Research Square

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A familial cluster of COVID-19 infection in a northern Chinese region

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Abstract

Background

Currently, coronavirus disease 2019 (COVID-19) has spread worldwide and become a global health concern. Here, we report a familial cluster of COVID-19 infection in a northern Chinese region and share our local experience.

Methods

A familial cluster of six patients infected with severe acute respiratory coronavirus 2 (SARS-CoV-2) was included for analysis. The demographic data, clinical features, laboratory examinations, and epidemiological characteristics of enrolled cases were collected and analyzed.

Results

Two family members (Cases 1 and 2) had Hubei exposure history and were admitted to the hospital with a confirmed diagnosis of COVID-19; eight familial members who had contact with them during the incubation period were isolated in a hospital. Finally, the condition of four members (Cases 3, 4, 5, and 6) was as follows. Case 3 had negative SARS-CoV-2 RT-PCR results but was suspected to have COVID-19 because of radiographic abnormalities. Cases 4 and 5 developed COVID-19. Due to positive SARS-CoV-2 RT-PCR results, Case 6 was considered an asymptomatic carrier. In addition, four close contacts did not have evidence of SARS-CoV-2 infection.

Conclusions

Our findings suggest that COVID-19 has infectivity during the incubation period and preventive quarantine is effective for controlling an outbreak of COVID-19 infection.

Background

In December 2019, a number of cases with viral pneumonia of unknown cause were reported in Wuhan, Hubei Province, China. On February 8, 2020, the disease was named as “Novel Coronavirus Pneumonia (NCP)” by the health administration of China. (China) Subsequently, the disease was recognized as coronavirus disease 2019 (COVID-19) and declared an epidemic on March 11, 2020 by the World Health Organization (WHO). (Organization) As of April 28, 2020, about 3 million cases of confirmed COVID-19 infection have been reported by the WHO and more than 200,000 individuals have died from the disease. The causative agent of this viral pneumonia of unknown cause, which was provisionally named 2019 novel coronavirus (2019-nCoV), was ultimately designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) based on phylogeny, taxonomy, and established practice.

Currently, accumulating evidence has indicated person-to-person transmission. (Wang et al., 2020) In most cases, respiratory and direct contact with contaminated surfaces is the two main infection routes of COVID-19. (Rothan and Byrareddy, 2020) Recently, COVID-19 nucleic acid was detected in fecal samples, and in an epidemiological

and clinical investigation of childhood COVID-19, the possibility of fecal-oral transmission was raised. (Holshue ML, 2020; Xu et al., 2020) Jilin Province is located at the northeast of China and is about 2000 miles from Hubei Province. In the early stage of the COVID-19 epidemic, imported infection was the most common source in Jilin Province. However, in the later stage, sporadic clusters of SARS-CoV-2 infection have become a major source of the epidemic. According to the Jilin Centers for Disease Control and Prevention report, a total of 93 confirmed COVID-19 cases were reported during the epidemic period. Among them, 54 cases (60%) can be interpreted as a cluster of SARS-CoV-2 infection. However, the epidemiological characteristics of sporadic clusters of SARS-CoV-2 infection remain unclear, and the quarantine strategy for COVID-19 control remains incomplete.

Hence, we report a familial cluster of COVID-19 infection in Jilin, a northern Chinese region, and share our experience in controlling COVID-19. This may significantly improve the quarantine measures for COVID-19.

Methods

Research Subjects

Between January 20, 2020 and February 23, 2020, a familial cluster of six patients infected with SARS-CoV-2 and four close contacts were included for analysis. The demographic data, clinical features, laboratory examinations, and epidemiological characteristics of enrolled cases were collected and analyzed.

Diagnostic Criteria

COVID-19 pneumonia was diagnosed according to the Diagnosis and Treatment Guideline for New Coronavirus Pneumonia (7th edition), issued by the National Health Commission of China. (China) All patients with COVID-19 pneumonia were confirmed by performing reverse transcription-polymerase chain reaction (RT-PCR)on their samples (e.g., pharyngeal swab and fecal sample) for SARS-CoV-2. A cluster of SARS-CoV-2 infection was defined as two or more cases reported from the same address (e.g., family, school, and office) and diagnosed within a 2-week interval.

Results

Table 1 shows the clinical and epidemiological characteristics of confirmed and suspected COVID-19 cases. Timeline of exposure and chronology of symptom onset in the family cluster of SARS-CoV-2 infection are depicted in Fig. 1. The relationship of relatives to cases is shown in Fig. 2.

Table 1
Clinical and epidemiological characteristics of confirmed and suspected COVID-19 cases.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Sex	Female	Male	Female	Male	Female	Female
Age (years)	50	57	54	28	50	51
Native place	Hubei Province	Jilin Province	Jilin Province	Jilin Province	Jilin Province	Jilin Province
Occupation	Building worker	Building worker	Housewife	Worker	Housewife	Housewife
Types of COVID-19	Common	Common	Suspected	Common	Severe	Asymptomatic infection
Medical history	Autoimmune hemolytic anemia	No	No	No	Encephalorrhagia	No
Incubation period (estimated, days)	9	14	11	13	17	17
Clinical characteristics						
Abnormal chest CT findings	Yes	Yes	Yes	Yes	Yes	No
Symptoms						
Fever	Yes	Yes	No	No	Yes	No
Cough	Yes	No	Yes	No	No	No
Fatigue	No	No	Yes	Yes	No	No
Rhinobyon	No	No	No	No	No	No
Sneeze	No	No	No	No	No	No
Sore throat	Yes	No	No	No	No	No
Chest pain	No	No	No	No	No	No
Diarrhea	No	No	No	No	No	No
Laboratory examinations						
White blood cell ($\times 10^9$/L)	2.15	5.16	4.48	3.82	6.69	4.73
Neutrophil ($\times 10^9$/L)	1.64	3.03	2.11	1.76	5.61	3.05

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Lymphocyte (× 10^9/L)	0.46	3.18	1.94	1.82	0.78	1.47
Platelet (× 10^9/L)	141	171	257	245	215	377
C-reactive protein (mg/L)	> 10	< 10	ND	ND	70.8	ND
Erythrocyte sedimentation rate (mm/h)	55	ND	ND	ND	10	ND
COVID-19 RT-PCR						
Throat swab (conversion)	+, Jan. 27	+, Jan. 30	-	+, Feb.	+, Feb. 4	Feb. 6
Throat swab (reversion)	-, Feb. 3	-, Feb. 26	-	-, Feb.	-, Feb. 9	-, Feb. 14
Viral shedding period (Throat swab)	7	26	-	1	3	8
Fecal samples	-	-	-	-	ND	+, Feb. 11
Antibody assays against COVID-19						
Date	Mar. 15	Mar. 26	Mar. 23	ND	March 15	ND
IgG	+	-	-		+	
IgM	+	-	-		+	

Index Cases

Case 1

was a 50-year-old woman, who lived in Hubei Province. On January 16, 2020, she took the train, returned from Xiantao (Hubei Province), and stopped in Wuhan (Hubei Province) before arriving in Gongzhuling (Jilin Province). On January 25, she had a fever (37.8 °C). Two days later, she was admitted to our hospital for fever, cough, and sore throat. RT-PCR for the detection of SARS-CoV-2 was performed and COVID-19 was confirmed. Laboratory examination revealed decreased levels of white blood cells (WBCs) (2.15×10^9/L, reference: $3.5–9.5 \times 10^9$/L), lymphocytes (0.46×10^9/L reference: $1.1–3.2 \times 10^9$/L), and neutrophils (1.64×10^9/L, reference: $1.8–6.3 \times 10^9$/L); and increased levels of C-reactive protein (CRP) (> 10 mg/L, reference: 2–10 mg/L; Table 1) and erythrocyte sedimentation rate (ESR) (55 mm/h, reference: 0–20 mm/h). Computed tomography (CT) images showed patchy ground-glass opacities in the lungs (Fig. 3A). Case 2 was the husband of Case 1; he arrived in Gongzhuling

together with Case 1. On January 30, 2020, he had a temporary fever. Chest CT showed lung infection; the radiological findings are shown in Fig. 3B. One day later, he was diagnosed with COVID-19 because of the positive SARS-CoV-2 RT-PCR results. He was given an anti-viral and also treated for his symptoms. On March 2, his clinical condition significantly improved, as revealed by CT findings.

A Familial Cluster Of Secondary Cases

After Case 1 was confirmed to have COVID-19 on January 27, 2020, close contacts were identified, immediately isolated, and screened for SARS-CoV-2 in the fever clinic of our hospital. Respiratory samples were collected and tested using RT-PCR for detection of SARS-CoV-2. Case 3 had dinner with Cases 1,2, and 4 on January 20. On January 31, she became ill with fatigue and cough. Chest CT scan was performed and multiple patchy shadows were observed (Fig. 3C). Although RT-PCR for detection of SARS-CoV-2 was performed several times, the results were all negative. Due to the COVID-19 contact history, clinical symptoms, and abnormal radiographic findings, the patient was diagnosed with suspected COVID-19. Case 4 presented with mild symptoms of fatigue. On February 2, COVID-19 was confirmed by RT-PCR. Chest CT revealed multiple patchy, flocculent, fuzzy, and high-density shadows in the lungs (Fig. 3D). Case 5 had contact with Cases 1 and 2 on January 18 and 23, respectively. She became ill on February 4, presenting with fever, transcutaneous oxygen saturation 86% at rest, and patchy consolidation on CT images (Fig. 3E). Subsequently, COVID-19 was confirmed by RT-PCR. Case 6 had contact with Cases 1 and 2 on January 19, and no symptoms were observed. On February 6, pharyngeal swabs, including fecal samples, were tested for SARS-CoV-2 and positive results were confirmed. In addition, a chest CT scan was done and appeared normal. Hence, the patient was considered to have asymptomatic infection. The remaining four cases, who had close contact with the two index cases, were not found to have COVID-19. The detailed investigation was follows. C1D (daughter of Cases 1 and 2) lived with Case 1 between January 17 and 19, reporting no symptoms, and had persistently negative RT-PCR for SARS-CoV-2, and normal radiographic appearance. C5H (husband of Case 5) invited Cases 1 and 2 for a dinner at the home and was isolated on January 28. He was also considered to not have infection, based on the combination of clinical characteristics, SARS-CoV-2 RT-PCR results, and chest CT scan. Similarly, C5S (son of Case 3, husband of C1D) and C6H (husband of Case 6) were also found to not have SARS-CoV-2 infection. The four cases were all followed until March 15. They were tested for antibodies (IgG and IgM) against SARS-CoV-2 and negative results were observed in all cases. In addition, the familial cluster of SARS-CoV-2 infection was all reported at home or at our hospital and no other COVID-19 patients in the district were reported. Therefore, the early quarantine of close contacts of index patients, especially within a family, plays an important role in preventing the transmission of COVID-19.

Discussion

Due to the epidemiological features of the infection, the case series described in our study were considered a familial cluster of COVID-19 infection. The cluster of COVID-19 infection, including two imported cases and four secondary cases, occurred within 12 days. In this cluster, our findings suggested that: 1) during the incubation period, COVID-19 patients could infect close contacts; 2) the early quarantine for close contacts of index patients remains a useful tool for controlling the epidemic; and 3) asymptomatic infection may be more common than previously thought. In fact, in the later stage of COVID-19 epidemic in Jilin, sporadic clusters of SARS-CoV-2 infection became a major source. Therefore, knowing the characteristics of a cluster of COVID-19 is useful to rapidly control the epidemic.

Respiratory and contact routes are proven transmission mechanisms for COVID-19 infection. However, in a recent study, SARS-CoV-2 RNA was detected in the fecal samples of COVID-19 patients, indicating the possibility of transmission via the fecal-oral route. (Jiang et al., 2020; Xu et al., 2020) In our study, respiratory and contact should be considered as the two main transmission mechanisms responsible for this cluster of infections. Moreover, an asymptomatic carrier was also suspected of being a source for transmission of COVID-19, (Bai et al., 2020b) and this key point was proved by Zhang et al. (Zhang et al., 2020) Although these new findings make the prevention and control of COVID-19 more complicated, they will lead to improved and more effective strategies. To avoid acquiring COVID-19, specific attention should be paid to factors such as environmental, direct contact, and social distance. (2020a; China)

Person-to-person transmission has been confirmed. It is unclear if during the incubation period, the virus is infective. A previous study by Yu et al. (Yu P, 2020) showed possible transmission of COVID-19 during the incubation period. Similarly, our data also supported that the virus remains infective during the incubation period. In this study, before the onset of symptoms of Case 1 (January 25), Cases 3 and 4 only had dinner with Case 1, as well as a dinner party, and Case 5 had another social contact with Case 1. Three cases were all infected with COVID-19. This special characteristic mentioned above is different from the transmission of SARS infection. In our study, the incubation period was relatively long and ranged from 9 to 17 days. Remarkably, although the incubation period of Case 1 was estimated at 9 days, the possibility remained of it being extended to longer than 9 days because of her residential location (Xiantao, Hubei). The incubation periods of Cases 5 and 6 were estimated from the first contact with Case 1, with the longest period being 17 days. Likewise, the incubation period of a secondary case has been reported over 14 days, (Guan et al., 2020) even reaching up to 20 days. (Yang et al., 2020b) Hence, a longer quarantine period, such as 2 or 3 weeks, may be required.

Usually, patients with COVID-19 present with fever, cough, or lung infiltrates. (Huang et al., 2020) In some cases, they may also have mild respiratory symptoms. More recently, asymptomatic infection has been reported. In Japan, the prevalence of asymptomatic infection is estimated at 41.6% (95% confidence interval: 16.7%, 66.7%) among COVID-19-infected individuals. (Nishiura et al., 2020) However, in China, a study of 72, 314 COVID-19 patients showed that asymptomatic carriers comprised 1.2% of all COVID-19 cases. (2020b) The difference in the prevalence of asymptomatic infection may be caused by sample size estimated and different subjects included between the two studies (high-risk vs. confirmed). In our study, due to positive SARS-CoV-2 RT-PCR results from fecal and pharyngeal samples, Case 6 was considered asymptomatic infection, the time of viral shedding was 8 days, longer than the time for Cases 4 and 5. We believe that asymptomatic infection is common. A similar result was reported in another familiar cluster of COVID-19 infection. Due to SARS-CoV-2 RT-PCR (+) and IgM assays (+), four cases without clinical symptoms were considered asymptomatic infection. (Bai et al., 2020a) Hence, on one hand, good personal hygiene is emphasized; on the other hand, due to no clinical symptoms and normal radiography, asymptomatic infection could be easily neglected. Hence, more attention should be given to improving the diagnostics and management of asymptomatic carriers, this would improve the prevention and control of the COVID-19 epidemic. (2020c)

For the diagnosis of COVID-19 patients, the sensitivities of IgM and IgG assays were 77.3%, and 83.3%, respectively, (Xiang et al., 2020) and RT-PCR for detection of COVID-19 has a lower sensitivity of 35%. (Mardani et al., 2020) It was then concluded that a significant proportion of COVID-19 would be diagnosed as suspected cases. Case 3, as a suspected COVID-19 case, presented with mild respiratory symptoms and abnormal radiography. Although RT-PCR for SARS-CoV-2 detection was performed several times, the case was not

confirmed. However, due to contact history with the index case, Case 3 was identified, isolated, and treated as a suspected case. Fortunately, until now, several new assays, such as an automated chemiluminescent immunoassay, a reverse transcription loop-mediated isothermal amplification assay, and antibody detection assay for the diagnosis of COVID-19, have been evaluated and good performance has been confirmed. (Baek et al., 2020; Infantino et al., 2020; Xiang et al., 2020; Yan et al., 2020; Yang et al., 2020a) These new assays may improve the diagnostic dilemma of current assays for COVID-19.

Accumulated evidence suggests that SARS-CoV-2 is more infectious than SARS-CoV and MERS-CoV. (Bai et al., 2020a) However, this study of a familiar cluster of COVID-19 infection demonstrated a differential susceptibility. Although C1D and C5S lived with Cases 1 and 2, it remains to be found without COVID-19 infection. The result suggests a difference in the susceptibility to COVID-19 among individuals. The SARS-CoV-2 has preferential tropism to human airway epithelial cells through the same cellular receptor as that for SARS, angiotensin-converting enzyme 2 (ACE2), which is a central body receptor for the surface glycoprotein S of the virus. (Munster et al., 2020) Therefore, the down regulation of ACE2 expression is thought to explain the lower susceptibility to COVID-19. In addition, the differential susceptibility suggested by the study implicated that interventions, such as vaccine trials and preventive measures, for the COVD-19 control should be evaluated their feasibility.

Conclusions

In terms of the control of sporadic clusters of COVID-19 infection, several recommendations can be made as a result of the study. 1) Cases who are exposed to COVID-19 patients during the incubation period should also be included as close contacts. 2) The diagnosis of COVID-19 infection could not reasonably rely on RT-PCR and antibody detection and all suspected cases should be treated as confirmed patients. Moreover, further research should be performed to look for a rapid, accurate, economic diagnostic assay for COVID-19. 3) A differential susceptibility to COVID-19 between individuals exists. Further investigation for the mechanism of the difference may be helpful to improve the management of the susceptible population. 4) Finally, it is better that all close contacts are isolated and observed in a centralized setting. (Qiu et al., 2020) Otherwise, home isolation and observation are required and a community supervision mechanism is needed.

Abbreviations

COVID-19
coronavirus disease 2019
SARS-CoV-2
severe acute respiratory coronavirus 2
NCP
Novel Coronavirus Pneumonia
RT-PCR
reverse transcription-polymerase chain reaction
WHO
World Health Organization
2019-nCoV
2019 novel coronavirus
WBCs

white blood cells
CRP
C-reactive protein
ESR
erythrocyte sedimentation rate
CT
Computed tomography
ACE2
angiotensin-converting enzyme 2

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the requirement of the Helsinki Declaration revised in 2013, and the research protocol was approved by the Ethics Committee of the First Hospital of Jilin University, Jilin Province, China. Written informed consent was obtained from all individual participants included in the study.

Consent for publication

All data published here are under the consent for publication. Written informed consent was obtained from all individual participants included in the study.

Availability of data and materials

The datasets generated and analyzed during the present study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no conflict of interest.

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Authors' contributions

Kai-yu Zhang and Yi-zhe Sun designed/performed most of the investigation; Lu-yao Sun and Zhi-hui Liu performed the data analysis and wrote the manuscript; Peng Zhang, Hai-ying Chen, Li-xin Lou, Xin Li and Wan-

guo Bao contributed to interpretation of the data and analyses. All of the authors have read and approved the manuscript.

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Not applicable

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Figures

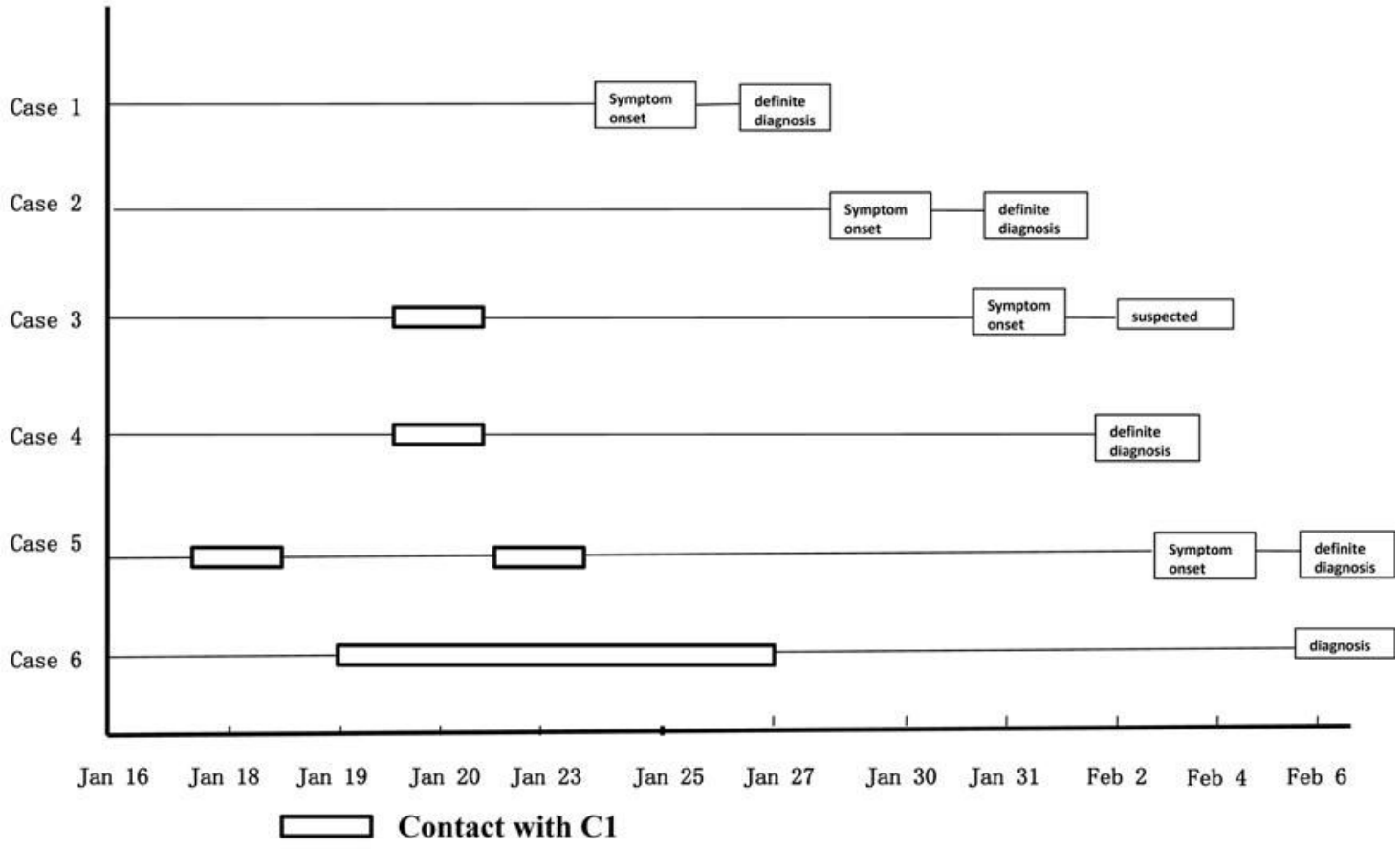

Figure 1

Timeline of exposure and chronology of symptom onset in the family cluster of SARS-CoV-2 infection.

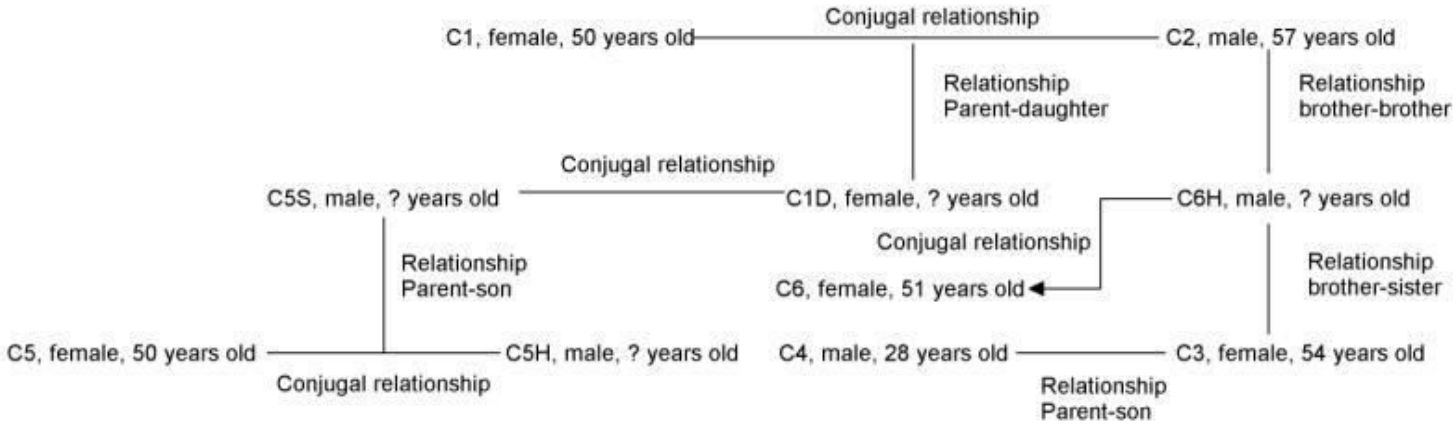

Figure 2

The relationship of relatives to the index cases (Cases 1 and 2).

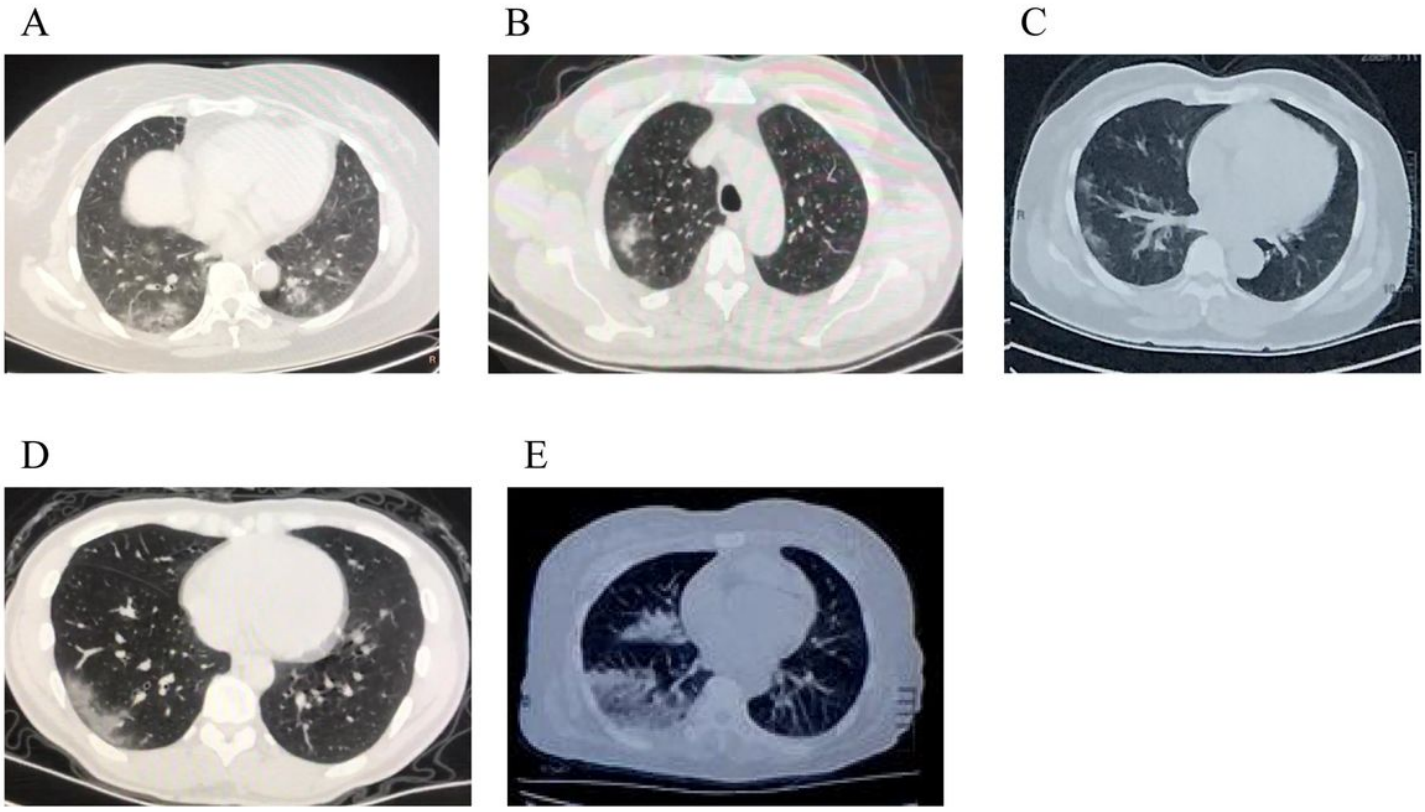

Figure 3

Chest scan of five cases. Case 1: patchy ground-glass opacities in the lungs (A); Case 2: abnormal findings with suspected lung infection (B); Case 3: multiple patchy shadows (C); Case 4: multiple patchy, flocculent, fuzzy, and high-density shadows in the lungs (D); Case 5: patchy consolidation (E).