Case Report

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Tuberculosis in a SARS Outbreak

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Preoccupied with the diagnosis of SARS (severe acute respiratory syndrome) in a SARS outbreak, doctors tend to overlook other endemic diseases, such as tuberculosis. Incorrectly labeling a patient as SARS may result in serious consequences. Single isolation being not always possible, the patient may have to be isolated with a group of SARS patients. The following article reports how a young girl suffering from pulmonary tuberculosis was erroneously diagnosed as SARS in an outbreak. Isolated with other SARS patients, she was infected with the virus. The treatment of SARS and tuberculosis resulted in liver dysfunction. Fortunately, the patient recovered uneventfully. The importance of keeping an open mind in an outbreak is highlighted.

Key Words
atypical pneumonia;
outbreak;
pneumonia;
SARS;
severe acute respiratory syndrome;
tuberculosis

During an outbreak of severe acute respiratory syndrome (SARS), a patient with respiratory symptoms, fever, and shadows on chest X-ray (CXR) will very likely be diagnosed as SARS till proven otherwise. The patient will often be isolated, to guard against the high infectivity of the virus. Since single isolation is not always feasible in many hospitals during an outbreak, the patient will often be isolated among other suspected patients, some of whom may be highly infective. The following reports a case in which a teenage patient suspected to have SARS, was isolated among SARS patients but later diagnosed as tuberculosis. Unfortunately, she was infected with SARS during her isolation. The importance of single isolation and accurate diagnosis is highlighted.

CASE REPORT

A teenage lady was admitted at the peak of a SARS outbreak in Hong Kong. She had fever for 2 days, rigor and myalgia for 2 weeks. There was no record of recent travel or contact with SARS patients. Three other residents in the same building of her flat had caught SARS. She had no past history of tuberculosis. Her temperature was 39 °C, physical examination was normal otherwise. CXR showed LUZ (left upper zone) haziness (Fig. 1A). WBC 9.5×10^9/L, lymphocyte 0.5×10^9/L. Arterial blood gas, renal and liver functions were normal. Cultures of blood, urine and sputum were normal. Septic screen and Widal reaction were negative. Immunofluorescence to *Influenza* A, B, *Parainfluenza* 1, 2, 3 and *adenovirus* were negative. Nasopharyngeal swab and stool for *coronavirus* were taken, results pending.

In view of possible contact, high fever and LUZ haziness, the patient was diagnosed as SARS on the day of admission. Due to limited availability of single isolation rooms, she was not isolated singly, but among a cohort of SARS patients. The standard regimen recommended by local authority at that time-10 days ribavirin 400 mg IV

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q8h and hydrocortisone 300 mg q6h with cephtriaxone and clarithromycin- were given.[1,2] Fever subsided the next day. Reverse transcriptase polymerase chain reaction (RT-PCR) of nasopharyngeal swab for *coronavirus* on Day 1 of admission returned negative. RT-PCR of stool on Day 2 and Day 12 were also negative. Both were assumed to be false negative.

The LUZ opacity persisted and slightly enlarged. On day 20 after admission, temperature suddenly rose to 39 °C. CXR showed dense LUZ shadow typical of tuberculosis, and a new ground glass opacity appeared in RMZ (right mid-zone). On Day 25, Ziehl-Neelsen stained positive for acid-fast bacilli (AFB) in sputum. Anti-tuberculosis drugs, isoniazid (INAH), rifampicin, pyrazinamide and ethambutol were prescribed. Serology for *coronavirus* on Day 1 and Day 14 again were negative. RT-PCR was repeated on nasopharyngeal swab and stool on Day 25. Both specimens were then positive for *coronavirus*. As fever persisted, anti-tuberculosis drugs were withheld due to the possibility of drug fever, but were resumed after 2 days. Another ground glass opacity appeared in the LMZ (left mid-zone) (Fig. 1B).

At that time, the efficacy of ribavirin and steroid in SARS treatment was queried by many authorities over the world.[3] Since our patient was likely to be infected while on ribavirin treatment, oral lopinavir®/ritonavir® (Kaletra, Abbott Laboratories, Illinois, USA) 300 mg bd and ribavirin 600 mg daily were prescribed. Kaletra was a protease inhibitor combination for treatment of HIV infection.[4,5] The patient was subsequently isolated in a single room. Temperature subsided on the next day. The patient developed nausea on the 4th day and pyrazinamide

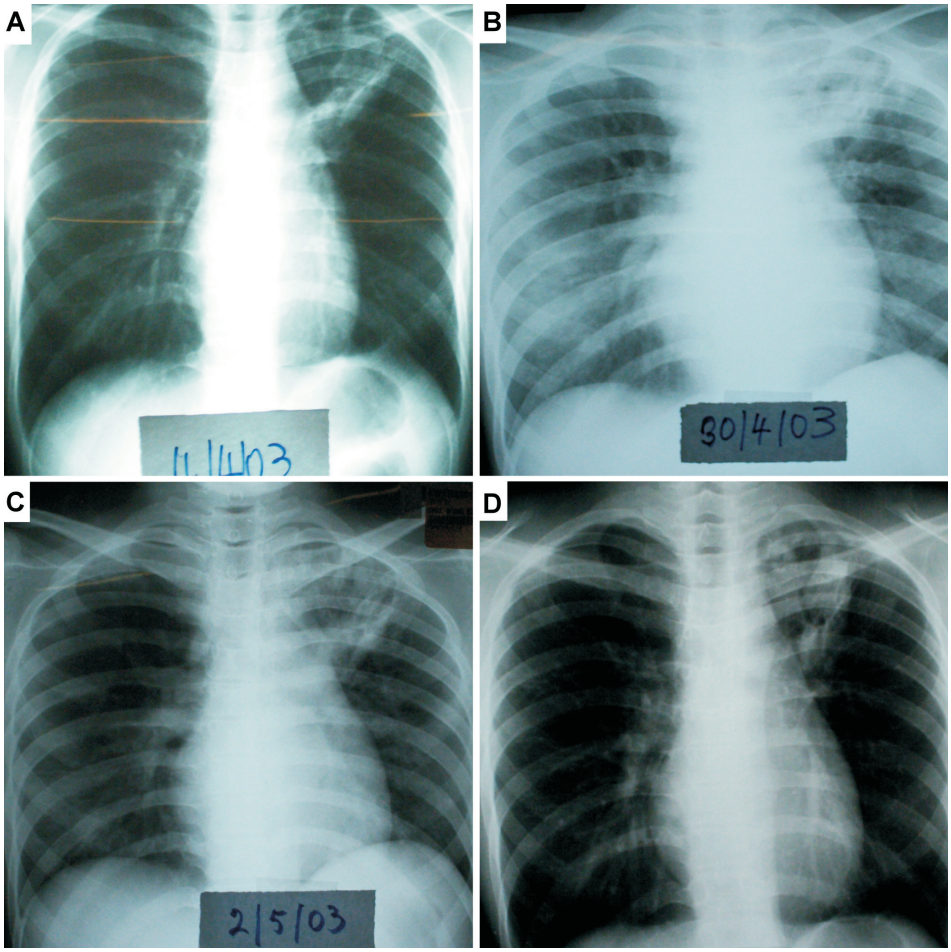

Fig. 1. (**A**) Day 1. Showing LUZ opacity with nodules and streaks. (**B**) Day 26 showing new RMZ and LMZ ground glass opacities. (**C**) Day 28 showing partial clearing of RMZ and LMZ opacities. (**D**) After 7 months LUZ showed remaining scars of tuberculosis.

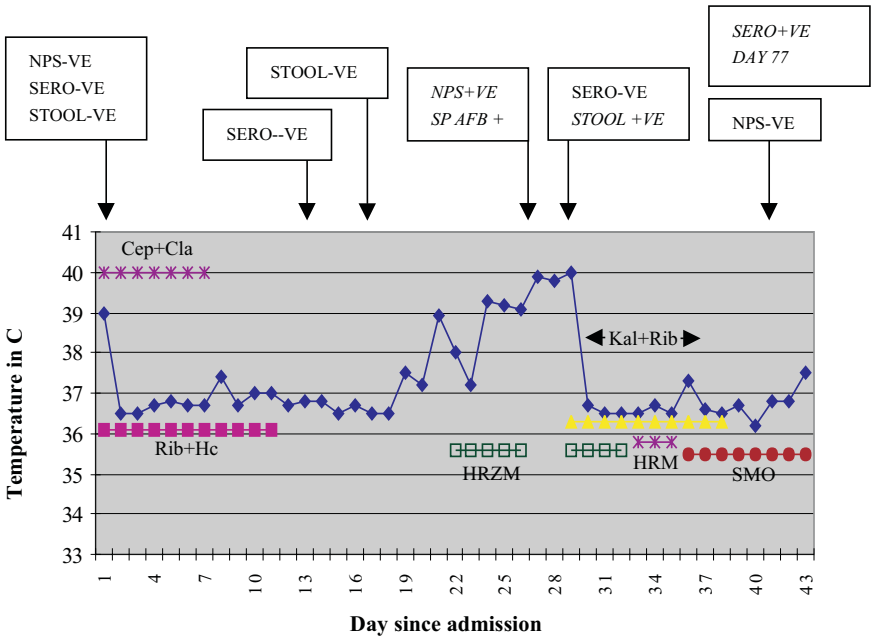

Fig. 2. The patient's stool was negative for *coronavirus* by RT-PCR on Day 56. The patient's sputum showed positive smear for acid-fast bacillus on Day 24. The specimen was identified as mycobacterium complex after culture for 9 weeks. The specimen was sensitive to isoniazid, rifamipicin, streptomycin and ethambutol. The sputum smear of the patient was converted negative at Day 103. Cep+Cla = Cephtriaxone + Clarithromycin; Rib+Hc = Ribavirin + Hydrocortisone; HRZM = INAH + rifampicin + pyrazinamide + ethambutolo; Kal+Rib = Kaletra + ribavirin; HRM = INAH + rifampicin + ethambutol; SMO = Streptomycin + ethambutol + ofloxacin; NPS-VE = Nasopharyngeal swab NEGATIVE for coronavirus using RT-PCR; NPS+VE= Nasopharyngeal swab POSITIVE for coronavirus using RT-PCR; SERO-VE = Serology NEGATIVE for coronavirus; SERO+VE = Serology POSITIVE for coronavirus; SP AFB + = Sputum Acid-fast bacillus smear positive.

was stopped. Three days later, the alanine transferase (ALT) rose to 250 IU/L. INAH and rifampicin were also stopped. Non-hepatotoxic streptomycin and ofloxacin were prescribed in addition. On the 28th day after admission, there was partial clearing of new shadows in right and left mid zones (Fig. 1C). ALT later rose to 350 IU/L. Kaletra and ribavirin were stopped. The chemotherapy prescribed was presented with the temperature chart (Fig. 2). The liver function returned to normal level on Day 52. Serology became positive on Day 77. The sputum cultured *mycobacterium tuberculosis* complex and direct smear for AFB remained persistently positive for 3 months.

Computerized tomogram (CT) of the thorax at 3 months showed small opacities at RUZ, and multiple wedged-shaped opacities at LUZ, which represented consolidation. Parts of this consolidation contained calcific foci and cavitation compatible with pulmonary tuberculosis. CXR at 7 months showed residual fibrosis in the LUZ only. The mid-zone opacities on both sides cleared up completely (Fig. 1D).

DISCUSSION

In the early days of the SARS outbreak, a 43-year-old man of Hong Kong descent, who presented with fever and extensive bi-basal infiltration, was treated as tuberculosis in Toronto.[6] He died, and autopsy diagnosed SARS. In contrast, our patient presented with fever, and infiltration at LUZ-a typical site for tuberculosis-but was misdiagnosed as SARS.

The aetiological agent of SARS is a novel *coronavirus* SARS-Co V, the incubation period of which is between 2 and 10 days.[7] Viral RNA can be detected by RT-PCR in nasopharyngeal aspirate or swab in 32% of SARS patients at Day 3, and 68% at Day 14. Viral RNA can be detected in 97% at Day 14. IgG sero-conversion occurs in 15% of patients at Day 15 and greater than 90% by Day 28.[8] The intervals are calculated from day of onset of illness.

Before admission, the patient had chills and myalgia for 2 weeks, which was longer than the incubation period of 2 to 10 days for SARS. Her presenting CXR showed shadow at LUZ, a typical site for pulmonary tuberculosis. The shadow displayed nodules and fibrosis, a typical feature of tuberculosis. Her nasopharyngeal swab and stool on Day 1 of admission and stool on Day 12 were negative by RT-PCR for *coronavirus.* The specimens would have been taken on the 14th and 26th day of onset of symptoms, respectively.[9] Serology of the patient taken on Day 1 and Day 14 of admission (14 and 28 days calculated from symptom onset) were negative. Since 68% of nasopharyngeal swabs would be positive for RT-PCR by 14 days and 90% would have sero-conversion by 28 days of symptom onset, it was highly unlikely that the patient was suffering SARS on admission.

After 19 days, high fever recurred with the appearance of new SARS-like CXR lesions. Sputum showed acid-fast bacilli. RT-PCR for *coronavirus* was repeated on Day 25, and it was positive in nasopharyngeal swab and stool. It may be argued that PCR may not be positive until the 6th day, thus the false negative result in the initial specimens. However, the recurrence of high fever, the delayed positive RT-PCR of stool and nasopharyngeal swab on Day 25, and the positive serology on as late as Day 77 from admission verified against the possibility of the presence of SARS on admission.[8]

Even in an outbreak of SARS, if the incubation period is incompatible, and if the CXR shows features of tuberculosis, supported by a negative RT-PCR, albeit in the early stage of disease, one should be on the alert for tuberculosis. The earliest feature of SARS on CXR is ground glass opacity, progressing to consolidation. Effusion is infrequent, and, even if present, is small. Cavitation is rare, and atelectasis is not a feature.[10] The serology result is usually too late to assist clinical decision. An early CT of the thorax can help to diagnose tuberculosis by providing additional information such as the 'tree-in-bud' sign. Early single isolation of the patient can avoid a hospital-acquired SARS infection.

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