Chapter 3

Severe Acute Respiratory Syndrome (SARS) Outbreak in a University Hospital in Hong Kong

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Epidemiology-University Hospital Experience

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Epidemiology – University Hospital Experience

In March 2003, there was an outbreak of atypical pneumonia in Hong Kong\(^1\,^2\) and our institution was at its epicenter. Epidemiological investigations revealed that the initial outbreak at our institution was related to a single index case admitted to one of our medical wards.

In the early phase of the outbreak, the index case infected
- 55 health care workers in the same ward
- 16 medical students who clinically examined the index case
- 54 patients who were either nursed in the same ward or had visited their relatives.

It is postulated that the use of nebulized salbutamol for muco-ciliary clearance may have potentiated its transmission\(^2\).

Diagnosis of SARS

At the time of writing, the diagnosis of SARS is still based on clinical and epidemiological information as in our previously reported cohort\(^2\). According to the WHO case definition\(^1\), patients are classified as “suspect” or “probable” cases, as discussed in the earlier chapter. Cases are excluded if an alternative diagnosis can fully explain their illness\(^3\). However, clinicians are advised that patients should not have their case definition category downgraded while awaiting results of laboratory testing or on the bases of negative results. It must be emphasized that the hallmark of this illness is an initial viral pneumonia followed by a ‘reactive phase’ producing inflammatory changes resembling Bronchiolitis Obliterans Organizing Pneumonia (BOOP), subsequently progressing to acute RDS / respiratory failure\(^4\). Thus radiological investigations play a major role in the diagnosis and management of this disease.

**Key Points**

- *Diagnosis is based on clinical grounds*
- *Mainly a diagnosis of exclusion (at the time of writing)*

The subsequent part of the chapter will discuss the clinical, laboratory features, and prognostic factors of the initial cohort of confirmed SARS patients admitted to our institution. The current status of virological tests will also be discussed briefly.
Clinical features

The clinical features of SARS have been remarkably consistent among all reported cohorts²-⁷. In brief, the time interval between exposure to the onset of fever ranged from 2-16 days. The median incubation period is approximately 6 days. In the cohort of patients at our institution, the most common symptoms at presentation were fever (100%), chills and/or rigor (73.2%), myalgia (60.9%), cough (57.3%), headache (55.8%), and dizziness (42.8%). Less common symptoms included sputum production (29%), sore throat (23.2%), coryza (22.5%), nausea and vomiting (19.6%), and diarrhea (19.6%). Physical examination on admission revealed high body temperature in most patients (median body temperature 38.4°C, range 35-40.3°C). Inspiratory crackles could be heard at the base of the lungs and wheezing was universally absent. Skin rash, lymphadenopathy and purpura were not found.

As the disease progressed into second week, high spike of fever, non-productive cough, shortness of breath, and in some cases re-emergence of diarrhoea, became the more prominent features⁵. One must note that progression into RDS and respiratory failure may develop during this time.

Key Points

- **Fever, chills and/or rigor, myalgia, cough, headache and dizziness are the main presenting symptoms in the first week of illness**
- **Resurgence of fever, non-productive cough, shortness of breath and diarrhoea are the main features in the second week**
- **Progression into RDS and respiratory failure may occur**

Laboratory features [²,⁶]

- Initial blood count showed leucopenia (total white cell count < 3.5 x 10⁹/L) in 33.9% of patients.
- While neutrophil (median 3.45 x10⁹/L; range 0.5-11.8 x10⁹/L) and monocyte counts were normal in most cases, moderate lymphopenia (absolute lymphocyte < 1.0 x 10⁹/L) was found in 69.6%.
- Thrombocytopenia (platelet count < 150 x 10^9/L) was documented in 44.8% of patients on presentation.
- The lymphocyte count continued to drop within the first 2 weeks after admission.
- Prolonged APTT (> 38 seconds) was noted in 42.8%, while the prothrombin time remained normal in most cases.
- In 45.0% of patients D-dimer levels were also elevated.
- Reactive lymphocytes were detected in peripheral blood films in 15.2% of cases.

Serum chemistry was normal in the majority of cases. There were, however, several abnormalities found in a substantial proportion of patients.
- Serum transaminase levels (ALT>45 IU/ml) were elevated in 23.4% of patients (mean 60.4 ± 150.4 IU/ml).
- Creatinine kinase (CPK) levels were elevated in 32.1% of patients (median 126 U/L, range 29-4644). CK-MB and troponin-T were assayed in those with elevated CPK levels and none was found to be abnormal, indicating that the source of CPK was unlikely to be from cardiac muscles.
- LDH level was elevated in 71.0% of patients.
- Hyponatremia (Na⁺ <134 mmol/L) was documented in 20.3% of patients and hypokalemia (K⁺ <3.5 mmol/L) in 25.2% of patients.

As the disease progresses, LDH level increased and was believed to correlate well with disease severity. It has been postulated that as the disease progresses, LDH is released into the circulation after pulmonary inflammation and necrosis.²,⁶

**Key Points**
- *Initial lymphopenia and its subsequent progression are the main hematological features*
- *LDH level is helpful in the initial diagnosis as well as disease monitoring*
- *Thrombocytopenia, prolonged APTT, elevated D-dimer, ALT and CPK levels are other important laboratory features of SARS*
Clinical outcomes and prognostic factors

Univariate analysis of our cohort revealed that:
- advanced age, male gender, peak CPK value, LDH on presentation and its peak value, higher initial absolute neutrophil count and low serum sodium levels were significant predictive factors for ICU admission and mortality ².
- the presence of co-morbidities appeared to confer a worse clinical outcome in another cohort ⁶.

With multivariate analysis, advanced age [Odds Ratio (for every 10 years) = 1.80; 95% C.I. = 1.16-2.81; p=0.009], high peak LDH level [Odds Ratio (for every 100 U/L) = 2.09; 95% C.I. = 1.28-3.42; p=0.003], and higher absolute neutrophil count on presentation [Odds Ratio = 1.60; 95% C.I. = 1.03-2.50; p=0.04] were independent predictive factor of adverse outcomes ².

Key Points

Prognostic indicators for adverse clinical outcome:
- Advanced age,
- High peak LDH level,
- High initial neutrophil count

Virological testing for SARS

The cause of SARS is ascribed to a novel Coronavirus (SARS-CoV) ²,³,⁸-¹⁰. It is genetically distinct from other known coronaviruses, and early evidence also suggested that it may be non-human in origin. There are now several laboratory tests available for the virological diagnosis, namely serology for SARS-CoV (by IF or ELISA), virus isolation (cell culture), and reverse-transcriptase (RT) PCR on clinical specimens of different sites (including nasopharyngeal aspirate, nasal swab, throat gargle, sputum, stool, urine, blood, etc).

According to WHO [1], positive SARS diagnostic test findings are either:
- (a) confirmed RT-PCR on at least 2 different clinical specimens (e.g. nasopharyngeal and stool) or the same clinical specimen collected on 2 or more days during the course of the illness (e.g. 2 or more nasopharyngeal aspirates), or 2 different assays or repeat
PCR using the original clinical sample on each occasion of testing.

- (b) Seroconversion by ELISA or IFA: negative antibody test on acute serum followed by positive antibody test on convalescent serum, or four-fold or greater rise in antibody titre between acute and convalescent phase sera tested in parallel.

- (c) Virus isolation: isolation in cell culture of SARS-CoV from any specimen plus PCR confirmation using a validated method.

It is now generally accepted that absence of antibody to SARS-CoV in convalescent serum obtained >21 days after symptom onset should suggest absence of infection. However at the time of writing, there is no properly evaluated rapid diagnostic test for SARS-CoV infection. As a result, clinical, epidemiological and radiological information 11 are crucial in the diagnosis and management of SARS.

**Key Points**

- **Serological testing (IF or ELISA) for SARS-CoV is generally considered as the “gold standard”; cases are excluded when seronegativity is confirmed 3 weeks after symptom onset**

- **RT-PCR offers rapid diagnosis; though multiple clinical specimens are needed to increase the sensitivity and specificity.**
References

1. WHO. Severe Acute Respiratory Syndrome (SARS). Available at http://www.who.int/csr/sars/en/