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World J Gastroenterol 2003;9(6):1135-1138
World Journal of Gastroenterology
 ISSN 1007-9327

• REVIEW •

Severe acute respiratory syndrome and its lesions in digestive system

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Received: 2003-05-20 **Accepted:** 2003-05-27

Abstract

Severe acute respiratory syndrome (SARS) is an infectious atypical pneumonia that has recently been recognized in the patients in 32 countries and regions. This brief review summarizes some of the initial etiologic findings, pathological description, and its lesions of digestive system caused by SARS virus. It is an attempt to draw gastroenterologists and hepatologists' attention to this fatal illness, especially when it manifests itself initially as digestive symptoms.

Zhang JZ. Severe acute respiratory syndrome and its lesions in digestive system. *World J Gastroenterol* 2003; 9(6): 1135-1138
http://www.wjgnet.com/1007-9327/9/1135.asp

INTRODUCTION

In November 2002, a so-called atypical pneumonia with unknown etiology appeared in Guangdong Province, China, followed by reports from Hong Kong, Vietnam, Singapore, Canada and Beijing of severe febrile respiratory illness that spread to household members and health care workers[1-6,23-26]. This disease was designated "severe acute respiratory syndrome (SARS)" later by the World Health Organization (WHO) and global efforts to understand the cause of this illness and prevent its spread were instituted in March 2003. Many cases could be linked through chains of transmission to a health care worker from Guangdong Province, China, who visited Hong Kong, where he was hospitalized with SARS and died. Till May 19, 2003, a cumulative total of 7 864 SARS cases were reported to WHO from 29 countries; 643 deaths (case-fatality proportion: 8.2 %) have been reported, in which most cases occurred in China (7291 cases)[7]. The incubation period for the disease is usually 2 to 7 days. Infection is characterized by fever, non-productive cough, and shortness of breath, and the presence of minimal auscultatory findings with consolidation on chest radiographs. Lymphopenia, leucopenia, thrombocytopenia, and elevated liver enzymes and creatinine kinase may also present in most cases.

In response to this outbreak, WHO coordinated an international collaboration that included clinical, epidemiologic, and laboratory investigation, and initiated efforts to control the spread of SARS. Rapid research progress has been made in last three months. This brief review is to focus on the etiologic and pathologic findings with an emphasis on the known lesions in the liver and intestine.

ETIOLOGICAL FINDINGS

The isolation of a novel coronavirus was obtained from the respiratory secretions of patients with SARS and subsequently demonstrating this virus or a serologic response to this virus, points to a possible etiologic association with SARS[5,6,17,20,22,27]. The discovery of this new virus occurred through a broad-based and multidisciplinary effort by clinical, epidemiologic, and laboratory investigators.

Researchers around the world have sequenced the genetic codes of SARS virus, and are searching for clues to the virus' s origins, behavior, and future. Science is set to publish online a paper analyzing the genome from the BCCA Genome Sciences Center in Vancouver, as well as one from the Centers for Disease Control and Prevention (CDC) in Atlanta (www.sciencemag.org/feature/data/sars). Now that sequencing technology has become cheap and widely available, almost every country or area affected by SARS is sequencing its own version, including Hong Kong, Singapore and China[8-10]. The viruses themselves are something of an oddity. With a genome of the complete -29 700 nucleotides, coronaviruses are relative giants, and they have a complex two-step replication mechanism. Many RNA virus genomes contain a single, large gene that is translated by the host' s cellular machinery to produce all viral proteins. Coronaviruses, instead, can have up to 10 separate genes. Most ribosomes translate the biggest one of these, called replicase, which by itself is twice the size of many other RNA viral genomes. The replicase gene produces a series of enzymes that use the rest of the genome as a template to produce a set of smaller, overlapping messenger RNA molecules, which are then translated into the so-called structural proteins - the building blocks of new viral particles. Most coronaviruses cause either a respiratory or an enteric disease, and some do both. But the differences among these types can be small. In 1999, for instance, a team led by Luí s Enjuanes of the Autonomous University of Madrid, Spain, showed that just two point mutations can change a mostly enteric virus that can kill piglets into a nondeadly one that excels at the respiratory route but replicates poorly in the gut[11].

Researchers have grouped coronaviruses into three categories based on cross-reactivity of antibodies backed up by genetic data; the two previously known human viruses fell into different groups. Investigators have hoped that the genome sequence of the new virus would help pinpoint its origins. But a first glance at the data has yielded few clues. The new coronavirus does not fit into any of the clusters but is a new one by itself. Phylogenetic analysis of the predicted viral proteins indicates that the virus does not closely resemble any of the three previously known groups of coronaviruses. The genome sequence will aid in the diagnosis of SARS virus infection in humans and potential animal hosts (using PCR and immunological tests), in the development of antivirals (including neutralizing antibodies), and in the identification of putative epitopes for vaccine development.

PATHOLOGICAL CHANGES IN THE LUNG

Pathological studies of patients who died of SARS from Guangdong, Hongkong, Beijing and Singapore showed diffuse

alveolar damage (DAD) in the lung as the most notable feature[5,6,12,15,21]. In those individuals with severe disease resulting in death, scattered type II pneumocytes showed marked cytologic changes including multinucleation, cytomegaly, nucleomegaly, clearing of nuclear chromatin, and prominent nucleoli. Although these changes were severe, they were within the spectrum of epithelial changes seen in other cases of DAD. Definite viral inclusions were not always found in the cytoplasm of epithelial cells. Nicholis *et al*[12] found that DAD was common but not universal. Morphologic changes identified were bronchial epithelial denudation, loss of cilia, and squamous metaplasia. Other findings included focal intraalveolar hemorrhage, hemophagocytosis, necrotic inflammatory debris in small airways, organizing pneumonia or secondary bacterial pneumonia.

DAD is a pattern of acute lung injury characterized, in the acute phase, by hyaline membranes, interstitial and intraalveolar edema, patchy type II pneumocyte hyperplasia, microthrombi, and scant interstitial infiltrates of mononuclear cells. The acute phase forms a continuum with the proliferative or organizing phase in which proliferation of interstitial fibroblasts and prominent type II pneumocyte hyperplasia are the histologic hallmarks. In addition to DAD, the autopsy cases showed acute bronchopneumonia and variable intravascular thrombosis, all of which are common as terminal events. Biopsy material from milder cases or earlier in the course of illness may better define the initial lesion in SARS.

Multinucleated syncytial cells were identified in the alveolar spaces in a few patients. These cells contained abundant vacuolated cytoplasm with cleaved and convoluted nuclei, which show either CD68 or cytokeratin positive. No obvious intranuclear or intracytoplasmic viral inclusions were identified, and electron-microscopical examination of a limited number of these syncytial cells revealed no coronavirus particles. No definitive immunostaining was identified in tissues from a patient with SARS, with the use of a battery of immunohistochemical stains reactive with coronavirus from antigenic groups I, II, and III. In addition, no staining of patient tissues was identified with the use of immunohistochemical stains for influenza viruses A and B, adenoviruses, Hendra and Nipah viruses, metapneumoviruses, respiratory syncytial virus, measles virus, *Myocoplasma pneumoniae*,and *Chlamydia pneumoniae*[14].

Evaluation of Vero E6 cells infected with coronavirus isolated from a patient with SARS revealed viral cytopathic effect that included occasional multinucleated syncytial cells but no obvious viral inclusions. Immunohistochemical assays with various antibodies reactive with coronavirus from antigenic group I, including human coronavirus 229E, feline infectious peritonitis virus 1, and porcine transmissible gastroenteritis virus, and with an immune serum specimen from a patient with SARS demonstrated strong cytoplasmic and membranous staining of infected cells. No staining was identified with any of several monoclonal or polyclonal antibodies reactive with coronavirus in antigenic group II (human coronavirus OC43, bovine coronavirus, and mouse coronavirus) or group III (turkey coronavirus and infectious bronchitis virus). Electron-microscopical examination of a bronchoalveolar-lavage specimen from one patient revealed many coronavirus-infected cells[14].

Ksiazek and colleagues[5] noticed that the primary histopathological lesions are consistent with a nonspecific acute response to lung injury that can be caused by infections, trauma, drugs, or toxic chemicals. The multinucleated syncytial cells without viral inclusions seen in the lungs of two patients, however, are suggestive of a number of viral infections including measles and parainfluenzavirus, respiratory syncytial virus, and Nipah virus infection. Multinucleated syncytial cells associated with some human coronavirus infections have occasionally been observed in cell culture, but most often in cell cultures inoculated with animal coronaviruses. To detect this novel coronavirus antigen, the investigators used an extensive panel of antibodies against coronaviruses that are representative of the three antigenic groups, including several group 1 antiserum specimens that reacted against Urbani SARS-associated coronavirus infected tissue-culture material. A possible explanation for the failure of this antiserum to react with antigens in these patients on immunohistochemical analysis is that the host immune response has cleared the virus from these tissues. The tissues were available late in the course of the illness, 14 to 20 days after its onset. For many viral respiratory infections, viral antigens and nucleic acids are cleared within two weeks after the onset of disease.

Electron microscopic examination showed that virus-like particles with 100-150 nm in diameter were found in cytoplasm and dilated reticular endoplasm of the infected alveolar epithelial cells and endothelial cells[5, 15-17]. Other agents, such as paramyxovirus, metapneumovirus and chlamydia, were also identified in the pulmonary tissues[16,22]. It could be that the coronavirus may by itself produce the disease but it may also open the door for other viruses, or nonviruses, to aggravate the disease.

The pathogenesis of this disorder remains to be determined. However, the mechanism of acute lung injury could involve direct damage by the virus to the alveolar wall by targeting either endothelial cells or epithelial cells. Alternatively, the virus could infect inflammatory cells with the injury mediated through cytokines, interleukins, or tumor necrosis factor-alpha. It is also possible that the tissue damage in SARS is not directly related to viral infection in tissues but is a secondary effect of cytokines or other factors induced by viral infection proximal to but not within the lung tissue. In influenza infections, viral antigens are seen predominantly in respiratory epithelium of large airways and are only rarely identified in pulmonary parenchyma, despite concomitant and occasionally severe interstitial pneumonitis.

LESIONS IN DIGESTIVE ORGANS

As previously described, most coronaviruses cause either a respiratory or an enteric disease, which is also transmitted by the faecal-oral route. During this outbreak of SARS, symptoms of gastrointestinal tract in the patients were noticed. Many investigators[13,19,24] found that gastrointestinal symptoms are not uncommon at presentation, including diarrhea (19-50 percent), nausea and vomiting (19.6 percent), and abdominal pain (13 percent) manifested in SARS patients.

As many as 66 % of the patients in the Amoy Garden SARS outbreak in Hong Kong also had diarrhea, contributing to a significant virus load being discharged in the sewerage, which caused 361 cases of SARS[3]. During hospitalization, some patients were present with mildly elevated aminotransferase levels (indicating liver damage), or developed dysfunction of the liver at the later stage of the disease. Some patients presented with severe acute abdominal pain requiring exploratory laparotomy. All these patients developed typical SARS. These clinical findings suggest that SARS virus does involve the digestive system, especially the epithelial cells of intestinal mucosa.

Pathologic evaluation of the fatal cases showed that, except the lung changes, hepatocytes underwent fatty degeneration, cloudy swelling, apoptosis and dot necrosis, with Kupffer cell proliferation and portal infiltrates of lymphocytes[15,16]. There were regional hemorrhages, vascular congestion and lymphocytic infitration in gastrointestinal walls of the patient. Suckling mice inoculated with SARS-infected samples also

demonstrated hepatocytic lesions, including swelling, vacuolar and hydropic degenerations, focal cellular condensation and necrosis. But no coronavirus-like particles were found in hepatocytes.

Epidemiologic investigation also showed that the virus could survive in stools for at least two days and in diarrhoeal stools, which has a higher pH, for up to four days. It can also survive on plastic surfaces for up to 48 hours, but it is not yet known how big a dose of the virus is required to cause infection[18].

According to the experience of Prince of Wales Hospital in Hong Kong[20], where SARS outbreak happened, the difficulty of making a firm diagnosis until chest radiographic changes appear has important implications for health-care personnel and for surveillance. Three major reasons for spread of infection to health-care workers are: failure to apply isolation precautions to cases not yet identified as SARS, breaches of procedure, and inadequate precautions. Every patient must now be assumed to have SARS, which has major long-term implications for the health-care system. Another reason for spread among health-care workers is infected workers continuing to work despite symptoms, such as mild fever. Such individuals must now cease working. However, staying at home can also have disastrous consequences for exposed family members. Potential cases therefore require early isolation from both workplace and household. Extreme measures are required to protect health-care workers, who account for about 20 % of cases. Therefore, gastroenterologists and hepatologists should pay more attention when contacting the patients.

SARS has been appropriately elicited because current knowledge regarding the transmission of this disease is rapidly evolving and clinicians must provide patient care while dealing with a degree of uncertainty. The Centers for Disease Control and Prevention have published and regularly update logical recommendations for preventing the spread of the causative agent. The causative organism appears to spread predominantly by contact and droplets and may spread by airborne routes as well. The use of N-95 masks, gowns, double gloves, hand hygiene, and eye protection seem well advised and appear to have substantially curtailed spread within hospitals.

Global efforts have described this new syndrome with dramatic speed, and identified and sequenced the apparent etiologic agents. With expedited efforts to develop a specific diagnostic test, effective infection-control techniques, and to develop effective therapies and vaccines for SARS-associated coronavirus, and to create a true global health network, there is much reason for optimism. To be prepared for that challenge, health care professionals must not forsake their patients, the research community must help provide answers to the unanswered questions, and health care leadership must take the knowledge from that research to rapidly implement whatever strategies necessary to better combat this newly emerging infectious disease[28].

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Edited by Zhu LH