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Outcome of Middle East Respiratory Syndrome (MERS) in hematology and oncology patients: A case series in Saudi Arabia

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ABSTRACT

Background: Middle East Respiratory Syndrome Coronavirus (MERS-CoV) is associated with a high fatality rate (34%), which is higher in the presence of co-morbidities. The aim of the current study was to assess the clinical course and the outcome in hematological or oncological malignancy cases, diagnosed with MERS-CoV.

Methods: This is a case series of hematological /oncological cases, diagnosed with MERS-CoV, in a tertiary care setting in 2015. The cases were identified based on the World Health Organization (WHO) MERS-CoV case definition. The demographic, clinical, and outcome data were retrieved from the patients' medical charts and electronic health records.

Results: In total, nine hematological or oncological cases were identified, diagnosed with MERS-CoV. The baseline malignant condition was hematological malignancy in seven patients, as well as colon cancer and osteosarcoma in one patient each. Six (67%) patients were male. The median age was 65 years (range 16–80 years). Co-morbidities included chronic kidney disease (n = 3.33%), diabetes mellitus (n = 3.33%), and hypertension (n = 2.22%). The presenting symptoms were shortness of breath (n = 6.66%), fever (n = 5.55%), cough (n = 2.22%), and diarrhea (n = 2.22%). Chest x-rays indicated bilateral infiltrates in 6 patients (66%). The PCR (polymerase chain reaction) test was repeated in six patients to confirm the diagnosis. The mortality rate was 100%, and the median time to death was 26 days (range 15–77 days).

Conclusion: MERS-CoV infection in this small cohort of hematology or oncology patients has a 100% mortality rate, regardless of the status of the underlying disease. The confirmation of the diagnosis may require repeated testing. Additional studies are required to verify the findings and to elucidate the disease pathogenesis in cancer patients.

Introduction

Middle East Respiratory Syndrome Coronavirus (MERS-CoV) is a β-coronavirus [1]. The first case was reported in Saudi Arabia in September 2012, and the virus spread to other Arab countries, including the United Arab Emirates, Jordan, Kuwait, Yemen, Lebanon, Oman, and Qatar [2]. According to the 2019 World Health Organization (WHO) report, 2494 laboratory-confirmed cases have been identified in 27 countries. The fatality rate is high in MERS-

Abbreviations: SARS, Acute Respiratory Distress Syndrome; MERS-CoV, Middle East Respiratory Syndrome Coronavirus; WHO, World Health Organization; SARS-CoV, Severe Acute Respiratory Syndrome Coronavirus; RT-PCR, Reverse Transcriptase Polymerase Chain Reaction; WBC, White Blood Cells.

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CoV cases (n = 858, 34.4%) [3]. The majority of the cases occurred in Saudi Arabia, with a case fatality rate of 37.1% [4]. The majority (75%) of the cases diagnosed with MERS-CoV had at least one co-morbidity [5].

Several countries reported MERS-CoV spreading through zoonotic transmission from dromedary camels [6–8]. The clinical presentation is comparable with Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) [3]. The symptoms in mild cases are low-grade fever, runny nose, sore throat, and aching muscles. Severe cases progress to acute respiratory distress syndrome [9,10]. In Korea, the MERS-CoV cases presented atypically [11]. The hospital outbreaks were due to human-to-human transmission [5].

The MERS-CoV diagnosis is confirmed with a Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) assay of a respiratory specimen [10,11]. Immunocompromised individuals are prone to MERS-CoV infection, with a higher mortality rate [5]. The current paper describes the clinical course and the outcomes of nine hematological or oncological cases diagnosed with MERS-CoV, admitted to the intensive care unit (ICU) in a tertiary care hospital in Saudi Arabia.

Methods

In total, 130 patients were diagnosed with MERS-CoV in June–September 2015, hospital outbreak [12]. The design of the study was a retrospective case series analysis of nine hematology or oncology patients diagnosed with MERS-CoV in the year 2015. The study was conducted at a tertiary care hospital in, Riyadh, Saudi Arabia. Ethical approval was obtained from the Institutional Review Board (IRB), with the approval number (RC16/095).

MERS-CoV case definition

The cases were identified based on a prior diagnosis of a hematological or solid organ neoplasm, with a confirmed MERS-CoV infection. The patients presented with acute respiratory illness, a thoracic image suggestive of pneumonia and acute respiratory distress syndrome (SARS), and a confirmation done with RT-PCR assays targeting upstream of the E gene and the open-reading frame gene 1a.

A case was considered *confirmed* MERS-CoV if the laboratory confirmation of the RT-PCR was available. A *probable* case had a febrile respiratory illness with clinical, radiological, or histopathological signs, but an inconclusive RT-PCR test [13]. In the case of a negative result, the test was repeated by the treating physician.

The patients were followed-up from admission until death. The data included patient demographic characteristics, co-morbidities, underlying diagnosis, history of contact with a MERS-CoV patient, presenting symptoms, exposure to camel urine or milk, laboratory, RT-PCR, length of hospital or ICU stay, radiological data, and the outcome. The relevant data were extracted from the electronic medical records. The laboratory data were assessed at multiple time points (day 1, 7, 14, 21, 28). A white blood cell (WBC) count lower than 4.0×10^9/L was considered as leukopenia and a platelet count less than 140×10^9 as thrombocytopenia. The liver enzymes were deemed elevated if they were more than twice the range of the upper reference limit.

The variables gender, primary disease diagnosis, co-morbidities, disease stage, presenting symptoms, chest x-ray findings, and type of specimen are displayed as frequency and percentage. The age, length of stay in the ward, and time to death are summarized as median and range. The repeated samples and the clinical course of the disease are displayed in figures. The descriptive analysis were done with SAS version 9.4 (SAS Institute, Cary, NC, USA).

Table 1
Cohort characteristics.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Age in years	16	27	33	41	65	75	77	78	80
Gender	Male	Female	Male	Male	Male	Male	Female	Female	Male
Primary Disease	T cell -ALL	B-ALL	Cutaneous T-cell lymphoma	Metastatic Osteosarcoma Right fibula	MF	Recto-sigmoidal carcinoma	CLL	CLL	MM
Primary Disease Status	Relapse	Relapse	Refractory	–	Active	Refractory	Refractory	Refractory	Refractory
Immunosuppressants	FLAG	FLAG Clofarabine/ Cyclophosphamide with Etoposide	CHOP GDP Hyper-CVAD part B	Methotrexate	Ruxolitinib	Xeloda and Oxaliplatin	Ibrutinib	None	Carfilzomib and Dexamethasone
Co-morbidities	None	None	None	CKD	DM, CKD	None	DM, HTN	DM, HTN, Atrial fibrillation	IHD, CKD
Exposure to Camel milk/urine	No	No	No	No	No	No	No	Yes	No
HSCT	Allogeneic HSCT	No	No	–	No	–	No	No	No
Clinical Presentation	Fever, SOB	Fever, SOB	Fever, cough	SOB	Fever, cough, SOB	SOB, bloody diarrhea	Fever, diarrhea	Cough, fever	SOB, hemoptysis
Other Pathogens	None	None	Gram negative bacteremia	None	None	Enterococcus	None	None	None
Chest x-ray	Left lower lobe consolidation	Bilateral infiltrates	Bilateral infiltrates	Bilateral infiltrates and pleural effusion	Bilateral interstitial opacities	Left lower lobe consolidation /pleural effusion	Bilateral infiltrates	Right side consolidation /pleural effusion	Bilateral infiltrates
Ventilation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Outcome	Died	Died	Died	Died	Died	Died	Died	Died	Died
Days post ICU admission	7	6	6	23	6	19	7	1	19

Abbreviations: MF, Myelofibrosis; MM, Multiple Myeloma; CLL, Chronic lymphocytic leukemia; ALL, Acute lymphoblastic leukemia; HSCT, Hematopoietic stem cell transplantation; CKD, chronic kidney disease; IHD, ischemic heart disease; DM, Diabetes mellitus; HTN, Hypertension; SOB, Shortness of Breath; ICU, intensive care unit.

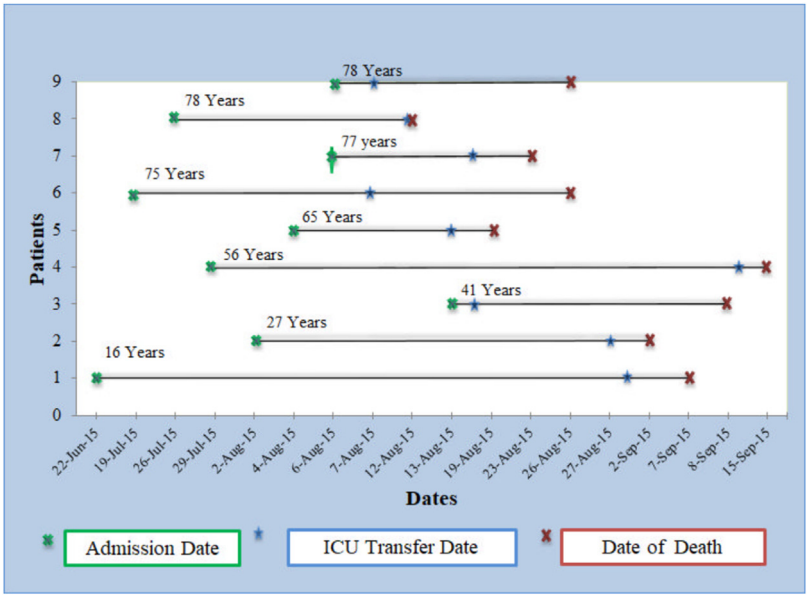

Fig. 1. Patients' disease course.

Results

Cohort characteristics

In total, in 2015 nine hematological or oncological patients had a confirmed diagnosis of MERS-CoV. All patients were exposed to the hospital environment during the 2015 hospital outbreak, and only one had a history of exposure to camels.

The majority of the patients (7/9) had a hematological malignancy, including chronic lymphocytic leukemia (CLL, n = 2), acute lymphocytic leukemia (B-ALL, n = 1), T cell ALL (n = 1), cutaneous T-cell lymphoma (n = 1), multiple myeloma (MM, n = 1), and primary myelofibrosis (PMF, n = 1). One patient was diagnosed with colon cancer and one with osteosarcoma. Six (67%) patients were male and the median age was 65 years, with the range 16–80 years. Half of the cohort (55%) was in a refractory disease stage when admitted. Four (44%) patients had no comorbid condition. Three (33%) patients had chronic kidney disease, three diabetes mellitus (33%), two hypertension (22%), and one was dialyzed. One patient had an allogeneic hematopoietic stem cell transplantation (HSCT) (Table 1).

Clinical presentation

The lower respiratory tract was primarily involved, with the most prevalent presenting symptoms shortness of breath (n = 6.66%) and fever (n = 5. 55%). Only 2 patients (22%) coughed or had flu, and diarrhea was observed in 2(22%) (Table 1). The chest x-ray demonstrated bilateral infiltrates in 6 patients (67%) (Table 2).

Table 2
Study Cohort Follow-up.

Variables	*n* = 9
Chest X-ray findings n (%)[a]	
Bilateral infiltrates	6 (66.6)
Pleural effusion	3 (33.3)
Consolidation	2 (22.2)
Length of stay in ward (days) (median, range)	16 (1–70)
Days stayed in ICU (median, range)	7 (6–19)
Time taken to death (days) (median, range)	26 (15–77)
Community exposure to infected person	1 (11)
In-hospital during an outbreak[b]	9 (100)
Type of specimen with positive PCR n (%)	
Tracheal Aspirate	6 (67)
Nasopharyngeal swab	2 (22)
Sputum	1 (11)

[a] not mutually exclusive.
[b] Referring to the outbreak period of mid-June to mid-September 2015.

Laboratory data

The laboratory parameters are summarized in Table 3. The median WBC count reduced from 12.75 × 10^9/L on day 1 to 5.50

Table 3
Laboratory Results of the Study Cohort Overtime.

Laboratory Parameters (median, range)	Day 1	Day 7	Day 14	Day 21	Day 28
WBC (4.00–11.00 × 10^9/L)	11 (4.7–31.3)	7.95 (0.10–25.2)	6.6-(0–25.3)	5.45 (0.2–16.7)	5.50 (0.40–24.9)
Neutrophils (2.00–7.50 × 10^9/L)	19 (4.0–56.0)	54.0 (5.0–54.0)	59.5 (2.0–86)	27.5 (8.0–47)	62.5 (36–86)
Hemoglobin (120–160 gm/L)	99.5 (68–157)	82.5 (71–142)	83 (72–120)	72 (54–87)	69 (63–102)
Platelet (150–400 × 10^9/L)	52.0 (7.0–256)	79.5 (14–168)	46.0 (11–261)	57.5 (2.0–378)	74.0 (10.0–335)
AST (5–34 U/L)	18.5 (10.0–77.0)	34.0 (9.0–50.0)	41.0 (8.0–65.0)	33.0 (22.0–41.0)	43.0 (5.0–246.0)
ALT (5–55 U/L)	14.0 (9.0–240.0)	19.0 (6.0–179.0)	27.5 (17.0–139)	26.0 (24.0–32.0)	20.0 (6.0–32.0)
Alkaline phosphatase (40–15 U/L)	114.5 (43–397)	86.0 (81–307)	183 (111–398)	86 (86–320)	119.5 (86–535)
Total Bilirubin (3.4–20.5 umol/L)	8.8 (5.0–53.4)	13.3 (9.8–37.2)	14.5 (9.2–50.45)	14.9 (8.9–17.9)	18.05 (9.0–89.2)
PT (9.38–12.34 s)	11.5 (10.7–16.4)	11.4 (10.0–17.4)	11.9 (9.40–41.0)	14.1 (10.3–15.2)	13.9 (10.9–16.7)
PTT (24.84–32.96 s)	33.05 (21.2–39.9)	29.2 (26.3–43.9)	35.2 (22.2–69.2)	35.0 (24.5–60.5)	35.4 (24.4–50.5)
INR (0.80–1.20)	1.06 (0.98–1.50)	1.05 (0.92–1.60)	1.09 (0.87–3.76)	1.29 (0.95–1.39)	1.28 (1.0–1.53)
Creatinine (50–98 mol/L)	71 (37–156)	52 (33–541)	80 (30–322)	51 (36–233)	49 (38–191)

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; PT: prothrombin time; PTT: partial thromboplastin time; INR: international normalized ratio.

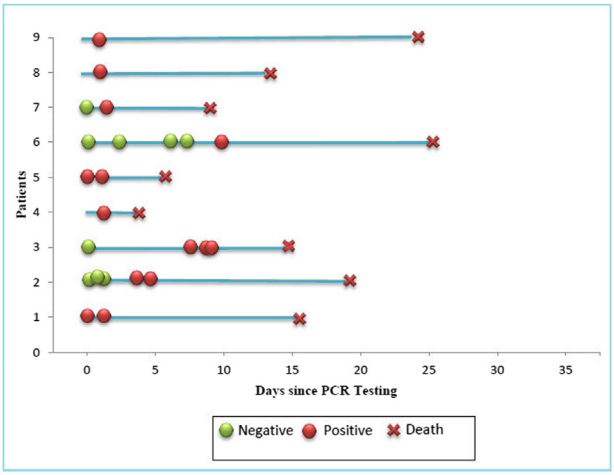

Fig. 2. Sequential RT-PCR results.

$\times 10^9$/L on day 28. The median hemoglobin reduced from 99.5 gm/L on day 1 to 69 g m/L on day 28. The median neutrophil count increased from 16% on day 1 to62.5% on day 28.

Treatment course

The patients' disease course is presented in Fig. 1. The length of stay in the ward was 16 days (range 1–70 days). The group of patients younger than 50 years stayed in the hospital longer than the group 50 years and older. The stay in ICU was shorter than the stay in the ward (Table 2). All patients required ICU admission and mechanical ventilation soon after the symptoms appeared. The management was mainly supportive, and antibiotics were used for bacterial co-infections, when required.

RT-PCR testing

The specimen was primarily taken from tracheal aspirate (n = 6. 67%) (Table 2). The diagnosis was confirmed through RT-PCR testing (Fig. 2). Six patients had repeated RT-PCR testing to obtain a positive result.

Outcome data

Two patients had central line related bacteremia, one gram-negative, and one enterococcus. The mortality rate was 100%. The median time to death was 26 days (range 15–77 days) (Table 3). The 30-day mortality was 55%.

Discussion

According to the 2018 WHO global summary and assessment of risk report, Saudi Arabia reported the majority of the MERS-CoV cases [14]. In this paper, we report nine hematological or oncological cases diagnosed with MERS-CoV in Saudi Arabia. All the patients presented with respiratory tract symptoms, including shortness of breath and cough, and some also had diarrhea [10,15,16]. A meta-analysis indicated that cough, fever, and shortness of breath were the most prevalent symptoms in patients diagnosed with MERS-CoV [17]. Multiple risk factors of acquiring MERS-CoV have been reported, including exposure to dromedary camels, diabetes mellitus, and cardiovascular disease [18]. In the current case series, only one patient was exposed to camels. Five patients had one co-morbidity, including diabetes mellitus, ischemic heart disease, or chronic kidney disease [14]. A systematic review reported that 50% of the patients diagnosed with MERS-CoV were diagnosed with diabetes and hypertension, and 30% with cardiac disease [17].

The mode of testing, with blood or body fluids, is important for the diagnosis. In the early phase, nucleic acid testing is diagnostic, however, antibodies are only detectable later in the disease course [19]. The diagnosis of MERS-CoV infection mainly depends on an RT-PCR assay of a respiratory specimen [20]. A RT-PCR was conducted for all the patients in the case series as it is the gold standard diagnostic test [21]. The samples were repeated at several time points based on the clinical judgement of the treating physician. The WHO recommends testing with upper and lower respiratory tract specimens. In our sample, a tracheal aspirate was done in 67%, and a nasopharyngeal swab in 22% [22].

In total, 130 cases were diagnosed with MERS-CoV during June–September 2015 hospital outbreak. Out of 130, 61(47%) had hospital acquired, while 26(20%) had community acquired MERS-CoV. The fatality rate was higher in hospital acquired infection 40/61(65.5%) compared with community acquired infection 11/26(42.3%) [12]. In the current case series, the overall mortality was 100%, however, the 30-day mortality was 55%, which is higher than reported by Ahmed et al., 28.3% in 660 MERS-CoV cases [23]. As reported, the mortality rate is higher in elderly patients (45.2%), compared to patients younger than 60 years (20%) [23–27]. In the current case series, the group aged 60–80 years died, on average, within 21 days (range 15–38 days). The mortality in hematological malignancy cases diagnosed with coronavirus disease 2019 (COVID-19) is 37% (198/536) [28]. However, in a recent case series with eleven HSCT patients, diagnosed with COVID-19, none required mechanical ventilation and there was no mortality [29]. In the current case series, only one patient had HSCT.

Clinical trials are ongoing to identify the optimal therapeutic management for MERS-CoV [30]. Human vaccine development remains a major challenge, but various vaccines against MERS-CoV have been developed and are being tested in clinical trials [31,32].

According to literature, MERS-CoV outbreaks were due to a lack of awareness of the infection, overcrowding, lack of isolation rooms, and inadequate infection control measures [33]. Infection control and prevention became more challenging with the COVID-19 pandemic.

Limitations

This case series is specific to MERS-CoV infection in hematology or oncology patients. The small sample size is a major limitation of the study, preventing the stratification of individuals between different clinical profiles, and precluding statistical analysis. The clinical findings cannot be generalized to patients diagnosed with malignancy and MERS-CoV. In addition, the retrospective nature of the data and the dependence on documentation for assessing the clinical presentation and outcomes, is a limitation of the study.

Conclusion

In conclusion, patients with MERS-CoV have high mortality rate in general. Patients with comorbidities are at a greater risk of mortality when developing MERS-CoV. In particular, we have observed a 100% mortality rate in hematology or oncology patients diagnosed with MERS-CoV, regardless of age and the underlying disease status. The clinical presentation is not distinctive and the confirmation of the diagnosis may require several respiratory samples. Additional studies are required to verify the findings and to elucidate the disease pathogenesis in cancer patients.

Authors' contributions

AA: conceived the idea, designed the study, reviewed results, and the manuscript.

NAS: descriptive analysis, reviewed the results, created the tables and figures and drafted the manuscript.

HR, MA and MAM: wrote the study proposal, developed the data collection form, and collected the data.

MB, HS, KA, GG, MD, BA, MAZ, AO, and AAH: reviewed the manuscript.

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Competing interests

None declared.

Ethics approval and consent to participate

The study was approved by King Abdullah International Medical Research Center (KAIMRC), Institutional Review Board (RC16/095).

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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