Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and Pulmonary Tuberculosis Co-Infection: Implications for Infection Control

Sarah H. Alfaraj[a], Jaffar A. Al-Tawfiq [b, c], Talal A. Altuwaijri [d], Ziad A. Memish [e, f]

[a] Corona Center, Infectious Diseases Division, Department of Pediatric , Prince Mohamed Bin Abdulaziz Hospital, Ministry of Health, Riyadh, Saudi Arabia

[b] Johns Hopkins Aramco Healthcare, Dhahran, Kingdom of Saudi Arabia

[c] Indiana University School of Medicine, Indianapolis, IN, USA

[d] Department of Surgery, Prince Mohamed Bin Abdulaziz Hospital, Ministry of Health, Riyadh, Saudi Arabia

[e] College of Medicine, Alfaisal University, Riyadh, Saudi Arabia

[f]. Infectious Diseases Division, Department of Medicine, Prince Mohamed Bin Abdulaziz Hospital, Ministry of Health, Riyadh, Saudi Arabia

Running title: MERS-CoV and Pulmonary Tuberculosis Co-Infection

Key word: Middle East Respiratory Syndrome Coronavirus; MERS-CoV; Tuberculosis

Correspondence:

Ziad A. Memish College of Medicine, Alfaisal University, P.O. Box 54146, Riyadh 11514, Kingdom of Saudi Arabia, zmemish@yahoo.com; Telephone: +966-50-5483515

Fax: +966-11-2616464

This is the author's manuscript of the article published in final edited form as:
Alfaraj, S. H., Al-Tawfiq, J. A., Altuwaijri, T. A., & Memish, Z. A. (2017). Middle East Respiratory Syndrome Coronavirus and Pulmonary Tuberculosis Coinfection: Implications for Infection Control. Intervirology, 60(1–2), 53–55. https://doi.org/10.1159/000477908

Abstract:

Objectives: Co-infection of Middle East Respiratory Syndrome (MERS-CoV) with tuberculosis had not been previously reported. Here, we present two cases with both MERS-COV and pulmonary tuberculosis.

Methods: A case series of two cases with MERS-COV and pulmonary tuberculosis.

Results: The first case was a 13 year-old patient who was admitted with a two-month history of fever, weight loss, night sweats and cough. The second patient was a 30 year old who had a four-week history of cough associated with shortness of breath and weight loss of 2 kg. The two patients were diagnosed to have pulmonary tuberculosis and had had positive MERS-CoV. Both patients were discharged home to complete the therapy for tuberculosis. It is likely that both patients had pulmonary TB initially as they had prolonged symptoms and then they developed MERS-COV infection.

Conclusions: It is important to carefully evaluate suspected MERS-CoV patients for the presence of other infectious diseases such as tuberculosis especially if cohorting is done for suspected MERS to avoid nosocomial transmission.

Introduction:

Middle East Respiratory Syndrome (MERS-CoV) was first discovered in Saudi Arabia in 2012 [1]. As of Jan 26, 2017, a total of 1888 laboratory confirmed cases of MERS-CoV infection, including at least 670 related deaths have been reported to WHO [2]. The clinical presentations, diagnosis and laboratory findings were previously described [3]. As highlighted in previous studies, none of the presenting symptoms helped distinguish patient with MERS-CoV infection from the patient presenting with influenza like illness (ILI) [4,5]. Even with access to full viral panel on all ILI patients and with evidence of influenza virus as the etiology, MERS-CoV cannot be ruled out. A previous study showed one of 5 patients with MERS-CoV had influenza co-infection [6]. Investigation of the initially described 47 MERS-CoV patients showed no co-infection with MERS-CoV as microbiological investigations excluded bacterial pathogens associated with community-acquired pneumonia [7]. Co-infection of MERS-CoV with other viruses such as influenza had been reported [8].

From April 2014 to November 2016, 295 confirmed cases were admitted to Prince Mohamed Bin Abdulaziz Hospital (PMAH), a MERS-CoV designated hospital in the capital Riyadh [5]. To our knowledge, co-infection of MERS-CoV and *Mycobacterium tuberculosis* was not reported previously. Here, we present two cases of co-infection of MERS-CoV and pulmonary tuberculosis.

Methods:

Patient data: We extracted the date of admission, gender, age, results/dates of MERS-CoV testing, and patients' outcomes. We included the initial laboratory data: White Blood Cell count (WBC) 10^9 per liter, Hemoglobin (Hgb) grams/deciliter, Platelets 10^9 per liter, Creatinine

micromoles per liter, Albumin gram per liter, Aspartate Aminotransferase (AST) units per liter, Alanine Aminotransferase (ALT) units per liter, and initial chest-X-ray (CXR) results. **The study complied with institutional ethical guidelines.**

MERS-CoV testing: Nasopharyngeal swabs were tested for MERS-CoV using real-time reverse-transcription polymerase chain reaction (RT-PCR) as described previously [7,9]. The test amplified both the upstream E protein (upE gene) and ORF1a. A positive case is considered if both assays were positive and controls were negative, as described previously[7]. The specimens were submitted to and testing was carried out at the Saudi Ministry of Health MERS-CoV regional laboratory.

CASE 1:

A 13 year-old girl was admitted with a two-month history of fever, weight loss, night sweats and cough. She had a history of contact with pulmonary tuberculosis patient in the past. Four days prior to her presentation, she had worsening respiratory symptom. No history of contact with camels or MERS-CoV patient.

On examination: she looked ill, cachectic, with respiratory distress. She was febrile T: 39°C, BP: 100/59 RR 38 SPO2 95%; weight 40KG. There was no lymphadenopathy. Chest: bronchial breathing and crepitation bilaterally.

Chest X-rays showed diffuse multi-nodular infiltration consistent with miliary TB (figure 1). CT-scan of chest and abdomen showed multiple pulmonary nodules randomly distributed in both lungs. Multiple areas of consolidation especially within the left upper lobe were also noted. Bilateral upper lobes multiple cystic areas probably representing cystic bronchiectasis changes were seen. There were necrotic mediastinal and enlarged hilar lymph node.

A nasopharyngeal swab collected upon presentation was positive for MERS-CoV and negative for infuenza and a repeated swab after 48 Hrs was negative MERS-CoV. A tuberculin skin test (TST) was 10 mm, and sputum AFB smears were negative, but gastric aspirate were positive for *M .tuberculosis* by PCR, mycobacterium culture was positive for *M. tuberculosis*. During hospitalization, the patient had respiratory distress and hypoxia requiring intensive care (ICU) admission for observation. Isoniazid, ethambutol, pyrazinamoide and rifampicin were started. The patient was discharged home in stable condition after hospitalization for 3 weeks to complete anti-TB therapy.

CASE 2

A 30 year-old Filipino female nurse had unprotected exposure to a patient with MERS-CoV on May 15, 2015. During that time, she was quarantined for 14 days in the hospital and two nasopharyngeal swabs for MERS-CoV were negative. A month later, she went to the Philippines. Two weeks after her arrival to Philippines, she manifested symptoms of dry cough and shortness of breath, and she took amoxicillin with no improvement. On August 7, she returned to Saudi Arabia. She was evaluated on August 12 for dry cough for 4 weeks, associated with shortness of breath associated with weight loss of 2 kg. She had no history of contact with TB patient and no history of recent contact with MERS-COV patient.

On examination, temperature 37 °C (Oral) BP: 133/88 SpO2: 94%; Chest examination revealed crepitation in the left upper lobe. Laboratory data showed: WBC 6.8, neutrophil 68%, ESR 90, and CRP: 0.39.

Chest x-ray showed non-homogenous opacity involving most of the left lung more prominent at the upper and middle left lung zones (figure 2).

A nasopharyngeal swab collected upon presentation was positive for MERS-CoV and negative for influenza. A repeated swab after 48Hrs was negative for MERS-CoV. Sputum AFB PCR, AFB smear were positive but TB culture was negative. She was treated with isoniazid, ethambutol, pyrazinamoide and rifampicin.

Discussion:

The presentation of these two patients is of particular interest due to the co-infection with MERS-CoV and pulmonary TB. We are not aware of any previous such report. Co-infection of MERS-CoV patients with influenza A, parainfluenza, herpes simplex, and *Streptococcus pneumoniae*, Herpes simplex virus type 1 and rhinovirus RNA14 were reported [8,10,11]. Co-infection with *M. tuberculosis* is of particular importance as the diagnosis of TB might be overlooked and shadowed by the concern about MERS-CoV infection as occurred during the SARS outbreak [12]. One patient contracted SARS when she was cohorted with SARS patient although she initially had TB [12]. In another report, a healthcare worker had healthcare-associated SARS infection and was diagnosed with pulmonary TB and two other patients were known to have pulmonary TB and had a superinfection with SARS-CoV after contact with other hospitalized SARS patients [13]. Another two patients had pulmonary TB after recovery from SARS [14]. In this report, the first patients was co-infected with MERS-CoV and pulmonary TB and might had been infected with both as the *M. Tuberculosis* culture was negative. Both MERS-CoV and TB may cause immune suppression and augment the infection of each other as was described with SARS and TB [13]. It is important to carefully evaluate suspected MERS-CoV for the presence of other infectious diseases such as TB especially if cohorting is done for suspected MERS to avoid nosocomial transmission of TB as was described with the SARS [15].

In the current cases it is likely that both patients had pulmonary TB initially as they had prolonged symptoms and then they developed MERS-COV infection.

Conflict of Interest:

Authors have no conflict of interest to declare

References:

[1] Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus ADME, Fouchier RAM. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med 2012;367:1814–20. doi:10.1056/NEJMoa1211721.

[2] WHO. Middle East respiratory syndrome coronavirus (MERS-CoV) n.d. http://www.who.int/emergencies/mers-cov/en/.

[3] Al-Tawfiq JA, Memish ZA. Managing MERS-CoV in the healthcare setting. Hosp Pr 2015;43:158–63. doi:10.1080/21548331.2015.1074029.

[4] Al-Tawfiq JA, Hinedi K, Ghandour J, Khairalla H, Musleh S, Ujayli A, et al. Middle east respiratory syndrome coronavirus: A case-control study of hospitalized patients. Clin Infect Dis 2014;59. doi:10.1093/cid/ciu226.

[5] Mohd HA, Memish ZA, Alfaraj SH, McClish D, Altuwaijri T, Alanazi MS, et al. Predictors of MERS-CoV infection: A large case control study of patients presenting with ILI at a MERS-CoV referral hospital in Saudi Arabia. Travel Med Infect Dis 2016;14:464–70. doi:10.1016/j.tmaid.2016.09.008.

[6] Yavarian J, Rezaei F, Shadab A, Soroush M, Gooya MM, Azad TM. Cluster of Middle East respiratory syndrome coronavirus infections in Iran, 2014. Emerg Infect Dis

2015;21:362–4. doi:10.3201/eid2102.141405.

[7] Assiri A, Al-Tawfiq JA, Al-Rabeeah AA, Al-Rabiah FA, Al-Hajjar S, Al-Barrak A, et al. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: A descriptive study. Lancet Infect Dis 2013;13:752–61. doi:10.1016/S1473-3099(13)70204-4.

[8] Alfaraj SH, Al-Tawfiq JA, Alzahrani NA, Altwaijri TA, Memish ZA. The impact of co-infection of influenza A virus on the severity of Middle East Respiratory Syndrome Coronavirus. J Infect 2017. doi:10.1016/j.jinf.2017.02.001.

[9] Corman VM, Müller MA, Costabel U, Timm J, Binger T, Meyer B, et al. Assays for laboratory confirmation of novel human coronavirus (hCoV-EMC) infections. Euro Surveill 2012;17:49.

[10] World Health Organization. WHO guidelines for investigation of cases of human infection with Middle East Respiratory Syndrome Coronavirus (MERS-CoV) 2013. http://www.who.int/csr/disease/coronavirus_infections/MERS_CoV_investigation_guideline_Jul13.pdf (accessed January 17, 2017).

[11] Drosten C, Seilmaier M, Corman VM, Hartmann W, Scheible G, Sack S, et al. Clinical features and virological analysis of a case of Middle East respiratory syndrome coronavirus infection. Lancet Infect Dis 2013;13:745–51. doi:10.1016/S1473-3099(13)70154-3.

[12] Wong C-Y, Wong K-Y, Law TSG, Shum T-T, Li Y-K, Pang W-K. Tuberculosis in a SARS outbreak. J Chin Med Assoc 2004;67:579–82.

[13] Liu W, Fontanet A, Zhang P-H, Zhan L, Xin Z-T, Tang F, et al. Pulmonary tuberculosis and SARS, China. Emerg Infect Dis 2006;12:707–9. doi:10.3201/eid1204.050264.

[14] Low JGH, Lee CC, Leo YS, Guek-Hong Low J, Lee C-C, Leo Y-S. Severe Acute Respiratory Syndrome and Pulmonary Tuberculosis. Clin Infect Dis 2004;38:e123–5. doi:10.1086/421396.

[15] Centers for Disease Control and Prevention (CDC). Nosocomial transmission of Mycobacterium tuberculosis found through screening for severe acute respiratory syndrome--Taipei, Taiwan, 2003. MMWR Morb Mortal Wkly Rep 2004;53:321–2.

Figure 1: Diffuse multi-nodular infiltration consistent with military tuberculosis

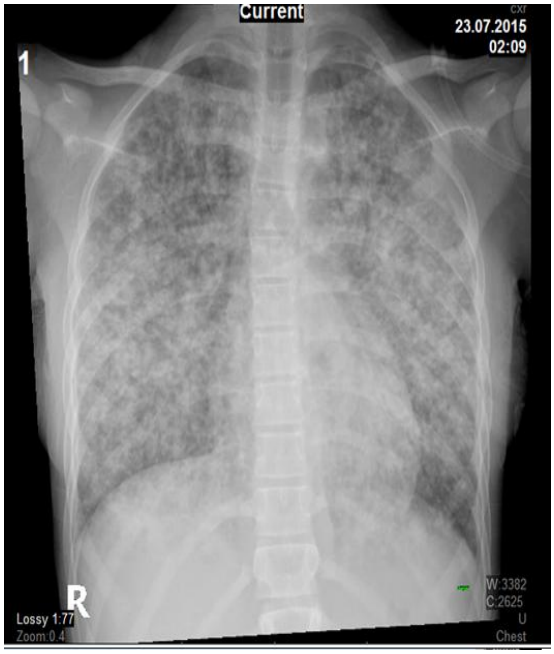

Figure 2: Chest X-ray showing a non-homogenous opacity involving most of the upper and middle left lung zones