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Case report

Bleeding pneumonia: Diffuse alveolar hemorrhage due to human metapneumovirus

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ABSTRACT

Diffuse alveolar hemorrhage is a condition with high morbidity and mortality. The majority of cases are caused by pulmonary capillaritis associated with systemic vasculitis. Infection disease has also been associated with this condition. A 62-year-old woman with a history of chronic alcohol abuse presented with shortness of breath, hemoptysis, constipation, and icterus. Chest x-rays on admission showed diffuse patchy opacities concerning for diffuse alveolar hemorrhage. The patient quickly developed acute respiratory failure requiring intubation. PCR identified human metapneumovirus and bronchoalveolar lavage confirmed alveolar hemorrhage. Despite all efforts, the patient ultimately developed multi-organ failure and died. Human metapneumovirus is usually associated with mild upper and lower respiratory tract infections in young children. Nevertheless, clinicians should recognize that this virus has recently emerged as a significant pathogen, particularly in adult patients with underlying conditions and the elderly population.

Introduction

Diffuse alveolar hemorrhage (DAH) is a catastrophic clinical syndrome potentially leading to respiratory failure [1]. It usually presents with hemoptysis, anemia, and diffuse alveolar infiltrates, but the findings are nonspecific [1,2]. Despite advances in the identification and management of DAH, mortality remains high ranging from 30 % to 100 %, depending on the underlying etiology [1]. Early recognition is crucial as prompt diagnosis and treatment increase the chances of survival [2]. Up to 88 % of the cases of DAH are caused by pulmonary capillaritis associated with systemic vasculitis [1,2]. In immunocompetent patients, lung infections are rarely reported as the etiology of DAH [3]. Human metapneumovirus (hMPV) mostly causes upper and lower respiratory tract infections in young children. Still, it is also a common unidentified trigger in adult patients with asthma and chronic obstructive pulmonary disease (COPD) [4,5]. Lethal hMPV infections in adults have been classically described in immunosuppressed patients [6]. We present a case of DAH secondary to human metapneumovirus infection in the setting of end-stage liver disease.

Case description

A 62-year-old woman with no known past medical history presented on February 23, 2020, with sudden onset shortness of breath at rest for one week associated with hemoptysis. On interrogation, she referred intermittent yellow sclera for one month, and her son mentioned heavy alcohol consumption. She migrated from Mexico more than 30 years ago and was never in contact with a known tuberculosis case. Given her illegal alien immigrant status, she had limited access to health care and had no regular follow-ups with primary care physicians.

On presentation in the emergency department, she was tachypneic and tachycardiac with significant respiratory distress. She was placed on a nonrebreather mask, started on broad-spectrum antibiotic therapy as per sepsis protocol, and transferred to a progressive care unit (PCU). In the PCU, she was further upgraded to bilevel positive airway pressure. Her exam was significant for scleral icterus and dried blood on lips and chin, diffuse crackles over bilateral lower lung fields, and bilateral lower extremity pitting edema.

Initial lab results showed a white blood cell count of 25.7 k/mm^3 (4.0–11.0 k/mm^3), hemoglobin of 10.1 g/dL (12.0–15.3 g/dL), and platelet count of 71,000 k/mm^3 (150–450 k/mm^3). Other lab values

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of note included albumin of 2.9 g/dL (3.5–5.7 g/dL), alkaline phosphatase 172 IU/L (35–104 IU/L), aspartate aminotransferase (AST) 133 IU/L (13–39 IU/L), alanine aminotransferase (ALT) 32 IU/L (7.0–52.0 IU/L), bilirubin 12.4 mg/dL (0.0–1.0 mg/dL), lactate 2.2 mmol/L (0.7–2.0 mmol/L), BNP 886 pg/mL (0.0–100 pg/mL), high-sensitivity troponin 449 pg/mL (0–12 pg/mL), D-Dimer 29,578 ng/mL (0–622 ng/mL), fibrinogen 183 mg/dL (163–463 mg/dL), elevated INR 1.8 (0.9–1.1), and PT 20.9 (10.1–13.1 sec).

Chest x-ray showed bilateral multifocal patchy opacities (Fig. 1a), and a CT chest showed extensive patchy parenchymal airspace opacities involving all lobes of the lung (Fig. 1b and c). CT abdomen revealed diffusely heterogeneous enhancement and nodularity throughout the liver parenchyma, suspicious for liver cirrhosis. The pancreas and spleen had a healthy contrast-enhanced CT appearance.

She subsequently developed severe respiratory acidosis, as manifested on a blood gas (pH 7.24, pCO2 68.9), prompting intubation and transfer to the intensive care unit (ICU). She was then started on intravenous (IV) steroids due to high suspicion for DAH secondary to systemic vasculitis. Bronchoalveolar lavage after intubation was performed. The airways were observed erythematous, and the lavage was with a bloody return, confirming alveolar hemorrhage. The cytology exam demonstrated benign respiratory epithelium with reactive changes, acute inflammation, macrophages, and red blood cells. Acid-fast stain and cultures were negative, as well as a *Pneumocystis jiroveci* smear.

Further laboratory testing was negative for autoimmune disease, including normal IgG and IgM cardiolipin antibodies, normal Beta-2-Glycoprotein IgG and IgM antibodies, negative anti-nuclear antibodies (ANA), negative anti-neutrophil cytoplasmic antibodies (P-ANCA and C-ANCA), negative rheumatoid factor, and negative anti-glomerular basement membrane antibody. Infectious disease workups were also negative, except for the respiratory viral panel collected from a nasopharyngeal swap that confirmed the presence of human metapneumovirus by PCR. These tests included negative HIV-1/2 antibodies and HIV-1 antigen, negative *Histoplasma* galactomannan urine antigen, negative *Legionella* and pneumococcal urinary antigens, negative Epstein-Barr DNA PCR, negative hepatitis viral panel, negative *Blastomyces dermatitidis* antibodies, negative *Aspergillus* galactomannan antigen and galactomannan index, negative *Mycoplasma,* West Nile virus, cytomegalovirus and dengue virus serum IgM and IgG antibodies, negative blood cultures, negative urine cultures, and negative bronchial brushing cultures (including negative fungal cultures). The Illinois Department of Public Health was contacted for coronavirus disease 2019 (COVID-19) testing, but the request was denied as the patient did not meet the criteria for trial at that point. She had no history of recent travels, no sick contacts, and community transmission was not suspected in the State of Illinois at that time.

On admission day 4, she was started on vasopressors due to shock. On day 8, she was placed in a prone position for 24 h due to worsening hypoxia. On days 9 and 10, she required hemodialysis for severe acute kidney injury (creatinine 4.83 mg/dL) with acidosis (pH 7.21). On day 11 she developed disseminated intravascular coagulation (platelet count 19 k/mm^3, D-Dimer 36,469 ng/mL and fibrinogen 91 mg/dL). CT head without contrast showed scattered small bilateral subarachnoid hemorrhages. She ultimately developed multi-organ failure, had a cardiac arrest, and was declared dead after unsuccessful attempts at resuscitation.

Discussion

Diffuse alveolar hemorrhage is a critical condition that presents with hemoptysis, anemia, diffuse radiographic pulmonary infiltrates, and hypoxemic respiratory failure [1,2]. DAH is characterized by the accumulation of intra-alveolar red blood cells originating from the bronchial vessels, the pulmonary vessels, or the microcirculation [1–3]. Bronchoscopy with bronchoalveolar lavage is the gold standard to confirm the diagnosis. Systemic autoimmune diseases such as anti-neutrophil cytoplasmic antibody-associated vasculitis, anti-glomerular basement membrane disease, and systemic lupus erythematosus, represent the most common cause of capillaritis associated with DAH. Although rare in immunocompetent patients, lung infections can also cause alveolar microcirculation injury, secondary to generalized or lung-specific disease, and DAH [2,3]. In our patient, likely the presence of chronic alcoholism, unmanaged end-stage liver disease, decompensated liver cirrhosis, and hence baseline predisposition for bleeding diastasis played an essential role in the development of infectious DAH.

Human metapneumovirus is an enveloped, non-segmented, negative-sense, single-stranded RNA virus [7]. It belongs to the order *Mononegavirales* in the family *Paramyxoviridae,* and it was the first human member of the *Metapneumovirus* genus in the subfamily *Pneumovirinae* of the family *Paramyxoviridae* [7,8]. Since its discovery, hMPV has been isolated on all continents and has a seasonal distribution, with outbreaks primarily occurring in the spring and winter months and accounting for up to 11 % of respiratory tract infections [4,5]. It is thought to be transmitted by direct or close contact with contaminated secretions, which may involve saliva, droplets, or large particle aerosols. It has an incubation period of 5–9 days, with a median of 5 days [9].

In general terms, hMPV infection cannot be distinguished from other respiratory viruses, and symptoms include fever, cough, rhinorrhea, and wheezing [5,9]. The severity of the illness varies considerably, from asymptomatic carriers to acute respiratory distress syndrome (ARDS). Severe disease has been mainly

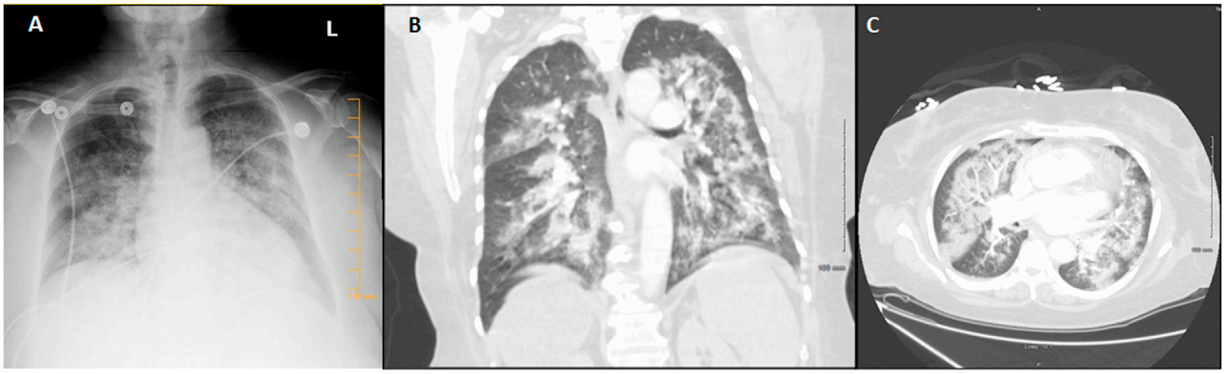

Fig. 1. Anteroposterior chest x-ray view (A) showing diffuse interstitial airspace opacities throughout the upper and lower lobes bilaterally. CT chest, coronal plane (B), and transversal plane (C), indicating extensive airspace opacities diffusely involving all lobes.

described in children, elderly and immunocompromised patients with underlying conditions, including asthma, cancer, and COPD [6,8,10]. DAH is an uncommon manifestation of severe hMPV infection in otherwise immunocompetent patients, in which the more common pathogens include influenza A (H1N1), dengue, leptospirosis, malaria, and *Staphylococcus aureus* infection [3].

hMPV should be considered an emerging respiratory pathogen with a significant burden of disease in adults. In a population-based surveillance study in the United States (US) by Jain [11], hMPV was isolated as a single pathogen in 4 % of hospitalized adults with community-acquired pneumonia. In one retrospective study by Hasvold [5], 31 % of hospitalized patients with hMPV infection required ICU admission, and 48 % of those patients met the criteria for ARDS. Furthermore, the latest data available from the CDC WONDER mortality database show that 72.6 % of the reported deaths in the US since 2011 from hMPV pneumonia or bronchiolitis (ICD-10 codes J12.3 and J21.1, respectively) occurred from 2016 onwards, the vast majority in patients 65 years old or older (45.3 %) [12].

Management of hMPV infection is primarily supportive care as there is no standard treatment; however, promising therapy with IV ribavirin and IV immunoglobulin (IVIG) has been reported [[13]]. Ribavirin is a nucleoside with activity against RNA viruses that have shown *in vitro* activity against hMPV and exhibited some efficacy in animal models and case series [[8],[9],[13]]. Commercial IVIG contains neutralizing action against hMPV that also has demonstrated prophylactic and therapeutic efficacy in animal models and case series [[8],[13]]. Most important, droplet respiratory precautions must be applied to prevent nosocomial transmission of this pathogen.

Lethal hMPV infections in adults have been classically described in immunosuppressed patients. Nevertheless, in recent years this pathogen has emerged as a significant respiratory virus that carries high morbidity and mortality, especially in the elderly population. Lower respiratory tract infections are rarely reported in association with DAH, but they should be considered in the differential diagnosis because of the therapeutic implications.

Author contribution

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in this work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication.

Informed consent

Written informed consent was obtained from the patient's next-of-kin for publication of this case report. A copy of the written consent is available for review by the Editor of this journal.

Ethical approval

Our institution does not require ethical approval for case reports

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Declaration of Competing Interest

The authors declared no conflict of interest.

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