CoV-2: a potential novel etiology of fulminant myocarditis

Coronaviruses

Coronaviruses are enveloped nonsegmented positive-sense RNA viruses, which are broadly distributed in humans and other mammals, including camels, bats, masked palm civets, mice, dogs, and cats [1]. Although most human coronavirus infections are mild, coronaviruses have caused two large-scale pandemics in the last two decades: severe acute respiratory syndrome (SARS) with a mortality rate of 10%, and Middle East respiratory syndrome (MERS) with a mortality rate of 37%, together causing more than 10,000 cumulative cases [2, 3].

In December 2019, the Chinese city of Wuhan became the center of an outbreak of pneumonia of unknown cause [4]. Several patients with viral pneumonia were found to be epidemiologically associated with the Huanan seafood market in Wuhan, where a number of non-aquatic animals such as birds and rabbits were also on sale [5]. Bronchoalveolar lavage fluid (BALF), oral swabs, anal swabs, and blood samples from patients with severe pneumonia were investigated for pathogen diagnosis at the early stage of the outbreak. Soon, a novel coronavirus was isolated from patients, and the SARS-CoV-2, previously named "2019 novel coronavirus" (2019-nCoV), was identified using next-generation sequencing [6].

Usually, RNA viruses have a high mutation rate, but a notable common characteristic of both SARS-CoV and MERS-CoV is that they have a low potential for sustained community transmission [7]. Thus, the mutation rate of coronaviruses might also be lower because of their genome-encoded exonuclease [4].

SARS-CoV-2 infection

At the early stage of the outbreak, most SARS-CoV-2-infected patients worked at or lived around the local Huanan seafood wholesale market. Among them severe acute respiratory infection symptoms were observed, and some patients even rapidly developed acute respiratory distress syndrome (ARDS), acute respiratory failure, and other serious complications [8].

Huang et al. first reported the clinical features of patients infected with SARS-CoV-2 in Wuhan, China [9]. A total of 41 patients admitted to hospital were identified as having laboratory-confirmed SARS-CoV-2 infection. Most of them were men (n=30, 73%). A minority of them had underlying diseases (n=13, 32%), including diabetes (n=8, 20%), hypertension (n=6, 15%), and cardiovascular disease (n=6, 15%). A majority of them (n=27, 66%) had been exposed to the Huanan seafood market, while one family cluster was found. Common symptoms at the onset of illness were fever (n=40, 98%), cough (n=31, 76%), and myalgia or fatigue (n=18, 44%); less common symptoms were sputum production (11/39, 28%), headache (3/38, 8%), hemoptysis (2/39, 5%), and diarrhea (1/38, 3%). All 41 patients had pneumonia with abnormal findings on chest computed tomography (CT). Complications included ARDS (n=12, 29%), RNAemia (n=6, 15%), acute cardiac injury (n=5, 12%), and secondary infection (n=4, 10%). Among the 41 patients, 13 (32%) were admitted to the intensive care unit (ICU) and six (15%) died. Meanwhile, Zhu et al. described the clinical features of two SARS-CoV-2 pneumonia patients, evidenced by whole-genome sequencing, direct polymerase chain reaction (PCR), and virus isolation [10].

One week later, a larger retrospective study with 99 SARS-CoV-2-infected patients was reported [8]. In line with the previous findings, the SARS-CoV-2 infection showed a clustering onset, a higher likelihood of affecting older males with comorbidities, and the possibility of resulting in severe and even fatal respiratory diseases such as ARDS. In particular, some patients worsened in a short period of time and died of multiple organ failure. Subsequently, cases of SARS-CoV-2 infection were confirmed in the United States and Germany [11, 12].

Recently, another retrospective, single-center case series of 138 consecutive hospitalized patients with confirmed SARS-CoV-2 infection reported that hospital-related transmission of SARS-CoV-2 was suspected in 41% of the patients, 26% of the patients received ICU care, and the mortality rate was 4.3% [13].

Together, the clinical presentations of SARS-CoV-2 greatly resemble SARS-CoV. Patients with severe illness developed ARDS and required ICU admission and oxygen therapy.

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Cardiac involvement during SARS-CoV-2 infection

Previously published research mainly reported the epidemiological and clinical characteristics of SARS-CoV-2. Although elevated cardiac troponin I (cTnI) levels and arrhythmia were recorded, no specific investigation of the effects of SARS-CoV-2 infection on the cardiovascular system was reported.

In our clinical center, we mainly focused on the treatment of critically ill patients with severe SARS-CoV-2 infection, especially with cardiovascular complications. Among the 120 SARS-CoV-2-infected patients included in our observation, elevated N-terminal pro B-type natriuretic peptide (NT-proBNP; n=33, 27.5%) and cTnI (n=12, 10%) levels were recorded, indicating that the effects of cardiovascular injury on systemic stability should not be ignored.

The pathophysiology of SARS-CoV-2 has not been completely understood. Studies have suggested that SARS-CoV-2-infected patients had high levels of interleukin (IL)-1 beta, interferon gamma (IFN-γ), IFN inducible protein (IP)-10, and monocyte chemoattractant protein (MCP)-1, which probably led to the activated T-helper-1 cell response [9]. Moreover, they found that compared with patients who did not require ICU admission, those requiring ICU admission had higher concentrations of granulocyte colony-stimulating factor (GCSF), IP-10, MCP-1, macrophage inflammatory protein (MIP)-1A, and tumor necrosis factor (TNF)-α, suggesting that the cytokine storm might affect the disease severity [2]. We noticed that the plasma IL-6 level was increased dramatically in SARS-CoV-2-infected patients with cardiac injury. Moreover, death was associated with the cardiac damage induced by fulminant myocarditis (FM). Considering that a cytokine storm is also the core pathophysiological mechanism in FM—which is often fatal, especially in patients with severe multiple organ dysfunction—SARS-CoV-2-associated FM should be given more attention.

Viral fulminant myocarditis

Fulminant myocarditis is a rare clinical syndrome with features of cardiac inflammation and a reported high mortality rate of approximately 40–70%. It is part of the clinical spectrum of acute myocarditis [14], but was not specifically mentioned in the Dallas Criteria [15] or in the report of the World Health Organization/International Society and Federation of Cardiology (WHO/ISFC) classification of cardiomyopathies [16].

According to the European Society of Cardiology (ESC) myocarditis taskforce classification [17] and the current literature on FM [18], FM can be categorized into the histologically defined entities of lymphocytic, eosinophilic, and giant cell myocarditis and sarcoid heart disease. The lymphocytic forms are subdivided into those of infective and noninfective origin. Whereas viral etiology is assumed but not proven in the majority of cases, biopsy studies of patients with acute myocarditis in Europe indicate that viral etiology ranges between 37.8% [19] and 77.4% [20]. In patients with severe heart failure (ejection fraction [EF] < 45%) and inflammation in the Marburg registry, 42.1% were virus positive.

The mortality rate of FM ranges from 40 to 70% in most centers [17, 21]. The current Chinese publication on "Life support-based comprehensive treatment regimen" demonstrated a mortality rate of less than 5% [22]. This treatment regimen included the early application of sufficient doses of immune-modulation drugs, e.g., sufficient doses of steroids and i.v. immunoglobins, neuraminidase inhibitors, and active mechanical life-support treatments. The life-support treatments comprised the application of mechanical respirators and circulatory support systems, of which intra-aortic balloon pulsation (IABP) or Impella implantation or extracorporeal membrane oxygenation (ECMO) as well as cardiac pacemaker are part of the current therapeutic armamentarium [23]. The important and life-saving role of IABP, Impella, and ECMO has been underlined also by European and American centers [24–26]. These measures follow the hemodynamic principle of unloading the inflamed myocardium [27].

Conclusion

The condition of some patients with severe SARS-CoV-2 infection patients might deteriorate rapidly with acute respiratory distress syndrome and septic shock, which is eventually followed by multiple organ failure and fulminant myocarditis. More attention should be paid to patients with extremely increased cardiac troponin I (cTnI) levels and new-onset arrhythmias. The application of mechanical respirators and circulatory support systems, including IABP, Impella, and ECMO, might have beneficial effects on these patients.

Corresponding address

Prof. Dao Wen Wang, MD, PhD
Division of Cardiology, Department of Internal Medicine, and Hubei Key Laboratory of Genetics and Molecular Mechanisms of Cardiological Disorders, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology
1095# Jiefang Ave., 430030 Wuhan, China
dwwang@tjh.tjmu.edu.cn

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