Severe Acute Respiratory Syndrome and Pulmonary Tuberculosis

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In Singapore, of 236 patients with probable severe acute respiratory syndrome (SARS), 2 were coinfected with tuberculosis, a phenomenon not previously reported. The patients' tuberculosis episodes only came to light after full recovery from SARS, when they presented with persistent respiratory symptoms and/or worsening chest radiography findings.

It is well documented that certain viral infections, such as measles, have been known to aggravate pulmonary tuberculosis (TB), presumably as a result of depressed cellular immunity [1, 2]. We report what is, to our knowledge, the first 2 cases of pulmonary TB associated with the acquisition of severe acute respiratory syndrome (SARS).

Case 1. The first patient was a 54-year-old cab driver who was a chronic smoker with a history of well-controlled type 2 diabetes mellitus. He presented to Tan Tock Seng Hospital (Singapore) on 18 April 2003 (during the height of the SARS epidemic in Singapore) with fever and respiratory tract symptoms of cough and sore throat of 4 days' duration. He was later confirmed to have had direct contact with another patient with SARS shortly before the onset of symptoms.

At admission, the patient was febrile (temperature, 39°C). Findings of the remainder of the physical examination were unremarkable. Routine blood tests revealed the following: a WBC count of 6400 cells/mm^3, with 90.7% neutrophils, 6.3% lymphocytes, and 3.0% monocytes; a hemoglobin level of 12.5 g/dL; and a platelet count of 189,000 platelets/mm^3. The patient's serum sodium level was 129 mmol/L and creatinine level was 106 μmol/L (i.e., 1.2 mg/dL). The patient's serum lactate dehydrogenase level was 759 U/L. His liver function test results showed mildly elevated aspartate transaminase and gamma glutaryl transaminase levels of 46 U/L and 107 U/L, respectively. His pulse oximetry reading was 98% on room air. Chest radiography revealed consolidation in the left upper and middle zones and right upper and lower zones. The results of blood cultures for bacteria and throat swab cultures for respiratory viruses were negative. On day 7 of illness, stool and throat swab samples had negative PCR results for SARS coronavirus, and serological testing results were negative for SARS coronavirus; however, the results of tests performed on convalescent serum samples were positive for coronavirus IgG antibody at day 80 of illness. The patient recovered well with supportive management and was discharged on 27 April 2003.

The findings of a chest radiograph made on 26 May 2003 during follow-up showed improvement in the previously reported consolidation, with the exception of a persistent area of consolidation with scarring over the left midzone. A second chest radiograph in July 2003 revealed similar changes with suggestion of a new cavitation. The patient remained well throughout this period with no new respiratory or systemic symptoms, and his weight returned to prehospitalization baseline values. However, the patient developed recurrence of dry cough in September 2003, and a chest radiograph at this time revealed a worsening cavitatory lesion in the left midzone. Acid-fast bacilli (AFB) smear of induced sputum samples showed 4+ AFB, and a subsequent culture was positive for *Mycobacteria tuberculosis* complex. This patient had previously undergone an annual chest radiograph screening in September 2002 as part of his job requirement, and the chest radiograph findings were reportedly normal at that time. The patient initiated a 4-drug regimen with rifampicin, isoniazid, pyrazinamide, and ethambutol. He remains well on follow-up.

Case 2. The second patient, a 39-year-old quality surveyor, had a history of stage 1 left testicular seminoma diagnosed in 2000 and had undergone curative orchidectomy and radiotherapy in the same year. He had remained well since that time. He was a chronic smoker and had well-controlled hypertension. He was admitted to our hospital on 11 May 2003 for evaluation of fever and respiratory symptoms of cough and productive sputum of 1 week's duration. Interestingly, he represented the last probable SARS case during the SARS epidemic in Singapore, and despite extensive epidemiological investigation, he had no known contact with patients with SARS. At admission, he had a temperature of 39.1°C. Respiratory examination revealed right-sided crackles over the midzone. The results of the remainder of the physical examination were unremarkable.

Routine blood studies revealed the following: a WBC count

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of 6900 cells/mm^3, with 89% neutrophils, 9.4% lymphocytes, and 1.6% monocytes; a hemoglobin level of 13.3 g/dL; and a platelet count of 228,000 platelets/mm^3. The patient's electrolytes were normal except for a sodium level of 133 mmol/L. His serum lactate dehydrogenase level was 936 U/L. Liver function test results showed mildly elevated aspartate transaminase and gamma glutaryl transaminase levels of 36 U/L and 151 U/L, respectively. His initial pulse oximetry reading was 94% on room air. Chest radiography revealed a focus of consolidation at the right lower zone and the periphery of the right middle zone, with mild cardiomegaly.

A therapeutic trial of antibiotics including levofloxacin was initiated after appropriate cultures were performed. The patient's condition deteriorated over the next 48 h, with respiratory compromise and worsening infiltrates visible on chest radiography, and the patient was transferred to the intensive care unit (ICU) on 13 May 2003. Intravenous ceftazidime was added to the regimen to treat possible *Burkholderia pseudomallei* infection. The patient was eventually intubated on 15 May 2003 (day 11 of illness) for severe respiratory distress. A PCR of an endotracheal tube specimen was positive for SARS coronavirus, and coronavirus IgM and IgG antibodies were present in blood samples obtained at day 14 of illness. Sputum and blood cultures for bacteria were repeatedly negative. The results of serological testing for mycoplasma, chlamydia, legionella, melioidosis, HIV, and dengue virus were negative. Cultures of secretions from sputum and endotracheal tube suction were negative for respiratory viruses, and smears were negative for AFB.

On the basis of the adopted treatment for SARS at that time, intravenous immunoglobulin was initiated at 0.4 g/kg and intravenous methylprednisolone at 200 mg for 3 days from 18 to 20 May 2003, followed by intravenous hydrocortisone at 100 mg every 6 h for another 5 days. The patient made an eventual recovery and was extubated on 24 May 2003. A chest radiograph on 2 June 2003 showed marked improvement, with resolution of bilateral consolidation and with some residual linear markings in the left upper zone. There was no recent chest radiograph available from before this admission for comparison. The patient was discharged well on 6 June 2003 and was asymptomatic during follow-up on 18 July 2003. An additional chest radiograph on 21 July 2003 did not reveal any lung abnormality.

An endotracheal specimen was obtained for culture on 22 May 2003 and yielded *Mycobacteria tuberculosis* complex after 8 weeks' incubation. As far as we know, this patient had a reportedly normal chest radiograph in the year 2000, when he was initially diagnosed with testicular seminoma. The patient was recalled on 25 July 2003, and a 4-drug regimen with rifampicin, isoniazid, pyrazinamide, and ethambutol was initiated. He remains well at follow-up.

Both of these patients did not have evidence of extrapulmonary TB. It is important to note that both of our patients did not have a history of pulmonary TB and had no known contact with people with active TB, either in the hospital or in the community. They were admitted directly into the hospital's isolation facility after triage in the emergency department. The first patient did not come into contact with other patients throughout his hospitalization. The second patient was asymptomatic for TB. A search for possible cross-contamination in the ICU confirmed that there were no patients with TB or anyone suspected to have TB around him during his stay in the ICU.

Discussion. TB is the prototype of infection that requires cellular immunity [3]. Coinfection with TB and HIV is well described in the literature [4, 5]. Singapore is endemic for the tubercle bacilli, with an annual reported incidence at 42.2 cases per 100,000 population in 2002 [6]. To our knowledge, these are the first 2 reports of patients with evidence of pulmonary TB occurring with SARS or shortly after treatment for SARS. The occurrence of 2 cases of pulmonary TB in the cohort of 236 patients with SARS far exceeded the incidence in the general population.

Cui et al. [7] reported a cohort of 38 patients with SARS and found lymphopenia in 84%, T lymphopenia in 95%, and reduction in the level of CD4$^+$ T lymphocytes in 100% of patients. Both of our patients had lymphopenia that lasted throughout their hospitalization. Unfortunately, CD4$^+$ T lymphocyte levels were not evaluated at that time. We acknowledge that the presence of diabetes mellitus in the first patient and the use of high-dose methylprednisolone in the second patient might have further compromised their host immunity. However, the fact that TB was isolated from the sputum sample only 4 days after initiation of intravenous methylprednisolone argues against corticosteroids as a contributing factor for immunosuppression.

In summary, we present the cases of 2 patients with recent SARS infections who were coinfected with pulmonary TB. It is highly likely that both of our patients developed active pulmonary TB after acquiring SARS because both presented with clinical syndromes consistent with SARS that were supported by laboratory findings, and they both recovered well, with initial biochemical and radiological improvement, without anti-TB therapy. It is possible that infection with the SARS coronavirus causes a temporary suppression of cellular immunity which further predisposed our patients to aggravated reactivation or new infection with TB, much as is the case with the measles virus and HIV.

Although both patients were chronic smokers and one had diabetes mellitus (albeit well controlled) and the other received a short course of high-dose corticosteroids, we think that illness with SARS may further increase the risk of developing progressive primary or reactivation TB in excess of other existing

risk factors. Hence, in regions endemic for TB, it will be prudent for clinicians treating patients who have recovered from SARS episodes to be aware and vigilant of the possibility of coinfection with TB, especially in the presence of persistent or worsening chest infiltrates.

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Conflict of interest. All authors: No conflict.

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