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Severe Acute Respiratory Syndrome (SARS) in a Liver Transplant Recipient and Guidelines for Donor SARS Screening

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Severe acute respiratory syndrome (SARS) is a recently described infectious entity with salient features of fever, headache and malaise, with rapid progression to pneumonitis. The etiology of SARS is likely a novel coronavirus. During the winter of 2003, an outbreak of SARS involving several hospitals occurred in Toronto, Canada. We describe a patient post liver transplant who contracted SARS and died during the outbreak, with subsequent infection of family and several health-care workers. A novel coronavirus was detected in respiratory specimens by PCR. Due to the potential severity of SARS in transplant recipients and the large number of cases of SARS in the community, in order to avoid transmission of SARS from a donor, we developed guidelines for SARS screening of organ donors. A screening tool based on potential hospital SARS exposure, clinical symptoms, and epidemiological exposure was used to stratify donors as high, intermediate or low risk for SARS. As SARS spreads throughout the world, it may become an increasingly significant problem for transplant patients and programs.

Key words: Coronavirus, donor screening, severe acute respiratory syndrome

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Introduction

SARS, or severe acute respiratory syndrome, is a new clinical disease of infectious etiology that has recently been reported in the literature. Thought to have first originated in Guangdong Province in China, the illness has spread rapidly to numerous other parts of the world, including Asia, North America, and Europe (1). The World Health Organization (WHO) identifies suspected and probable SARS cases on the basis of clinical and epidemiologic case definitions (2). A suspect case includes fever with cough and either exposure to a suspect or probable case of SARS in the 10 days prior to illness onset, history of travel to an area affected by SARS, or residing in an affected area. A probable case includes the above with chest radiograph infiltrates. The incubation period ranges from 2 to 11 days, and illness typically begins with fever, headache and myalgias, which may progress to lower respiratory tract symptoms that in some cases require mechanical ventilation. The agent of SARS has been speculated to be a novel coronavirus and is likely transmitted via droplets (3–5).

As of 22 April 2003, there have been 3947 SARS cases and 229 deaths reported from 25 countries (http://www.who.int). Within Canada, there have been 324 SARS cases (probable and suspect) in 6 provinces with 14 deaths. The vast majority of these cases have occurred in the Toronto area (http://www.hc-sc.gc.ca). Epidemiological investigations have linked the Canadian outbreak to the index case of a traveler returning from Hong Kong (6). Due to the large number of SARS cases and the infection of several health care workers, a number of infection control measures were taken by Ontario Hospitals. These included strict handwashing, high filtration masks, gowns, gloves for all patient contacts, a no visitors policy, cancellation of all elective surgery, and limiting the number of active hospital employees. Infection control precautions for dealing with SARS patients are available at http://www.cdc.gov/ncidod/sars.

There have been no descriptions of SARS occurring in organ transplant recipients. To date, no reports have linked adverse events from SARS to comorbid conditions such as transplant. We report a liver transplant patient who died of SARS. Also, in the setting of a SARS outbreak in our region, we developed guidelines for screening of potential organ donors in order to avoid the risk of transmission of SARS through organ donation.

Materials and Methods

Patient data were obtained from chart review. Information about contacts was provided by the Toronto Public Health Department. Coronavirus-specific RT-PCR was performed on RNA extracted from clinical samples using the TRizol reagent (Life Technologies), as per the manufacturer’s recommendations. Reverse transcription was performed as described (7) using the primer 5′GCATAGGCGAGTGCCATC3′. This was followed by PCR using primers targeting highly conserved regions of the coronavirus pol 1b coding region, namely 5′TGATGGGATGGGACTATCCTAAGTG3′ and...
His AST was slightly elevated at 51 U/L but ALT and with a lymphocyte count of 0.2 bil/L; platelets were 74 bil/L. globin was 87 g/L; total white blood cell count was 2.0 bil/L.

Initial laboratory investigations were as follows: hemoglobin, and multisystem organ failure. Death occurred on day 18 of his illness.

Case Report

A 74-year-old male was admitted to the Intensive Care Unit of our hospital with respiratory failure and was diagnosed with SARS. He was 9.5 years post orthotopic liver transplant for alcoholic cirrhosis. His current immunosuppression was cyclosporin 100 mg twice daily and prednisone 5 mg/day. His other medication included insulin and trimethoprim/sulfamethoxazole prophylaxis. The patient visited Hospital A for an outpatient podiatry appointment 5 days prior to the onset of his illness. He spent most of the day in the hospital but no specific exposure to an ill person was recounted. Hospital A was subsequently quarantined by the Public Health authority due to an unrecognized exposure and outbreak of SARS in this facility. Numerous people, of whom the majority were health care workers, developed SARS at this facility. Approximately 5 days after his outpatient appointment at Hospital A, the patient developed high fever, chills, nonproductive cough, and myalgias. He subsequently developed progressive shortness of breath and, after visiting his family physician, presented again to the Hospital A emergency. Due to impending respiratory failure, he was immediately transferred to the intensive care unit of another facility (Hospital B). In Hospital B, he required mechanical ventilation and was commenced on Ceftriaxone and levofloxacin for community-acquired pneumonia. Full isolation precautions were not used at this time as SARS was not suspected. Within 24 h, since he was a transplant patient, he was transferred to our facility’s intensive care unit for ongoing care. On arrival at our hospital, the patient was placed in negative-pressure isolation with full precautions due to the suspicion of SARS.

On admission, he was febrile (38.8°C) and hypotensive, requiring inotropic therapy for blood pressure support. His initial laboratory investigations were as follows: hemoglobin was 87 g/L; total white blood cell count was 2.0 bil/L; platelets were 74 bil/L. His AST was slightly elevated at 51 U/L but ALT and bilirubin were normal. His arterial blood gas on 100% FiO2 was pH 7.45, PO2 57 mmHg, PCO2 34 mmHg. Chest radiograph demonstrated bilateral airspace and interstitial disease, more prominent on the right side (Figure 1). Investigations including a broncho-alveolar lavage (BAL) were performed and he was treated with ceftriaxone and azithromycin. In addition, he received ribavirin 2g intravenously loading and 1g every 6h intravenously for presumptive SARS. His cyclosporin was discontinued. The hospital course was complicated by progressive hypoxemia, and multisystem organ failure. Death occurred on day 18 of his illness.

Microbiology investigation

A BAL at the time of admission was negative for routine bacterial, fungal and mycobacterial stains and culture. Direct fluorescent antibody stains of BAL fluid were negative for influenza, parainfluenza, respiratory syncytial virus and adenovirus. Culture was negative for routine respiratory viruses, cytomegalovirus, and Legionella. Special stains for Legionella and Pneumocystis were negative, as were PCR for Mycoplasma and Chlamydia. CMV antigenemia, and urine Legionella antigen were negative.

A coronavirus-specific RT-PCR was performed on BAL fluid and was positive. We obtained an amplicon of the expected size of 216bp, which was sequenced. The sequence was identical to that found in another patient with SARS reported previously (6). The sequence internal to the primers was 100% homologous to the expected segment of the pol 1b coding region of the SARS coronavirus complete sequence from a Canadian isolate (BCCA Genome Science Center, British Columbia; GenBank accession number AY274119). We also performed RT-PCR for coronaviruses on plasma samples and peripheral blood mononuclear cells purified by buffy coat obtained on the first and fifth day of hospitalization, but coronavirus was not detected in these samples.

Contact tracing

The patient had not been in isolation until reaching our facility. During the course of his illness, several persons were exposed. These included his wife and two children, family physician (FP), FP’s office staff and several other patients in the waiting room. At Hospital A, due to a large outbreak, it was not possible to determine those exposed as a direct result of this patient as several other SARS exposures had occurred at the same time. However, hundreds of individuals from this hospital were placed in
isolation. The patient had two visitors during his emergency visit at Hospital A. Exposure also occurred in 11 individuals involved in transfer of the patient to hospital B and 68 staff at Hospital B, primarily those involved in the patient’s ICU care. Subsequent illness compatible with suspect or probable SARS occurred in 10 persons: the patient’s wife, family physician, two visitors at Hospital A, and six staff at Hospital B, resulting in one death due to SARS. This is likely an underestimate as we were unable to determine how many at Hospital A were exposed specifically due to this patient.

**Guidelines for donor screening**

Due to this outbreak of SARS in the greater Toronto area, all transplant programs in the city were temporarily closed. Prior to re-starting the transplant program, concern arose about unrecognized SARS in potential cadaveric organ donors, with the largely unknown potential for spread to multiple recipients. A donor may be at risk of incubating SARS or have active SARS due to exposure in a health care facility or specific epidemiological exposure within the community. Therefore, a donor SARS screening tool was developed and is shown in Figure 2. The screening tool is based on information regarding potential hospital exposure, clinical symptoms, and contact history. In section A, the category of the donor institution is listed. Hospital categorization is based on Canada’s Ministry of Health guidelines and ranges from category 0 (no SARS cases in institution) to category 3 (SARS exposure and further spread from the exposed person to others) (Figure 2). This information is readily available from the infection control practitioner at a given institution. Section B is based on determining if any clinical or radiological evidence of SARS is present. Section C evaluates contact exposure to either someone with SARS (suspected or probable) or due to travel to areas with high risk of SARS exposure based on current governmental travel advisories (available at www.cdc.gov in the United States). With the above information, donors can be classified into high risk, intermediate (or indeterminate) risk, or low risk, based on categories shown at the bottom of Figure 2. Since implementation of the screening tool, our practice has been to accept low-risk donors and intermediate-risk donors, and generally exclude high-risk donors. This is done in discussion with the transplant team and the recipient. The screening tool can be modified for living related donors by labeling section A as category 0 if the donor has not visited any hospital within the previous 10 days. We have also implemented a modified version of this screening tool for potential recipients, to ensure that a patient incubating SARS is not inadvertently transplanted.

**Discussion**

Transplant recipients are exposed to several emerging new illnesses, such as West Nile Virus, Chagas Disease and now SARS. We describe the first reported case of SARS in a solid organ transplant recipient. There are several factors that support the diagnosis of SARS in this patient. First, the patient’s symptoms were compatible with those described in the literature for SARS and with the current WHO guidelines for probable SARS (8). The most common presenting symptoms reported in the literature are fever (100% of cases), chills (73.2%), headache (55.8%), and myalgias (60.9%) (9). Patients may then develop cough and shortness of breath, with pulmonary infiltrates. In addition, laboratory abnormalities including lymphopenia, thrombocytopenia and mild elevations of aminotransferase levels have been described in many SARS patients and were seen in our patient (6,9). Other epidemiological evidence that is consistent with the diagnosis of SARS is the subsequent spread of infection to numerous contacts, including healthcare workers who subsequently developed illnesses fitting the WHO case definition for suspect or probable SARS. Our patient died, despite therapy with antibiotics, ribavirin and a prompt reduction in immunosuppression. Similar therapy with antibiotic coverage for atypical pneumonia and ribavirin for antiviral effect has been commonly used for treatment of SARS. Recently, steroid therapy in conjunction with ribavirin has been proposed. However, the efficacy of all such treatments is largely unknown (6,9). At the time of this writing, there are no published or reported data on other therapies.

Recently a novel coronavirus has been implicated in the etiology and pathogenesis of SARS (3–5). The implicated coronavirus has now been sequenced and the full sequence is available through GenBank (accession number AY274119). We were also able to amplify a segment of the polymerase gene of a coronavirus from BAL fluid of our patient by RT-PCR, the sequence of which was completely homologous to the sequence of the SARS coronavirus. This finding strongly supports the diagnosis of SARS and is consistent with viral investigations in other groups of patients with probable SARS that point to a new coronavirus as the most likely etiology of SARS (3–5). Coronaviral RNA was detected in 22 of 44 nasopharyngeal samples from SARS patients in the Hong Kong outbreak (3). Additionally, all 32 patients in whom acute and convalescent sera were available showed a greater than 4-fold rise in antibody titer to the virus. Although a detailed discussion of laboratory testing for the SARS coronavirus is beyond the scope of this study, diagnostic evaluation for SARS is a rapidly evolving field. SARS virus specific serology with acute and convalescent titers can be diagnostic, but its utility in assessing acute illness may be limited due to delays in seroconversion. RT-PCR is a more rapid method, and may prove more useful for diagnosis of acute illness. However, the optimal method and its sensitivity in clinical specimens are not known (http://www.cdc.gov). Human metapneumovirus, as a single agent or in conjunction with coronavirus, has also been isolated from patients with SARS in
DONOR SARS SCREENING TOOL

SECTION A: Donor Hospital Category

- Category 0  Hospital has no known cases of SARS.
- Category 1  SARS cases in hospital but no unprotected SARS exposure in either staff or patients.
- Category 2  Any unprotected SARS exposure within the last 10 days with or without transmission to staff or patients
- Category 3  Unprotected SARS exposure plus transmission from exposed person to others in the hospital

If the donor has entered any other institution in a higher category in the last 10 days mark that category instead.

SECTION B: Clinical evaluation: Has the donor had any of the following symptoms in the past 10 days (unexplained symptoms only)

| Symptom                          | Yes | No |
|----------------------------------|-----|----|
| Fever (≥38 °C)                   |     |    |
| Flu-like symptoms (Myalgias, headache) | Yes | No |
| Cough                           | Yes | No |
| Shortness of Breath             | Yes | No |
| CXR showing infiltrates         | Yes | No |

SECTION C: Contact history

Has the donor had contact with a person with or under investigation for SARS in the last 10 days?  □ Yes  □ No

Has the donor traveled to an area listed in the current travel advisory in the last 10 days.  □ Yes  □ No

(Based on most recent SARS travel advisory at http://www.sars.gc.ca)

High Risk donor: ANY of
- Section A category 3 exposure or
- Section B any Yes answer AND Section A Category 2 exposure or
- Section C any Yes answer

Low Risk donor: ALL of
- Section A category 0 or 1 exposure
- Section B all no answers
- Section C all no answers

Intermediate or Indeterminate Risk donor: any other combination

Figure 2: A SARS donor-screening tool. SARS travel advisory for United States available at http://www.cdc.gov.

the Canadian outbreak (6), although in more recent reports evidence for this virus as an agent for SARS is lacking (3–5). 

There are a number of implications for the emergence of SARS in transplantation. First, the post-transplant patient on immunosuppression may be more likely to develop
symptomatic SARS if exposed. Also, although difficult to determine from a single case report, it is likely that more severe disease with a higher mortality rate may be seen in transplant patients. The overall mortality from SARS has been reported at 3–4% (1). Multivariate analyses of the outbreak in Hong Kong have determined advanced age to be predictive of an adverse outcome but have not found any comorbid conditions to be predictive of death or ICU admission (9). Our patient was elderly and also had diabetes, which may have contributed to the poor outcome. However, data from other respiratory viruses do suggest greater morbidity and mortality in transplant recipients (10).

In addition, it is possible that transplant recipients with SARS may shed large amounts of virus for prolonged periods of time, resulting in spread to a greater number of contacts, i.e. so-called ‘super-spreaders’. ‘Super-spreaders’ have recently been identified in certain SARS outbreaks in Hong Kong (9) and Singapore (http://www.who.int) and may in part be responsible for the rapid spread of SARS across the world. This may lead to stricter infection control precautions for this group of patients.

Due to the outbreak of SARS in our community, all the transplant programs in the Greater Toronto Area (Hospital For Sick Children, St Michael’s Hospital and the University Health Network) were temporarily closed. This was due to concerns regarding recipient safety in the hospital and ensuring that donors were safe to use. It is likely that use of an organ from a donor with active or incubation SARS could potentially infect organ recipients. The highest likelihood of this may be in the lung transplant setting since this appears to be the primary site of disease. We did not find evidence of viremia in our patient, suggesting that viremia may be short lived or of low-titer. However, other recent studies have found detectable coronavirus in serum, sputum, and stool and a variety of tissues including lung, kidney and bone marrow from patients with SARS (4,5). Therefore, it is likely that transmission of SARS through nonpulmonary organ transplantation is also possible. Additionally, the finding of virus in serum implies the potential for viral transmission via blood products. With the lack of rapid diagnostic techniques for SARS, a clinical screening tool may be useful in risk-stratifying donors for the potential of disease transmission. Even with the use of a rapid clinical test such as RT-PCR, donors incubating SARS or with early SARS may be missed. We have therefore developed a donor screening tool for SARS risk stratification. Although just recently initiated, we believe it allows clinicians and patients to formulate a more structured understanding of the potential risks for SARS in a donor. Based on this screening tool, donors can be classified into high, intermediate and low risk. High-risk donors are generally excluded and low-risk donors are used. Intermediate-risk donors are further discussed on a case-by-case basis to reach a decision about use of organs. A slightly modified screening tool is used on potential recipients to avoid inadvertently transplanting someone who may be incubating SARS. As further experience and validation are gained with this screening tool, modifications will undoubtedly be made. Similarly, as more information is gained about the etiology and epidemiology of SARS, and as diagnostic tests are developed further, screening for SARS will continue to evolve. As SARS continues to spread around the world, it is likely that more and more transplant programs will be faced with similar issues.

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