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Original Article

Nosocomial Outbreak of COVID-19 in a Hematologic Ward

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) outbreaks occur in hospitals in many parts of the world. In hospital settings, the possibility of airborne transmission needs to be investigated thoroughly.
Materials and Methods: There was a nosocomial outbreak of COVID-19 in a hematologic ward in a tertiary hospital, Seoul, Korea. We found 11 patients and guardians with COVID-19 through vigorous contact tracing and closed-circuit television monitoring. We found one patient who probably had acquired COVID-19 through airborne-transmission. We performed airflow investigation with simulation software, whole-genome sequencing of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
Results: Of the nine individuals with COVID-19 who had been in the hematologic ward, six stayed in one multi-patient room (Room 36), and other three stayed in different rooms (Room 1, 34, 35). Guardian in room 35 was close contact to cases in room 36, and patient in room 34 used the shared bathroom for teeth brushing 40 minutes after index used. Airflow simulation revealed that air was spread from the bathroom to the adjacent room 1 while patient in room 1 did not used the shared bathroom. Airflow was associated with poor ventilation in shared bathroom due to dysfunctioning air-exhaust, grill on the door of shared bathroom and the unintended negative pressure of adjacent room.
Conclusion: Transmission of SARS-CoV-2 in the hematologic ward occurred rapidly in the multi-patient room and shared bathroom settings. In addition, there was a case of possible airborne transmission due to unexpected airflow.

Keywords: SARS-CoV-2; COVID-19; Hematologic malignancy; Multi-patient room; Airborne transmission

INTRODUCTION

Nosocomial severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can occur in hospitals. SARS-CoV-2 infection in hospitalized patients with underlying disease is associated with a poor prognosis, and rapid SARS-CoV-2 transmission makes containment of

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the outbreak challenging. In addition, there is growing evidence for airborne-transmission of SARS-CoV-2 [1-4] and previous studies suggest that thorough investigation should be performed including the possibility of airborne-transmission [5-7].

We recently experienced a nosocomial outbreak in a hematologic ward in a tertiary care hospital. Our unique experience regarding control of the outbreak may provide crucial information on the risk of transmission in multi-patient rooms, and the possible airborne transmission from a shared bathroom to an adjacent room. We herein describe the outbreak investigation with containment measures in detail.

MATERIALS AND METHODS

1. Setting

We experienced coronavirus disease 2019 (COVID-19) outbreak in a hematology unit in Asan Medical Center, a 2,700-bed tertiary care center in Seoul, Korea during September 2020. The hematologic ward was divided into 16 rooms. Eight were individual positive pressure rooms reserved for hematopoietic stem cell transplantation, equipped with high-efficiency particulate air filters, and the remaining eight with ambient air were rooms for patients with hematologic malignancy. The latter eight rooms were where the outbreak occurred; four were six-patient rooms, two were two-patient rooms, and two were single-patient rooms. The ward had two shared bathrooms containing a shower room and toilet separated according to sex. The shared male bathroom was made built by splitting Room 1 into two entities. There was a shower booth and toilet in the shared male bathroom, with a direct air supply in the toilet, and an air exhaust in the shower booth. The floor plan of the ward is shown in **Fig. 1A**.

2. Transmission route investigation and infection control

After the first case of COVID-19 had been confirmed, patients were admitted to a negative-pressure isolation room, and deep terminal cleaning using quaternary ammonium compounds

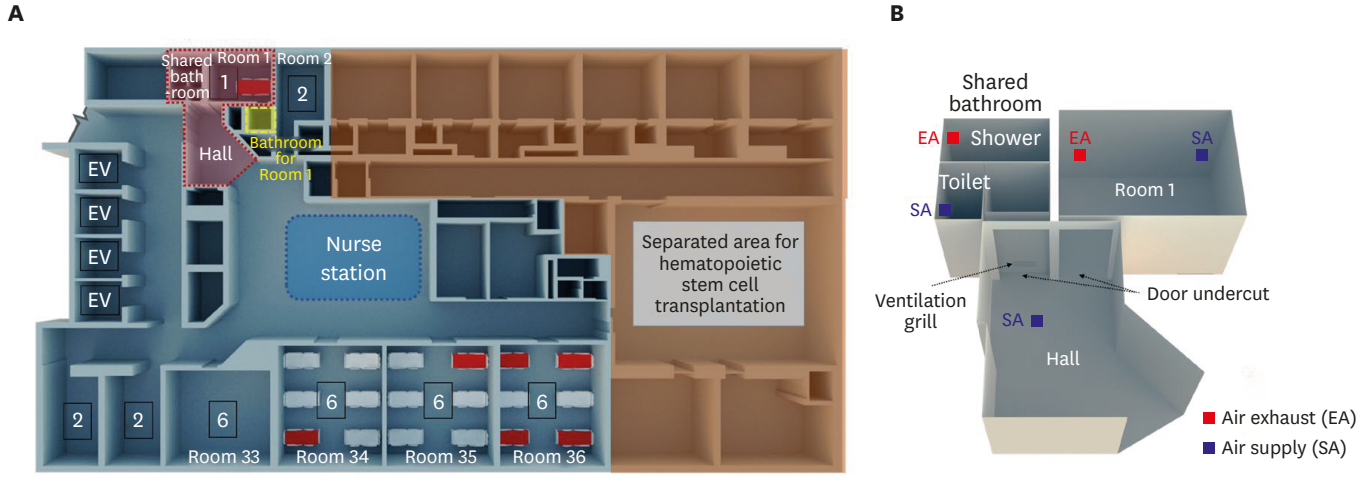

Figure 1. Floor plan of the entire hematologic ward (A) and floor plan of the shared shower room and Room 1 (B). The red box indicates the beds of patients with COVID-19.
COVID-19, coronavirus disease 2019.

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Conflicts of interest

No conflicts of interest.

Author Contributions

Conceptualization: JJ, SHK. Data curation: JJ, JL. Funding Acquisition: MSP, SHK. Investigation: JJ, JL, SJ, YJL, SHK, MJH, EOK. Methodology: JJ, JL, SJ, SB, JYK, HHC. Software: JL, SJ. Validation: JYB, CK, MSP. Visualization: JJ, JL, SJ. Writing - original draft: JJ, JL, SJ. Writing - review & editing: MS, MSP, SHK.

was performed across the hematologic ward. We reviewed the closed-circuit television (CCTV) footage to identify patient contacts, which included other patients, guardians, visitors, and health care workers (HCWs) who had previously stayed at or visited the ward. All contacts were interviewed and categorized according to the nature of their activity, duration of exposure, and the personal protective equipment (PPE) worn at the time of exposure.

Close contacts were defined as patients or guardians who shared the same room with the case patient, or those who were nearby (<2 meters) for >3 minutes while not wearing masks. Casual contacts were defined as those who did not meet the close contact criteria but had possible temporal or spatial contact with the confirmed patient. HCWs were considered close contacts if they had direct contact with the index patient without appropriate PPE (N95 or FFP2 equivalent respirator, face shield/goggles, gown, and gloves).

SARS-CoV-2 polymerase chain reaction (PCR) was carried out in nasopharyngeal swab samples and sputum, if available. The Allplex™ 2019-nCoV kit for SARS-CoV-2 genes (Seegene, Seoul, Korea) was used for PCR.

3. Whole-genome sequencing

To determine the viral genomic sequences from the original sample, viral RNA was extracted using a QIAamp viral RNA Mini Kit (Qiagen, Hilden, Germany). To isolate pure SARS-CoV-2 RNA only, human ribosomal RNA was depleted using the NEBNext rRNA Depletion Kit (New England Biolabs, Ipswich, MA, USA). Library preparations were performed using the Truseq RNA sample prep kit v2 (Illumina, San Diego, CA, USA) protocol. The enriched libraries were quantified using the Kapa Library Quantification Kit (Roche, Basel, Switzerland), and all sequencing described in this study was performed using the Miseq platform (Illumina, USA) with Miseq reagent kit v2 (300 cycles) (Illumina, USA). Sequencing analysis was performed using a CLC Genomics Workbench 10 (QIAGEN, Hilden, Germany). Base-called reads in FASTQ were trimmed and mapped to a reference sequence (NCBI Reference: NC_045512).

4. Airflow simulation

Airflow simulation was conducted to observe the possibility of airborne transmission during the visit of Case 6 to the bathroom, which was adjacent to Room 1 (**Fig. 1B**). The simulation was carried out using the conventional computational fluid dynamics (CFD) program STAR-CCM+ ver.2020 (Siemens, Munich, Germany). Room 1, the shared bathroom, and the adjacent hall were modeled to scale. The hall was partially modeled for simulation efficiency, and the ventilation grill was placed on the bottom side of the bathroom door. The door undercut was modeled on both the bathroom and Room 1 door. Approximately 0.5 million trimmer meshes were created in the simulation domain and meshes were densely created near doors and diffusers to observe accurate contaminant dispersion. The supply and exhaust air volume of diffusers used in the simulation were measured with the airflow meter (testo 417 and flow hood). The realizable k-ε model was used for the turbulence model. In the simulation scenario, the contaminant was released from the toilet for 11 minutes to represent Case 6's time spent there. After 31 minutes, the door of Room 1 was opened.

5. Research ethics

This study was approved by the Institutional Review Board of our hospital with a waiver of the requirement of patient consent (IRB no. 2020-2560).

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RESULTS

1. Transmission route investigation and infection control

Case 1 was admitted into a six-patient room on the hematologic ward (Room 36) on August 28, and the universal screening SARS-CoV-2 PCR test on admission day was negative. On September 2, he developed fever and the second SARS-CoV-2 PCR was positive. Case 1 was promptly admitted to a negative-pressure isolation room. The hematology ward in which the index patient had stayed was put under cohort isolation and cleaned. The adjacent rehabilitation department was also placed under cohort isolation because two wards shared the utility room. Upon contact tracing, we identified a total of 184 close and casual contacts (121 HCWs, 27 in-patients, seven already discharged patients, and 29 caregivers) in the hematologic ward, and all performed SARS-CoV-2 PCR testing with antibody testing. We performed SARS-CoV-2 PCR testing for all in-patients and their guardians in the cohort isolation wards every 2 - 3 days, and as soon as symptoms developed. In addition, already discharged patients and caregivers were tested for SARS-CoV-2 PCR at their local community health center.

On September 2, two other patients with hematologic malignancy (Cases 4, 6) and three caregivers (Cases 2, 3, 5) were positive for SARS-CoV-2 PCR (**Supplementary Table 1**, **Fig. 2**). Cases 2, 3, 4 had stayed with Case 1 in Room 36, Case 5 had remained in Room 35 (adjacent to Room 36) since August 29, and Case 6 had stayed in Room 34. On September 4, the patient (Case 7) in Room 1 was positive for SARS-CoV-2 PCR, and on September 5, the patient (Case 8) who had stayed in Room 36 and had been discharged on August 30 tested positive for the virus. His wife and son who did not come to our hospital also had positive SARS-CoV-2 PCR results (Cases A, B) on September 5. Finally, the husband of Case 2 (Case 9) tested positive for COVID-19 on September 6. We performed SARS-CoV-2 antibody testing for eight confirmed cases who remained in the hospital (Cases 1 - 7, Case 9) on September 3, and all had negative SARS-CoV-2 IgM and IgG.

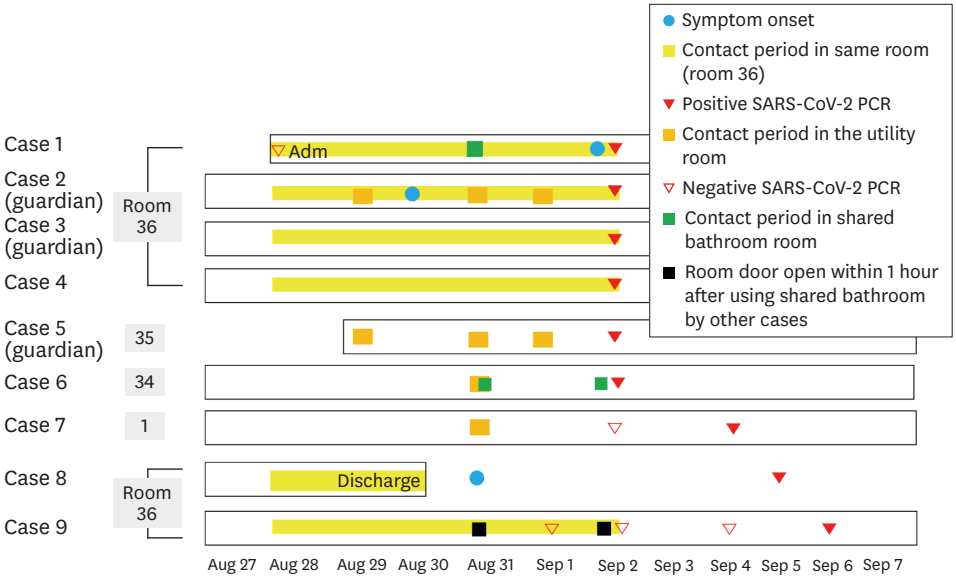

Figure 2. Chronology of the 9 patients with COVID-19 including contact history and SARS-CoV-2 PCR results.
COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; PCR, polymerase chain reaction.

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We actively traced the visitors who had met the patients with COVID-19 and performed PCR testing, but all returned negative results (**Supplementary Table 1**). Two other patients discharged from Room 36 on August 28 had negative SARS-CoV-2 PCR results on September 3 and September 4, respectively. All remaining patients, caregivers, and HCWs had negative SARS-CoV-2 PCR and IgM/IgG results and were released from isolation on September 16, which was 2 weeks from the start of the isolation period.

In an interview, Case 2 stated that she talked with Case 1 for 1 - 2 minutes on August 28. CCTV footage revealed that Case 2 often did not wear masks, frequently used the shared bathroom and utility room, and was intimate with Case 3. Case 5 talked with Case 3 while wearing a mask, and used the shared bathroom and utility room at the same time as Case 2 (**Fig. 2**). Case 1 used the shared bathroom on August 31, and 40 minutes later, Case 6 (Room 34 occupant) used the shared bathroom for teeth brushing. CCTV footage revealed that 10 minutes after 6 had used the shared bathroom, the door of Case 7's room 1 (adjacent to the bathroom) was opened. Case 7 (Room 1) did not use the shared bathroom. Similarly, 30 minutes after Case 6 briefly used the shared bathroom, the door of Room 1 was left open on September 2. In an interview, Case 7 stated that he did not wear a mask in Room 1, where he was isolated because of the colonization of carbapenem-resistant *Enterobacteriaceae*. Case 7 stopped by the shared utility room once or twice daily to deliver his food plate, and he used the shared utility room with Case 2 (both wore masks) at the same time for 30 seconds on August 31 (**Fig. 2**).

In the male shared bathroom, the air supply was located on the toilet ceiling, and ventilation was located on the shower room ceiling; however, this was not functioning adequately (**Fig. 1A, 1B**). Additionally, the shared bathroom had a grill on the lower part of the door. There was unintended negative pressure (-1.5 Pa) in Room 1 due to an imbalance of the air supply and ventilation system.

The rehabilitation ward located on the same floor as the hematology ward and shares the utility room, all patients and caregivers (38 in-patients and 35 caregivers) in the rehabilitation ward underwent SARS-CoV-2 PCR testing every 3 days. All patients and caregivers of the rehabilitation ward also received negative SARS-CoV-2 PCR tests.

2. Whole-genome sequencing

We sequenced the virus from nine patients using stored upper or lower respiratory samples. The viral genomes from all but one patient were 100% identical and phylogenetically grouped to clade GH (**Fig. 3**). The remaining sample had a difference of 1 nucleotide (C1023T of the *ORF* gene in the N protein), indicating that synonymous mutations and SARS-CoV-2 came from the same point of origin.

3. Airflow simulation

To identify the transmission route of Case 7, airflow analysis was performed and modeled on the case of patient 6 visiting the shared bathroom for 11 minutes. According to the field airflow analysis, the air supply allowed bathroom to maintain positive pressure compared with the hall due to dominant supply air in bathroom. Smoke was observed spreading toward the hall through ventilation grill and undercut of the bathroom door when smoke was released from the shared bathroom to visualize the airflow. Airflow simulation results are shown in **Fig. 3**. While Case 6 was in the bathroom, the contaminant spread to the hall through the ventilation grill and undercut of the bathroom door due to the bathroom's

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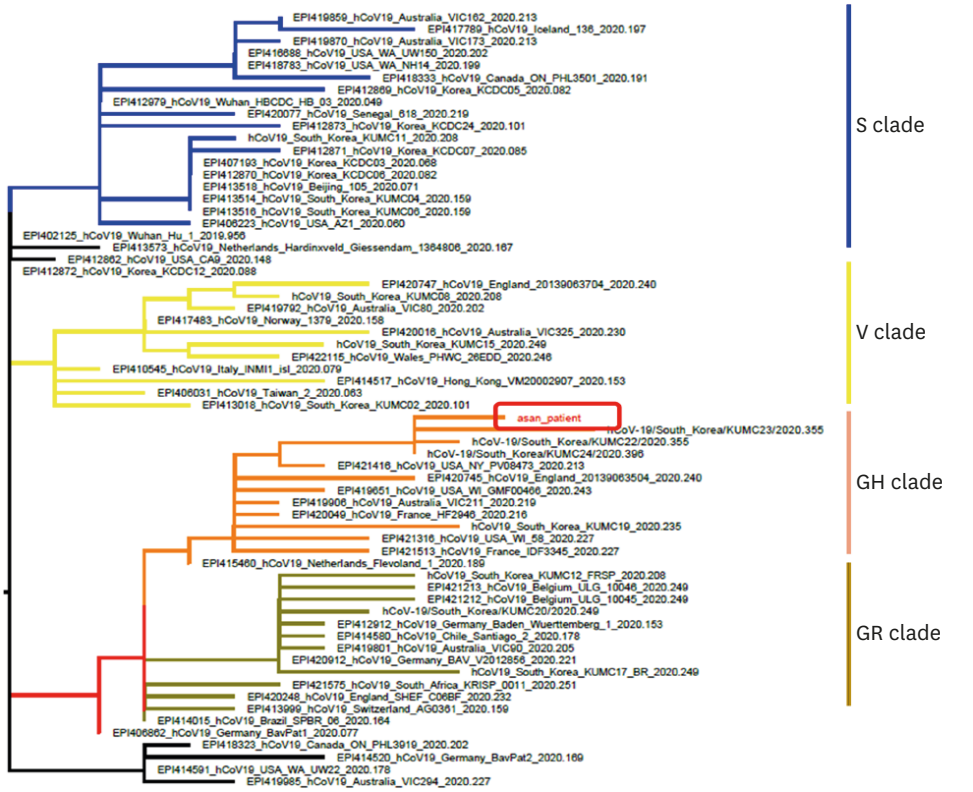

Figure 3. Phylogenetic analysis of the sequenced SARS-CoV-2 genomes.
SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

positive air pressure as observed in smoke test and towards Room 1 through the Room 1 door undercut. Room 1's door was open for a total of 31 minutes, which allowed the contaminant to infiltrate (**Fig. 4A**). The average concentration of the contaminant in Room 1 rose gradually and peaked after 20 minutes. The average volume concentration of contaminant in Room 1 was 3.1% of that in the bathroom, and the peak concentration in Room 1 was 21.0% compared with the bathroom concentration (**Fig. 4B, 4C**). Opening the door caused the peak concentration in Room 1 to increase by 26.1%.

DISCUSSION

In this nosocomial outbreak, we identified 10 additional cases involving patients with hematologic malignancy and their caregivers from the index patient within 6 days of admission. All patients had negative SARS-CoV-2 PCR results at the time of admission, suggesting that the outbreak was triggered by presymptomatic transmission at least 4 days from symptom onset. The multiple occupancy room setting with a close-contact guardian, shared bathroom, and possible airborne transmission from a shared bathroom to an adjacent room facilitated this outbreak.

Spatiotemporal analysis and epidemiologic analysis revealed that the most likely index was Case 1; Cases 2, 3, 6, 8 were secondary cases, and Cases 4, 5, 7, and 9 were tertiary (**Fig. 5**). Of the nine patients with COVID-19, six stayed in Room 36; therefore, we assume that the index patient was probably an individual in Room 36. Assuming no possibility of transmission on

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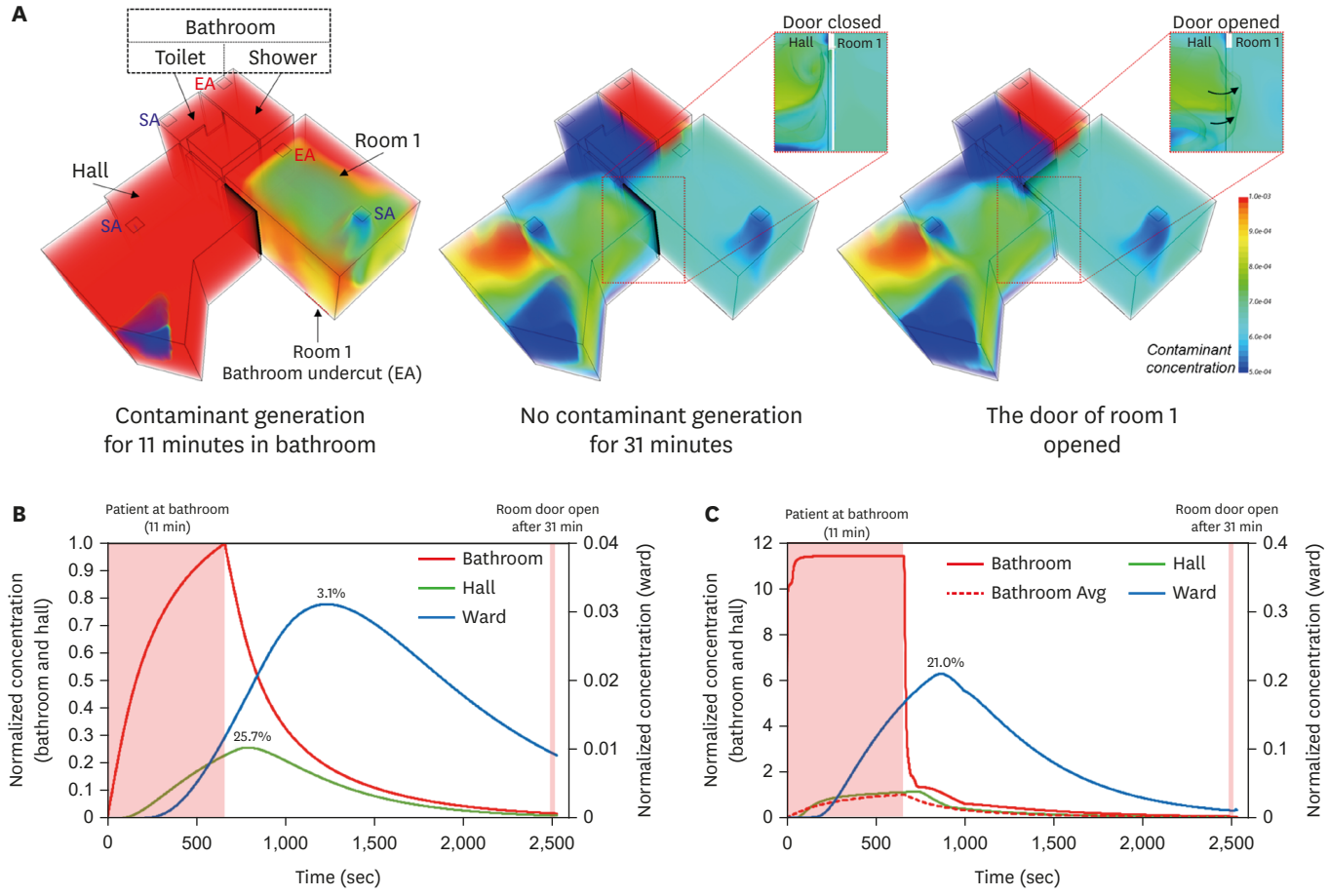

Figure 4. (A) Passive tracer distribution in male shared bathroom, hall, and Room 1 during aerosol generation for 11 minutes in bathroom, no aerosol generation for 31 minutes in bathroom, and the door of Room 1 opened. (B) Average cumulative concentration of tracer in Room 1 compared with that of the bathroom. (C) Highest concentration of tracer in Room 1 compared with the average concentration of the tracer in the bathroom.

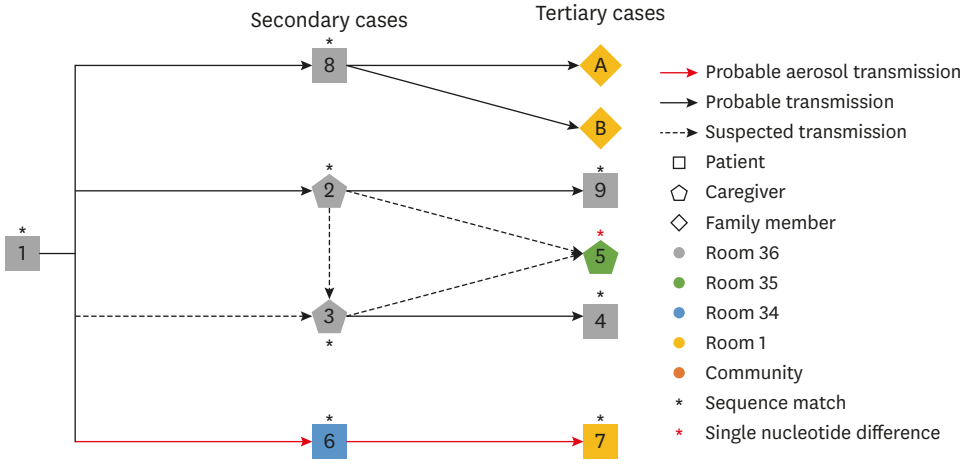

Figure 5. Suspected transmission routes between cases.

the day of the negative PCR test, transmission likely began between August 29 and August 30 because Case 1 was admitted to Room 36 on August 28, and Case 8, who was hospitalized for >3 weeks, was discharged on August 30. In addition, there were no other patients, caregivers,

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or HCWs with positive SARS-CoV-2 antibodies, suggesting no other possible sources of transmission. Negative SARS-CoV-2 antibody test results indicate that transmission occurred within 1 week of admission and, although Case 2 had the earliest symptom onset, she had been admitted 10 days before August 29, and there was no other identified source in the hospital. Based on these findings, we have determined that Case 1 was likely the index patient. As Case 2 talked with case 1 on August 28, case 6 may have acquired the infection from Case 1 in the shared bathroom, and case 8 discharged on August 30, they were considered as secondary cases. Case 4, 5, 7 and 9 may be tertiary case, because Case 4 did not move and might acquire SARS-CoV-2 from his guardian (Case 3), Case 5 had contacts with Case 2 and 3 in the utility room or female shared bathroom, Case 7 had negative PCR result on September 2 and he may have acquired the infection from Case 1 or Case 6 through airborne transmission in the shared bathroom and Case 9 had negative PCR results on September 4 and might acquire the infection from Case 2. We performed whole-genome sequencing, which showed all but one patient had identical sequences, while the remaining one had a single nucleotide difference, suggesting nosocomial transmission from one source.

There is a possibility of Case 5 and 6 acquired SARS-CoV-2 by the contaminated surface, because contamination on bathroom surfaces used by patients infected with SARS-CoV-2 has previously been reported [8, 9]. However, the recent CDC guidelines indicate that surface contamination is not the main route by which SARS-CoV-2 spreads, and the risk is considered to be low [10]. In the bathroom, patients usually did not wear masks; therefore, airborne SARS-CoV-2 may come from patients' breath or the aerosolization of the virus-laden aerosol from feces [8]. Recent studies have detected viable SARS-CoV-2 in air samples from rooms occupied by COVID-19 patients where there were no aerosol generating events, and from the car of an infected person [11, 12]. In addition, data has now suggested aerosol transmission of SARS-CoV-2 as a major mode of transmission [1-4]. We performed an airflow simulation and demonstrated that air was spread from the poorly ventilated bathroom to the adjacent Room 1, where Case 7 stayed. Air flowed from the shared bathroom to the hall and Room 1 due to the air supply to the toilet area, poor shared bathroom ventilation, grill of the door and the unintended negative pressure (-1.5 Pa) of Room 1. Case 7 in Room 1 was isolated in single-patient isolation room due to the colonization of carbapenem-resistant Enterobacteriaceae. He exclusively used the bathroom located in Room 1 and did not use the shared bathroom adjacent to Room 1. In addition, we observed that none except HCWs entered room 1 on CCTV. So, it is less likely that he got the virus via the contaminated surface in the shared bathroom. We cannot exclude the possibility that Case 7 acquired the virus in the shared utility room because he met with Case 2 in this location for 30 seconds on August 31. However, many patients and caregivers, including those in the adjacent rehabilitation ward who used the shared utility room, had negative SARS-CoV-2 PCR tests, except Cases 2, 3, and 5 who had other spatiotemporal close relationships. Therefore, it is less likely that Case 7 acquired the virus from the shared utility room via contaminated surfaces. Considering the airflow simulation study, it is likely that he acquired SARS-CoV-2 due to airborne transmission from shared bathroom. Similar to our findings, previous airflow simulation studies have shown that Middle East respiratory syndrome coronavirus spread from inadequately ventilated rooms through the airflow [13]. It is vital that ventilation systems are checked, especially air exhaust locations, and that function in the patient care area in the hospital is thoroughly examined.

It is worth noting that the index patient in this outbreak transmitted the virus at least 4 days before symptom onset (fever). The previous study reported that approximately 15% to 81% of patients with COVID-19 transmitted the virus during the presymptomatic period,

and the earliest presymptomatic contact event occurred 5 days before symptom onset [14]. In this context, our cases consolidated the importance of presymptomatic transmission in the nosocomial outbreak, suggesting that the contact tracing period should be as early as 4 to 5 days before symptom onset. Furthermore, although we performed universal SARS-CoV-2 PCR screening tests on the day before or of admission, the incubation period might have caused a negative result. Case 1 had a negative PCR test on admission but a positive test when his fever spiked 5 days after admission, and there were 10 additional cases involving secondary and tertiary cases in the hospital and community. Factors including underlying hematologic malignancy, multi-patient room setting, and caregiver interaction might have contributed to the rapid transmission observed in this case study. Therefore, follow-up testing may be warranted in patients with high-risk factors (*i.e.*, those with immunosuppression, hematologic malignancy [15], hospitalization in the rehabilitation unit [16], or history of stay in a long-term care facility [17]) or those who develop symptoms.

There are several limitations to our study. First, we tried to identify the index patient using CCTV tracing, visitor tracing, and large-scale PCR and antibody testing, but there was no clear epidemiologic association in the community for this patient. We therefore cannot rule out the possibility of a missing index patient. However, 19% of confirmed patients with COVID-19 had no identifiable source in South Korea between August 16 and August 29 [18], so we believe that Case 1 may be the index patient when considering the temporal relationship. Finally, secondary cases could be misclassified as tertiary cases.

In conclusion, the rapid transmission of SARS-CoV-2 in the hematologic ward occurred as a result of the multi-patient room setting, resident caregiver interaction, and shared bathroom, which was triggered by presymptomatic transmission. There is a possibility of airborne transmission due to poorly ventilated shared bathroom in the hospital. Infection control practitioners should thoroughly examine the ventilation system in the hospital.

SUPPLEMENTARY MATERIAL

Supplementary Table 1

Characteristics of patients with COVID-19

Click here to view

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