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The Impact of Co-infection of Influenza A Virus on the on Severity of Middle East Respiratory Syndrome Coronavirus

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Ho and colleagues recently drew attention to the consequences of co-infection with Influenza and HIV [1]. We present four cases of combined infection with influenza and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection. Nasopharyngeal swabs or tracheal aspirates were tested for MERS-CoV using real-time reverse-transcription polymerase chain reaction (RT-PCR) [2,3]. Samples were tested for Influenza A, B and H1N1 by rapid molecular test (GenEXper for detection of flu A, B and 2009 H1N1, Cepheid).

CASE 1:

A 39 year-old male, health care worker, an engineer who became ill seven days before admission. He had fever > 38°C, cough and sore throat. He also had no nausea, vomiting, diarrhea and shortness of breathing (SOB). He had no history of travel or contact with positive case or camels. He was febrile with a temperature of 39.5^0C. Chest X-ray showed non homogenous opacity at the lower right lung zone. A nasopharyngeal swab was positive for MERS-CoV with Ct value UPE GENE 34 ORF1A 34 (Table 1). The test was negative for influenza but a repeat swab after 48 hrs was negative for MERS-CoV and positive for H1N1. The patient received azithromycin, ceftriaxone and oseltamivir. The patient was discharged home after two negative swabs of MERS-CoV and being asymptomatic for 48 hours.

CASE 2:

A 61 year-old female with diabetes mellitus and dyslipidemia was admitted with a three-day history of shortness of breath and productive cough. She also had no nausea, vomiting and diarrhea. She has no history of travel or contact with positive case or camels. She was afebrile with a temperature of 37^0C. Chest x-ray showed patchy opacities involving middle and lower zones of both lung fields.

A nasopharyngeal swab was positive for MERS-CoV with Ct value upE gene 34 ORF1A 35 and negative for influenza. A repeated swab after 48 hrs was negative for MERS-CoV but positive for H1N1. She required BIPAP and she was subsequently intubated and was started on mechanical ventilation. She was extubated after 13 days. The patient received piperacillin – tazobactam, and erythromycin. The patient was discharged home after she had 2 negative swabs of MERS-CoV and being asymptomatic for 48 hours.

CASE 3:

A 29 year-old housekeeper female was admitted with two days history of fever and cough. She had no nausea, vomiting, diarrhoea nor shortness of breathing. She had a history of contact with MERS-CoV positive case. She was afebrile with a temperature of 36.9^0C. Chest x-ray was normal. A nasopharyngeal swab collected upon presentation was positive for MERS-CoV with CT value upE gene 32 ORF1A 32. The swab was negative for influenza. A repeated swab after 48hrs was positive MERS-CoV and positive for H1N1. The patient received oseltamivir, azithromycin and ceftriaxone. The patient was discharged home after she had 2 negative swab of MERS-CoV and she was asymptomatic for 48 hours.

CASE 4:

The patient was a 73 year-old female with a history of hypothyroidism, heart failure, lymphoma, and lung fibrosis. She has no history of travel or contact with positive case or camels. Four days prior to her presentation, she had productive cough and shortness of breath. She had no fever, diarrhea, vomiting or nausea. She was afebrile with a temperature of 36.7^0C. Chest X-ray showed bilateral diffuse (Figure 1). A nasopharyngeal swab was positive for MERS-CoV with Ct value upE gene 37; ORF1A 36 and negative for Influenza. A repeat swab after 3 days was

negative for MERS-CoV but positive for influenza A. The patient was treated with piperacillin-tazobactam for six days and oseltemavir for 5 Days. The patient was discharged home after two negative MERS-CoV and she was asymptomatic for 48 hours.

These patients highlight the co-infection with MERS-CoV and influenza. The exact reason to have a negative influenza test at the time of positive MERS-CoV is not completely understood. It is possible that the presence of MERS-CoV inhibits the PCR reaction for influenza virus. However, an earlier case of MERS-CoV tested initially positive for influenza A(H1N1)pdm09 [4]. On the other hand, the positivity of nasal swabs for influenza is specimen and method dependent [5]. Thus, initially negative influenza tests could be a false test result. Positive results for viral respiratory pathogens should not preclude testing for MERS-CoV because co-infection can occur [6]. Only a small number of MERS cases had co-infection with influenza A, parainfluenza, herpes simplex, and *Streptococcus pneumoniae* [7]. In one case, a co-infection with Herpes simplex virus type 1 DNA13 and rhinovirus RNA14 were detected by RT-PCR [8]. The investigation of the first 47 cases showed no co-infection with MERS-CoV [2]. There is a controversy regarding the risk of increased or decreased severity of co-infections. For example co-infections with Respiratory Syncytial Virus (RSV) and human meta-pneumovirus (hMPV) causes more severe infection than either virus alone with longer hospitalization and oxygen requirement [9]. Other studies did not demonstrate these effects [10]. The association and the impact of co-infection with MERS-CoV and influenza viruses deserve further evaluation and studies.

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Table 1: A Summary of the Four Cases of Co-Infection of MERS-CoV and Influenza

#	Age	Gender	Symptoms	Comorbidity	Sample Type	Viral Load CT Value (upE gene)	Co-Infection	CXR	Intensive Care	Outcome	Days ill before Hospitalisation	Oxygen requirement
1	39	Male	Fever, cough, sore throat	None	NPS	34	H1N1	Non-homogenous opacity in lower right lung zone. clear both	NO	Discharged home	7	Nil
2	61	Female	Productive cough, SOB	DM , hypothyroidism	NPS	35	H1N1	Patchy opacities involving middle and lower zones of both lung fields	YES	Discharged home	3	Ventilator for 13 days
3	29	Female	Fever, cough	None	NPS	32	H1N1	Normal	NO	Discharged home	2	Nil
4	73	Female	SOB, productive cough	CHF, hypothyroidism	NPS	36	Influenza A	Bilateral diffuse infiltrate	NO	Discharged home	4	Nasal Canula

NPS=nasopharyngeal swab; DM=diabetes mellitus; SOB=shortness of breath; CHF=congestive heart failure

Figure 1: A Chest Radiograph showing bilateral diffuse opacities