

SARS: clinical features and diagnosis

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Severe acute respiratory syndrome (SARS) is a highly infectious disease with a significant morbidity and case fatality. The major clinical features include persistent fever, chills/rigor, myalgia, malaise, dry cough, headache and dyspnoea. Less common symptoms include sputum production, sore throat, coryza, dizziness, nausea, vomiting and diarrhoea. Older subjects may present with decrease in general well-being, poor feeding, fall/fracture and delirium, without the typical febrile response. Common laboratory features include lymphopenia with depletion of CD4 and CD8 lymphocytes, thrombocytopenia, prolonged activated partial thromboplastin time, elevated D-Dimer, elevated alanine transaminases, lactate dehydrogenase and creatinine kinase. The constellation of compatible clinical and laboratory findings, together with the rather characteristic radiological features especially on HRCT and the lack of clinical response to broad-spectrum antibiotics, should quickly arouse suspicion of SARS.

The positivity rates of urine, nasopharyngeal aspirate and stool specimen have been reported to be 42%, 68% and 97%, respectively, on day 14 of illness, whereas serology for confirmation may take 28 days to reach a detection rate above 90%. Recently, quantitative measurement of blood SARS CoV RNA with real-time RT-PCR technique has been developed with a detection rate of 80% as early as day 1 of hospital admission but the detection rates drop to 75% and 42% on day 7 and day 14, respectively.

Key words: clinical features, laboratory diagnosis, severe acute respiratory syndrome.

INTRODUCTION

Severe acute respiratory syndrome (SARS) is an emerging infectious disease with a significant morbidity and mortality. From November 2002–7 August 2003, 8422 cases have been reported worldwide with a death toll of 916.¹ During the recent epidemic and before the identification of the SARS coronavirus (CoV), the diagnosis of SARS has relied on recognition of certain clinical, laboratory and radiological features in addition to identification of any epidemiological linkage to an index case.

CLINICAL FEATURES

The incubation period of SARS is generally between 2 and 10 days although it has been estimated to be 6.4

days (95% CI 5.2–7.7) with the mean time from onset of clinical symptoms to hospital admission between 3 and 5 days.² The frequency of clinical features on presentation from several case series is summarised in Table 1. The major clinical features include persistent fever, chills/rigor, myalgia, malaise, dry cough, headache and dyspnoea. Less common symptoms include sputum production, sore throat, coryza, dizziness, nausea, vomiting and diarrhoea.^{3–6} Watery diarrhoea has been reported in 73% of a group of patients one week down the clinical course in a community outbreak linked to a faulty sewage system, presumably due to involvement of the gastrointestinal tract via the faecal oral route.⁷ Nevertheless, these clinical symptoms are rather non-specific and may mimic influenza or atypical pneumonia of other causes such as mycoplasma, chlamydia and legionella. Older subjects may present with decrease in general well-being, poor feeding, fall/fracture,⁸ and in some cases, delirium, without the typical febrile response.^{8,9} Physical examination of patients with SARS may reveal fever, tachycardia, tachypnoea and inspiratory crackles at the lung bases in some cases.^{3–6}

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LABORATORY AND RADIOLOGICAL FINDINGS

Laboratory features from a large case series are summarized in Table 2. Lymphopenia, features of low grade disseminated intravascular coagulation (thrombocytopenia, prolonged activated partial thromboplastin time, elevated D-Dimer), elevated alanine transaminases (ALT), lactate dehydrogenase (LDH) and creatinine kinase (CPK) are commonly observed in SARS patients with active disease. These laboratory features, together with the clinical features, may help in the clinical diagnosis of the disease.³⁻⁷ Lactate dehydrogenase, ALT and CPK tend to improve along with clinical and radiological improvement. The CD4 and CD8 T lymphocyte counts fall early in the course of SARS, whereas low counts of CD4 and CD8 at presentation are associated with adverse outcome.¹⁰

Previous studies have shown that radiologists cannot reliably distinguish bacterial from non-bacterial

pneumonia based on radiographic features.¹¹ The radiographic appearances of SARS indeed share common features with pneumonia of other causes. It is noteworthy that about 20–25% of patients with SARS may have normal chest radiographs on presentation,^{4,6,12} and HRCT of the thorax is useful in detecting parenchymal opacities early.¹³ Characteristic radiographic and HRCT features of SARS are described in detail in the previous article.

CLINICAL COURSE

The clinical course of SARS appears to follow a typical pattern in many cases.⁷ Phase 1 (viral replication) is associated with increasing viral load and clinically characterised by fever, myalgia and other systemic symptoms that generally improve after a few days. Phase 2 (immunopathological damage) is characterised by recurrence of fever, oxygen desaturation, radiological progression of pneumonia with falls in viral load. The majority of patients will improve with a combination of ribavirin and intravenous pulse steroid therapy but 20–36% may require ICU admission, and 13–26% may progress into acute respiratory distress syndrome (ARDS) necessitating invasive ventilatory support.^{4,7,14,15} Compared with adults and teenagers, SARS seems to run a less aggressive clinical course in younger children and none of the children aged below 13 years required supplemental oxygen in a case series.¹⁶

Despite the use of low volume and low pressure mechanical ventilation, the incidence of barotrauma was higher than expected. Pneumothorax has been observed in 3% of cases⁶ and 12% of patients developed spontaneous pneumo-mediastinum over a period of 3 weeks in another case series.⁷

The average hospital length of stay for the majority of patients during the recent epidemic in Hong Kong was 21 days with a 21-day mortality between 3.6 and 10%.^{4,14} Some of the patients received physiotherapy as outpatients while about 15% of patients required a period of rehabilitation as inpatients. The prognostic

Table 1 Clinical features of SARS on presentation³⁻⁶

Symptom	% of patients with symptom
Persistent fever > 38C	99–100
Non-productive cough	57–75
Myalgia	45–61
Chills/rigor	15–73
Headache	20–56
Dyspnoea	40–42
Malaise	31–45
Nausea and vomiting	20–35
Diarrhoea	20–25
Sore throat	13–25
Dizziness	4.2–43
Sputum production	4.9–29
Rhinorrhoea	2.1–23
Arthralgia	10.4

Table 2 Laboratory results during the first week from a large case series⁴

Mean ± SD	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Haemoglobin g/dL	13.5 ± 1.7	13.1 ± 1.5	13.1 ± 1.7	13.1 ± 1.7	13.0 ± 1.6	13.1 ± 1.5	12.9 ± 1.7
Platelet × 10 ⁹ /L	150.2 ± 60.1	147.6 ± 53.1	153.2 ± 61.3	157.6 ± 63.8	164.9 ± 70.7	185.4 ± 72.5	206.3 ± 89.9
White cell count × 10 ⁹ /L	5.1 ± 2.1	4.5 ± 2.0	5.1 ± 2.7	5.2 ± 3.0	6.0 ± 3.4	8.0 ± 6.3	8.3 ± 4.9
Neutrophil count × 10 ⁹ /L	3.9 ± 2.0	3.2 ± 1.9	4.0 ± 2.7	4.0 ± 2.7	5.0 ± 3.3	7.0 ± 6.6	7.2 ± 4.7
Lymphocyte count × 10 ⁹ /L	0.9 ± 0.7	0.8 ± 0.4	0.8 ± 0.7	0.7 ± 0.4	0.7 ± 0.4	0.6 ± 0.3	0.6 ± 0.4
Prothrombin time s.	11.2 ± 4.7	12.2 ± 8.0	12.7 ± 8.6	11.7 ± 5.9	11.2 ± 4.6	12.8 ± 9.3	11.3 ± 4.0
Activated partial thromboplastin time sec.	41.6 ± 8.9	43.8 ± 8.9	44.8 ± 12.8	42.6 ± 9.8	41.2 ± 8.1	39.8 ± 11.1	36.3 ± 6.9
Sodium mmol/L	135.6 ± 3.4	135.6 ± 3.6	135.9 ± 3.5	137.0 ± 3.9	137.0 ± 4.4	138.0 ± 5.1	139.2 ± 4.9
Potassium mmol/L	3.7 ± 0.4	3.8 ± 0.4	3.8 ± 0.5	3.8 ± 0.4	3.8 ± 0.4	4.0 ± 0.4	3.9 ± 0.4
Urea mmol/L	4.7 ± 5.1	4.9 ± 5.7	4.5 ± 4.5	4.8 ± 4.4	4.6 ± 3.8	5.4 ± 4.4	6.3 ± 7.2
Creatinine µmol/L	99.0 ± 111.8	97.4 ± 88.6	94.3 ± 100.4	91.2 ± 59.0	82.8 ± 23.8	82.4 ± 23.8	82.7 ± 27.2
Bilirubin µmol/L	10.0 ± 19.4	11.6 ± 29.5	10.7 ± 17.8	14.4 ± 33.0	12.5 ± 19.3	18.6 ± 47.1	14.3 ± 16.3
Alanine transferase Iu/L	60.4 ± 150.4	45.4 ± 49.6	67.4 ± 113.7	79.3 ± 104.9	69.4 ± 72.3	79.5 ± 77.0	89.8 ± 104.5

factors associated with a poor outcome (ICU admission or death) include advanced age,^{2,4,7,15} chronic hepatitis B treated with lamivudine,⁷ high initial LDH,¹⁵ high peak LDH,⁴ high neutrophil count on presentation,^{4,15} diabetes mellitus or other comorbid conditions^{6,14} and low CD4 and CD8 lymphocyte counts at presentation.¹⁰

DIAGNOSTIC CRITERIA OF SARS

Both the WHO and the CDC have issued updated case definitions for SARS during the outbreak. A suspected case has been defined by the WHO (revised 1 May 2003)¹⁷ as a person presenting after November 1, 2002 with:

- Fever > 38°C; and
- Cough or difficulty breathing; and
- Either close contact with a person who is a suspect or probable case of SARS and/or history of travel or residence in an area with recent local transmission of SARS within 10 days of symptom onset.

Patients with an unexplained fatal acute respiratory illness who fit the above epidemiologic criteria, but on whom no autopsy has been performed are also classified as suspected cases.

A probable case is defined as:

- A suspected case with radiographic findings of pneumonia or acute respiratory distress syndrome (ARDS); or
- A suspected case positive for SARS CoV in one or more laboratory assays; or
- A suspected case with autopsy evidence of ARDS with unknown cause.

The WHO definitions have been established to assist in the definition of hospital cases. The reason for retaining the clinical and epidemiological basis for the case definitions is that there is as yet no validated,

widely and consistently available rapid test for SARS CoV infection. The WHO definitions have recently been evaluated in the context of screening patients before admission to hospital.¹⁸ In the early stages of SARS, the main discriminating features are fever, chills, malaise, myalgia and rigors rather than cough and breathing difficulty. Documented fever (> 38°C) may not occur in the early stages in some cases and radiological evidence of pneumonic changes often precedes fever. The WHO case definitions for suspected SARS have a low sensitivity of 26% and a negative predictive value of 85% for detecting SARS in patients who have not been admitted to hospital.¹⁸ The WHO has recently revised the case definitions in the post outbreak period with inclusion of radiographic and laboratory findings for public health purposes (Table 3).¹⁹

The CDC case definitions of SARS are based on clinical, epidemiologic and laboratory criteria (Table 4).²⁰ The case definitions and exclusion criteria have been revised to allow exclusion of cases with a convalescent phase serum sample, collected >28 days after symptom onset, that is negative for antibody to SARS CoV.²⁰

LABORATORY DIAGNOSIS

The detection rates for SARS CoV using reverse transcriptase polymerase chain reaction (RT-PCR) are generally low in the first week of illness. The positivity rates on urine, nasopharyngeal aspirate and stool specimen have been reported to be 42%, 68% and 97%, respectively, on day 14 of illness whereas serology for confirmation may take 28 days to reach a detection rate above 90% (Table 5).⁷ Recently, quantitative measurement of blood SARS CoV RNA with real-time RT-PCR technique has been developed with

Table 3 WHO case definitions of SARS in the postoutbreak period¹⁹

Clinical case definition of SARS:

A person with a history of:

Fever ≥ 38C

AND one or more symptoms of lower respiratory tract illness (cough, difficulty breathing, shortness of breath)

AND Radiographic evidence of lung infiltrates consistent with pneumonia or Respiratory distress syndrome (RDS) OR autopsy findings consistent with the pathology of pneumonia or RDS without an identifiable cause.

AND No alternative diagnosis can fully explain the illness.

Laboratory case definition of SARS:

A person with symptoms and signs that are clinically suggestive of SARS and with positive laboratory findings for SARS CoV based on one or more of the following diagnostic criteria:

(a) PCR positive for SARS CoV

PCR positive using a validated method from:

At least 2 different clinical specimens (e.g. nasopharyngeal aspirate or stool) OR

The same clinical specimen collected on 2 or more occasions during the course of the illness (e.g. sequential nasopharyngeal aspirates) OR

Two different assays or repeat PCR using a new RNA extract from 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 phase serum tested in parallel OR

Fourfold 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 and PCR confirmation using a validated method.

Table 4 CDC updated interim case definition for SARS²⁰**Clinical criteria:**

Asymptomatic or mild respiratory illness

Moderate respiratory illness (temp > 100.4F or 38C) and at least one respiratory features (cough, dyspnoea, difficulty breathing, or hypoxia)

Severe respiratory illness (one or more respiratory features as above and radiographic evidence of pneumonia, or respiratory distress syndrome, or autopsy findings consistent with pneumonia, or respiratory distress syndrome without an identifiable cause).

Epidemiologic criteria:

Travel (including transit in an airport) within 10 days of onset of symptoms to an area with current or recently documented or suspected community transmission of SARS, or

Close contact within 10 days of onset of symptoms with a person known or suspected to have SARS infection.

Laboratory criteria:

(a) Confirmed:

Detection of antibody to SARS-CoV in specimens obtained during acute illness or 21 days after illness onset, or

Detection SARS-CoV RNA by reverse- transcriptase polymerase chain reaction (RT-PCR) confirmed by a second PCR assay, by using a second aliquot of the specimen and a different set of PCR primers, or

Isolation of SARS-CoV

(b) Negative:

Absence of antibody to SARS CoV in a convalescent phase sample obtained > 28 days after symptom onset

(c) Undetermined: Laboratory test either not performed or incomplete

Case classification:

A case of *probable SARS* is defined as having met the clinical criteria for *severe* respiratory illness of unknown aetiology and epidemiologic criteria for exposure, laboratory criteria confirmed or undetermined

A case of *suspect SARS* is defined as having met the clinical criteria for *moderate* respiratory illness of unknown aetiology, and epidemiologic criteria for exposure, laboratory criteria confirmed or undetermined

Exclusion Criteria:

A case may be excluded as a suspect or probable SARS case if:

An alternative diagnosis can fully explain the illness.

The case has a convalescent phase serum sample (i.e. obtained > 28 days after symptom onset) for which is negative for antibody to SARS-CoV

The case was reported on the basis of contact with an index case that was subsequently excluded as a case of SARS, provided other possible epidemiologic exposure criteria are not present

Table 5 Diagnostic tests for SARS CoV⁷

RT-PCR	Detection rate
Nasopharyngeal aspirate	32% Day 3, 68% Day 14
Stool	97% Day 14
Urine	42% Day 15
Serology	15% Day 15
IgG seroconversion to SARS CoV	60% Day 21 >90% Day 28

a detection rate of 80% as early as day 1 of hospital admission but the detection rates drop to 75% and 42% on day 7 and day 14, respectively.²¹

CONCLUSION

With the recent SARS epidemic worldwide, research in the development of diagnostic tests is urgently needed. The availability of the genome sequence of the SARS CoV²²⁻²⁴ will hopefully facilitate efforts to develop new and rapid diagnostic tests. The WHO¹⁷ and CDC case definitions of SARS during the outbreak period relied heavily on epidemiological linkage to increase the specificity of the diagnostic criteria. Nev-

ertheless, in the postepidemic period, epidemiological links to cases of SARS and areas reporting recent local transmission are no longer useful in defining incident cases.¹⁹ The clinical and laboratory features of SARS are non-specific and may be indistinguishable from other cases of atypical pneumonia. However, the constellation of compatible clinical and laboratory findings, together with the rather characteristic radiological features, especially on HRCT, and the lack of clinical response to broad-spectrum antibiotics, should quickly arouse our suspicion of SARS. Until rapid diagnostic tests with a high rate of early detection (e.g. blood SARS CoV RNA using real time RT-PCR technique) become readily available, the diagnosis of SARS will remain a clinical decision in the early stage.

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