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Original Article

Clinical Implications of 5 Cases of Middle East Respiratory Syndrome Coronavirus Infection in a South Korean Outbreak

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SUMMARY: The Korea Middle East respiratory syndrome coronavirus (MERS-CoV) was first confirmed on May 20, 2015, with a subsequent outbreak in South Korea. Five patients with suspected MERS-CoA infection were admitted to our hospital during this outbreak. One patient had no major symptoms upon admission, but pneumonia was identified upon chest radiography. Two patients progressed rapidly to acute respiratory failure and required ventilator-assisted respiration. One patient required extracorporeal membrane oxygenation to treat refractory hypoxemia, and one patient died of shock with multiorgan failure. All the patients had fever, myalgia, leucopenia, normal procalcitonin level, and pneumonia. Importantly, clinicians should test for pneumonia in all suspected patients with MERS-CoV infection, even in the absence of respiratory symptoms. The pneumonia usually affected the lower lobes. A shorter incubation period was associated with more severe disease and greater risk of mortality, and the severity of fever predicted the prognosis of MERS-CoV infection-related pneumonia. Therefore, in cases of lower-lobe pneumonia that occur during an MERS-CoV outbreak and are unresponsive to antibiotics, clinicians should consider the possibility of MERS-CoV infection.

INTRODUCTION

In September 2012, the Middle East respiratory syndrome coronavirus (MERS-CoV) was first reported in Saudi Arabia, in 2 patients with severe pneumonia (1). This virus causes sporadic infections, as well as intrafamilial and health-care-associated infections (2,3). Over the past 3 years, the numbers of MERS-CoV cases has continued to increase and, as of May 31, 2015, 1,187 laboratory-confirmed cases have been recorded, with 485 deaths (up to 40% mortality) (4). Since April 2014, travel-associated cases have been detected in 8 countries outside the Arabian Peninsula (5). Herein, we report on the clinical course, imaging, and laboratory findings from 5 cases of MERS-CoV in a South Korean outbreak.

The index case involved a 68-year-old man who had travelled to the Middle East (Bahrain, United Arab Emirates, Saudi Arabia, and Qatar) from April 18 to May 3, 2015. His symptoms began on May 11 and consisted of fever (38.9°C), cough, and myalgia. He visited a local clinic in Seouleuwon (Clinic A), on May 12, 14, and 15. He was then admitted to the Pyeongtaek Saint Mary Hospital (Hospital B) on May 15. On May 17, he developed dyspnea and cough developed, and he was transferred via local Clinic C (Yulineuwon) to the Samsung Medical Center (Hospital D). The possibility of MERS-CoV infection was first considered on May 18. At that time, the patient was isolated and individual precautions were implemented. MERS-CoV infection was confirmed on May 20. On the same day, the patient was transferred to the National Medical Center (Hospital E), where he was admitted to a specialized unit equipped with maximal precautions, including a negative pressure room. The South Korean outbreak was the largest case cluster of MERS outside of the Middle East.

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MATERIALS AND METHODS

Clinical histories and physical findings: We ascertained clinical histories and possible exposures to MERS-CoV by direct interview with patients and family members. All physical, laboratory, and radiological data were obtained retrospectively from medical records, and Institutional Review Board (IRB) approval was obtained for retrospective evaluation of patients with MERS-CoV infection.

Specimen collection: Oropharyngeal swab, sputum, and tracheal aspiration samples were collected from each patient at various times. Two sets of oropharyngeal swab samples, or sputum samples and serum samples, were collected from all patients at initial diagnosis. Follow-up sets of specimens were collected on admission days 12–14, as well as 2 days after the pneumonia had resolved, and 2 days after symptoms had disappeared. Samples were tested at the Korean Center for Disease Control (KCDC) within 48 h of collection.

MERS-CoV laboratory testing: Specimens were test-

ed using a MERS-CoV real-time reverse transcription PCR (RT-qPCR) method had been developed by the KCDC. All PCR procedures were done at the KCDC.

Antiviral treatment: Treatment was modified from previously published protocols (6,7). Pegylated interferon α-2a (Pegasys; Roche, Basel, Switzerland) was administered via subcutaneous injection at a dose of 180 μg/week for 2 weeks. The dose of oral ribavirin (Copegus; Roche) was adjusted in accordance with calculated creatinine clearance and continued for 8–10 days (6,7). Patients with a creatinine clearance >0.833 mL/sec/m^2 received a 2,000 mg loading dose, followed by 1,200 mg every 8 h for 4 days, then by 600 mg every 8 h for 4–6 days. Patients with a creatinine clearance of 0.333–0.833 mL/sec/m^2 received a 2,000 mg loading dose, followed by 600 mg every 8 h for 4 days, then by 200 mg every 6 h for 4–6 days. Patients with a creatinine clearance <0.333 mL/sec/m^2, or who were on dialysis, received a 2,000 mg loading dose, followed by 200 mg every 6 h for 4 days, then by 200 mg every 12 h for 4–6 days (7). Convalescent sera were recommended in a recent study (6).

Data analysis: Basic descriptive analyses were conducted in all patients.

RESULTS

Patient 1: A 46-year-old woman without comorbidities was diagnosed with MERS-CoV infection on May 29 after contact with the index case (case number 1) of the South Korean outbreak. The patient was a nurse at Clinic A and had been in contact with the index case on May 15. During the latent period, the patient shared a room with a family member. On May 23, defined as day 1 of illness, while still in good health, the patient developed a headache, fever, and loose stool. The fever subsided after she took acetaminophen. On May 26, she experienced fever again but had no respiratory complaints; physical examination was normal, but MERS-CoV PCR was performed because of the close contact with the index case. The result was negative. A second MERS-CoV PCR performed on the evening of May 29 proved positive, and she was diagnosed with MERS-CoV infection. Clinical symptoms improved after May 28. Laboratory findings of blood samples showed leukopenia and mildly increased C-reactive protein level (5.46 mg/dL; normal range, 0–0.8 mg/dL). Other laboratory blood findings were normal. No respiratory symptoms were evident. Chest radiography revealed multiple small ground-glass appearance on both lungs, as well as infiltration with atelectasis in the left upper lobe. The patient was treated for MERS-CoV using interferon α-2a (180 μg), high-dose ribavirin, and kaletra (Abbvie; North Chicago, IL, USA). Antimicrobial agents (cefepime and azithromycin) were also prescribed. During the administration of high-dose ribavirin, the patient developed bradycardia (38–48 beats/min). The patient recovered satisfactory after treatment.

Patient 2: A 47-year-old man visited Hospital C to visit the mother of a friend on May 15. He developed fever and cough on May 21. He visited the local hospital 3 times as a result. Symptoms persisted, and the patient learned that both his friend and his friend's mother had been diagnosed with MERS-CoV infection. Therefore, he visited our hospital to be tested for MERS-CoV infection using PCR. The test was positive, and he was diagnosed with MERS-CoV infection on June 2. Chest radiography performed upon admission showed bilateral enhanced pulmonary hilar vascular shadows that were more prominent on the left lung and accentuated broncho-vascular lung markings. Laboratory findings revealed leukopenia as well as mildly increased C-reactive protein levels (1.77 mg/dL) and aspartate transaminase (AST: 111 U/L; normal range, <42 U/L). Other laboratory blood findings were normal. Following the diagnosis, the patient was treatment for MERS-CoV infection using interferon α-2a (180 μg), high-dose ribavirin, and kaletra. Antimicrobial agents (piperacillin/tazobactam and azithromycin) were also prescribed. The patient developed bradycardia during high-dose ribavirin (42–52 beats/min) treatment. The patient recovered satisfactory after treatment.

Patient 3: A 65-year-old man was diagnosed with MERS-CoV infection on June 6. He had come in contact with another patient with MERS-CoV infection (Case number 16) in the hospital while visiting his wife. He developed fever, myalgia, and headache on May 31, as well as diarrhea and abdominal pain on June 5. At admission, his temperature was 37.8°C (maximum, 39.4°C), his heart rate was 90 beats/min, and his blood pressure was 119/72 mm Hg. Physical examination was unremarkable, although he showed mild and diffuse abdominal tenderness. Laboratory blood findings revealed leukopenia and normal C-reactive protein levels (0.35 mg/dL). Other laboratory blood findings were normal. Chest radiography showed an ill-defined, patchy consolidation in the left lower lung zone. Antiviral and antimicrobial treatment as described above (Patient 2) was initiated on June 6. During high-dose ribavirin administration, the patient developed bradycardia (32–44 beats/min). His lung condition deteriorated, and symptoms became aggravated. We changed the antimicrobial agents used to meropenem and teicoplanin. Until June 12, the patient experienced diarrhea 4 to 8 times per day. On June 15, mechanical ventilation was implemented to support his respiration. His liver function values, amylase and lipase levels were elevated and aggravated after June 10. Renal function progressively deteriorated after June 15. Pneumonia progressed and right ventricular heart failure developed on June 22; inotropics were needed to maintain blood pressure. Cardiopulmonary resuscitation was necessary on June 23, and he died of shock with multiorgan failure on June 24; fever was sustained until death. While the patient was intubated, bronchoscopic toileting was the only way to clear his respiratory secretions because they were thick and cream soup-like.

Patient 4: A 27-year-old man came in contact with another patient who had MERS-CoV infection at the emergency department (Case number 6). He developed fever, myalgia, and abdominal pain on June 7 and diagnosed with MERS-CoV infection on June 8. Antiviral and antimicrobial treatment (ceftriaxone and azithromycin) was started on June 8. Chest radiography revealed ill-defined peribronchial consolidation in the left lower lung zone and retrocardiac area at admission. Laboratory blood findings showed leukopenia and nor-

mal C-reactive protein levels (0.67 mg/dL). His symptoms had resolved 5 days after admission. The patient recovered satisfactory after treatment.

Patient 5: A 35-year-old police officer from Pyeongtaek where the South Korean outbreak occurred was diagnosed with MERS CoV infection on June 10. He had developed fever and myalgia on May 31. He visited a local clinic where a PCR test yielded weakly positive results for MERS CoV. He was transferred to a specialized unit. Another MERS-CoV PCR test on June 2 was negative. He was discharged from the hospital, and his quarantine was cancelled. His symptoms persisted, and he began to cough on June 3. He was admitted to a local hospital where he stayed from June 5–9. The pneumonia and symptoms worsened, despite broad-spectrum antibiotic treatment. He was transferred to our hospital for treatment of the pneumonia. We determined that the pneumonia to be atypical considering his age, health status, imaging data, laboratory data, and clinical course. Therefore, MERS-CoV PCR was performed, even though no definite epidemiological evidence was present and despite a prior negative test result. This time the MERS-CoV PCR was positive. At admission, his breathing sounds were coarse, with a crackle on the right lower anterior aspect of the chest. The abdomen and other organs were normal. All vital signs were stable, except for body temperature 38.0°C. Laboratory and arterial blood gas analysis (ABGA) data were as follows; pH 7.51; arterial partial pressure of oxygen ($PaCO_2$), 27 mmHg; PaO_2, 48 mmHg; HCO_3^-, 21.5 mmol/L; arterial oxygen saturation (SaO_2), 88%; leukocyte count 3,680 /mm^3 (segmented neutrophils, 87.2%); hemoglobin, 13.3 g/dL; hematocrit, 37.0%; platelet count, 159,000 /mm^3; C-reactive protein, 16.72 mg/dL; procalcitonin, 0.118 ng/mL; AST/ALT, 137/75 U/L; total protein, 5.8 g/dL; and albumin, 3.5 g/dL. Chest radiography revealed a lobar consolidation in the right lower lung zone and ill-defined lobar consolidation with air bronchogram in the right middle and lower lobes. Antiviral and antimicrobial treatment (meropenem and vancomycin) was started on June 10. Despite the use of broad-spectrum antibiotics and antiviral agents, the patient's condition continues to worsen, and his pneumonia deteriorated. At that time, we started to search for a donor for convalescent plasma and thereby protect his lungs from further viral attack. Amylase and lipase levels increased abruptly (amylase 703 U/L, lipase 2,457 U/L), and the antiviral agent was discontinued on 12 June. Oxygen was provided via a high flow nasal cannula at a flow rate of 40 L/min and a fraction of inspired oxygen (FiO_2) 0.8 to reverse hypoxemia, nonetheless the results of ABGA were getting worse, pH 7.45; $PaCO_2$, 16 mmHg; PaO_2, 54 mmHg; HCO_3^-, 11.1 mmol/L; SaO_2, 89%. Mechanical ventilation was begun on June 11. Despite immediate intubation and conventional management, oxygenation continued to worsen. The arterial PaO_2 to FiO_2 ratio (PaO_2/FiO_2) was 53 with a positive end-expiratory pressure 10 cm H_2O. Extracorporeal membrane oxygenation (ECMO) was began on June 12; the ECMO was established promptly using the Seldinger technique, 4 h after the start of mechanical ventilation. ECMO treatments were venovenous (Maquet Rotaflow Centrifugal Pumps with Quadrox-D oxygenators; Maquet, Rastatt, Germany), and biocoated circuits were used. A femorojugular venovenous ECMO was established using the Seldinger technique. We started steroid treatment as the Meduri protocol on June 11. We then found a donor who had been discharged from hospital on June 10. Convalescent plasma was transfused to the patient on the same day. On June 18, the ECMO was removed, and on June 20, the mechanical ventilator was removed. On June 23, the patient was extubated and pleural effusion was drained using a chest tube on June 27. The patient recovered satisfactory after treatment.

The timeline of clinical symptoms, laboratory findings, and chest radiography findings for the 5 patients are summarized in Table 1.

DISCUSSION

As of July 9 2015, 186 people have been confirmed as having MERS-CoV infection, and 35 have died since the index case was detected. The median incubation period for secondary cases associated with limited human-to-human transmission is approximately 8 days (range; 2–13 days). One patient had no epidemiologic links or exposure history. The median time from illness onset to hospitalization was approximately 7 days (range; 2–12 days). One patient had no major symptoms at admission, but she showed pneumonia upon chest radiography. Two patients progressed rapidly to acute respiratory failure and required a ventilator to support respiration, and 1 patient required extracorporeal membrane oxygenation due to refractory hypoxemia. One patient died of shock with multiorgan failure; the time from onset to death was 20 days.

The radiographic findings of MERS-CoV infection may include bilateral patchy densities or opacities, interstitial infiltrates, consolidation, and pleural effusions. Pneumonia typically involves the lower lobes. All patients showed fever, myalgia, leucopenia, mildly increased C-reactive protein level, normal procalcitonin level, and pneumonia at admission. Although all patients had pneumonia, respiratory symptoms such as cough and sputum were rare or not prominent during the initial course of the disease. One patient had no respiratory symptoms at admission, and the other 4 patients had non-productive cough. None of the patients had sputum during the initial course of the disease. This lack of definitive symptoms often delayed diagnosis. In Patinet 5, results had been negative before admission to our hospital. In patients without sputum, an oropharyngeal swab was used to obtain a specimen.

Two patients required ventilator support and had thick, bloody, cream soup-like respiratory secretions. Bronchoscopy was required to eliminate the secretion. After repeated bronchoscopy, chest radiography showed that the haziness had improved. All patients developed fever during progression of pneumonia. After the fever subsided, progression of lung involvement appeared to slow or stop (Table 1). Furthermore, other inflammatory markers such as C-reactive protein or procalcitonin, did not predict or correlate with pneumonia progression on chest radiography (Table 1). Early diagnosis might have contributed to survival in Patients 1, 2, 4, and 5; in any case, a short incubation period is associated with mortality (8). In Patient 3, the only fatal

Table 1. Timeline of clinical symptoms, laboratory findings, and chest radiography findings

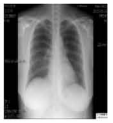
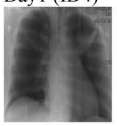
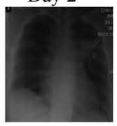
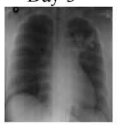
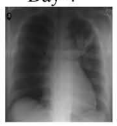
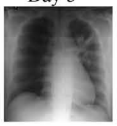
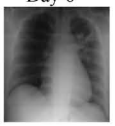
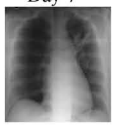
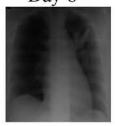
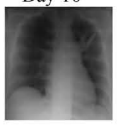
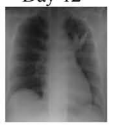
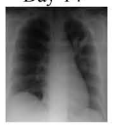
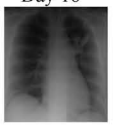
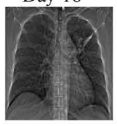
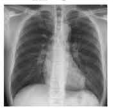
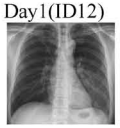
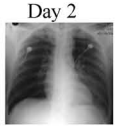
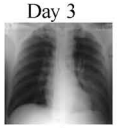
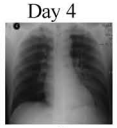
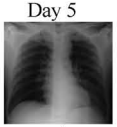
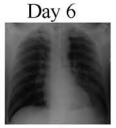
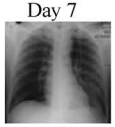
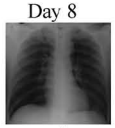
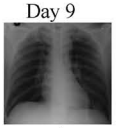
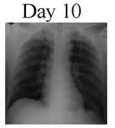
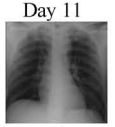
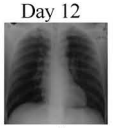
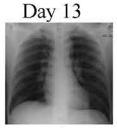
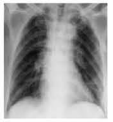
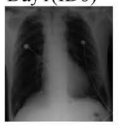
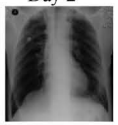
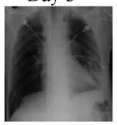
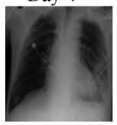
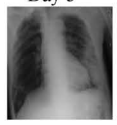
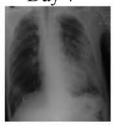
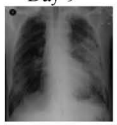
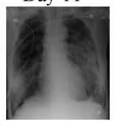
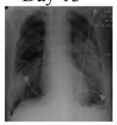
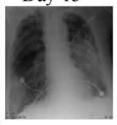
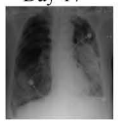
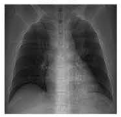
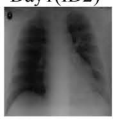
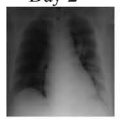
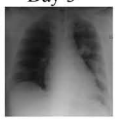
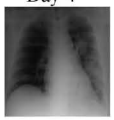
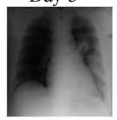
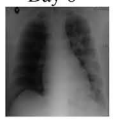
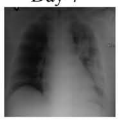
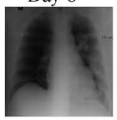
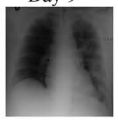
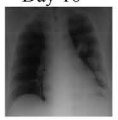
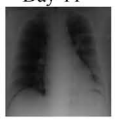
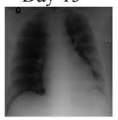
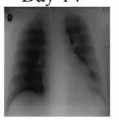
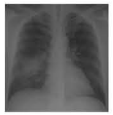
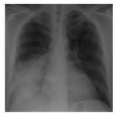
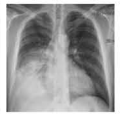
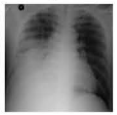
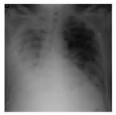
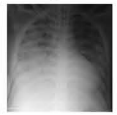
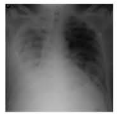
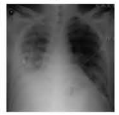
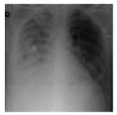
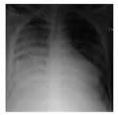
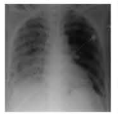
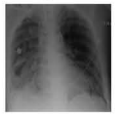
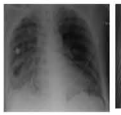
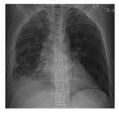
Patient 1	ID[1)] 1	Day1 (ID4)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 10	Day 12	Day 14	Day 16	Day 18
Incubation period: 9 days														
Fever/Myalgia	38.3℃/+	38.2℃/+	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-
Cough/Sputum	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-
CRP (mg/dL)		2.46	1.22	0.72	0.46	0.30	0.15	0.08	0.18	0.08	0.06	0.08	0.11	
WBC/monocyte (%)		3990/5.8	3850/9.6	3840/11.7	3400/11.5	2870/9.1	2990/12.7	3710/8.1	3760/9.8	3970/11.3	3160/14.2	3660/12.8	3400/12.9	4200/5.5
AST/ALT (U/L)		26/23	29/25		29/32	20/27	42/37	56/44	55/59	46/59	35/51	26/41	20/30	18/24
Amylase/Lipase (U/L)		48/42	40/34		45/42	40/32	44/35	44/30	58/38	43/30	40/27	18/22	21/19	24/20
Creatinine (mg/dL)		0.73	0.56		0.54	0.47	0.48	0.52	0.57	0.58	0.60	0.60	0.60	0.61
PCR		+							+			-	-	-
Patient 2	ID 8	Day1(ID12)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13
Incubation period: 7 days														
Fever/Myalgia	38.6℃/+	37.8℃/+	37.8℃/+	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-
Cough/Sputum	-/-	-/-	-/-	-/-	+/-	+/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-
CRP (mg/dL)	5.98	1.77	1.02	0.89	0.52	0.25	0.23	0.39	0.25	0.16	0.12	0.09	0.10	0.14
WBC/monocyte (%)	2430/9.9	3140/15.3	3570/17.9	4030/23.8	4310/29.2	4510/27.9	5850/17.9	5900/15.1	4970/17.5	4980/14.5	4420/18.3	4760/16.6	4900/13.7	5640/17.6
AST/ALT (U/L)		111/43	140/59	215/124	163/123	103/20	105/22	102/24	102/21	101/23	104/26	104/23	101/26	98/20
Amylase/Lipase (U/L)		64/45	78/54	79/56	74/41	71/37	71/32	76/37	51/69	65/81	48/70	44/57	35/51	29/44
Creatinine (mg/dL)		0.87	0.71	0.73	0.67	0.74	0.79	0.94	0.84	0.86	0.80	0.95	0.88	0.93
PCR		+							+				-	-
Patient 3	ID 4	Day1(ID6)	Day 2	Day 3	Day 4	Day 5	Day 7	Day 9	Day 11	Day 13	Day 15	Day 17	Day 18	Day 20
Incubation period: 2–4 days														
Fever/Myalgia	39.4℃/+	38.8℃/+	37.7℃/+	38.1℃/+	38.4℃/+	37.8℃/+	38.4℃/+	38.3℃/+	38.3℃/	39.2℃/	38.8℃/	39.5℃/	38.4℃/	39.4℃/
Cough/Sputum	-/-	-/-	-/-	±/-	±/-	+/-	+/-	+/+	/+	/+	/+	/+	/+	/+
CRP (mg/dL)		0.35	0.32	0.43	1.81	4.06	4.25	7.68	14.99	13.49	6.76	7.05	5.74	2.61
WBC/monocyte (%)		2740/17.9	2940/13.3	3200/7.5	4250/5.9	3580/5.6	4500/4.2	6390/5.5	8210/3.7	5590/6.3	7160/8.2	8110/6.8	10290/10.3	14110/9.1
AST/ALT (U/L)		18/10	20/10	17/6	32/9	76/26	123/28	96/41	83/42	59/39	53/35	59/39	665/220	25520/3588
Amylase/Lipase (U/L)		44/33	41/30	50/32	71/78	64/61	42/33	48/39	32/19	50/54	54/294	78/176	239/277	290/3259
Creatinine (mg/dL)		0.76	0.86	0.72	0.70	0.57	0.63	0.60	1.33	1.88	2.14	2.52	3.80	4.47
PCR	+	+						mechanical ventilator →						

Table 1.

Patient 4	ID 1	Day1(ID2)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 13	Day 14
Incubation period: 13 days														
Fever/Myalgia	38.9℃/+	38.1℃/+	37.7℃/+	37.7℃/+	36.8℃/-	37.0℃/-	36.8℃/-	36.6℃/-	36.5℃/-	36.9℃/-	36.5℃/-	36.4℃/-	36.8℃/-	36.6℃/-
Cough/Sputum	-/-	-/-	-/-	-/-	+/-	+/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-
CRP (mg/dL)		0.63	1.97	1.93	2.60	3.00	2.61	1.12	0.62	0.44	0.31	0.29	0.28	0.14
WBC/monocyte (%)		3170/8.2	3130/5.9	3320/8.4	3740/11.6	4300/15.3	4150/12.3	3990/15.6	5110/10.0	5190/11.1	6040/11.2	7050/11.1	6330/8.4	6580/9.4
AST/ALT (U/L)		132/116	194/128	308/209	188/167	154/154	129/149	104/131	80/114	59/101	48/86	40/76	31/65	30/57
Amylase/Lipase (U/L)		53/71		59/107	52/83	43/57			39/49					
Creatinine (mg/dL)		1.12	1.12	0.95	0.96	0.82	0.87	0.93	0.81	0.76	0.68	0.72	0.67	0.63
PCR	+	+				+	±						-	-

Patient 5	ID5	ID8	Day1(ID9)	Day 2	Day 3	Day 4	Day 5	Day 7	Day 10	Day 12	Day 15	Day 19	Day 22	Day 25
Incubation period: (2–4) days														
Fever/Myalgia	38.9℃/+	38.0℃/+	38.0℃/+	38.4℃/+	38.2℃/+	-/-	-/-	-/-	-/-	-/-	38.0℃/	-/-	-/-	-/-
Cough/Sputum	±/-	+/-	+/-	+/-	+/-	/+	/+	/+	/+	/+	/+	-/+	-/-	-/-
CRP(mg/dL)			16.72	16.01	14.97	13.00	4.67	0.97	4.86	6.81	28.99	2.75	1.88	0.43
WBC/monocyte (%)			3680/2.2	3410/5.6	3350/11.2	2320/14.0	2570/17.6	7170/36.3	21340/7.4	18750/5.1	13420/6.4	9270/10.8	8730/13.2	9950/9.2
AST/ALT(U/L)			137/75	233/170	358/283	171/189	91/106	54/107	28/76	40/49	56/42	37/48	18/26	27/17
Amylase/Lipase(U/L)			44/37	69/42	367/901	703/2457	416/1484	202/588	121/138	77/100	47/45			
Creatinine(mg/dL)			0.78	0.75	0.90	0.75	1.09	0.81	0.54	0.84	0.89	0.79	0.72	0.63
					mechanical ventilator →									
					extracorporeal membrane oxygenation →									
					PT [2]									
			antiviral therapy →											
PCR			+	+			+				+	±		-

[1]: Illness day. [2]: Plasma transfusion.

case in this study, the incubation period was 2–4 days, the patient already had pneumonia 2 days before diagnosis. However, he did not receive any treatment before diagnosis. And he died of shock with multiorgan failure. However, Patients 1, 2, and 4 had longer incubation periods of 9, 7, and 13 days, respectively. They had pneumonia, but their clinical symptoms and disease course were mild. In particular, Patients 1 and 4 had longer incubation periods. Patient 1 had fever at admission and was asymptomatic 1 day after admission, despite having pneumonia. Patient 4 also had pneumonia, but his clinical symptoms and disease course were mild.

All patients showed bradycardia or relative bradycardia during administration of high-dose ribavirin. The bradycardia disappeared after the dose was reduced from 3.6 g/day to 1.8 g/day. All patients were administered antiviral agents, although these were discontinued in Case 5 because of acute pancreatitis.

In summary, MERS-CoV infection can cause severe acute respiratory failure with high mortality. In our cases, early application of ECMO was crucial for treatment. Flexible bronchoscopy to clear lung excudates should be considered because thick, cream soup-like respiratory secretions often develop in critically ill patients. A short incubation period is associated with mortality and severity. Three patients had no respiratory symptoms, while other 2 patients had non-productive cough. Hence, it can be difficult to acquire specimens with which to perform MERS-CoV PCR. High-dose ribavirin therapy will likely cause bradycardia. Pneumonia usually affected the lower lobes and possibility of pneumonia should be considered in all patients with MERS-CoV infection, even in the absence of prominent respiratory symptoms. Fever can predict the prognosis of pneumonia in MERS-CoV infections. Taken together, MERS-CoV infection should be considered in cases of lower lobe pneumonia that do not respond to antibiotics during a MERS-CoV outbreak.

Ethical approval: IRB was obtained for this publication.

Conflict of interest None to declare.

REFERENCES

1. Zaki AM, van Boheemen S, Bestebroer TM, et al. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med. 2012;367:1814-20.
2. Joint Kingdom of Saudi Arabia/WHO mission. Middle East respiratory syndrome coronavirus. Riyadh, Saudi Arabia, 2013. Available at <http://www.who.int/csr/disease/coronavirus_infections/MERSCov_WHO_KSA_ Mission_Jun13u.pdf>. Accessed December 12, 2013.
3. Al-Tawfiq JA, Assiri A, Memish ZA. Middle East respiratory syndrome novel corona MERS-CoV infection. Epidemiology and outcome update. Saudi Med J. 2013;34:991-4.
4. Zumla A, Hui DS, Perlman S. Middle East respiratory syndrome. Lancet. 2015;386:995-1007.
5. Centers for Disease Control and Prevention. First confirmed Middle East respiratory syndrome coronavirus (MERS-CoV) infection in the United States and updated information on the epidemiology of MERS-CoV infection and guidance for the public, clinicians, and public health authorities–May 2014. MMWR Morb Mortal Wkly Rep. 2014;19:431-6.
6. Momattin H, Mohammed K, Zumla A, et al. Therapeutic options for Middle East respiratory syndrome coronavirus (MERS-CoV)–possible lessons from a systematic review of SARS-CoV therapy. Int J Infect Dis. 2013;17:e792-8.
7. Omrani AS, Saad MM, Baig K, et al. Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. Lancet Infect Dis. 2014;14:1090-5.
8. Virlogeux V, Fang VJ, Wu JT, et al. Incubation period duration and severity of clinical disease following severe acute respiratory syndrome coronavirus infection. Epidemiology. 2015;26:666-9.