CLINICAL VIGNETTE

Hospitalization of an Immunocompromised Patient with Neutropenic Fever Due to Human Metapneumovirus Infection

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A 64-year-old man presented to the emergency department during the springtime with recurrent fevers over 100.4°F. His past medical history was significant for stage IV chronic lymphocytic leukemia. He was undergoing chemotherapy with completion of the fourth cycle of rituximab, fludarabine, cyclophosphamide six weeks prior to hospitalization. His fifth cycle of chemotherapy was scheduled earlier during the week of presentation, but was postponed due to thrombocytopenia. He had also reported having "a tickle in the back" of his throat. Throughout the week, he subsequently developed chills, rhinorrhea with postnasal drip, nonproductive cough, and a headache when he coughed. On presentation to the hospital, review of systems were negative for diaphoresis, chest pain, nausea, abdominal pain, vomiting, diarrhea, constipation, dysuria, myalgias, arthralgias, rash, hemoptysis, melena, hematochezia, easy bruising, and hematuria.

Other past medical history included coronary artery disease, dyslipidemia, paroxysmal atrial fibrillation, gastroesophageal reflux disease, and pancytopenia. His father and mother had heart disease. He did not smoke or use illicit drugs. He drank alcohol occasionally and lived at home with his wife who was healthy. He was unaware of any sick contacts. He was compliant with his home medications, which included prophylactic trimethoprim sulfamethoxazole and valacyclovir.

The initial physical exam was benign. Vital signs were normal with oral temperature of 98.7 °F, heart rate 62 beats/minute, respirations 18 breaths/minutes, blood pressure 116/58, and pulse oximetry 98% on room air. Chemistry panel was unremarkable. However, his complete blood count revealed pancytopenia with white blood cell count 400/CMM, hemoglobin 11.2 gm/dL, and platelets 16,000/CMM. The absolute neutrophil count was 164/CMM.

Respiratory PCR panel detected human metapneumovirus. Other pathogens tested that were not detected included Adenovirus, Coronavirus 229E, Coronavirus HKU1, Coronavirus NL63, Coronavirus OC43, Human Rhinovirus/Enterovirus, Influenza A, Influenza B, Para-influenza Virus 1, Parainfluenza Virus 2, Parainfluenza Virus 3, Parainfluenza Virus 4, Respiratory Syncytial Virus, Bordetella pertussis, Chlamydophila pneumoniae, and Mycoplasma pneumoniae.

The patient was admitted for neutropenic fever due to human metapneumovirus. He was placed on empiric vancomycin and piperacillin/tazobactam for risk of bacterial superinfection given his immunocompromised state. He continued on viral prophylaxis with valacyclovir. Supportive measures included intravenous ketorolac for his headache and saline nasal spray for congestion. He received a unit of platelets for thrombocytopenia. Hematology/oncology was consulted and chemotherapy continued to be held and the patient received daily filgrastrim. Antibiotics were discontinued 48 hours after his last fever and blood, urine, and sputum cultures remaining negative. He discharged home in stable condition with symptoms resolved. His ANC was 504/CMM on discharge.

Discussion

Human metapneumovirus (hMPV) is an enveloped, negative-sense, single-stranded RNA virus belonging to the *Paramyxoviridae* family that was discovered in the Netherlands in 2001.[1,2] The *Paramyxoviridae* family also includes measles, mumps, respiratory syncytial virus (RSV) and parainfluenza virus.[1,2] It is the leading cause of upper and lower respiratory disease worldwide and a cause of significant morbidity and mortality in premature infants, immunocompromised patients, and the elderly (age > 60 years).[2,3] Most individuals are infected with hMPV by the age of 5, but reinfections can occur throughout life due to incomplete immunity.[2,3] Transmission is through direct or close contact via large-particle aerosols, droplets, and fomites.[3] Nosocomial infection is a concern, especially in elderly patients with prolonged hospitalizations or with cardiopulmonary disease.[3] The incubation period is thought to be 5-6 days with increased incidence of infection during the winter and spring.[3,4] Symptoms in mild cases are similar to RSV infection and may include cough, wheezing, rhinorrhea, sore throat, fever.[2,4] Infection can cause otitis media, pneumonia, asthma exacerbations, or bronchiolitis.[2-4] Rapid diagnosis is based on reverse transcriptase PCR.[2,5] Use of nucleic acid amplification based-techniques, such as RT-PCR, is highly recommended in immunocompromised patients.[6]

Direct fluorescent antibody test, serology, and viral culture can also be used to detect the virus.[3] Use of chest x-ray for diagnosis is not recommended; however, CT scan of the chest may reveal bronchial wall thickening and interstitial infiltrates suggestive of lower respiratory tract infection.[6]

Prevention of hMPV infection developing into lower respiratory tract infections (LRTI) is important in patients with cancer, as LRTI is associated with a higher mortality in these patients.[5] In patients with cancer, a few studies have found possible risk factors for infection with hMPV developing into lower respiratory tract infections. These factors include recent steroid use, low lymphocyte count, early onset of hMPV infection after hematopoietic cell transplant, nosocomial infection, and hypoxia at presentation.[5]

Treatment of hMPV is usually supportive. Home remedies and non-steroidal anti-inflammatory drugs may be used for a placebo effect on severity and duration of infection, as long as there is no associated harm in their use.[6] Ribavirin 600mg three times a day and IVIG have been used in cases of severe hMPV infections; however, they are not routinely used due to adverse reactions, expense, and lack of data showing any antiviral being effective in humans.[2,3,5,6] Use of steroids has not been shown to be effective in treatment of hMPVn infection and, therefore, is not recommended.[6]

Prevention of the disease includes early infection control via hand hygiene, use of face masks, avoiding contact with large-particle aerosols and droplets, and limiting visitation of persons at risk of severe infection.[3,5,6] Guidelines from the Infectious Disease Working Party of the German Society for Hematology and Medical Oncology recommend follow up testing two weeks or longer in patients with cancer and continuing contact isolation precautions until repeat testing is negative.[6]

Studies for potential vaccines are underway in animal models and have yet to be tested in humans.[1,2] Ren et al reviewed efforts for hMPV vaccine development specifically looking at inactive vaccines, viral protein-based vaccines, and live attenuate vaccines.[1] Formalin inactivated vaccines have not proven suitable.[1] However, further investigation into other inactivation techniques is required.[1] The most promising studies are of viral protein-based vaccines involving the most immunogenic protein, fusion protein F, which facilitates viral fusion and entry.[1,2] Vaccines for other hMPV proteins, specifically P & G proteins, are underway.[1] Further trials include vaccines that are retroviral core particles, alpha virus replicon-based, or fusion protein-based.[1] Live attenuated vaccines are also being studied. Other treatment options being investigated include monoclonal antibodies, fusion inhibitors, and small interfering RNAs.[1,5]

Conclusion

This case highlights the importance of considering viral etiologies in immunocompromised patients presenting with neutropenic fever. The patient in this case had a mild case of hMPV infection based on his symptoms. However, his immunocompromised state placed him at greater risk of developing a LRTI and increased mortality. Supportive care was provided during his hospitalization. Ribavirin and IVIG have not been found beneficial in current literature review and were not recommended in this patient. Continued preventive measures, such as hand washing and limiting exposure to sick contacts, were recommended, as hMPV infection can recur.

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