

Severe Acute Respiratory Syndrome : An Update

Maj Gen SR Mehta, vsm*, Wg Cdr VK Sashindran⁺, Wg Cdr K Kumar[#], Maj A Gupta^{**}

MJAFI 2007; 63 : 52-55

Key Words : Severe acute respiratory syndrome

Introduction

The medical community will long remember the winter of 2002. An outbreak of an unusual form of respiratory illness started in the Southern Chinese province of Guangdong. It was characterised by a severe form of pneumonia caused by typical or atypical organisms. It also had a propensity to spread among household contacts and healthcare providers [1]. It spread quickly from mainland China, to Hong Kong, Taiwan, Singapore, Vietnam, Canada, USA and UK. The Public Health Specialist's nightmare of a rapidly spreading infection carried on the wings of modern jet airliner was a reality. A total of 8098 cases were reported, from 01 November 2002 to 31 July 2003 [2,3]. India was also affected with three probable cases and 10 suspect cases reported. Statistics from the most affected regions are listed in Table 1.

The overall mortality rate was 11% and the attack rate was 53%. The disease mainly spreads by droplets or close person to person contact. Contact with contaminated skin, secretions and excreta of patients are also postulated to be the modes of spread. The rapid spread of cases in the Amoy Gardens Apartment complex in Hong Kong and Metropole Hotel in Singapore have raised questions about airborne and vector borne (rats) transmission [3,4]. Majority of patients may not effectively transmit the virus, but some are "super-spreaders" and they transmit the virus to a large number

of individuals [4]. These super-spreaders and nosocomial amplifications were responsible for the early 2003 outbreaks.

Initially, the disease was thought to be a type of 'bird flu', after all, an avian flu epidemic had occurred in Hong Kong in 1997. On 26 February 2003, a Chinese-American businessman was admitted to a French Hospital in Hanoi with fever, dry cough and difficulty in breathing. Dr Carlo Urbani (the World Health Organisation (WHO) public health specialist in Vietnam, who later succumbed to severe acute respiratory syndrome), attended him. The rapid deterioration in the patient's condition and occurrence of similar symptoms in ten other persons working in the hospital made him suspect that this was not a simple epidemic of avian flu. He notified the WHO and a team of experts was rushed to investigate the outbreak [5]. WHO also formed a Severe Acute Respiratory Syndrome (SARS) working group comprising of 11 research laboratories all over the world to try and identify the causative agent and develop diagnostic tests [6]. The initial suspects were a paramyxovirus and human metapneumovirus. These organisms were however found in only a few clusters of cases. The turning point was the detection of an agent that produced a distinct cytopathic effect on Rhesus monkey kidney cells [7]. Electron microscopy further revealed virus-like particles. The very next day, a laboratory in United States identified these to be corona virus particles. Primers against corona virus were used to test samples all over the world and a high positivity was reported. Three pathogenic families of corona viruses are known. They cause a number of veterinary diseases like porcine gastroenteritis, avian infectious bronchitis and feline infectious peritonitis. The human pathogenic forms usually cause a mild upper respiratory tract infection (human corona virus – hCoV 229E). The culture requirements and cytopathic effect of the viral

Table 1
SARS statistics (01 November 2002 to 31 July 2003)

Region	Cases	Deaths
Mainland China	5327	348
Hong Kong	1755	298
Taiwan	671	84
Canada	250	38
India	03	—

*Senior Consultant (Medicine), Office of DGAFMS, Ministry of Defence, 'M' Block, New Delhi. *Reader (Medicine), Armed Forces Medical College, Pune. # Classified Specialist (Medicine), 5 Air Force Hospital, C/o 99APO. ** Graded Specialist (Medicine), 166 MH, C/o 56 APO.

particles isolated from patients with SARS were distinct from the known pathogenic strains. Hence the infection was thought to be due to a novel corona virus. Since then, the viral genome has been sequenced and many rapid diagnostic kits are available [8]. Koch's postulates have also been proven by growth and isolation of the virus in cynomolgus macaques[9]. Preliminary research suggests that the SARS – associated coronavirus (SARSCoV) may have originated in small mammals like the Himalayan palm civet or in livestock (chicken or duck). Mutation may have then allowed its transmission to humans. The proximity in which humans and livestock exist in rural China could have aided this process.

Clinical Features

An asymptomatic incubation period of 4-7 days (median 6 days) occurs after infection [9-11]. This is followed by a flu-like illness that lasts for 3-7 days. It is marked by fever, malaise, headache, chills, anorexia and fatigue. Diarrhoea may occur rarely. The lower respiratory phase usually begins 3-7 days after onset of symptoms when most patients complain of dry cough and breathlessness. About 10- 20 % of the patients will develop severe hypoxaemia which requires ventilatory support. The frequency of occurrence of various clinical features (a meta-analysis of 4 major clinical reports) is shown in Table 2 [10-13].

Fever is the commonest symptom in SARS. Chills, myalgia, headache and cough are other common complaints. When compared with the radiological findings, respiratory symptoms and auscultatory findings are disproportionately mild thus making it akin to the atypical pneumonias. The mean time between onset of symptoms and worsening is 8.3 days. Risk factors associated with severe complicated disease include old age, severe lymphopenia, raised alanine aminotransferase values and exposure to a household contact. Transient leucopenia occurs in the first week in about 64% of the cases and is followed by leucocytosis in 61% cases in the succeeding two weeks. Lymphopenia is common and reaches its nadir in the second week of illness. The lymphocyte count normally recovers by the third week. The CD4 and CD8 cell counts are reduced during the early phase of the illness.

Table 2
Frequency of clinical features in SARS (Meta-analysis of 4 studies)

Clinical feature	Occurrence (%)
Fever	95
Chills/rigors	62.6
Dry cough	52.7
Myalgia	51.8
Headache	48.2

A low CD 4 and CD 8 count at presentation may be a poor prognosticator [14]. Transient thrombocytopenia also occurs in 55% cases. Low serum albumin (68%), elevated creatinine phosphokinase (up to 3000 IU/L seen in 26%), and raised alanine aminotransferase (up to 2-6 times the normal seen in 34%) are common biochemical abnormalities.

The radiological changes are varied. A peripheral or pleural-based opacity may be the only abnormality seen in the early stages. Widespread opacification is seen in advanced cases with a ground glass appearance. The lesions mainly occur in the lower zones. Calcifications, pleural effusion, cavitation and lymphadenopathy are not seen in SARS. High resolution computed tomography (CT) scan shows similar changes[15,16]. The typical postmortem findings in the lungs include bronchial epithelial denudation, loss of cilia, squamous metaplasia and giant cell infiltration [17].

The diagnosis of SARS CoV infection is done by detection of IgG and IgM antibodies by an enzyme linked immunosorbent assay (ELISA) test. This test usually becomes positive 21 days after the onset of the illness. An immunofluorescence assay test that can detect antibodies by the tenth day of infection is also available. Reverse transcriptase polymerase chain reaction (PCR) can detect the SARS CoV RNA in serum, nasal secretions and stool samples within the first 10 days of illness. The diagnosis of SARS will however remain clinical and epidemiological until standardised reagents are adequately tested in the field.

CDC Guidelines for Diagnosis

In view of the evolving nature of the illness, the Centre for Disease Control (CDC) has issued guidelines that are periodically updated [18].

A suspect case is defined as a respiratory illness of unknown aetiology with onset after 01 February 2003 associated with measured temperature > 100.4° F, one or more clinical findings of respiratory illness and travel within ten days of onset of symptoms to an area with / suspected to have community transmission of SARS or close contact within 10 days of onset of symptoms with a suspect case of SARS.

A probable case is a suspect case with radiographic evidence of pneumonia or respiratory distress syndrome or an autopsy findings consistent with respiratory distress syndrome without an identifiable cause.

A contact is a person who has cared for, lived with, or had direct contact with respiratory secretions and/or body fluids of a patient known to be suspect SARS case.

Management

The suspect/probable case of SARS should be isolated

or hospitalised. The investigations to exclude both typical and atypical community acquired pneumonia should be done. Chest radiographs, complete blood counts, creatinine phosphokinase, hepatic transaminases, and electrolyte levels measurements should be done. Paired sera should be preserved for virological studies.

At the time of admission, the use of antibiotics for treatment of community-acquired pneumonia with atypical cover (like newer macrolides or levofloxacin) is recommended. Scrupulous precautions should be taken during procedures like nebulisation, bronchoscopy, chest physiotherapy and gastroscopy. Standard precautions like hand washing and eye protection should be made mandatory for all care takers. Contact precautions like use of gloves, gowns and masks should be enforced for all people coming in contact with the patient or his surroundings. N-95 respirators (a type of face mask) are recommended. Patients should be managed in isolation rooms with negative pressure.

Ribavirin with or without steroids has been tried. Good results have been reported from China [19], but these have not been corroborated elsewhere. Pending randomized controlled trials, ribavirin therapy is not recommended. Oseltamivir phosphate (a neuraminidase inhibitor) and human immunoglobulins, have also been found to be ineffective. Lopinavir-ritonavir coformulation, used in combination with ribavirin, is claimed to decrease mortality [20], but further trials are required to substantiate this. In vitro trials using interferon alpha seem promising.

The patients can be discharged once they have remained afebrile for more than 48 hours, their cough and chest radiograph have started resolving, and the blood counts and biochemistry have started normalizing. On discharge, the patients should be advised to record their temperature twice daily and remain indoors for at least 14 days [4]. They should also be advised to avoid contact with others and report to hospital for a review after one week. A viral serology test should be repeated after three weeks. The contacts should be educated about the disease and kept under surveillance for at least 10 days. They should also be advised voluntary home isolation. Telephonic surveillance is a practical method of keeping a daily check on these people. Daily temperature record is advised, as fever is the most consistent first symptom.

Conclusion

Unprecedented cooperation amongst the scientific community was the key behind rapid isolation of the SARS CoV. Vigorous case detection and energetic quarantine procedures have played a major role in containing the SARS epidemic. The WHO has already cautioned the world about the resurgence of the

epidemic. The diagnosis of SARS in a scientist in Taiwan and another confirmed case in China has re-awakened fears of another outbreak. Public awareness and vigilance on part of healthcare workers will continue to play a major role in containing the spread of SARS till a cure or vaccine is discovered. A genetically engineered vaccine for SARS, found effective in rhesus macaques, holds the promise for an early vaccine against this disease [21].

Conflicts of Interest

None identified

References

1. WHO. Severe acute respiratory syndrome (SARS) Weekly Epidemiol Rep 2003; 78: 86.
2. World Health Organization. Summary of probable SARS cases with onset of illness from 01 November 2002 to 31 July 2003. Revised September 23, 2003. (cited 2004 Apr 30). Available from <http://www.who.int/csr/sars.htm>.
3. Chang – Yeung M, Yu WC. Outbreak of severe acute respiratory syndrome in Hong Kong special administrative region: case report. *BMJ* 2003; 326: 850-2.
4. CDC. Severe acute respiratory syndrome – Singapore 2003, *MMWR* 2003; 52: 405-11.
5. Fleck F. Carlo Urbani- World Health Organization who raised the alarm over severe acute respiratory syndrome. *BMJ* 2003; 326: 825-7.
6. Stohr K. A multicenteric collaboration to investigate the cause of severe acute respiratory syndrome. *Lancet* 2003; 361: 1730-3.
7. Peiris JSM, Lai ST, Poon LLM, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet* 2003; 361: 1319-25.
8. Marra MA, Jones SJM, Astell CR, et al. The Genome Sequence of the SARS associated corona virus. *Science* 2003; 300: 1399-1404.
9. World Health Organization Update 4: SARS case fatality ratio, incubation period. May 7, 2003. (cited 2004 Apr 30). Available from www.who.int/crs/sarsarchive.htm.
10. Lee N, Hui D, Wu A, et al. A major outbreak of Severe Acute Respiratory Syndrome in Hong Kong. *N Eng J Med* 2003; 348: 1986-94.
11. Booth CM, Matukas LM, Tomlinson GA, et al. Clinical features and short-term outcomes of 144 patients with SARS in Greater Toronto area. *JAMA* 2003; 289: 2801-9.
12. Peiris JS, Chu CM, Cheng VC, et al. Clinical progression of viral loads in a community outbreak of coronavirus associated SARS pneumonia: a prospective study. *Lancet* 2003; 361: 1767-72.
13. Donnelly CA, Ghani AC, Leung GM, et al. Epidemiological determinants of spread of causal agent of Severe Acute Respiratory Syndrome in Hong Kong. *Lancet* 2003; 361: 1761-6.
14. Wong R, Wu A, To KF, et al. Haematological manifestations in patients with severe acute respiratory syndrome: retrospective analysis. *BMJ* 2003; 326: 1358-62.
15. Wong KT, Antonio GE, Jui D, et al. Severe Acute Respiratory

- Syndrome: Radiographic appearances and pattern of progression in 138 patients. Published online before print. May 20, 2003b. (cited 2004 Apr 30). Available from <http://radiology.rsna.org/cgi/conens/full/228203053v1>.
16. Wong KT, Antonio GE, Jui D, et al. Thin section CT of Severe Acute Respiratory Syndrome: Evaluation of 73 patients exposed to or with the disease. Published online before print on May 8, 2003a. (cited 2004 Apr 30). Available from <http://radiology.rsna.org/cgi/conent/full/2283030541v1>.
 17. Nichols JM, Poon LM, Lee KC, et al. Lung pathology of fatal severe acute respiratory syndrome. *Lancet* 2003; 361: 1773-8.
 18. World Health Organization. Updated Interim US Case definition for severe acute respiratory syndrome (SARS), July 11, 2003. (cited 2004 Apr 30). Available from www.who.int/csr/sars/case_definition.
 19. Zhao Z, Zhang F, Xu M, et al. Description and clinical treatment of an early outbreak of SARS in Guangzhou PR China. *J Med Microbiol* 2003; 52: 715-20.
 20. Sung J. Clinical diagnosis and management of SARS. WHO Global conference on severe acute respiratory syndrome (SARS), Malaysia. June 2003. <http://SARSreference.com/link.phpid=18>.
 21. Gao W, Tamin A, Soloff A, et al. Effect of a SARS-associated coronavirus vaccine in monkeys. *Lancet* 2003; 362: 1895-6.

Answer to Quiz

The mistakes made were as follows:

- a) The patient was not examined nor was the case sheet perused to check the operation notes and the procedure the patient had undergone.
- b) The radiograph was being treated and not the patient.
- c) Only a postero anterior view of the chest was taken. A lateral view of the chest would have prevented all the confusion (Fig. 2).

The fluid level seen in the chest radiograph was saline that had been instilled in the tissue expander, inserted in the sub-pectoral plane as the first stage of delayed breast reconstruction. The tissue expander outline and the port for filling the expander are clearly visible in the lateral radiograph. Putting a needle through the tissue expander would have been a disaster and necessitated removal of the tissue expander and nullification of the surgery done. The patient was overly anxious and the pain chest and breathing difficulty were probably psychosomatic than physical.



Fig. 2 : Chest radiograph lateral view