

One nosocomial cluster following with a familial cluster of COVID-19 cases: the potential transmission risk in patients with negative swab tests

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Research article

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Abstract

Background

In December 2019, a cluster of cases of acute respiratory illness, novel coronavirus-infected pneumonia, occurred in Wuhan, Hubei Province, China. Health care workers exposure to a high density of patients are at extremely high risk of becoming infected at the early outbreak of this disease for not realizing the fact of human-to-human transmission among close contacts at that time. The false-negative nasopharyngeal swabs of SARS-CoV-2 caused the delayed diagnosis of COVID-19. The nosocomial transmission of SARS-CoV-2 in negative nasopharyngeal swabs cases were not reported previously. We wish to alert the potential transmission risk in COVID-19 patients with negative swab tests to the clinicians and stress the role of serological detection of anti-SARS-CoV-2.

Methods

This study evaluated a total of 6 cases and four of them were health care providers who worked in the same ward. All epidemiological and clinical information was collected. Respiratory samples of the patients were tested for influenza A, influenza B and respiratory syncytial virus (RSV) RNA. The reverse-transcription–polymerase chain reaction (RT-PCR) assay of SARS-CoV-2 RNA was conducted and serological detection of anti-SARS-CoV-2-IgG/IgM is performed by chemiluminescence immunoassay kit.

Results

We reported two related clusters of COVID-19 cases. The first cluster is a nosocomial infection of four health care providers at early January in one ward of university hospital. One of them made sequential familial cluster of infection. For total six cases, four of them (66.7%) showed negative RNA of SARS-CoV-2 by nasopharyngeal swabs. All patients received either self-quarantined at home or were admitted to hospital for isolated treatment. All recovered and had anti-SARS-CoV-2 IgG and/or IgM positive (100%) for serological detection of SARS-CoV-2 at recovery stage.

Conclusions

Our study provides a cautionary warning that negative results of nasopharyngeal swabs of suspected SARS-CoV-2 infection can increase the risk of nosocomial infection among health care providers. Serologic detection for anti-SARS-CoV-2 IgG and/or IgM is an important test in the assistant diagnosis of COVID-19.

Background

In December 2019, a cluster of cases of acute respiratory illness, novel coronavirus-infected pneumonia occurred in Wuhan, Hubei Province, China^{1,2}. As of March 1, 2020, there have been over 80000 confirmed cases of coronavirus disease 2019 (COVID-19) with over 2800 deaths globally, the majority in China³. This outbreak was confirmed to be caused by severe acute respiratory syndrome coronavirus 2 (SARS-

CoV-2), which is in the same family as the viruses responsible for severe acute respiratory syndrome (SARS)⁴. Most patients with COVID-19 presented with fever, dry cough, dyspnea with bilateral ground-glass opacities in the peripheral areas under the pleura on chest computed tomography (CT) scans⁵. Health care providers' exposure to a high density of patients places them at extremely high risk of becoming infected, especially during January, when many did not realize that human-to-human transmission among close contacts was possible⁶. Nasopharyngeal swabs of SARS-CoV-2 analyzed using reverse-transcription–polymerase chain reaction (RT-PCR) were the gold-standard diagnostic test for COVID-19⁷. However, some patients with typical chest CT findings may present with repeated negative RT-PCR tests for SARS-CoV-2⁸. Patients with false-negative RT-PCR swab results can delay the diagnosis and hence increase the risk of disease transmission. Early diagnosis of COVID-19 is crucial for disease treatment and control so any suspected COVID-19 cases with false-negative RT-PCR swab results needs to be critically focused. The nosocomial transmission of SARS-CoV-2 in negative nasopharyngeal swabs cases were not reported previously. Here, we report a cluster nosocomial infection of four cases in early January in one ward of one university hospital. One of the four cases made sequential familial cluster of infection. For total six cases, four of them (66.7%) showed negative RT-PCR results for SARS-CoV-2. When the serological detection can be carried out in Wuhan in late February, all cases in this study performed anti-SARS-CoV-2 IgG and/or IgM detection of SARS-CoV-2 at recovery stage. The purpose of this study was to review the potential for human-to-human transmission from people with negative nasopharyngeal swabs and discuss the future application of serological detection of anti-SARS-CoV-2.

Methods

This study evaluated a total of 6 cases and four of them were health care providers who worked in the same ward. We designated cases of health care providers from 1 to 4 according to the chronological order of the disease onset. We defined the first day of symptom onset as day 1(d1). Case 3 included a nurse with her two family members who lived in a same household. The timeline of illness onset and diagnostic information of nosocomial and following familial cluster cases were clearly depicted in Fig. 1.

Respiratory samples of the patients were tested for influenza A, influenza B and respiratory syncytial virus (RSV) RNA by Xpress Flu/RSV Assay (Cepheid, USA) using GeneXpert Dx System (Cepheid, USA). RNA was extracted from oropharyngeal swabs of patients using the respiratory sample RNA isolation kit. The reverse-transcription–polymerase chain reaction (RT-PCR) assay (Shanghai Huirui Biotechnology Co.,Ltd., China) of SARS-CoV-2 RNA was conducted to amplified and tested two target genes including open reading frame1ab and nucleocapsid protein. Serological detection of anti-SARS-CoV-2-IgG/IgM is performed by chemiluminescence immunoassay kit (Snibe Diagnostic, China); the results less than 0.90 AU/mL defines negative results; the results between 0.90 ~ 1.10 AU/mL defines suspicious positive; the results greater than 1.10 AU/mL defines positive results.

Results

Nosocomial cluster of infection

The first patient (case 1) is a 46-year-old female nurse with no significant medical history. She presented with 2 days of sore throat and dry cough starting on January 1. Then, she gradually developed mild fever (37.8°C) two days later, and her symptoms were relieved by nonsteroidal anti-inflammatory drugs. She took oseltamivir (75 mg) orally twice a day for five days, but she had a fever again (37.5°C to 38.5°C) and felt shortness of breath after general physical activity. Routine blood testing showed normal white blood cell (WBC) count ($5.08 \times 10^9/L$) with lower lymphocyte counts ($1.06 \times 10^9/L$). High-sensitivity C-reactive protein (hsCRP) test results were within the normal ranges (0.5 mg/L, normal <8.0 mg/L). Throat swabs were negative results for influenza A, influenza B and respiratory syncytial virus. She had chest CT with multiple ground glass-like-lung lesions indicative of viral pneumonia on d10 (Figure 2). Nasopharyngeal and throat swabs for SARS-CoV-2 were performed twice but negative for SARS-CoV-2 RNA under RT-PCR. As a suspicious case of COVID-19, she was self-quarantined at home from d18 (January 18). Based on the established therapeutic and triage strategy of Wuhan Union Hospital⁹, she was treated with oral of 200mg arbidol three times a day and 0.4 moxifloxacin once daily for 10 days. Her symptoms gradually resolved and repeat chest CT showed absorbance of lesions after 4 weeks (Figure 2). She returned for follow-up two weeks later and tested positive for anti-SARS-CoV-2 IgM and IgG under serological detection at recovery stage. She now remains well and symptom free.

Cases 2 to 4 worked in the same ward with case 1. Case 2 was a 33-year-old male surgeon with no significant medical history. He presented with mild fever (37.8 °C), fatigue and muscle soreness on January 8. He had typical changes in lymphocyte counts. His chest CT on d4 showed multiple ground glass-like lung lesions (Figure 2). The nucleic acid tests were negative for SARS-CoV-2 RNA twice. He was self-quarantined at home and treated with 300mg intravenous ribavirin for 7 days, along with oral of 200mg arbidol three times a day and 0.4 moxifloxacin for 10 days. Absorbance of glass-like lung lesions in chest CT was visible one week later (Figure 2). He showed positive anti-IgG for serological detection of SARS-CoV-2 and confirmed previous infection.

Case 3 was a 54-year-old female nurse with a 10-years history of primary hypertension. She presented with fatigue and diarrhea starting January 8. She was confirmed to have COVID-19 with positive SARS-CoV-2 RNA and typical chest CT findings on January 18 (Figure 2). She was then admitted to hospital for isolated treatment. After supportive care, antiviral drugs (arbidol) and intravenous dexamethasone, she soon recovered, with chest CT absorbance and cessation of symptoms after six days of hospitalization. The SARS-CoV-2 RNA of the nasal swabs was not detected after treatment. She showed positive anti-IgM/IgG for serological detection of SARS-CoV-2 at recovery stage.

Case 4 is a 31-year-old female nurse with no significant medical history. She presented with fatigue and dry cough since January 18. She had typical chest CT findings (Figure 2) with WBC change and confirmed COVID-19 diagnosis on d8 (January 26) with positive SARS-CoV-2 RNA by nasal swab. She was admitted to the hospital for isolated treatment when confirmed. After supportive care, antiviral drugs (arbidol), intravenous antibiotics (moxifloxacin) and dexamethasone, she recovered with chest CT

absorbance and cessation of symptoms after 25 days of hospitalization. No SARS-CoV-2 was detected in a nasal swab after treatment. She showed positive anti-IgM and IgG for serological detection of SARS-CoV-2. The clinical and laboratory examination results of this cluster SARS-CoV-2 nosocomial infection are outlined in Table 1.

Familial cluster of infection following the first cluster

For case 3, her 59-year old husband and 29-year old daughter who lived in the same household with case 3 were presented respiratory symptoms several days later, but both were negative nasopharyngeal swab tests of SARS-CoV-2 RNA. As a highly suspicious cases due to the close contact of case 3 and their typical chest CT findings (Figure 2), they received isolated treatment soon. Both were recovered after 13 days of hospitalization. Both had positive anti-IgG for serological detection and proved their previous SARS-CoV-2 infection. For the other three health care providers, no familial cases of SARS-CoV-2 infection were identified. The clinical and laboratory examination results of this sequential familial cluster are outlined in Table 1.

Discussion

In this paper, we evaluated two related clusters with SARS-CoV-2 infection as early as January 1. This is an early cluster of nosocomial outbreaks of COVID-19 among health care providers in one ward. All patients presented typical clinical symptoms and chest CT findings of COVID-19 from the first scan. In early January, the lack of attention paid to human-to-human transmission made nosocomial infection more likely¹. So far more than 1,700 bedside clinicians have been confirmed infected¹⁰. From retrospective review of our cases, although the first case had negative nasopharyngeal and throat swab results, she and later case 2 still capable of transmitting the virus to other coworkers and/or family members who live in the same household. Due to the inadequate medical beds at the increasing outbreak period of this disease, some suspicious cases with negative results of nasopharyngeal were suggested to receive the isolated home care. The reported familial cluster cases^{11,12} and our study showed that isolated home care is not the ideal plan and should be cautious used in other outbreak regions around world. In addition, the review of these cases suggested that the nosocomial infection has occurred in this ward as early as January 1, but no effective measures to prevent the nosocomial outbreak were taken at that time. Most people including health care providers mistook their symptoms for seasonal influenza.

Swab tests for SARS-CoV-2 RNA by RT-PCR assay plays a vital role in determining hospitalization and isolation for individual patients. Currently, there is a strong debate that whether negative swab tests with typical clinical and CT manifestation should be considered clinically confirmed cases and be placed under quarantine⁸. Some argue that chest CT had higher sensitivity for diagnosis of COVID-19 as compared with initial RT-PCR from swab samples in the epidemic area of China¹³ and should replace the RT-PCR from swab samples. Insufficient viral load and/or swab location cause numerous false-negative results, especially in Wuhan, the epicenter of COVID-19 outbreak. In the fifth version of new coronavirus pneumonia prevention and control program issued by the Chinese National Health Commission, these

groups of patients were included as clinically confirmed cases¹⁴. Later, the sixth version of this guideline⁷, swab test for SARS-CoV-2 RNA was again the most important tests. Among our cases, 66.7% had negative results in nasopharyngeal swab and there was considerable risk of disease spread from hospital to community. All cases showed positive anti-IgG and/or IgM SARS-CoV-2 during the recovery stage, indicating the importance of this test. We, therefore, recommend adding serologic detection to the repertoire of diagnostic processes for COVID-19. Since most hospitals only had ability to carry on serologic test in the middle or late February. It can be broadly used for the rapid screening of patients in non-fever or fever clinics in any outbreak places, including symptomatic or asymptomatic SARS-CoV-2 carriers, in hospitals, clinics, and test laboratories¹⁵. Since all the cases in this study showed positive results after 30 days of first swab, the sensitivity and specificity at earlier stage should be investigated as soon as possible.

Conclusions

Our study provides a cautionary warning that negative results of nasopharyngeal swabs of suspected SARS-CoV-2 infection can increase the risk of nosocomial infection among health care providers. Serologic detection for anti-SARS-CoV-2 IgG and/or IgM is an important test in the assistant diagnosis of COVID-19. It can help doctors to confirm diagnosis of COVID-19 for suspected cases and may be incorporated into revised diagnostic criteria soon.

Declarations

Abbreviations

COVID-19: Coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome corona virus 2; SARS: severe acute respiratory syndrome; RT-PCR: reverse-transcription–polymerase chain reaction; CT: computed tomography

Ethics approval and consent to participate

This study was approved by the Medical ethics committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology.

Consent for publication

All patients gave written consent for their clinical details along with any identifying images to be published in this study. A copy of the written consent form is available for the journal, if requested.

Availability of data and materials

The data supporting the findings of the article is available from the corresponding author by request

Competing interests

All authors listed above have no relations with industry or any conflicts of interest to declare.

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Authors' contributions

GC, JW and LM conceived the study designed the study. ST, GC and LM supervised the overall study. DY and WS collected specimen. DY, WS and GC collected clinical data and CT images. RW took care of the patients. CL did the RT-PCR. HW did the serological tests and analyzed the data. JW and GC searched the literatures. JW wrote the manuscript. LM revised the manuscript.

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Table

Due to technical limitations, Table 1 is only available for download from the Supplementary Files section.

Figures

Figure 3

The representative Chest CT imaging of case 1 to case 4 at early and recovery stage. All cases at diagnosis showed multi-focal ground glass-like lung lesions compatible with viral pneumonia.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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