SEVERE ACUTE RESPIRATORY SYNDROME
Aetiopathogenesis and Morphological Changes
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INTRODUCTION

The recent outbreak of Severe Acute Respiratory Syndrome (SARS) began in
November 2002 in the Guangdong province of the Peoples' Republic of China. SARS
assumed epidemic proportions between February and July 2003, rapidly spreading
to involve a reported 8437 individuals in at
least 32 countries. Over 90% of reported
cases occurred in China and the Asia Pacific
region.  

Although none of the confirmed cases of
SARS officially documented by the World
Health Organisation (WHO) occurred in
Africa, the WHO acknowledged the death of
a Taiwanese businessman in Kano on 28
February 2003, with features suggestive of
SARS. Subsequently, The Nigerian federal
government adopted measures aimed at
ensuring that the epidemic did not enter the
most populous African country with a
population of over 126 million. These
included provision of special masks, gloves,
protective gowns, infrared digital
thermometers, spray machines, and
chemicals to ports of entry for easy
identification of probable cases. In addition,
Nigeria has installed facilities at the nation's
six international airports in Abuja, Lagos,
Calabar, Enugu, Kano, and Port Harcourt for the
screening of arriving passengers. There was
also mass mobilization of the media to educate
the people about the symptoms of SARS. In
Lagos, the largest commercial city in the West
African country, more than 4,000 people
arriving from SARS-infected countries and
regions around the world were screened during
the period the federal government began its
surveillance for the disease. Similarly, five
Nigerians deported from Southeast Asia, where
the infection has a high prevalence rate, were
quarantined for at least 10 days to ascertain their
state of health.

Such was the global hysteria associated with
this condition that a radio station in Port
Harcourt, Nigeria was closed down by
government officials following a false
unverified report of an outbreak of SARS
among Chinese workers at a local restaurant.

Another outcome of the SARS epidemic
directly affecting Nigeria was the cancellation
by the Nigerian Football Association of an
international football match scheduled for June
11 in Japan between the Nigerian and Japanese
national teams because of the purported risk of
SARS. Fortunately, no confirmed case of
SARS has been documented in Nigeria to date.

SARS is due to a novel virus belonging to the
family Coronaviridae, which is transmitted through respiratory droplets, contact with fomites, and aerosolised respiratory secretions. This virus has been designated the SARS coronavirus (SARS-CoV). This virus has a propensity to spread to healthcare workers and household members, resulting in community-wide outbreaks.

There has been one unsubstantiated report linking SARS to a human metapneumovirus in a study of 48 patients in Hong Kong. These patients apparently fulfilled the WHO clinical criteria listed below for SARS, and 25 of them (52.1%) had metapneumovirus RNA detected on reverse transcription polymerase chain reaction. However, no autopsy or surgical biopsy morphological studies were performed on these patients. The human metapneumovirus is a paramyxovirus first described in 2001, which has been linked to community-acquired respiratory tract infections. It is noteworthy that eleven (23%) of these patients had coronavirus infections, six being mixed metapneumovirus and coronavirus infections, and five being isolated coronavirus infections. This report awaits verification by further studies, and the prevailing consensus of the scientific community is that clinically verified cases of SARS are due to the SARS-CoV.

AETIOPATHOGENESIS
Coronaviruses are enveloped, RNA viruses possessing a single positive strand, which infect both humans and animals. The message sense RNA genome and the viral nucleocapsid phosphoproteins form a helical nucleocapsid. A corona of large, distinctive spikes in the envelope makes possible the identification of coronavirus by electron microscopy. Coronaviruses possess the largest viral RNA genomes known to date (27.7 to 31Kb). There are three groups of coronaviruses, groups 1 and 2 containing mammalian viruses, and group 3 avian viruses. Within each group, coronaviruses are classified into distinct species by host range, antigenic relationships, and genomic organization. Coronaviruses typically have narrow host ranges and are fastidious in cell culture. The known human coronaviruses can cause serious infections of the lower respiratory tract in children and adults and necrotising enterocolitis in newborns. These agents are able to survive on environmental surfaces for up to 3 hours. Coronaviruses might be transmitted by close person-to-person contact via droplets, hand contamination, fomites, and small particle aerosols. Body fluids such as blood and faeces are another possible vehicle of transmission. Epidemiological evidence for the importance of close contact in transmission of SARS-CoV may be adduced from the occurrence of relatively large numbers of cases in North America, Singapore, and Vietnam, accounting for 7-10% of global SARS cases, predominantly among those with close cultural ties to China. As a corollary, despite the geographic proximity of Japan to the epicentre of the SARS contagion, there was a striking paucity of Japanese SARS cases. This has been postulated to be due to the largely closed nature of the traditional Japanese society, which does not allow for mingling of natives with non-Japanese.

It is believed that the origin of SARS could be traced to three small mammals, the masked palm civet (Pargama latava), raccoon dog, and possibly the Chinese ferret badger, which are eaten as delicacies in China. The SARS-associated coronavirus could have arisen as a mutant of a human coronavirus that acquired new virulence factors, as a mutant of an animal coronavirus that can infect human cells, or as a recombinant of two human coronaviruses or a
human coronavirus and an animal coronavirus. Antibodies to the SARS-associated coronavirus were found in serum samples obtained from patients with SARS during convalescence but not in human serum samples banked before the SARS outbreak, suggesting that the SARS-associated coronavirus is new to the human population.

**MORPHOLOGICAL CHANGES**

The Centre for Disease Control and Prevention (CDC) has issued guidelines for the safe conduct of autopsies on cases of SARS. These include strict adherence to standard procedures, such as the use of personal protective equipment such as double surgical gloves or interposed mesh gloves, goggles, surgical cap, impervious gown, or apron, and shoe covers. Respiratory protection by respirators or powered air-purifying respirators is also recommended. Facilities in which such autopsies are performed should also have negative pressure air handling systems, with laminar airflow in the dissecting area.

Autopsies of fatal cases of SARS have demonstrated that the predominant pathology in the lungs is diffuse alveolar-damage (DAD). Generally, the causes of DAD include a large number of toxic insults including infections, inhalants, ingestants, drugs, shock, sepsis, radiation, and miscellaneous injuries such as acute pancreatitis, burns, and uraemia.

Gross findings in the post-mortem lung tissue include oedema, with lung weights of up to 1000-2000g, with a greyish brown consolidated cut surface. The consolidation was irregular and patchy, or less commonly more diffuse in distribution. Mucopurulent material may be seen in the tracheobronchial tree.

DAD (diffuse alveolar damage) is a pattern of acute lung injury characterised, in the acute phase, by hyaline membranes, interstitial and intra-alveolar oedema, patchy type II pneumocyte hyperplasia, microthrombi, and inflammation. In contrast to typical diffuse alveolar damage in which neutrophils and fibroblasts are the main cellular agents and macrophages have a lesser role, fatal SARS is associated with interstitial infiltrates of CD68 positive macrophages, which constitute the predominant leukocytes in the alveoli, even in the early stages of the disease.

The acute phase of DAD forms a continuum with the proliferative or organising phase in which proliferation of interstitial fibroblasts and prominent type II pneumocyte hyperplasia is the histologic hallmark. In SARS, scattered type II pneumocytes showed marked cytological changes including multinucleation, cytomegaly, nucleomegaly, clearing of nuclear chromatin, and prominent nucleoli. In patients surviving up to 8 days squamous metaplasia of the bronchial mucosa with loss of cilia may occur.

Although definite viral inclusions are usually not seen on light microscopy, electron microscopy reveals dilated Golgi bodies in the cytoplasm of pneumocytes containing 90 nm viral particles with characteristic small external spikes typical of coronaviruses.

The multinucleated giant cells in the lungs in cases of SARS are usually positive for the macrophage marker CD68. However, in one case, they were positive for the epithelial marker AE3.

In addition to DAD, autopsy cases showed acute bronchopneumonia and variable intravascular thrombosis, all of which are common as terminal events. Cultures were positive for Pseudomonas aeruginosa in one case and methicillin resistant Staphylococcus aureus in another.
The finding of haemophagocytosis in the lung and white pulp atrophy of the spleen identified in SARS is reminiscent of that reported in foetal influenza subtype H5N1 disease in 1997. Haemophagocytosis has been attributed to cytokine dysregulation. Lymphopenia is another feature common to both SARS-CoV and H5N1 influenza pneumonia. Intriguingly, both viruses have crossed to human beings from animals.\textsuperscript{9}

The recent WHO case definition of SARS includes autopsy demonstration of DAD without an identifiable cause. The absence of DAD makes the diagnosis of SARS very unlikely, and is a major exclusion criterion. However, in serologically confirmed cases, there is a range of morphological changes in SARS and in disease of less than 10 days duration. The changes of respiratory distress syndrome may be focal and dissimilar to those previously published cases. Pathologists undertaking these autopsies should be aware of the varied range of these morphological changes.\textsuperscript{25}

**MANAGEMENT**

The mainstay of therapy is intensive and good supportive care, with or without antiviral agents. Intravenous ribavirin, in combination with high dose corticosteroids such as 2mg/kg/day intravenous methylprednisolone, and intravenous immunoglobulin 1gm/kg/day, may produce some clinical improvement in critically ill patients.\textsuperscript{17,27,29}

The case fatality of reported cases of SARS ranges from 6\% to 50\%, depending on the age group affected, with an overall estimate of case fatality of 14\% to 15\%.\textsuperscript{25,26} Factors independently associated with an adverse clinical outcome include advanced age, as well as high neutrophil counts, and high lactate dehydrogenase levels at the time of presentation.\textsuperscript{16}

Combination antibiotic therapy, including azithromycin, amnoglycosides, ceftriaxone, doxycycline, and ciprofloxacin, predictably do not cause any clinical improvement. However, antibiotics may be beneficial in the prevention of secondary bacterial infections.\textsuperscript{17}

Respiratory protection and barrier nursing are advised for all health care workers and visitors in close with reported cases.\textsuperscript{17}

**CONCLUSION**

There are several lessons that have been gained from the recent epidemic of SARS.\textsuperscript{27} The epidemic was effectively curtailed by the timely declaration of a Global Alert for the first time in the history of the World Health Organisation (WHO). This was followed by a concerted multinational effort to institute simple public health control measures while searching for the aetiological agent of this new global scourge. A network of 13 laboratories in 10 countries assembled by the WHO was responsible for the identification of the SARS-CoV, elucidating its molecular genetics, and demonstrating that the SARS-CoV could induce respiratory illness in monkeys.\textsuperscript{27,29} There is now an ongoing coordinated effort to identify and test effective vaccines for the prevention of SARS. Although the apogee of the epidemic has been eclipsed, and the disease has all but vanished from the face of the earth, these efforts are still crucial in order to facilitate quelling of any future resurgence of this monstrous disease.\textsuperscript{29}

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Centres for Disease Control and


